Optimising Outcomes for Patients with Early Inflammatory Arthritis

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The candidate confirms that the work submitted is her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapters 7 and 9 include work presented in jointly authored publications by Dr Sarah Horton, Dr Ai Lyn Tan, Dr Jane Freeston, Dr Richard Wakefield, Prof Maya Buch and Prof Paul Emery. The aims of the study were set by Dr Horton, Prof Buch and Prof Emery. Dr Horton was involved in the recruitment and clinical management of patients in the study, performed a significant proportion of the clinical assessments, validated the clinical data, planned and performed the statistical analyses, produced the initial draft of the article and was responsible for integrating all co-author revisions. All authors were involved in the design of the prospective cohort study and approved the final articles. Other authors involved in the recruitment and clinical management of patients in the study were Dr Tan, Dr Freeston, Dr Wakefield and Prof Emery. Dr Tan, Dr Freeston and Dr Wakefield also performed a proportion of ultrasound assessments within the study.

The papers are as follows:

- Sarah Horton, Ai Lyn Tan, Jane Freeston, Richard Wakefield, Maya Buch and Paul Emery. Ultrasound-detectable grey scale synovitis predicts future fulfilment of the 2010 ACR/EULAR RA classification criteria in patients with new-onset undifferentiated arthritis. RMD Open 2017, 3(1): e000394.
- Sarah Horton, Ai Lyn Tan, Jane Freeston, Richard Wakefield, Maya Buch and Paul Emery. Discordance between the predictors of clinical and imaging remission in patients with early rheumatoid arthritis in clinical practice: implications for the use of ultrasound within a treatment-to-target strategy. Rheumatology 2016, 55(7): 1177-87.

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Abstract

Background: Early and effective treatment of inflammatory arthritis (IA) is essential to preserve patients' functional ability and prevent joint damage. Recent strategies for optimising care have included implementing treatment-to-target management and utilising ultrasound to guide treatment decisions. The 2010 ACR/EULAR rheumatoid arthritis (RA) classification criteria were also recently developed with the aim of facilitating the study of early IA.

Aims: To determine the phenotype, management and outcomes of patients with early IA, defined using the 2010 RA criteria, in clinical practice. Specific objectives were to risk stratify patients according to future disease severity, determine their response to treatment and assess the potential utility of ultrasound within a treatment-to-target strategy.

Methods: An audit and a prospective longitudinal observational study were conducted in patients attending the Leeds Early Arthritis Clinic. Patients were classified as undifferentiated arthritis (UA) or RA according to the 2010 RA criteria at baseline. Logistic regression methods were used to identify baseline predictors of outcome and treatment response.

Results: Ultrasound detectable synovitis at baseline was independently associated with a higher rate of methotrexate use, persistence of IA and development of new ultrasound erosions at one year in patients with UA and RA, as well as progression from UA to RA in the subset of patients with UA at baseline. A lack of concordance was observed between clinical and ultrasound-determined remission in RA patients receiving treatment-to-target management. In this sub-group, objective baseline measures of disease were predictive of imaging remission in comparison to the predominantly subjective parameters, which were predictive of clinical remission.

Conclusions: This verifies the value of ultrasound as a prognostic tool in the risk stratification of patients with early IA, over and above the clinical application of the 2010 RA criteria and clinical assessments. It supports future research in the use of ultrasound within a treatment-to-target strategy.

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Chapter 1 : **Introduction**

Over the past decade the management of early inflammatory arthritis (IA), and consequently the prospects for patients, has advanced dramatically. Early, effective therapy with tight monitoring towards a pre-defined target (clinical remission or at least low disease activity) is now recognised to be of key importance in patients at risk of persistent disease/rheumatoid arthritis (RA) (Smolen et al., 2010; Singh et al., 2012; Singh et al., 2016; Smolen et al., 2016; Combe et al., 2017; Smolen et al., 2017). With a range of conventional disease-modifying anti-rheumatic drugs (DMARDs) and biologic therapies now available, remission is a realistic target for treatment. This has led to a changing perception of RA from that of a frequently progressive and chronic disease towards a readily treatable and potentially even curable or preventable condition. However, none of these drugs are universally effective and some patients prove to have severe disease resistant to several of these therapies.

The 2010 ACR/EULAR RA classification criteria are now available to aid the prompt diagnosis, management and study of patients with RA at an early stage in their disease (Aletaha, D. et al., 2010). Furthermore, ultrasound is becoming increasingly used in clinical practice, both as a tool to guide diagnosis and in directing treatment decisions in patients with IA (Colebatch et al., 2013; D'Agostino, M.A. et al., 2016).

A literature review was undertaken to identify gaps in the existing research of patients with early IA, relevant to the management of patients in a contemporary clinical practice setting (Chapter 2). Pubmed was used to search for English language articles concerning four main areas of recent research in patients with early IA (including patients with undifferentiated arthritis, UA, and/or RA). These are displayed in Table 1, along with the selection criteria used to identify articles for review. References of the selected papers were also searched to identify additional, relevant articles. Literature searches were initially conducted in 2012 and were last updated in October 2016. Subsequently, a central hypothesis, aims and objectives for this research were devised (Chapter 3) and study methods were established (Chapter 4). Results, pertaining to the relevant objectives, and their implications for

future clinical practice and research, are presented and discussed in Chapters 5-9, and summarised in the final discussion (Chapter 10).

Table 1. Literature searches conducted for review.

Research Area	Selection Criteria	Section of Thesis
Performance of the 2010 ACR/EULAR RA classification criteria	Cohort studies evaluating outcomes in patients with early IA, classified using the 2010 ACR/EULAR RA criteria. Excluding historic cohorts in which anti-citrullinated peptide antibody (ACPA) testing (a factor with high weighting in the new criteria) was not available.	2.1
Risk stratification for future disease progression/severity	Prospective, longitudinal studies conducted in patients with early IA. Studies were restricted to those in which patients were disease-modifying anti-rheumatic drug (DMARD)-naïve, enrolled after 1990 (since availability of modern day DMARDs including methotrexate) and investigating baseline clinical, laboratory or imaging characteristics widely available in clinical practice (i.e. excluding studies restricted to hand bone densitometry, magnetic resonance imaging [MRI] and experimental serological or synovial biomarkers). Due to the volume of literature available in patients with RA, studies exclusive to these patients which were restricted to univariable analyses were excluded.	2.2
Effectiveness of ultrasound for use as a clinical tool	Articles reporting aspects of validity and/or the discriminative ability of ultrasound in detecting ultrasound pathology relevant to IA, i.e. synovitis, tendon abnormalities and bone erosions.	2.3
Efficacy of treatment strategies	Observational and intervention studies in patients with early IA reporting patient outcomes according to specific treatment strategies. Due to the volume of literature available in patients with RA, studies exclusive to these patients were restricted to randomised controlled trials and other intervention studies with a strict treatment protocol, including treatments and treatment dosing schedules in frequent use in current daily practice.	2.4

Chapter 2 : **Literature Review**

2.1 What is Inflammatory Arthritis and How is it Classified?

Inflammatory arthritis is an arthropathy primarily caused by an inflammatory process, as distinct from arthritis caused by a degenerative process (for example with aging, repetitive use or trauma). Its hallmark, synovitis, manifests as joint pain, stiffness (particularly in the morning or after inactivity) and swelling. There are several causes of IA including infection, crystal deposition disease, and autoimmune or autoinflammatory diseases including RA, connective tissue diseases and spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and reactive arthritis). This thesis focuses on RA and undifferentiated arthritis (UA, inflammatory arthritis not explained by any other specific disease category).

2.1.1 Rheumatoid Arthritis

Rheumatoid arthritis is characterised by persistent synovial inflammation, usually affecting multiple small joints in a symmetrical distribution. Persistent synovitis is associated with erosive joint damage (van der Heijde et al., 1995) and may lead to significant long-term disability (Yelin et al., 1987; Scott et al., 2000). It is a systemic autoimmune disorder that is associated with extra-articular complications, co-morbidity and excess mortality; primarily driven by increased cardiovascular disease due to atherosclerosis (Agca et al., 2016).

2.1.1.1 Prevalence and Incidence

Rheumatoid arthritis is the commonest cause of IA with a prevalence of approximately 1% (Symmons et al., 2002). Annual incidence rates across Northern Europe are estimated to be of the order of 20-40/100,000 (Söderlin et al., 2002; Savolainen et al., 2003; Pedersen et al., 2009; Humphreys et al., 2013).

2.1.1.2 Aetiology and Pathogenesis: Seropositive versus Seronegative disease

The pathogenesis of RA is understood to be quite heterogeneous. In particular, serological status appears to differentiate patients into distinct disease subsets.

Rheumatoid factor (RF) is an autoantibody detectable in the serum of approximately 60% of patients with RA (Miller et al., 2015; Ajeganova et al., 2016). It is directed against the constant fragment of immunoglobulin (Ig) G. Rheumatoid factor and IgG may combine to form immune complexes which may contribute to the disease process. However, its presence is not specific to RA, occurring in approximately 10% of healthy individuals and at higher frequencies in other autoimmune connective tissue diseases and chronic infections. Hence, investigations into the presence of other autoantibodies in RA have led to the development of new serological tests which include the detection of anti-cyclic citrullinated peptide antibodies (ACPAs). These are present in approximately two-thirds of patients with established RA (Nielen et al., 2004; Demoruelle et al., 2013), but have a high specificity of around 95% (Nishimura et al., 2007)

Genetic differences between seropositive and seronegative patients have been observed. The shared epitope alleles HLA-DRB1*01, DRB1*04, and DRB1*10 (which code a for a sequence of five amino acids in HLA-DRβ1 chains) are associated with increased risk of ACPA-positive RA (Huizinga et al., 2005; van der Helm-van Mil et al., 2006; Ding et al., 2009), whereas association of DRB1*03 with ACPA-negative disease has been described (Irigoyen et al., 2005; Verpoort et al., 2005). A further 31 genetic risk loci have been identified amongst seropositive patients (Stahl et al., 2010), whilst association of ACPA-negative RA with a single locus (IRF5) has been reported (Sigurdsson et al., 2007).

Smoking is recognised as a risk factor in the aetiology of ACPA-positive RA but not in ACPA-negative disease, via interaction with the shared epitope region of HLA-DRβ1 chains (Klareskog et al., 2006; Too et al., 2012). It has been hypothesised that smoking contributes to the production of citrullinated antigens which bind with shared epitope (Hill et al., 2003), leading to the activation of T cells (Law et al., 2012) and subsequent generation of ACPAs by B cells.

Interesting histological and immunological differences have also been observed. In patients with established RA undergoing therapeutic arthroscopic lavage of an inflamed knee joint, synovial analysis demonstrated greater infiltration of lymphocytes in ACPA-positive (n=34) versus ACPA-negative (n=23) patients (van Oosterhout et al., 2008). There was also significantly less fibrosis and less hypertrophy of the synovial lining layer. Of note, this was a heterogeneous patient group; disease durations and previous treatments were variable, which included the prior use of tumour necrosis factor (TNF)-inhibitors in 17 patients. Significant clinical differences between ACPA groups were also apparent, with lower disease activity scores (DAS) and a high proportion of males being observed amongst the ACPA-negative group.

Immunological differences have been implicated in early IA. In Birmingham, synovial fluid was aspirated from a knee or ankle joint in 36 patients with very early IA, with symptoms for less than three months (Raza et al., 2005b). A distinct cytokine profile, with elevated levels of T cell, stromal cell and macrophage related cytokines, was observed in eight patients who fulfilled 1987 ACR RA criteria over the following 18 months (seven of whom were RF and ACPA positive) in comparison to the remaining 28 patients who did not develop RA (only one of whom was ACPA positive), the majority of whom had resolving or persistent UA. In Leeds, a cross-sectional analysis of peripheral blood samples from 60 patients with early IA (with symptoms for less than one year, 25 of whom were fulfilling 1987 ACR RA criteria) identified differences in T cell populations, and levels of cytokines involved in T cell differentiation, between ACPA-positive and ACPA-negative individuals (Cuthbert et al., 2010). Patients with ACPA-positivity had lower concentrations of naïve and regulatory T cells and higher numbers of cytokine-activated T cells, in comparison to ACPA-negative patients in whom T cell profiles appeared similar to healthy controls. However, disease activity may have been a substantial confounder: C-reactive protein (CRP) level was associated with the concentration of cytokine-activated T cells and there was a trend towards higher CRP in patients with ACPA positive disease. Larger studies in well-defined patient cohorts are needed to further discern any pathological differences.

Further evidence for a divergence in pathogenesis is provided by clinical data illustrating disparity of response to treatments including rituximab and possibly

methotrexate. Data from clinical trials and registries illustrate superior rates of response to rituximab (B-cell depleting therapy) in patients who are seropositive for RF and/or ACPA (Emery et al., 2006; Cohen et al., 2007; Isaacs et al., 2009; Strangfeld et al., 2009; Van Vollenhoven et al., 2009a; Mease et al., 2010; Sellam et al., 2010; Tak et al., 2011). Studies suggesting a divergence in the response to methotrexate are discussed further in section 2.4.2.4 (van Dongen et al., 2007; Wevers-de Boer, K. V. C. et al., 2012; Nam et al., 2014b).

2.1.1.3 Classification Criteria for Rheumatoid Arthritis

- *1987 ACR RA Classification Criteria*

Until recently, the 1987 American College of Rheumatology (ACR) RA criteria were widely used in research to identify patients with RA (Arnett et al., 1988). They were originally developed to differentiate patients with established RA from other types of established arthritis. They stipulate a minimum duration of symptoms of six weeks and include consequences of chronic inflammation (rheumatoid nodules and radiographic changes) as two of the seven criteria. Meta-analyses have demonstrated they have poor sensitivity and specificity in identifying patients with early RA versus expert opinion (Banal et al., 2009).

- *2010 ACR/EULAR RA Classification Criteria*

The importance of early, aggressive treatment pushed the need for new classification criteria to facilitate the diagnosis, management and study of patients with early RA. The 2010 ACR/European League Against Rheumatism (EULAR) RA criteria were developed with the aim of classifying patients at risk of persistent IA. Data from patient cohorts and expert opinion was utilised to determine a set of criteria that would identify patients likely to require methotrexate as an indicator of persistence and severity (Aletaha, D. et al., 2010). To fulfil the criteria patients with at least one clinically swollen joint are required to score at least six points or demonstrate definite erosive disease, defined by the presence of typical radiographic erosion affecting at least three of the following joints: proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist or metatarsophalangeal (MTP) joints (van der Heijde et al., 2013).

- *Performance of the 2010 ACR/EULAR RA Classification Criteria*

The new criteria have been retrospectively applied to early IA patient cohorts. Improved sensitivity of the 2010 ACR/EULAR criteria, in comparison to the 1987 ACR criteria, has been demonstrated for various outcomes including the need for methotrexate, the need for DMARDs, expert opinion of RA, persistent IA and erosive disease (Table 2). However, specificity estimates indicate there is a risk of misclassification of a proportion of patients as RA under the criteria, highlighting the need for further study of prognostic factors in this patient group. Of note, the majority of studies were published prior to the formulation of the EULAR definition of erosive disease; hence, the 2010 criteria were most frequently applied considering a score of at least six points as the sole criterion for a definition of RA.

Table 2. Cohort studies evaluating performance of the 2010 ACR/EULAR RA criteria.
Excludes historical cohorts in which ACPA testing (a factor with high weighting in the new criteria) was not available.

Study Population	Years of patient recruitment	n	Inclusion Criterion	Study Design	Outcomes	2010 Criteria				1987 Criteria		Reference
						Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	
Leiden (Netherlands)	1993-2009	2258	• Symptoms <2 yrs • 'Arthritis' ≥1 joint	Prospective (2010 criteria applied retrospectively)	MTX use 1 yr; DMARD use 1 yr; Persistent arthritis (absence of sustained DMARD-free remission) 5 yrs	88; 79; 77	54; 68; 56	-	-	61; 54; 53	74; 87; 75	(van der Linden et al., 2011)
Brittany (France, multicentre)	1995-1997	270	• Symptoms <1 yr • Clinical swelling with tenderness or reduced ROM	Prospective (2010 criteria applied retrospectively)	RA (expert opinion) 2 yrs with use of DMARD or steroid	58	86	71	78	64	80	(Varache et al., 2011)
Jyväskylä (Finland)	1997-1999	221	• 'Recent onset' (median symptoms 6 mths) • 'Synovitis' • Excluded non-RA diagnoses	Patient invite to 10 year follow-up visit (2010 criteria applied retrospectively)	Erosive disease at 10 years	87	44	68	72	70	47	(Mäkinen et al., 2013)
France (multicentre)	1998-2002	310	• Symptoms <6mths • Swelling >4wks • ≥2 swollen joints • Excluded non-RA diagnoses	Prospective (2010 criteria applied retrospectively)	RA (expert opinion) at 6 yrs; Erosive (EULAR definition*) at 2 yrs	84*; 100*	71*; 36*	85*; 11*	70*; 100 *	78; 100	64; 39	(Le Loët et al., 2015)

Amsterdam (Netherlands)	2000 onwards	455	• Symptoms <2 yrs • DMARD-naïve	Prospective (2010 criteria applied retrospectively)	MTX use 1 yr; RA (expert opinion) at 1 yr; Erosive disease at 3 yrs	85; 90; 91	50; 48; 21	86; 79; 22	49; 69; 91	-	-	(Britsemmer et al., 2011)
Nagasaki (Japan)	2001 onwards	166	• UA** <6mths duration • Excluded 1987 ACR RA and non-RA diagnoses	Prospective (2010 criteria applied retrospectively)	DMARD start over 1 yr; 1987 ACR RA criteria at 1 yr	62; 61	83; 78	83; 76	61; 63	-	-	(Tamai et al., 2014)
Seville (Spain)	2002-2006	201	• Swelling ≥4 wks and ≤1 yr • ≥2 swollen joints • Excluded non-RA diagnoses	Prospective (2010 criteria applied retrospectively)	MTX use within 1 yr; DMARD start over 1 yr; RA (expert opinion) over 1 yr	80; 75; 87	62; 73; 73	90; 98; 91	43; 14; 64	58; 56; 69;	64; 91; 94	(Reneses et al., 2012)
Amsterdam (Netherlands)	2002-2010	301	• Symptoms <1 yr • Clinical arthritis by expert opinion	Prospective (2010 criteria applied retrospectively)	1987 ACR RA criteria at 2 yrs	83	76	77	91	-	-	(de Hair et al., 2012)
SAVE (international, multicentre study)	2004-2006	303	• Symptoms ≤16 wks • 'Arthritis' ≤1 joint	Prospective study, all patients receiving 120mg methylprednisolone IM or placebo (2010 criteria applied retrospectively)	DMARD start over 1 yr; RA (expert opinion) over 1 yr	80; 85	63; 64	71; 68	73; 82	55; 65	76; 80	(Biliavska et al., 2013)
REACH (Netherlands, multicentre)	2004-2008	231†	• Symptoms <1 yr • Clinical swelling or pain/reduced ROM in ≥2 joints with ≥2 other factors††	Prospective (2010 criteria applied retrospectively)	MTX use 1 yr; Persistent arthritis (synovitis present or DMARD use) 1 yr	74; 69	66; 72	76; 87	63; 46	-	-	(Alves et al., 2011)

Umea (Sweden)	2004-2009	313	• Symptoms <1 yr • Synovitis ≥1 joint (excluding DIPs, 1st CMCs and 1st MTPs) • Excluded non-RA diagnoses	Retrospective (2010 criteria applied retrospectively)	MTX use within 1 yr; RA (expert opinion) at 1 yr	84; 91	54; 65	-	-	68; 72	79; 83	(Berglin and Dahlqvist, 2013)
Christchurch (New Zealand)	2004-2010	79	• Symptoms <1 yr • ≥1 swollen joint • Excluded non-RA diagnoses	Prospective (2010 criteria applied retrospectively)	DMARD use at 2 yrs; Erosive disease at 2 yrs	79; 88	83; 33	98; 31	29; 88	-	-	(Raja et al., 2012)
Tokyo (Japan)	2009-2010	82	• Any symptom duration (mean 18 wks) • Clinical swelling • Excluded non-RA diagnoses	Retrospective (2010 criteria applied retrospectively)	RA (expert opinion) over follow-up (at least 3 mths follow-up)	74	71	93	36	47	93	(Kaneko et al., 2011)
Birmingham (UK)	Not stated	205	• Symptoms <3 mths • Clinical swelling • Excluded if later fulfilled non-RA diagnosis	Prospective (2010 criteria applied retrospectively)	MTX use 1.5 yrs; DMARD use 1.5 yrs	68; 62	72; 78	57; 75	81; 66	42; 38	88; 93	(Cader et al., 2011)

PPV: positive predictive value, NPV: negative predictive value, MTX: methotrexate, ROM: range of movement, SAVE: Stop arthritis very early, IM: intra-muscular, REACH: Rotterdam early arthritis cohort, DIP: distal interphalangeal joint, CMC: carpometacarpal joint.
*Patients fulfilling the EULAR definition for erosive disease considered as fulfilling the criteria regardless of clinical score (typical radiographic erosion in ≥3 joints) (van der Heijde et al., 2013).
**Includes 13 patients without clinical joint swelling and 2 patients with typical radiographic erosion.
†Excludes patients from the REACH cohort whose data were used in phase 1 of development of the 2010 criteria.
††Morning stiffness for more than 1 hour; unable to clench a fist in the morning; pain when shaking someone's hand; pins and needles in the fingers; difficulties wearing rings or shoes; a family history of RA; unexplained fatigue for less than 1 year.

2.1.2 Undifferentiated Arthritis

This term is used to categorise patients with IA in whom it is not possible to establish a specific diagnosis. Historically UA has been defined as IA not fulfilling 1987 ACR RA criteria, or criteria for other rheumatic diseases. Outcomes within this patient group are wide-ranging, varying from self-limiting disease to erosive RA. Studies demonstrate 14-53% of patients with UA may progress to RA (defined by non-fulfilment and fulfilment of 1987 ACR criteria, respectively) over one to three years (Quinn et al., 2003; Caro-Oleas et al., 2008; van Der Helm-van Mil et al., 2008; Salaffi et al., 2010; de Rooy et al., 2011; Tamai et al., 2014). Differences in the rate of progression across these studies may be, at least in part, due to differences in inclusion criteria.

Differences between patients with UA defined by non-fulfilment of 1987 ACR RA criteria and UA defined by non-fulfilment of 2010 ACR/EULAR RA criteria have been demonstrated in the Leiden early IA cohort (Krabben et al., 2012). The latter UA group had milder disease characteristics at baseline and superior outcomes including a higher rate of sustained remission over 7 years; rates were 46% in patients with non-fulfilment of 2010 criteria (n=776) versus 34% in patients with non-fulfilment of 1987 criteria (n=1166) (HR [hazard ratio] 1.5, 95% confidence interval [CI] 1.2-1.7).

Despite milder disease characteristics, UA defined by non-fulfilment of the 2010 criteria is not a benign condition. In a UK study, 10% of such patients with very early disease (symptoms for less than three months) progressed to fulfil 2010 ACR/EULAR RA criteria over 18 months (Cader et al., 2011). Of patients fulfilling neither 2010 ACR/EULAR criteria nor 1987 ACR RA criteria, 10% and 21% of patients progressed to fulfil the 2010 and 1987 criteria, respectively. In a Japanese cohort, a rate of progression to 1987 ACR RA of 32% was observed over one year, in a similarly defined UA group but with symptoms for up to six months (Tamai et al., 2014).

The other studies displayed in Table 2 also indicate that there is a proportion of patients with UA, not fulfilling 2010 ACR/EULAR RA criteria, who are destined to require DMARDs (including methotrexate), develop persistent disease and receive a diagnosis of RA by their physician. The potential for these patients to benefit from

early intervention (discussed further in section 2.4.2) emphasises the need to identify these at risk patients early.

2.2 Predicting Prognosis in Patients with Early Inflammatory Arthritis

Summaries of the studies identified and reviewed are presented in Tables 3 to 7 (see Table 1 for selection criteria). When available, results of multivariable analyses are presented preferentially (demonstrating independently predictive characteristics). The main findings are summarised with respect to the main outcomes assessed in section 2.2.2, below.

The prognostic value of the majority of predictive factors identified seems plausible and results are largely consistent across studies. Differences in treatment regimens as well as other study methods may have contributed to some of the variation in results observed across studies. Generally, later cohorts are more likely to have included more aggressive treatment strategies, in line with the increasing awareness of the importance of such an approach in optimising patient outcomes. The strengths and limitations of study methods in respect to the areas of patient selection, outcomes assessed and statistical methods are discussed below.

2.2.1 Populations

The majority of studies selected patients from early arthritis clinics (EACs) in secondary or tertiary care settings. Implications of this include the potential for exclusion of patients with short, self-limiting episodes of IA. However, this is not the main population of interest and inclusion of such patients (for example post-viral illnesses) may introduce difficulty in the interpretation of results. Indeed, eligibility criteria for several studies include a minimum duration for symptoms.

In the Norfolk Arthritis Register, in which patients with at least four weeks of symptoms were recruited from primary care, 73% of patients were referred to hospital over three years (Harrison and Symmons, 2000). However, since the time of this study there has been increasing awareness of the importance of early

diagnosis and several guidelines have been published emphasising the need for early referral (Luqmani et al., 2006; www.nice.org.uk, 2009). Therefore, restricting the population to secondary/tertiary care in more recent studies seems reasonable.

- *Prognosis in patients with UA, RA and non-RA (Table 3)*

It may be argued that to enable the application of results to all patients with early IA, it may be inappropriate to exclude specific diagnoses. Classification criteria (including 1987 ACR RA criteria) have been shown to have a low sensitivity and specificity in early IA cohorts (Banal et al., 2009) and it is plausible that an initial physician impression at presentation may be revised at a later date, perhaps with the exception of clearly identifiable cases of crystal arthropathy or culture-positive infective or reactive arthritis. However, it may be difficult to draw meaningful conclusions from studies which allow for inclusion of such a variable patient population.

- *Prognosis in patients with UA and RA (Table 4)*

Studies excluding non-RA diagnoses provide more consistency in patient selection. Hence, their results may be easier to interpret and more translatable into daily practice. Most studies included patients with swelling of at least two joints. These studies often reported that a substantial proportion of their patients fulfilled 1987 ACR criteria for RA at baseline. This perhaps explains the poor outcomes observed in these studies (Bukhari et al., 2002). Therefore, results of a number of these studies may not be applicable to a proportion of patients with UA initially presenting with monoarthritis.

- *Prognosis in patients with UA (Table 5)*

Historically UA has been defined as IA not fulfilling 1987 ACR RA criteria or criteria for other rheumatic diseases. These studies therefore potentially include patients who would now be classifiable as RA according to the 2010 ACR/EULAR RA criteria. The definition of ‘arthritis’ also varied considerably across these studies, although joint swelling was a requisite for inclusion in the majority of studies. In 2011, a multinational expert group (the 3E initiative) agreed a definition of UA of at least one swollen joint and no clear diagnosis after rheumatologic assessment (Machado et al., 2011).

- *Prognosis in patients with RA (Tables 6 and 7)*

The majority of studies were conducted in patients fulfilling 1987 ACR RA criteria, either at or during follow-up. However, a small number of studies are available investigating prognostic factors in patients with RA defined according to a physician impression of RA (Contreras-Yanez et al., 2012; da Mota, L. et al., 2012; Ma et al., 2012) or likely RA (Wevers-de Boer, K. V. C. et al., 2012).

Variable definitions of UA and RA across these studies suggest the need for further investigation of the prognostic factors in patients with early IA in well-defined patient groups, relevant to contemporary clinical practice, i.e. in patients with UA or RA defined according to the 2010 ACR/EULAR RA criteria.

2.2.2 Outcomes

- *Predicting persistence of disease or progression to RA, providing guidance for commencement of DMARD therapy*

Persistence of IA (defined by ongoing synovitis and/or concurrent treatment) and progression to RA have been shown to be associated with factors now included in the 2010 ACR/EULAR RA criteria (seropositivity for rheumatoid factor [RF] and/or ACPA, longer symptom duration, greater small joint involvement and higher levels of inflammatory markers such as CRP) (Tables 3 to 5). Additional poor prognostic factors include older age (Boire et al., 2005), female gender (Harrison et al., 1996; Quinn et al., 2003), initial symptoms in the upper limbs (de Rooy et al., 2011), presence of the shared epitope (de Rooy et al., 2011), poor physical function (greater Health Assessment Questionnaire [HAQ] score) (Quinn et al., 2003) and existing radiographic erosive damage (Boire et al., 2005).

The need for DMARD therapy, or methotrexate therapy in particular (recommended as the optimal first-line therapy for patients with RA or those at risk of persistent disease (Combe et al., 2017; Smolen et al., 2017)), has been used as a proxy for disease which is likely to be persistent, such as in the development of the 2010 ACR/EULAR RA criteria. Progression to RA has been largely defined using 1987 ACR criteria. In clinical practice, knowledge of the predictors of persistence of disease may arguably be of greater value for the management of individual

patients, especially considering poor sensitivity of these criteria in early IA and the possibility that commencement of therapy may have prevented progression in a subset of patients in these cohorts.

- *Predicting severity or propensity of disease to cause radiographic damage and long-term disability, providing guidance as to whom may benefit from aggressive early treatment such as initial combination DMARD therapy or biologic therapy*

A selection of studies of patients with early IA have evaluated severity outcomes, identifying prognostic value of ACPA-positivity (Visser et al., 2002), RF-positivity (Bukhari et al., 2002; Funck-Brentano et al., 2013), age (Bukhari et al., 2002; Jansen et al., 2002), involvement of the hands (Jansen et al., 2002), symptom duration (Boire et al., 2005) and radiographic damage at baseline (Bukhari et al., 2002). Outcomes employed varied from presence of radiographic erosions at follow-up (Bukhari et al., 2002), development of new radiographic erosions (Funck-Brentano et al., 2013) or progression in radiographic scores (Visser et al., 2002), to combined outcomes of radiographic progression and/or significant disability (Jansen et al., 2002; Boire et al., 2005).

Follow-up times varied from one to five years. It is conceivable that in studies with shorter follow-up, a number of potentially erosive patients may not yet have developed erosions visible on x-ray. Furthermore, it is plausible that the frequency of radiographic progression in early IA may be reduced in later studies due to the increased awareness of the need for early, aggressive treatment, and therefore large numbers of patients may be needed to provide significant power in later cohorts.

Other severity outcomes studied in early RA include loss of bone mineral density (Deodhar et al., 2003; Boyesen et al., 2009; Hoff et al., 2009), specific aspects of functional ability (such as mobility, grip strength and self-care) (Evers et al., 1998), psychosocial outcomes (Smedstad et al., 1997), quality of life (Cohen et al., 2006; da Mota, L.M. et al., 2012) and work disability, including the continued ability to work (Albers et al., 1999; Verschueren et al., 2009) and work productivity (Puolakka et al., 2005).

- *Predicting response to therapy, providing guidance for the choice of treatment*

Investigations of factors predictive of treatment response have largely been conducted in studies with protocolised treatment, in a selection of open-label (Verschueren et al., 2009; Bosello et al., 2011; Saevarsdottir et al., 2011; Wevers-de Boer, K. V. C. et al., 2012; Gremese et al., 2013), single-blind (Wessels et al., 2007; Heimans et al., 2013) and double-blind studies (Takeuchi et al., 2014). Baseline factors consistently identified as predictive of poor response are older age (Verschueren et al., 2009; Saevarsdottir et al., 2011; Heimans et al., 2013), female gender (Wessels et al., 2007; Bosello et al., 2011; Saevarsdottir et al., 2011; Wevers-de Boer, K. V. C. et al., 2012; Takeuchi et al., 2014), smoking (Wessels et al., 2007; Saevarsdottir et al., 2011), higher body mass index (BMI) (Wevers-de Boer, K. V. C. et al., 2012; Heimans et al., 2013), greater disease activity (Wessels et al., 2007; Saevarsdottir et al., 2011; Wevers-de Boer, K. V. C. et al., 2012), greater disability (Saevarsdottir et al., 2011; Wevers-de Boer, K. V. C. et al., 2012; Takeuchi et al., 2014) and longer symptom duration (Bosello et al., 2011; Saevarsdottir et al., 2011; Wevers-de Boer, K. V. C. et al., 2012; Gremese et al., 2013). An early response to therapy is also associated with superior long-term response outcomes (Verschueren et al., 2009).

The majority of studies were conducted in patients with RA (fulfilling 1987 ACR criteria). Evidence of the predictors of treatment response in early UA or RA fulfilling 2010 criteria is more limited, with a small number of intervention studies available suggesting response to methotrexate may be more rapid in patients with seropositive disease (see section 2.4.2.4, below) (Wevers-de Boer, K. V. C. et al., 2012).

Various measures of response have been validated for use in clinical trials. The studies summarised here have largely assessed predictors of remission, or at least low disease activity. These outcomes are particularly pertinent to the management of patients with IA in modern-day clinical practice. Remission (or at least low disease activity) is now widely accepted as a realistic treatment goal and currently recommended as the ideal target for treatment in patients with RA or those at risk of persistent disease (Smolen et al., 2010; Smolen et al., 2016; Combe et al., 2017;

Smolen et al., 2017). However, remission may be defined by several composite measures, varying from definitions such as the 1981 ACR definition (Pinals et al., 1981) which includes criteria not uniformly assessed in contemporary studies or clinical practice, such as tendon sheath swelling, to the more recently developed 2011 ACR/EULAR Boolean remission criteria (Felson et al., 2011). Most of these composite measures include joint tenderness and/or patient-reported assessments which may be affected by chronic pain. Consequently, a higher level of pain may explain some of the poor response observed in females and patients with higher BMI (Verschueren et al., 2009; Saevarsdottir et al., 2011; Heimans et al., 2013). Implications of the choice of definition for remission as an outcome measure and as a target for treatment are discussed further in section 2.4.1.5.

2.2.3 Statistical Methods

Sample sizes and the number of candidate predictive factors considered varied across studies. Limited sample sizes and high numbers of relevant prognostic variables imply analyses may be underpowered to detect some independently predictive factors. Very few of the studies planned sample sizes on the basis of the number of variables to be included in statistical modelling for the prediction of outcome and the desired predictive power of such models (Reneses et al., 2009).

Automated step-wise selection procedures have been commonly used, however this approach introduces error through multiple testing. It is also plausible that confounding factors, whilst modifying the predictive strength of any particular variable may not be significant independent predictors of outcome themselves, therefore being excluded from final models. Some studies made allowance for this, for example using goodness-of-fit testing after re-entry of excluded variables. Others have entered pre-determined variables considered to be significant confounders or potential predictors of outcome.

The candidate variables included in statistical modelling also varied across studies. Knowledge of ACPA status or x-ray data, for example, was not available in all cohorts. Inclusion of factors with strong co-linearity (such as ACPA and shared epitope status) may also have led to missing potentially relevant factors. A large number considered only baseline variables, whilst others accounted for choice of

initial treatment, early response and disease activity or radiographic progression over follow-up. The foremost method is particularly pertinent to enable prediction of prognosis in patients at the onset of IA, in order to tailor therapy on an individual basis. It may be an appropriate means of assessing predictors of disease persistence or other outcomes in studies with uniform treatment protocols. However, for outcomes relating to disease activity, functional impairment and radiographic progression, adjustment for treatment in observational studies with inconsistent intervention strategies is essential in the interpretation of results, as efficacy of different regimens may vary substantially. Treatment is a likely confounder, being associated with baseline parameters such as disease activity as well as these disease outcomes.

As pathogenic mechanisms in UA and RA are recognised to be heterogeneous, it is likely that some factors may influence disease course more strongly in certain patient groups. For example, differences between seropositive and seronegative disease mechanisms suggest factors, such as smoking, may have a different effect in these patient groups (previously discussed in section 2.1.1.2). However, only a selection of studies made allowance for this, fitting interaction terms within models or testing in serologically defined sub-groups (Wessels et al., 2007).

The methods of fitting variables within models may be particularly relevant to some disease characteristics. For example, several studies enter symptom duration as a continuous variable, according to a linear trend, however its relationship with outcomes such as DMARD-free remission may be non-linear (van Nies et al., 2015). Sensitivity analyses, assessing the effect of categorisation of continuous variables, were conducted in a small number of studies.

Studies also differed in their handling of missing data. The most common means of dealing with this has been exclusion of cases with missing baseline and/or follow-up data which may introduce bias if not missing at random. Some studies imputed missing data (for example using the last observation), with sensitivity analyses employed to test the effect of including or excluding such patients on results.

Table 3. Longitudinal, prospective, inception cohort studies assessing prognostic factors in patients with UA, RA and non-RA.

Study Population	Years patients recruited	n	Total number of patients seen by clinic/study group	Inclusion Criterion	Proportion of patients with RA (1987 criteria) at baseline	Treatment Protocol, if applicable	Outcome	Statistical Methods of Analysis and Predictive Factors with Statistical Significance (baseline variables unless otherwise stated, results of multivariable analyses are presented preferentially over univariable analyses where available)	Reference
Leiden (Netherlands)	1993-1996	524	566	• Symptoms <2 yrs • 'Arthritis' ≥1 joint	30% (UA in 11%)	-	Persistent disease at 2 yrs (arthritis ≥1 joint and/or DMARDs/steroids within preceding 3 mths) in 40%	Logistic continuation ratio model by 2-step process: backwards step-wise selection entering all clinical variables (retained if p≤0.10), followed by entry of laboratory and radiographic variables with retention if independently predictive. • Model included: symptom duration, EMS ≥1 hr, 'arthritis' ≥3 joint areas, bilateral MTP squeeze positive, RF-positivity, ACPA-positivity, erosions. AUC 0.84 (SEM 0.02)	(Visser et al., 2002)
							In patients with persistent disease: persistent erosive disease at 2 yrs (modified Sharp erosion score ≥1 in hands/feet) in 60%	Given persistence, logistic continuation regression model developed as above: • Model included variables as above. AUC 0.91 (SEM 0.02)	
Brittany (France, multicentre)	1995-1997	270	Not reported	• Symptoms <1 yr • Synovitis ≥1 joint (swelling and tenderness or decreased ROM)	36% (SpA, ESSG criteria, in 19%)	-	RA over follow-up (physician impression) in 52% (median follow-up 30 mths)	Rate of RA in patients grouped according to joint involvement at baseline (Chi-square test): • 45% in oligo/polyarthritis • 61% in monoarthritis at presentation with patient-reported history of more extensive arthritis • 0% in monoarthritis alone (p<0.001 for both comparisons to other groups)	(Binard et al., 2007)
Kuopio (Finland)	2000	138	188	• Any symptom duration • ≥1 swollen joint or imaging evidence of synovitis in the sacroiliac, shoulder or hip joints	14%	-	Remission at 7-24 mths follow-up (5 of 1981 ACR remission criteria, excluding fatigue with/without treatment) in 25% of patients with RA at baseline and 58% of UA	Multivariable logistic regression, entering pre-determined clinical and laboratory variables: • Older age (p=0.01)	(Savolainen et al., 2007)

CHUS (Canada)	Up to 2004	149	Not reported	• Symptoms <1 yr • Synovitis ≥3 joints	81%	-	Persistent disease at 30 mths (synovitis ≥1 joint and/or current DMARD use, or ≥10 mg/day prednisone) in 84%	Multivariable logistic regression, entering pre-determined clinical, laboratory and radiographic variables: • Symptom duration ≥4 mths (OR not given)	(Boire et al., 2005)
							Severe disease at 30 mths (upper third of SHS or modified HAQ ≥1) in 38%	Multivariable logistic regression, as above: • Age (OR 1.05, 95% CI 1.02-1.08) • SHS erosion score (OR 3.8, 95% CI 1.4-10.1)	
NOR-VEAC (Norway, multicentre)	2004-2006	287	384	• Symptoms ≤16 wks • ≥1 swollen joint	Not reported	-	Persistent disease over 1 yr (≥1 swollen joint at ≥2/3 follow-up assessments) in 26%	Multivariable logistic regression, entering variables with p<0.25 on univariable analysis: • ACPA-positivity (OR 4.5, 95% CI 2.2-9.3) • Small joint swelling (OR 2.1, 95% CI 1.2-3.8) • HAQ score (OR 1.7, 95% CI 1.7-2.7) • CRP (OR 0.98, 95% CI 0.98-1.00)	(Mjavatten et al., 2009)
							RA (physician diagnosis) at 1 yr in 18%	Multivariable logistic regression, as above: • ACPA-positivity (OR 19, 95% CI 6.8-54) • RF (OR 5.0, 95% CI 1.5-17) • Small joint swelling (OR 3.5, 95% CI 1.2-9.9) • 28TJC (OR 1.09, 95% CI 1.02-1.16)	
							DMARD-use over 1 yr in 28%	Multivariable logistic regression, as above: • ACPA-positivity (OR 8.1, 95% CI 3.6-19) • Small joint swelling (OR 3.9, 95% CI 2.0-7.4) • HAQ score (OR 1.8, 95% CI 1.1-2.7)	
Leeds (UK)	Not reported	51	Not reported	• Symptoms <1 yr • Oligoarthritis: synovitis (≥2 of: swelling, tenderness, decreased ROM) in 1-5 joints (excluding DIPs alone)	Not reported	Methylprednis-olone IA in joints with synovitis +/- NSAIDs, sulfasalazine considered after 12 wks	Persistent synovitis at 1 yr in 49%	Multivariable logistic regression, entering pre-determined clinical and laboratory variables: • Synovitis at 2 wks (OR 18, 95% CI 4-88) • RF-positivity (OR 12, 95% CI 2-115) • Symptom duration (wks) (OR 1.1, 95% CI 1.03-1.21)	(Green et al., 2001)

Birmingham (UK)	Not reported	96	Not reported	• Symptoms ≤12 wks • Synovitis ≥1 joint	Not reported	-	Persistent RA at 18 mths (1987 criteria and swelling ≥1 joint and/or DMARDs/steroids within preceding 3 mths) in 20%	Multivariable logistic regression, entering pre-determined clinical and laboratory variables: • Age (OR 1.08, 95% CI 1.01-1.2) • Symmetrical arthritis (OR 10, 95% CI 1-96) • ACPA and RF-positivity (OR 80, 95% CI 8-850)	(Raza et al., 2005a)
		58	Not reported	As above, with US available	21% (2010 ACR/EULAR RA in 45%)	-	RA (1987 criteria) at 18 mths in 51% (Other outcomes persistent UA in 9%, other persistent IA in 14%, self-liming in 28%)	Multivariable logistic regression, entering clinical, laboratory and US (number of joints with GS/PD ≥grade 1 and total GS/PD scores [sum of grades 0-3 at each joint] in all 38 jts [bilateral shoulders, elbows, wrists, MCP1-5, PIP1-5, knees, ankles, MTP2-5] and by jt region) variables with significance on univariable analysis and the Leiden prediction score (van der Helm-vanMil et al., 2007) (separate models constructed for each US variable): Global assessments: • Total GS score (AUC 0.96), total PD score (AUC 0.96), number of joints PD ≥grade 1 (AUC 0.96) Reduced joint assessments/jt regions: • Total PD score in 12 jts (wrists, MCP2-3, knees and MTP2-3) (AUC 0.95), in 10 jts (wrists, MCP2-3., MTP2-3) (AUC 0.96) • Number jts GS ≥grade 1 hands (AUC 0.94), MCPs (AUC 0.94) • Number jts PD ≥grade 1 hands (AUC 0.94), MCPs (AUC 0.94). • Presence of GS ≥grade 2 wrists (AUC 0.94) • Presence of PD ≥grade 1 MTPs (AUC 0.93) (all p<0.05, OR not given) (N.B AUC for model with no US variable 0.91)	(Filer et al., 2011)

EMS: early morning stiffness, AUC: area under the receiver operating characteristic curve, SEM: standard error of the mean, SpA: spondyloarthropathy, ESSG: European Spondylarthropathy Study Group, CHUS: Centre hospitalier universitaire de Sherbrooke, OR: odds ratio, SHS: Sharp/van der Heijde score (total score unless otherwise specified), NOR-VEAC: Norwegian Very Early Arthritis Cohort, TJC: tender joint count, IA: intra-articular, GS: grey scale, PD: power Doppler activity, US: ultrasound.

Table 4. Longitudinal, prospective, inception cohort studies assessing prognostic factors in patients with UA and RA.

Study Population	Years patients recruited	n	Total number of patients seen by clinic/study group	Inclusion Criterion (excluding patients with non-RA diagnoses)	Proportion of patients with RA (1987 criteria) at baseline	Treatment Protocol, if applicable	Outcome	Statistical Methods of Analysis and Predictive Factors with Statistical Significance (baseline variables unless otherwise stated, results of multivariable analyses are presented preferentially over univariable analyses where available)	Reference
NOAR (UK)	1990-1994	312	992	• Symptoms>4 wks and <1 yr • ≥2 swollen joints • RF available	52%	-	DMARD/steroid-free remission (no swollen joints) at 2 yrs in 25%	Multivariable logistic regression model, developed with data from 60% randomly selected patients (n=199) using backwards step-wise selection (retention if p<0.20) entering baseline variables with a likelihood ratio of ≥1.3 on univariable analysis and DMARD/steroid use over 2 yrs: • No DMARDs/steroids over 2 yrs (OR 8.7, 95%CI 3.6-21), male gender (OR 3.9, 95%CI 1.7-8.7), TJC <6 (OR 3.8, 95%CI 1.2-12)	(Harrison et al., 1996)
	1990-not reported	439	Not reported	• Symptoms>4 wks and <1 yr • ≥2 swollen joints • X-rays available within 2 yrs of baseline (patients fulfilling ≥2 of 1987 ACR RA criteria) and at 5 yrs	52%	-	Radiographic damage at 5 yrs (Larsen score) (49% of patients with evidence of radiographic erosion at 5 yrs)	Multivariable negative binomial regression, entering pre-determined clinical and laboratory variables (data complete for RF n=390, CRP n=340, shared epitope n=269: n with all variables complete not given): • RF titre (coefficient 2.7, 95% CI 1.8-4.7), CRP (coefficient 2.0, 95% CI 1.4-3.0), shared epitope both alleles positive (coefficient 2.5, 95% CI 1.3-4.7) With adjustment for Larsen score at first x-ray (within 2 yrs of baseline) only RF titre remained a significant predictor (coefficient not given).	(Bukhari et al., 2002)
Leeds (UK)	1995-1997	63	Not reported	• Symptoms<1 yr • Synovitis (≥2 of: swelling, tenderness, decreased ROM)≥2 joints • ≥1 of: symptoms<3 mths, asymmetric, symmetric MCPs involvement and prognostic score low*	51%	Single dose of steroid (methylpred-nisolone ≤140mg total IA or 120 mg IM if SJC >5)	DMARD/NSAID-free remission at 6 mths (absence of symptoms) in 22%	Multivariable logistic regression, entering pre-determined clinical and laboratory variables: • Symptoms ≤12 wks (OR 4.9, 95%CI 1.3-17)	(Green et al., 1999)

Amsterdam (Netherlands)	1995 onwards	545	1854	• Symptoms <3 yrs • 'Arthritis' ≥2 joints	Not reported at baseline (63% at 1 yr)	-	Disease activity (DAS28), disability (HAQ) and radiographic damage (SHS) at 2 yrs	Analysis of ACPA and RF titres at baseline, and change in titres over 1 yr, using Spearman's rank correlation: • Significant correlation with baseline RF and SHS only (after adjustment for baseline SHS); correlation coefficient 0.14 (p=0.002)	(Ursum et al., 2010)
STIVEA (UK, multicentre)	2002-2006	253	572	• Symptoms 4-11 wks • ≥2 swollen joints (with ≥1 swollen wrist, MCP or PIP)	Not reported	Randomised to placebo or 80mg methylpred-nisolone IM injections at week 0, 1 and 2.	DMARD/oral steroid use and/or SJC28≥3, TJC28≥6, EMS≥45min and ESR≥28mm/hr at 6 months in 68%	Univariable logistic regression of individual clinical and laboratory variables with adjustment for age, gender and treatment group: • DAS28-ESR3variables (OR 1.6, 95%CI 1.2-2.0) • Pain (VAS) (OR 1.02, 95%CI 1.01-1.03) • Fatigue (VAS) (OR 1.02, 95%CI 1.00-1.03) • Physician disease activity VAS (OR 1.02, 95%CI 1.00-1.03) • RF-positivity (OR 4.3, 95%CI 2.1-8.7) • HAQ (OR 2.3, 95%CI 1.5-3.6) • SF-36 physical component (OR 0.93, 95%CI 0/89-0.98) • EQ-5D (OR 0.1, 95%CI 0.1-0.4)	(Verstappen et al., 2011)
		222					RA (physician impression) at 1 yr in 55%	Logistic regression, as above: • DAS28-ESR3variables (OR 1.4, 95%CI 1.1-1.8) • Pain (VAS) (OR 1.01, 95%CI 1.00-1.03) • Fatigue (VAS) (OR 1.01, 95%CI 1.00-1.02) • Physician disease activity VAS (OR 1.02, 95%CI 1.01-1.04) • RF-positivity (OR 10, 95%CI 4.8-22) • HAQ (OR 1.8, 95%CI 1.2-2.8) • EQ-5D (OR 0.3, 95%CI 0.1-0.8) • Current vs never smoker (n=148) (OR 3.4, 95% CI 1.2-10)	
ESPOIR (France, multicentre)	2002-2005	731	813	• Symptoms >6 wks and <6 mths • ≥2 swollen joints	Not reported	-	RA over 1 yr (1987 criteria and investigator's VAS ≥75/100 supporting diagnosis) in 51%	Multivariable logistic regression, entering variables with p<0.20 on univariable analysis using a backwards step-wise selection (retention if p<0.05). Separate models planned to include clinical variables only, clinical and radiographic variables only, or all clinical, laboratory and radiographic variables. • Greatest AUC (0.84) for model based on clinical, laboratory and radiographic variables. Included SJC, EMS, erosions, RF and ACPA	(Gossec et al., 2010)

ESPOIR (contd.)	2002-2005	673	813	As above, with x-rays available	72%	-	Radiographic progression (increase in SHS from baseline >1) at 1 yr	Multivariable logistic regression, entering variables with significance on univariable analysis using forwards step-wise selection (inclusion if p<0.15): • ACPA-positivity (OR 4.1, 95% CI 2.6-6.5), SHS >median score (OR 2.4, 95% CI 1.6-3.7), HLA-DRB1-01 or 04 both alleles positive (OR 2.7, 95% CI 1.3-5.6) or one allele positive (OR 1.7, 95% CI 1.0-2.7), ESR >median (OR 2.1, 95% CI 1.4-3.3)	(Mouterde et al., 2011)
		573	813	As above, with 5 yr data available	75% (82% fulfilling 2010 RA criteria at baseline, 93% fulfilling 2010 RA criteria over follow-up)	-	DMARD use within 5 yrs in 90%	Multivariable logistic regression, entering variables with p<0.15 on univariable analysis using forwards step-wise selection (inclusion if p<0.05) (continuous variables dichotomised by median): • Pain (VAS)>median (OR 2.2, 95% CI 1.4-3.5), fulfilling 2010 RA criteria (OR 2.5, 95% CI 1.6-4.0), ACPA-positivity (OR 4.9, 95% CI 2.5-9.6).	(Combe et al., 2013)
							Biologic use within 5 yrs in 22%	Multivariable logistic regression, as above: • Pain VAS>median (OR 2.2, 95% CI 1.4-3.3), TJC28>median (OR 2.3, 95% CI 1.5-3.6), ACPA-positivity (OR 3.1, 95% CI 1.8-5.4), RF-positivity (OR 1.9, 95% CI 1.1-3.4).	
							Poor function (HAQ >median) at 5 yrs	Multivariable logistic regression, as above: • Age>median (OR 1.9, 95% CI 1.3-1.8), female (OR 1.6, 95% CI 1.0-2.5), rest pain (VAS)>median (OR 1.7, 95% CI 1.2-2.4), HAQ (OR 2.9, 95% CI 2.0-4.2).	
							Radiographic progression (increase in SHS from baseline >1) at 3 yrs	Multivariable logistic regression, as above: • ACPA-positivity (OR 2.2, 95% CI 1.4-3.4), SHS erosion score (OR 2.3, 95% CI 1.4-3.8).	
		661	813	As above, with x-rays available	73% (79% fulfilling 2010 RA criteria at baseline)	-	DMARD use within 6 mths of onset of swelling in 47%	Multiple logistic regression, entering pre-determined variables (age, gender, erosion, comorbidity, symmetric arthritis, involvement of hands and others below) to develop propensity score. Final score included: • DAS28, CRP, involvement of >3 jt groups, RF-positivity, ACPA-positivity, research centre, symptom duration at first rheumatology visit.	(Lukas et al., 2011)

ESPOIR (contd.)	2002-2005	661	813	As above, with x-rays available	73% (79% fulfilling 2010 RA criteria at baseline)	-	Radiographic progression (change in SHS from baseline) at 1 yr	Generalised linear model, assessing early DMARD (excluding HCQ, within 3 mths of onset of swelling, n=140) vs. no early DMARD (includes n=387 starting DMARD 3mths-1yr after onset of swelling) with covariate propensity score, as above: • Early DMARD (estimated marginal mean 0.8 units vs 1.7 units no early DMARD p=0.03).	(Lukas et al., 2011)
		500	813	As above, with x-rays available (and excluding n=35 patients receiving TNF-inhibitor, none of whom had rapid radiographic progression)	71%	-	Rapid radiographic progression (change in SHS from baseline >5 per year, [5 units equivalent to sever destruction in 1 joint]) in yrs 2 and 3 in 18%	Multiple logistic regression, entering clinical, laboratory and radiographic variables and cytokine levels with p<0.1 on univariable analysis, using backwards step-wise selection: • Score for serology within 2010 RA criteria (0-3) (OR 6), IL-6 (OR 1.5), baseline SHS erosion score (OR 3), rapid radiographic progression in SHS erosion score (change from baseline >2.5) at 1 yr (OR 5) (95% Cis not given).	(Tobón et al., 2013)
		127	813	As above, for patients with US available	77%	-	Radiographic erosion at 2 yrs in 39%	Multivariable logistic regression, entering age, DAS28, CRP, ESR, RF-positivity, ACPA-positivity, steroid use and presence of US erosion: • RF-positivity (OR 5.0, 95%CI 1.8-14), presence of US erosion (OR 1.44, 95%CI 1.04-1.98).	(Funck-Brentano et al., 2013)
							Rapid radiographic progression (increase in SHS erosion score ≥5) at 1 yr in 9%	Multivariable logistic regression, entering clinical, laboratory, treatment (steroid/DMARD/biologic use) and US (number of jts with GS and number of jts with PD [and total PD score by sum of grades 0-3 each jt] of bilateral MCP2-5 and MTP5 and presence of erosion [and erosion score by sum of grades 0-4] at bilateral MCP2, MCP5 and MTP5]) but NOT radiographic variables, with p<0.3 on univariable analysis, using backwards step-wise selection: • RF-positivity (OR 7.4, 95%CI 1.4-40), total PD score (OR 1.2, 95%CI 1.04-1.42), number of joints with PD ≥grade 1 (OR 1.33, 95%CI 1.04-1.69).	
							Radiographic progression (change in SHS erosion score from baseline) at 1 yr	Multiple linear regression, entering variables as above: • CRP (parameter estimate 0.02, p=0.002), presence of any PD (parameter estimate -0.9, p=0.003), total PD score (parameter estimate 0.8, p<0.001), presence of any US erosion (parameter estimate 0.8, p<0.001).	
		93		As above, in patients with no erosions at baseline	Not reported	-	Radiographic erosion at 2 yrs	Multivariable logistic regression, as above. • RF-positivity (OR not given).	

NOR-VEAC (Norway, multicentre)	2004-2007	376	572	• Symptoms ≤16 wks • ≥1 swollen joint	19%	-	Persistent disease at 1 yr (≥1 swollen joint and/or DMARD-use) in 46%	Multivariable logistic regression, entering pre-determined clinical and laboratory variables: • ACPA-positivity (OR 3.6, 95%CI 1.6-8.1), RF-positivity (OR 2.7, 95%CI 1.2-6.2)	(Mjaavatten et al., 2010)
IMPROVED trial (Netherlands, multicentre)	2007-2010	610	730 screened	• DAS >1.6 Either: • RA (1987 ACR criteria) and symptoms <2 yrs Or: • Physician impression likely early RA, ≥1 arthritic joint, ≥1 other painful joint, any symptom duration	60% fulfilled 1987 RA criteria (2010 RA criteria in 79%)	MTX 25 mg/week and high dose of prednisone (60 mg/day, reducing over 7 weeks to 7.5 mg/day).	Remission (DAS44 <1.6) at 4 mths in 61%	Multivariable logistic regression, entering clinical and laboratory variables with p<0.1 on univariable analysis (separate models including DAS44 or number of swollen and/or tender small and large joints): • With DAS44: male (OR 2.0, 95%CI 1.3-3.1), BMI (OR 0.94, 95%CI 0.90-0.98), symptom duration (OR 0.99, 95%CI 0.98-0.997), DAS44 (OR 0.6, 95%CI 0.5-0.8), HAQ (OR 0.7, 95%CI 0.5-0.9), ACPA-positivity (1.6, 95%CI 1.1-2.3). • With small and large joint involvement: male (OR 2.0, 95%CI 1.3-3.1), BMI (OR 0.94, 95%CI 0.90-0.98), symptom duration (OR 0.99, 95%CI 0.98-0.997), no. small joints (OR 0.96, 95%CI 0.93-0.99), no. large joints (OR 0.8, 95%CI 0.7-0.9), HAQ (OR 0.6, 95%CI 0.5-0.9).	(Wevers-de Boer, K. V. C. et al., 2012)
		488			80% fulfilled 2010 RA criteria	As above, then (if DAS44≥1.6) randomised to combination DMARD plus prednisolone or MTX plus adalimumab	Radiographic progression (change from baseline in SHS≥0.5) at 2 yrs in 10%.	Multivariable logistic regression, entering clinical and laboratory variables with p<0.2 on univariable analysis (Anti-CarP and ACPA status entered as combined variable due to co-linearity): • Age (OR 1.03, 95%CI 1.00-1.06), AntiCarP and ACPA both positive (vs. both negative) (OR 2.5, 95% CI 1.2-5.6), symptom duration<12 wks, ESR≥28mm/hr and SHS all included (p=NS)	(Akdemir et al., 2016)

CATCH (Canada, multicentre)	2007-2011	1244/1205	Not reported	• Symptoms 6-52 wks Either: • ≥ 2 swollen joints Or: • 1 swollen MCP/PIP and ≥1 of: positive RF, positive ACPA, EMS >45 min, response to NSAIDs, or a positive MTP squeeze	Not reported	-	Sustained remission over follow-up (for ≥ 6 mths or 2 consecutive visits for remission definitions below) (length of follow-up available not known): • ACR Boolean (using 28-joint counts and omitting CRP) in 25% of n=1244 • SDAI in 23% of n=1205	Multivariable logistic regression, method unclear (including whether patients with missing data were excluded). Entered pre-determined confounders (including initial treatment [MTX monotherapy or combination DMARD within 3 months and biologic within 6 months with those in models below], stating other clinical, laboratory and radiographic variables were not predictive. • Boolean definition: age (OR 0.98, 95%CI 0.96-0.99), female (OR 0.6, 95%CI 0.4-1.0), pain (VAS) (OR 0.99, 95% CI 0.98-0.99), time to remission (OR 0.997, 95%CI 0.996-0.998). • SDAI definition: age (OR 0.98, 95%CI 0.96-0.99), pain (VAS) (OR 0.98, 95% CI 0.98-0.99), time to remission (OR 0.997, 95%CI 0.996-0.998).	(Kuriya et al., 2012)
	2007-2012	523	1431	As above	With baseline serology available (n=841), 89% RA (2010 or 1987 criteria)	-	Remission (DAS28<2.6) at 1 yr. Rate not given.	Multiple logistic regression, entering pre-determined clinical, laboratory, radiographic and treatment variables, using forwards step-wise selection (inclusion if p<0.1) and serological status (ACPA-/RF-, ACPA+/RF-, ACPA-/RF+ or ACPA+/RF+): • Age, SJC28, CRP, DAS28, HAQ (OR not given).	(Barra et al., 2014)
		392					Remission (DAS28<2.6) at 2 yrs. Rate not given.	Multiple logistic regression, as above: • Age, HAQ (OR not given).	
		233					New radiographic erosion(s) at 1 yr. Rate not given.	Multiple logistic regression, as above: • ACPA+/RF- (vs -/-) (OR 5.5, 95% CI 1.4-21), ACPA+/RF+ (vs -/-) (OR 3.7, 95% CI 1.1-12).	
		192					New radiographic erosion(s) at 2 yrs. Rate not given.	Multiple logistic regression, as above: • DAS28 (OR not given).	

CATCH (cont.)	2007-2012	342/520	1431	As above	67% 1987 RA and 75% 2010 RA (of n=342 with ACPA available) and 65% 1987 RA and 72% 2010 RA (of n=520 with RF status available)	-	Remission (DAS28<2.6) at 1 yr in 53% of 342 (with known ACPA status) and 52% of 520 (with known RF status) .	Multiple logistic regression, entering pre-determined clinical, radiographic and baseline treatment if p<0.1 on univariable analysis and ACPA or RF status (low positive or moderate/high positive vs negative): • With ACPA (n=342): Age, gender, smoking status, SJC28, DAS28 and HAQ (OR not given). • With RF (n=520): as ACPA above.	(Barra et al., 2013)
		277/376					Remission (DAS28) at 2 yrs in 57% of 277 (ACPA model) and 59% of 376 (RF model).	Multiple logistic regression, as above: • With ACPA (n=277): Age, DAS28 and HAQ (OR not given). • With RF (n=376): as ACPA above.	
		249/322					Any radiographic erosion(s) at 1 yr in 27% of 249 (ACPA model) and 27% of 322 (RF model).	Multiple logistic regression, as above: • With ACPA (n=249): CRP (OR not given), presence of erosions at baseline (OR not given), ACPA moderate/high positive (≥3xULN) (OR 3.4, 95% CI 1.6-7.2). • With RF (n=322): CRP, presence of erosions at baseline (OR not given).	
		198/247					Any radiographic erosion(s) at 2 yrs in 28% of 198 (ACPA model) and 27% of 247 (RF model).	Multiple logistic regression, as above: • With ACPA (n=198): DAS28, presence of erosions at baseline (OR not given). • With RF (n=247): DAS28 (OR not given), presence of erosions at baseline (OR not given), RF high positive (≥3xULN) (OR 2.4, 95% CI 1.1-5.2).	

NOAR: Norfolk Arthritis Register, SJC: swollen joint count, NSAID: non-steroidal anti-inflammatory drug, STIVEA: Steroids in Very Early Arthritis, ESR: erythrocyte sedimentation rate, DAS: disease activity score, VAS: visual analogue scale, SF-36: Short Form-36, EQ-5D: Euro-Qol-5 Dimensions (quality of life measure), ESPOIR: Étude et Suivi des Polyarthrites Indifférenciées Récentes (study and follow-up of early undifferentiated polyarthritis), HCQ: Hydroxychloroquine, IL: interleukin, IMPROVED: Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease, Anti-CarP: anti-carbamylated protein antibodies, CATCH: Canadian Early Arthritis Cohort, SDAI: simplified disease activity index, ULN: upper limit of normal.

*Composite score including RF, shared epitope, high HAQ, CRP, gender (Fries et al., 1980).

Table 5. Longitudinal, prospective, inception cohort studies assessing prognostic factors in patients with UA. Undifferentiated arthritis is defined as IA not fulfilling 1987 RA criteria, unless otherwise stated.

Study Population	Years patients recruited	n	Total number of patients seen by clinic/study group	Inclusion Criterion (excluding 1987 ACR RA and non-RA diagnoses, unless otherwise stated)	Treatment Protocol, if applicable	Outcome	Statistical Methods of Analysis and Predictive Factors with Statistical Significance (baseline variables unless otherwise stated, results of multivariable analyses are presented preferentially over univariable analyses where available)	Reference
Leiden (Netherlands)	1993-2005	570	~1900	• Symptoms <2 yrs • Physician impression of IA	-	RA (1987 criteria) at 1 yr in 31%	Multivariable logistic regression model, entering clinical and laboratory variables with p<0.05 on univariable analysis using backwards step-wise selection (retention if p≤0.10): • Age, female gender, localisation of symptoms (small joints, symmetrical and in upper +/- lower extremities), EMS severity (VAS), TJC, SJC (of 66), CRP, RF-positivity, ACPA-positivity (OR not given). Discriminative ability (ROC curve analysis) of Leiden prediction rule, with categorisation (except age, as more predictive as continuous variable) and weighting (using regression coefficients) of variables in the above model: AUC 0.89 (SD 0.02).	(van der Helm-vanMil et al., 2007)
		538	~1900	As above	-	Persistent disease at 5 yrs (absence of sustained DMARD-free remission defined as no swollen joints for ≥1 yr after cessation of DMARD) in 39%	Univariable logistic regression: • Female (OR 1.5, 95%CI 1.0-2.1), symptom duration (wks) (OR 1.01, 95%CI 1.00-1.02), EMS severity (OR 1.07, 95%CI 1.01-1.13), SJC (OR 1.07, 95%CI 1.02-1.13), CRP (OR 1.01, 95%CI 1.00-1.01), RF-positivity (OR 4, 95%CI 2-6), ACPA-positivity (OR 6, 95%CI 3-11)	(de Rooy, van der Linden et al. 2011)
		518	~1900	As above	-	RA (1987 criteria) at 1 yr in 31%	Number of erosive joints added to the multivariable logistic regression model above. Not an independent predictor.	(Thabet et
Amsterdam (Netherlands)	1995-1998	77	320	• Symptoms <3 yrs • 'Arthritis' ≥2 joints • Excluded physician impression RA 1-3 wks after baseline	-	Progressive disease at 1 yr (≥1 of: increase in SHS ≥4, SHS ≥10, HAQ ≥1) in 42%	Multivariable logistic regression, entering clinical, laboratory and radiographic variables with p<0.05 on univariable analysis with forwards step-wise selection: • Age (OR 1.05, 95% CI 1.01-1.09), 'arthritis' of hands (OR 4.2, 95% CI 1.04-17)	(Jansen et al., 2002)

Leeds (UK)	1996-1999	97	1877	• Symptoms <1 yr • History, examination or laboratory data suggestive of IA • Hand symptoms Synovitis (≥2 of: swelling, tenderness, decreased ROM) in 53% at baseline.	Step-up treatment protocol: 1) NSAIDs 2) Single dose of corticosteroid 3) DMARDs	RA (1987 criteria) at 1 yr in 14%	Multivariable logistic regression, stepwise procedure, other details unclear: • RF-positivity (OR 31, 95% CI 6-160), painful joint count (OR 1.06, 95% CI 1.00-1.12)	(Quinn et al., 2003)
						DMARD-use over 1 yr in 30%	Multivariable logistic regression, as above: • Greatest strength of association with synovitis at 12 wks (OR 49, 95% CI 13-180), other results not reported.	
						Persistent synovitis over 1 yr in 36%	Univariable analysis (Student's t-test and Wilcoxon's rank sum test): • RF-positivity, ≥1 swollen joint, synovitis (see definition across) (all p<0.05).	
						DMARD/NSAID-free remission at 1 yr (absence of symptoms without treatment) in 13%	Univariable analysis (Student's t-test and Wilcoxon's rank sum test): • Lower HAQ, shorter symptom duration, less synovitis at 12 weeks, male gender (all p<0.05).	
Seville ROP (Spain)	2002 onwards	56	322	• Symptoms ≥4 wks and ≤1 yr • 'Inflammation' ≥2 joints • Excluded patients developing RA (1987 criteria) and non-RA diagnoses after 1 yr follow-up	-	RA (1987 criteria) after 3 further yrs follow-up in 20%	Rate of RF and/or ACPA-positivity in patients grouped according to outcome (no statistical testing): • 8/11 who developed RA versus 0/44 who remained as UA.	(Caro-Oleas et al., 2008)
TEACH (Canada)	2003 onwards	105	Not reported	• Symptoms ≥6 wks and ≤1 yr • ≥2 swollen joints or ≥1 swollen MCP/PIP with ≥1 of: positive RF or ACPA, EMS ≥45 min, NSAID response or pain on MTP squeeze	-	RA (1987 criteria) over ≥6 mths follow-up (mean [SD] 19 [9] mths) in 76%	Univariable analysis (Student's t-test and Chi-square test): • TJC (of 44) (p<0.001), SJC44 (p<0.001), DAS28-ESR (p<0.001), HAQ (0.006), RADAI (p=0.003), RF-positivity (p=0.001) and ACPA-positivity (p<0.001).	(Kuriya et al., 2009)
Berlin (Germany)	2004 onwards	155	Not reported	• Symptoms ≥4 wks and ≤1 yr • 'Synovitis' ≥2 joints	-	RA (1987 criteria) at 1 yr in 37%	Leiden prediction rule re-derived (using data from Leiden cohort) substituting EMS duration for EMS severity. Discriminative ability (ROC curve analysis) of re-derived Leiden prediction rule: • AUC 0.82 (SEM 0.04).	(van Der Helm-van Mil et al., 2008)
Birmingham (UK)	Not reported	99	Not reported	• Symptoms ≤3 mths • ≥1 swollen joint	-	RA (1987 criteria) over 18 mths in 31%	Discriminative ability (ROC curve analysis) of re-derived Leiden prediction rule (using EMS duration, see above): • AUC 0.83 (SEM 0.04).	

Pavia (Italy)	2005-2012	215	Not reported	• UA (not fulfilling 2010 ACR/EULAR RA criteria) Symptom/disease duration not reported.	MTX if fulfilled 1987 ACR RA criteria, otherwise HCQ as first-line (given to 169 [79%]). Then treatment to target (DAS28<3.2).	Remission (DAS28<2.6) within 1 yr in 124 (58%). Median (IQR) follow-up 12 (6-12) months.	Cox regression for clinical variables, single items of the 2010 classification score and US (bilateral wrists and MCPs) variables, adjusted for age, gender, glucocorticoids and DMARDs (excluding HCQ) over time: • Age (HR 0.98, 95% CI 0.97-0.99), female (HR 0.6, 95% CI 0.5-0.9), • ACPA and/or RF titre (as per 2010 classification score) (HR 3.3, 95% CI 1.3-8.6), • Number of joints PD>0 (HR 1.2, 95% CI 1.0-1.3) or PD>1 (HR 1.3, 95% CI 1.1-1.6) or total PD score (HR1.1, 95% CI 1.0-1.2).	(Sakellariou et al., 2014)
Cairo (Egypt)	Not reported	173	Not reported	• Symptoms <6 mths • Synovitis ≥ 2 joints (≥2 of: swelling, tenderness, decreased ROM) • EMS >30 min • Pain on MCP/MTP squeeze	Step-up protocol: 1) NSAIDs 2) Single dose of corticosteroid 3) DMARDs	Persistent disease at 6 mths (MRI findings of active inflammatory arthritis) in 46%	Multivariable logistic regression, entering clinical and laboratory variables with p<0.25 on univariable analysis, Hosmer and Lemeshow goodness of fit testing to identify most predictive final model including independent predictors (p<0.05): • EMS duration (OR 1.16, 95% CI 1.09-1.22), ACPA-positivity (OR 11.2, 95% CI 1.7-75), change in HAQ at 3 mths (1.0, 95% CI 1.0-1.1)	(El Miedany et al., 2008)
Ancona (Italy)	Not reported	149	Not reported	• Symptoms <16 wks • ≥1 swollen joint in hands • ≥1 of: positive RF, positive ACPA, EMS >30 min, pain on MTP squeeze	Italian Society for Rheumatology guidelines	RA (1987 criteria) at 1 yr in 42% (Other outcomes: persistent UA in 32%, non-persistent UA in 15% and alternative non-RA/non-UA diagnosis in 12%)	Multivariable logistic regression, clinical (not including swollen and tender joint counts), laboratory and US (number of joints with any GS and PD>grade 1 of bilateral wrists, MCP2-5 and PIP2-5) variables with p<0.05 on univariable analysis. Backwards step-wise selection (retention if p≤0.10) (continuous variables categorised as per 2010 RA criteria): • ACPA and/or RF: high positive (OR 11, 95% CI 2.6-47), low positive (OR 5.8, 95% CI 1.6-21), abnormal CRP/ESR (OR 5.3, 95% CI 1.6-18), symptoms ⩾6 wks (OR 5.0, 95% CI 1.4-18), EMS >30 min (OR 3.2, 95% CI 1.1-9.5), PD⩾ grade 2 (with GS⩾grade 1): 1 joint (OR 9.9, 95% CI 2.3-43), 2-3 joints (OR 18, 95% CI 4.7-65), ⩾4 joints (OR 49, 95% CI 8.7-272).	(Salaffi et al., 2010)

ROC: Receiver Operating Characteristic curve, SD: standard deviation, ROP: Recent Onset Polyarthritis unit, TEACH: Toronto Early Arthritis Cohort, RADAI: Rheumatoid Arthritis Disease Activity Index (5 item questionnaire for patient-reported disease activity).

Table 6. Observational and non-randomised open-label prospective studies assessing prognostic factors using multivariable analysis, in patients with early DMARD-naïve RA.
Rheumatoid arthritis is defined according to fulfilment of 1987 RA criteria, unless otherwise stated.

Study Population	Years patients recruited	n	Total number of patients fulfilling inclusion criteria	Inclusion Criterion (patients fulfilling 1987 ACR RA criteria, unless otherwise stated)	Treatment Protocol (if applicable)	Outcome	Statistical Methods of Analysis and Predictive Factors with Statistical Significance (baseline variables unless otherwise stated)	Reference
NOAR (UK)	1990-1993	105	239	• Symptoms <6 mths	-	Radiographic erosions (Larsen score ≥2 in any joint of the hands or feet) ≥1 yr after symptom-onset in 35%.	Multivariable logistic regression, entering clinical and laboratory variables, backwards selection (retention if p≤0.05): • RF-positivity, symptoms ≥3 mths, involvement ≥2 large joints independent predictors (OR not given).	(Brennan et al., 1996)
EURIDISS (France, Norway, Netherlands)	1991 onwards	318	706	• Time from diagnosis <4 yrs	-	Radiographic damage (SHS) at follow-up (average 30 mths)	Multiple linear regression, entering age, gender, country, follow-up duration and other clinical, laboratory and radiographic variables with p≤0.10 on univariable analysis, using forwards and backwards step-wise selection: • Time from diagnosis (coefficient -0.1, p=0.03), ESR (coefficient 0.02, p<0.001), RF-positivity (coefficient 5, p=0.05), VAS general health (coefficient 0.01, p=0.002), baseline SHS (coefficient 1.0, p<0.001).	(Guillemin et al., 2003)
		125	706	As above	-	Radiographic progression (change in SHS from baseline ≥10 units) at 10 yrs in 59%	Multivariable logistic regression, entering clinical, laboratory and radiographic variables with p<0.15 on univariable analysis (+/- radiographic progression at baseline=SHS/disease duration): • Without adjustment for baseline radiographic progression: female (OR 3.3, 95% CI 1.3-7.6), ESR >20mm/hr (OR 3.2, 95% CI 1.2-7.6), ACPA-positivity (OR 4.0, 95% CI 1.6-10), RF-positivity (OR 3.1, 95% CI 1.2-7.9). • With adjustment for baseline radiographic progression: female (OR 3.2, 95% CI 1.1-9.4), ESR >20mm/hr (OR 3.1, 95% CI 1.3-7.8), ACPA-positivity (OR 3.1, 95% CI 1.2-8.4), RF-positivity (OR 2.7, 95% CI 1.0-7.3).	(Syversen et al., 2008)

EURIDISS (contd.)	1991 onwards	125	706	As above	-	Radiographic progression (change in SHS from baseline ≥10 units) at 10 yrs in 59%	Multivariable logistic regression, entering pre-determined variables (age, gender, CRP, ESR, RF-positivity and ACPA categorised as negative, low-moderate positive and high positive): • High ACPA (>200 U.ml) (OR 9.9, 95% CI 2.7-37) (low-moderate positive not significant vs ACPA negative, significance of other variables not given)	(Syversen et al., 2008)
Leipzig (Germany)	1992 onwards	2 yr data in n=87, 4 yr data in n=48	93	• Symptoms <2 yrs • Non-RA diagnoses within 1 yr of follow-up excluded	SSZ 2g/day or MTX 15mg/wk, + low dose prednisolone	Radiographic progression (mean yearly change in Larsen score) over 4 yrs	Multiple linear regression, entering pre-determined clinical, laboratory and radiographic variables using backwards step-wise selection: • IgA RF titre (IU/mL) (coefficient 0.01, 95% CI 0.00-0.02), shared epitope (coefficient 3.2, 95% CI 0.9-5.6), time of x-ray assessment (≤2yrs vs >2 yrs since baseline) (coefficient -3.1, 95% CI -5.6 to -0.5).	(Kaltenhäuser et al., 2001)
Mo-Co-To (France, multicentre)	1993-1994	172	191	• Disease duration <1 yr	-	Radiographic progression (increase in SHS from baseline ≥upper boundary of 95% CI of the differences [3.2]) at 3 yrs in 41%	Multiple logistic regression, entering clinical, laboratory and radiographic variables with p≤0.15 on univariable analysis, using step-wise selection (retention if p<0.05) (continuous variables dichotomised using median): • ESR ≥median mm/hr (OR 3.4, 95% CI 1.4–8.5), RF-positivity (OR 3.9, 95% CI 1.4–11), shared epitope (OR 2.9, 95% CI 1.2–7.0), SHS erosion score ≥median (OR 5.1, 95% CI 2.2–12.1).	(Combe et al., 2001)
						High radiographic progression (increase in SHS from baseline >median [4]) at 3 yrs	Multivariable logistic regression, as above: • Pain VAS ≥59mm (OR 2.4, 95% CI 0.8–6.6), RF-positivity (OR 2.9, 95% CI 0.9–9.2), shared epitope (OR 2.9, 95% CI 1.0–8.0), SHS (OR 31, 95% CI 10-95).	
		134	191	As above	-	Remission (DAS44<1.6) at 3 yrs in 36% of patients included in analysis	Multivariable logistic regression, as above (separate models with and without DAS44 due to overlap with other candidate variable identified on univariable analysis, RAI): • With DAS44: DAS44<4 (OR 5.7, 95% CI 2.3-14), EMS>60min (OR 2.5, 95% CI 1.3-7.0), SHS (OR 2.5, 95% CI 0.9-6.6). • Without DAS44: RAI<17 (OR 2.7, 95% CI 1.1-6.7), EMS>60min (OR 2.3, 95% CI 0.9-6.0), HAQ>1.25 (OR 2.3, 95% CI 0.9-5.7), SHS (OR 2.9, 95% CI 1.2-7.0).	(Gossec et al., 2004)

Mo-Co-To (contd.)	1993-1994	134	191	As above	-	Sustained remission (DAS44<1.6 at 3 and 5 yrs) in 22% of patients included in analysis	Multivariable logistic regression, as above: • With DAS44: DAS44<4 (OR 5.5, 95% CI 1.7-18), CRP <14.5mg/l (OR 2.5, 95% CI 0.8-7.4), SHS (OR 2.7, 95% CI 0.9-8.1). • Without DAS44: RAI<17 (OR 4.2, 95% CI 1.4-12.1), CRP <14.5mg/l (OR 3.1, 95% CI 1.0-9.0), SHS (OR 2.7, 95% CI 0.9-8.0).	(Gossec et al., 2004
		112	191	As above	-	High radiographic progression (increase in SHS from baseline >median) at 10 yrs	Multivariable logistic regression, as above (except p≤0.10 on univariable analysis used as cut-off for entry into model): • SHS erosion score (OR 5.6, 95% CI 1.8–17.9). After excluding the baseline radiographic variables: • ESR (OR 3.2, 95% CI 1.2–8.8), ACPA-positivity (OR 3.9, 95% CI 1.2–12.8),	(Courvoisier et al., 2008)
		156	191	As above	-	HAQ score at 5 yrs	Multiple linear regression, other details not specified: • RAI (coefficient 0.02, p=0.05), ESR (coefficient 0.01, p=0.006), CRP (coefficient 0.01, p=0.001), HAQ score (coefficient 0.4, p<0.001), presence of erosion (p=0.05).	(Combe et al., 2003)
BARFOT (Sweden, multicentre)	1993-1999	355	839	• Disease duration <1 yr	No protocol for DMARD therapy. Randomisation to +/- low dose prednisolone in n=166	Radiographic progression (SHS >smallest detectable change [5.8]) at 2 yrs	Multivariable logistic regression, entering variables at baseline and 1 yr (including change in hand BMD) with p<0.1 on univariable analysis: • With change in SHS from baseline at 1 yr: change in SHS (OR 2.7, 95% CI 2.0-3.5), ACPA-positivity (OR 3.1, 95% CI 1.7-5.8). • Without change in SHS at 1 yr: SJC at 1 yr (OR 1.1, 95% CI 1.0-1.2), ACPA-positivity (OR 3.1, 95% CI 1.7-5.8), presence of erosion at baseline (OR 2.6, 95% CI 1.5-4.5), change in hand BMD at 1 yr (OR 0.97, 95% CI 0.96-0.99).	(Forslind et al., 2012)
	1993-1997	379	453	As above	As above	Radiological progression (change from baseline in Larsen score >median [8]) at 2 yrs	Multiple logistic regression, entering clinical, laboratory and radiographic variables with p<0.05 on univariable analysis, using forwards step-wise selection (continuous variables dichotomised using median): • ESR (OR 1.8, 95% CI 1.0-3.1), ACPA-positivity (OR 3, 95% CI 2-5), baseline Larsen score (OR 9, 95% CI 5-16),	(Forslind et al., 2004)
						High radiographic damage (Larsen score >median [10]) at 2 yrs	Multivariable logistic regression, as above: • Baseline Larsen score (OR 15, 95% CI 8-28), ACPA-positivity (OR 5, 95% CI 3-9), ESR (OR 2.0, 95% CI 1.1-3.5).	

BARFOT (contd.)	1993-1999	608	698	As above	As above	Sustained remission (DAS28<2.6 at ≥2 consecutive visits, with/without treatment) at 18mths, 2 yrs and 5 yrs in 20%	Multiple logistic regression, entering clinical and laboratory variables with p<0.1 on univariable analysis, using backwards step-wise selection (retention if p<0.05): • Male (OR 2.6, 95% CI 1.6-4.3), disease duration (mths) (OR 0.9, 95% CI 0.8-1.0), DAS28 (OR 0.8, 95% CI 0.6-0.9), HAQ (OR 0.6, 95% CI 0.4-0.9), RF-positivity (OR 0.5, 95% CI 0.3-0.8).	(Forslind et al., 2007)
	1993-2004	1271	1587	As above	As above	EULAR response (good and/or moderate) at 1 yr	Multiple logistic regression, entering pre-determined variables (age, RF, HAQ, steroid use and those below): • Female (OR 0.5, 95% CI 0.4-0.7), disease duration (mths) (OR 0.94, 95% CI 0.90-0.98), current smoker (OR 0.7, 95% CI 0.5-1.0), DAS28 (OR 0.8, 95% CI 0.7-0.9), DMARD start at baseline (OR 1.5, 95% CI 1.1-2.0).	(Söderlin and Bergman, 2011)
Leiden (Netherlands)	1993-1999	95	Not reported (152 patients with RA, x-rays and 1yr data available)	• Symptoms <2 yrs • RA (1987 criteria but without the criterion of symptoms >6 wks) at/within 3 mths of first presentation to the clinic	1993-1996: initial therapy analgesics then chloroquine; 1996-1998: initial therapy chloroquine or SSZ; After 1998: initial therapy SSZ or MTX.	Radiographic progression (increase in SHS from baseline >0) at 1 yr	Multivariable logistic regression, entering all pre-determined clinical, laboratory and radiographic variables (sensitivity analysis including choice of initial DMARD did not change results): • SJC (of 22: PIPs, DIPs, MCPs and MTPs each scored as 1 joint for right and 1 for left) (coefficient 1.7, p=0.01), RF-positivity (coefficient 10, p=0.003)	(de Vries-Bouwstra et al., 2006)
		285	285 (total 1009 patients with IA including UA, RA and non-RA)	• Symptoms <2 yrs • Fulfilled 1987 RA criteria within 1 yr of enrolment	As above	Radiographic damage (SHS) at 1 yr	Multivariable logistic regression, entering clinical and laboratory variables (including swelling at individual joint sites), using backwards step-wise selection (retention p<0.10): • Symptom duration (coefficient 0.2, p<0.001), SJC (of 22, as above) (coefficient 0.9, p=0.03), CRP (coefficient 0.02, p<0.01), ACPA-positivity (coefficient 8, p<0.001).	(Linn-Rasker et al., 2007)
	1993-2002	454	590	• Symptoms <2 yrs • Fulfilled 1987 RA criteria	As above	Drug-free remission (physician judgement with no swollen joints and no DMARD/steroid over 1 yr) during follow-up (maximum 10 yrs) in 15%	Multivariable Cox regression, entering baseline clinical and laboratory variables with p<0.10 on univariable analysis (SHS not included due to co-linearity with symptom duration), using backwards step-wise selection (retention if p≤0.10): • Symptom duration (HR 0.95, 95% CI 0.90-1.00), CRP (HR 0.99, 0.98–1.00), ACPA-positivity (HR 0.09, 95% CI 0.04-0.20)	(van der Woude et al., 2009)

Leiden (contd.)	1993-2002	424	Not reported	• Symptoms <2 yrs • Fulfilled 1987 RA criteria • Excluding patients enrolled in BeSt	As above	Sustained drug-free remission at 5 yrs (DAS44<1.6 for ≥1 yr after cessation of DMARD/steroid) in 11%	Multivariable logistic regression, entering clinical, laboratory and radiographic variables with p<0.10 on univariable analysis, using backwards step-wise selection (retention if p≤0.10) (period of enrolment as surrogate for initial therapy not significant predictor on univariable analysis, therefore not included in model) (multiple imputation in n=50 with missing baseline data): • Symptom duration (wks) (OR 0.99, 95% CI 0.97-1.00), ACPA-positivity (OR 0.09, 95% CI 0.04-0.24).	(van der Woude et al., 2012)
	1993-2006	598	Not reported (total 1881 patients with IA including UA, RA and non-RA)	• Symptoms <2 yrs • Fulfilled 1987 RA criteria	As above	Radiographic progression (change in SHS from baseline) over follow-up (maximum follow-up 6 yrs, median 4 yrs).	Repeated-measures analysis assessing symptom duration at first rheumatology assessment (<12 weeks, n=186, vs ≥12 weeks, n=412) with adjustment for age, gender and period of enrolment: • Symptom duration ≥12 wks (coefficient 1.3, p=0.001). No adjustment for disease activity.	(van der Linden et al., 2010)
		557			As above	Drug-free remission (physician judgement with no swollen joints and no DMARD/steroid over 1 yr) during follow-up (median 3 yrs) in 13%	Multivariable Cox regression, with adjustment for variables above: • Symptom duration ≥12 wks (HR 1.9, 95% CI 1.2-3.0). No adjustment for disease activity.	
Amsterdam (Netherlands)	1995-1996	111	145	• Symptoms <3 yrs • Fulfilled 1987 RA criteria within 1 yr of presentation	-	Disability (HAQ >median [0.53]) at 1 yr	Multivariable logistic regression, entering clinical, laboratory and socioeconomic variables with p<0.1, using forwards step-wise selection: • Pain (VAS) (OR 1.02, 95% CI 1.00-1.04), baseline HAQ (OR 3.0, 95% CI 1.5-5.9).	(Jansen et al., 2000)
		114	142	As above	-	Radiographic Progression (change in SHS from baseline >median[3]) at 1 yr	Multivariable logistic regression, entering pre-determined clinical, laboratory and radiographic variables, using forwards step-wise selection: • CRP≥20mg/dL (OR 3.6, 95% CI 1.5-8.4), baseline SHS (OR 1.1, 95% CI 1.0-1.1), RF-positivity (OR 2.6, 95% CI 1.1-6.0).	(Jansen et al., 2001)

Barcelona & Sabadell (Spain)	1998-2000	60	65+	• Symptoms <2 yrs	1st yr: gold IM (50mg/week) + methylprednisolone 4mg/day +/- addition of MTX at 6 mths	Radiographic progression (change in modified Larsen score ≥ minimal clinically important difference [2] from baseline) at 1 yr in 37%	Multivariable logistic regression, entering clinical, laboratory and radiographic variables with p<0.15 on univariable analysis, using backwards selection: • Pain (VAS) (OR 1.02, 95% CI 1.02–1.09), baseline Larsen score (OR 1.1, 95% CI 1.1–1.6).	(Sanmarti et al., 2003)
						Radiographic progression (increase in number of erosive joints from baseline) at 1 yr in 27%.	Multivariable logistic regression, as above: • Pain (VAS) (OR 1.02, 95% CI 1.00–1.07), shared epitope (OR 5.7, 95% CI 1.1–26).	
	1998-2003	105	115	As above	As above	Remission (DAS28<2.6) at 2 yrs in 32%.	Multivariable logistic regression, entering clinical, laboratory and radiographic variables with p<0.25 on univariable analysis, using step-wise selection: • DAS28<5.1 (OR 4.1, 95% CI 1.6-11).	(Vazquez et al., 2007)
						Disability (modified HAQ >0) at 2 yrs in 73%	Multivariable logistic regression: clinical, laboratory, radiographic and socioeconomic variables with p<0.1 on univariable analysis, forwards step-wise selection; • Age (OR 1.1, 95% CI 1.0-1.1), RF-positivity (OR 3.8, 95% CI 1.2-12), baseline modified HAQ> 0.5 (OR 4.0, 95% CI 1.4-12).	(Graell et al., 2009)
						Radiographic progression (change in modified Larsen score ≥minimal clinically important difference [4] from baseline) at 2 yrs in 32%	Multivariable logistic regression, entering clinical, laboratory and radiographic variables with p<0.25 on univariable analysis, using step-wise selection: • Female (OR 5.5, 95% CI 1.1-28), shared epitope (OR 3.2, 95% CI 1.1-9.0).	(Sanmartí et al., 2007)
Leuven (Belgium)	2001-2005	89	Not reported	• Disease duration <1 yr	Step-down therapy (SSZ + MTX + prednisolone, randomised to SSZ or MTX at wk 40) or step-up (initial DMARD monotherapy) according to physician judgement 35% received step-down therapy	Remission (DAS28 <2.6) at time of analysis (median disease duration 18mths) in 69%.	Multivariable logistic regression, entering clinical, laboratory and treatment (initial step-up or step-down treatment) with significance on univariable analysis (in addition to pre-determined confounders: age, gender and symptom duration): • Remission (DAS28-CRP<2.6) at 4 mths (OR 19, 95% CI 3.6-96)	(Verschueren et al., 2009)
						Normal function (HAQ=0) at time of analysis (median disease duration 18mths) in 38%.	Multivariable logistic regression, as above (additional pre-determined confounders age, symptom duration and baseline DAS28-CRP): • Excluding HAQ=0 at 4 mths: female (OR 0.09, 95% CI 0.02-0.5), baseline HAQ (OR 0.1, 95% CI 0.03-0.6), good EULAR response at 4 mths (OR 6.6, 95% CI 1.3-33). • Including 4 mth HAQ: female (OR 0.04, 95% CI 0.003-0.5), HAQ=0 4 mths (OR 47, 95% CI 0.4-561)	

ERAN (UK, multicentre)	2002-2005	194	808 (Kiely et al., 2009)	• Physician diagnosis new-onset RA 62% of all enrolled (n=808) fulfilled 1987 RA criteria (Kiely et al., 2009)	-	Remission (DAS28<2.6) at 2 yrs in 30%	ROC curve analysis assessing predictive ability of model developed using multiple logistic regression for same outcome (entering clinical, laboratory and radiographic variables with p≤0.05 on univariable analysis) in n=379 CARDERA patients (UK multicentre double-blind RCT [MTX/ MTX+ciclosporin/ MTX+prednisolone/ MTX+ciclosporin+prednisolone] patients with 1987 ACR RA, disease duration <2 yrs, 3 of: SJC≥3, TJC≥6, EMS≥45min, ESR≥28mm/hr: 14% of all n=467 randomised had received prior DMARD). • Model including age, gender and TJC28: AUC 0.70 (95% CI 0.62-0.78).	(Ma et al., 2012)
SWEFOT (Sweden, multicentre)	2002-2005	322	487	• Symptoms <1 yr • DAS28 >3.2	1st phase open-label MTX: 10mg increasing to 20mg over 4 weeks	EULAR response (good and/or moderate) at 3-4 mths in 73%	Multivariable logistic regression, entering pre-determined clinical, laboratory and treatment (concurrent prednisolone and NSAID use) variables (excluding patients discontinuing MTX, treated as non-responders in sensitivity analysis n=355 with similar result) (separate models including DAS28 and HAQ due co-linearity): • Age (by decade) (OR 1.3, 95% CI 1.1-1.5), female (OR 0.5, 95% CI 0.3-0.8), symptom duration (mths) (OR 1.3, 95% CI 1.1-1.5), current smoker (OR 0.4, 95% CI 0.2-0.6), DAS28 (OR 0.6, 95% CI 0.5-0.8), HAQ (OR 0.6, 95% CI 0.4-0.8), concurrent prednisolone (OR 2.8, 95% CI 1.4-5.6).	(Saevarsdottir et al., 2011)
						Remission (DAS28, SDAI and CDAI definitions) at 3-4 mths in 18%, 11% and 12%, respectively	Multivariable logistic regression, as above entering baseline DAS28, SDAI or CDAI for models testing respective remission outcomes: • HAQ (OR not given) for all remission outcomes.	
Seville (Spain)	2002-2006	134	897	• Symptoms >4wks and <1 yr • SJC ≥2 • Fulfilled 1987 RA criteria at presentation and/or during follow-up	-	Radiographic damage (SHS erosion score) at 1yr	Multiple linear regression, entering serological (RF and ACPA), treatment (steroid and no. DMARDs over 12 mths), genetic (genotype TNFα promoter, shared epitope) and baseline SHS erosion score, using backwards step-wise selection (retention if p<0.15) • Shared epitope (double positive vs double negative) (coefficient 1.8, 95% CI 1.5-3.0), baseline SHS erosion score (coefficient 1.6, 95% CI 1.4-1.7).	(Reneses et al., 2009)

Umea (Sweden)	Not reported	43	Not reported	• Symptoms <1 yr	-	Radiographic progression (change in Larsen score from baseline) at 2 yrs	Multivariable logistic regression, entering variables (some pre-determined and some informed by univariable analysis: including age, gender, HAQ, CRP and those below): • SJC28 (coefficient 0.7, 95% CI 0.02-1.3), shared epitope (coefficient 9.3, 95% CI 1.9-17), baseline Larsen score (coefficient -0.4, 95% CI -0.7 to -0.1), EULAR response at 6 mths (good vs none coefficient -15, 95% CI -24 to -5) (moderate vs none coefficient -11, 95% CI -20to -3).	(Berglin et al., 2003)
Leeds (UK)	Not reported	182	182	• Symptoms <2yrs • Fulfilling 1987 ACR RA criteria at baseline or follow-up	-	Disability (HAQ and change in HAQ from baseline ordered by quartiles) at 1 and 2yrs	Multivariable ordinal regression, entering clinical, laboratory and radiographic variables, using forwards step-wise selection: • HAQ at 1 and 2 yrs: baseline HAQ (p<0.001). • Change in HAQ at 1 and 2 yrs: baseline HAQ (p<0.05) RF-positivity (p<0.05) (OR not given).	(Quinn et al., 2006)
						Radiographic erosions at 1yr in 51%	Multivariable logistic regression, entering clinical, laboratory and radiographic variables, using forwards step-wise selection: • CRP 13.5-43.5mg/L (p<0.05), RF-positivity (p<0.05), shared epitope (p<0.05) (OR not given).	
		118				Radiographic progression (change in Larsen score from baseline ordered by quartiles) at 1yr and 2 yrs	Multivariable ordinal regression, entering clinical, laboratory and radiographic variables, using forwards step-wise selection: • At 1 yr: no variables with p<0.05. • At 2 yrs: shared epitope (p<0.05). In RF-negative subgroup (n=67): • At 2 yrs high positive ACPA (p<0.05).	
Multicentre (Austria, Hungary, Slovenia)	Not reported	172	180	• Symptoms <3 yrs	-	Poor outcome over 3 yrs (≥1 of: increase in HAQ from 6mths to 3yrs ≥1, increase in HAQ from 6mths to 3yrs ≥0.3 and 6 mth HAQ≥2, new extra-articular RA feature [excluded sicca, Reynaud's, nodules], drop-out due to: biologic/ cyclophosphamide/ azathioprine/pulse steroid, joint/tendon surgery, disability due to RA, death) in 24%.	Multivariable determinant analysis, entering clinical,, laboratory (including experimental biomarkers such as cartilage oligomeric matrix protein [COMP]) and radiographic variables, using backwards and forwards step-wise selection: • DAS44, SJC (of 68), HAQ score, RF-positivity (IgM or IgG), COMP and Larsen score in feet in final model (effect sizes not given).	(Wagner et al., 2007)

3 centres, Italy	2007-2009	481	481	• SJC ≥2 for >2 wks and <1 yr • DAS28>3.2 (All fulfilled 1987 and 2010 RA criteria)	As per physician with loose protocol advised: initial MTX, step-up at/after 3 mths to combination DMARD if DAS28≥2.6 or TNF-inhibitor if DAS28≥3.2	Remission (DAS28<2.6) at 1 yr in 34%	Multivariable logistic regression, entering clinical, laboratory and radiographic variables with p≤0.1 on univariable analysis, using backwards step-wise selection: • Symptom duration <3 mths (OR 2.0, 95% CI 1.3 to 3.3) and starting DMARD within initial 3 mths (OR 1.7, 95% CI 1.1 to 2.7).	(Gremese et al., 2013)
CATCH (Canada, multicentre)	2007-2013	1840	1897	• Symptoms 6-52 wks • Fulfilling 1987 or 2010 RA criteria Either: • ≥ 2 swollen joints Or: • 1 swollen MCP/PIP and ≥1 of: positive RF, positive ACPA, EMS >45 min, NSAID-response, or a positive MTP squeeze	-	Sustained remission (for ≥ 6 mths or 2 consecutive visits for remission definitions below) over follow-up (maximum 5 yrs): • ACR Boolean (using 28-joint counts) in 19%. • SDAI in 23%.	Multivariable logistic regression, entering clinical, laboratory, radiographic, initial treatment (steroid and DMARD use within first 3 months) and time to remission variables if p<0.1 on univariable analysis, using backwards step-wise selection (retention if p<0.05 or pre-determined variable: age, gender, symptom duration, DAS28) (missing data for serology and x-rays imputed): • ACR Boolean definition: initial steroids (OR 0.5, 95% CI 0.3-0.7), initial combination DMARD (OR 1.6, 95% CI 1.1-2.3), time to remission (mths) (OR 0.94, 95% CI 0.92-0.96). • SDAI definition: initial steroids (OR 0.5, 95% CI 0.4-0.8), initial combination DMARD (OR 1.5, 95% CI 1.1-2.1), time to remission (mths) (OR 0.94, 95% CI 0.92-0.95).	(Kuriya et al., 2014)
Rome (Italy)	Not reported	121	Not reported	• Symptoms <1 yr • Fulfilling 1987 and 2010 RA criteria	Initial MTX +/- low dose steroid. Addition of Adalimumab or Etanercept if DAS44 >2.4	Remission (5 of 1981 ACR remission criteria at 2 visits for ≥3 months without flare [DAS44>0.6] or change in DMARD/steroid within prior 6 mths) at 1 yr in 25%	Multivariable logistic regression, entering clinical, laboratory and radiographic variables with p<0.25 on univariable analysis, using backwards step-wise selection: • Symptoms<3 mths (OR 5.3, 95% CI 2.1–13).	(Bosello et al., 2011)
						Remission (DAS44<1.6 at 2 visits for ≥3 mths without flare [DAS44>0.6] or change DMARD/steroid for previous 6 mths) at 1yr in 46%.	Multivariable logistic regression, as above: • Male (OR 2.5, 95% CI 1.1–5.9), ESR<35 mm/hr (OR 2.4, 95% C 2.2–5.1).	
						Radiographic erosion(s) at 1 yr in 40%	Multivariable logistic regression, as above: • Symptoms ≥3 mths (OR 3.9, 95% CI 1.5–11).	

EURIDISS: European Research on Incapacitating Diseases and Social Support, SSZ: sulfasalazine, Mo-Co-To: Montpellier-Cochin-Tours/Toulouse cohort, BARFOT: Better Anti-Rheumatic Pharmacotherapy, BMD: bone mineral density, ERAN: Early RA Network, CARDERA: Combination Anti-rheumatic Drugs in Early Rheumatoid Arthritis, RCT: randomised controlled trial, SWEFOT: Swedish Pharmacotherapy Trial, CDAI: clinical disease activity index, CATCH: Canadian Early Arthritis Cohort.

Table 7. Randomised trials assessing prognostic factors using multivariable analysis, in patients with early DMARD-naïve RA. Rheumatoid arthritis is defined according to fulfilment of 1987 RA criteria, unless otherwise stated.

Study Population	Years patients recruited	n	Total number of patients randomised	Inclusion Criterion (patients fulfilling 1987 ACR RA criteria, unless otherwise stated)	Treatment Protocol	Outcome	Statistical Methods of Analysis and Predictive Factors with Statistical Significance (independent variables are variables at baseline unless otherwise stated)	Reference
Utrecht (Netherlands)	1990 onwards	128	Not reported	• Disease duration <1 yr	Initial NSAID vs. initial HCQ vs. initial IM gold vs. initial MTX (open-label)	Radiographic progression (change in SHS from baseline >0) at 1 yr in 75%	Multivariable logistic regression, entering clinical, laboratory, radiographic and treatment variables using forwards step-wise selection: • joint score (joint swelling and tenderness, with weighting by size of joint)(Thompson et al., 1987) (OR 1.9, 95% CI 1.0-3.5), RF-positivity (OR 12.3, 95% CI 3.4-4.6), baseline SHS (OR 5.0, 95% CI 1.3-20).	(van der Heide et al., 1995)
	1990-1998	397	562	As above	1st yr: as above. 2nd yr: switch if no response (>50% improvement in ≥3 of: pain VAS, Thompson joint score, EMS, ESR) NSAIDs→DMARD, HCQ→auranofin, IM gold→penicillamine, MTX→SSZ. Yrs 3-4: no protocol.	Remission (EMS≤15 min, VAS pain≤10mm, Thompson joint score≤10, ESR≤30 mm/hr for ≥6 months) over 4 yrs in 36%	Multivariable Cox regression analysis, entering clinical, laboratory, radiographic variables and response at 6 mths using step-wise selection (not further specified): • Thompson joint score (coefficient 1.00, 95% CI 0.996-1.00), pain (VAS) (coefficient 0.98, 95% CI 0.97-0.99), RF-negativity (coefficient 1.6, 95% CI 1.2-2.3), good 6 mth response (as defined in treatment protocol) (coefficient 4.8, 95% CI 3.2-7.0).	(Verstappen et al., 2005)
Sample from 2 RCTs (Netherlands, multicentre)	1990-1998	78	394+	• Disease duration <1 yr	Protocol for DMARD therapy for first 2 years (van Jaarsveld et al., 2000; van Everdingen et al., 2002) (open-label)	Disease activity (composite score based on SJC and TJC of 38 joints and ESR) at 3 and 5 years	Multiple linear regression, entering baseline disease activity and clinical, laboratory and psychosocial variables with p<0.05 on univariable analysis, using sequential selection: • 3yrs: baseline disease activity (correlation coefficient 0.4, p<0.01), passive avoidance coping (correlation coefficient 0.3, p<0.01) social support (correlation coefficient -0.2, p<0.05). • 5yrs: baseline disease activity (correlation coefficient 0.3, p<0.05), passive avoidance coping (correlation coefficient 0.3, p<0.05).	(Evers et al., 2003)

FIN-RACo (Finland)	1993-1995	157	199	• Symptoms <2 yrs • SJC ≥3 • ≥3 of: ESR ≥28 mm/hr or CRP >19 mg/l, EMS ≥29 min, SJC>5, TJC>10	MTX + SSZ + HCQ + prednisolone vs. initial SSZ +/- low dose prednisolone (open-label)	Remission (1981 ACR remission criteria excluding fatigue and EMS) at 6 mths in 23% combination group vs. 9% initial SSZ group	Multivariable logistic regression per treatment group, entering pre-determined variables (age, gender, symptom duration, SJC, TJC, ESR, RF-positivity and those below): • Combination group (vs initial SSZ) (OR 4.4, 95% CI 1.6-12), soluble IL2 receptor (OR 4.7, 95% CI 1.4-15).	(Kuuliala et al., 2005)
		165	199	As above	As above	Remission (5 of 1981 ACR remission criteria: EMS ≤15 min, no joint pain, TJC=0, SJC=0, ESR <30 mm/hr in women or <20 mm/hr in men) at 2 yrs in 42% combination group vs. 17% in initial SSZ group	Multivariable logistic regression per treatment group, entering pre-determined variables (age, gender, number of ACR criteria fulfilled, shared epitope and symptom duration): • Combination group: no variables independently predictive. • Initial SSZ: symptom duration <4mths (p=0.01).	(Möttönen et al., 2002)
COBRA (Netherlands, Belgium)	1993-1995	135	156	• Time from diagnosis <2 yrs	Initial combination therapy (MTX, SSZ + high dose prednisolone) vs. SSZ + placebo (single-blind)	Radiographic progression (increase in SHS ≥1) at 1 yr at the joint level (n=2,700 joints)	Conditional logistic regression, entering baseline swelling score (0-2), tenderness score (0-3) and SHS for individual joints: • Swelling score (OR 2.8, 95% CI 1.9-4.1), tenderness score (OR 1.8, 95% CI 1.3-2.4), SHS (OR 2.0, 95% CI 1.6-2.6).	(Boers et al., 2001)
		148	156	As above	As above	Mean change in SHS score per yr	Multivariable generalised estimating equations, entering pre-determined variables (as below, plus age, gender, symptom duration, shared epitope, ESR and treatment use over follow-up): • Treatment group SSZ vs. combination (coefficient -3.2, 95% CI -5.6 to -0.8), baseline DAS28-ESR (coefficient 1.2, 95% CI 0.2 to 2.2), RF-positivity (coefficient 3.6, 95% CI 1.2 to 5.0), baseline SHS (coefficient 0.2, 95% CI 0.1 to 0.3).	(Landewé et al., 2002)
CAMERA (Netherlands, multicentre)	1999-2003	205	299	• Symptoms <1 yr	1-2 yrs: initial MTX with dose escalation and addition of ciclosporin depending on response (determined by physician assessment every 3 months or computer program every 4 weeks) (open-label)	Radiographic progression (mean yearly change in SHS from baseline) over 5 yrs (4 or 6 yr data used in n=76)	Multiple linear regressions, entering all pre-determined variables (age, gender, DAS28, RF-positivity, treatment arm, baseline SHS, and 6 mth response): • EULAR good response at 6 mths (coefficient -0.4, 95% CI -0.7 to -0.1), RF-positivity (coefficient 0.3, 95% CI0.1-0.6), SHS (coefficient 0.07, 95% CI 0.04-0.10).	(Bakker et al., 2011)
						DAS28-ESR at 5 yrs (4 or 6 year data used in n=34)	Multiple linear regressions, as above: • EULAR good response at 6 mths (coefficient -0.8, 95% CI -1.2 to -0.3)	

CIMESTRA (Denmark)	1999-2002	130 in MRI sub-study	160	• Disease duration <6 mths • SJC ≥2	Yrs 1-2: MTX + ciclosporin vs. MTX + placebo, with IA steroid +/- addition HCQ ≥wk 68 (double-blind to initial therapy)	Radiographic progression (change in SHS from baseline >0) at 2 yrs in 30%	Multivariable logistic regression, entering radiographic and MRI wrist variables with p<0.05 on univariable analysis and clinical and laboratory variables (age, gender, DAS28, shared epitope, ACPA, smoking) using backwards step-wise selection: • MRI bone marrow oedema score (OR not given).	(Hetland et al., 2009)
					Yrs 1-2 as above. Yrs 3-5: step-up if required to MTX + SSZ + HCQ, then TNF-inhibitor	Radiographic progression (change in SHS from baseline >0) at 5 yrs in 53% (intention-to-treat analysis)	Multivariable logistic regression, entering pre-determined clinical, laboratory, radiographic and MRI wrist baseline variables (including age, gender, DAS28, MRI bone marrow oedema score, MRI erosion score, MRI synovitis score and those below): • ACPA-positivity (OR 4.0, 95% CI 1.7-9.8), baseline SHS (OR 1.12, 95% CI 1.03-1.21).	(Hetland, Stengaard-Pedersen et al. 2010
BeSt (Netherlands, multicentre)	2000-2002	Not given	508	• Disease duration <2yrs • SJC (of 66) ≥6 and TJC (of 68) ≥6, • Either ESR ≥28 mm/hr or a VAS global health ≥20 mm	Sequential DMARD monotherapy; step-up to combination DMARD therapy; initial DMARD combination therapy including high dose prednisone; or initial MTX + Infliximab (single-blind)	Radiographic progression (increase in SHS from baseline >smallest detectable change [4.6]) at 2 yrs in 40%, 34%, 19% and 18% across treatment groups, respectively	Multivariable logistic regression, entering RF or ACPA-positivity (separate models) with confounders (variables associated with RF or ACPA on univariable analysis with p<0.05: gender, smoking, DAS44-ESR, SHS erosion score ≥0.5) in patients grouped by treatment arm: • RF-positivity (OR 4.7, 95% CI 1.5-14.5), ACPA-positivity (OR 13, 95% CI 3-52) with sequential monotherapy. • No significance in other treatment groups.	(de Vries-Bouwstra et al., 2008)
		465	508	As above	As above	Rapid radiographic progression (increase in SHS from baseline ≥5) at 1 yr in 33% initial monotherapy, 13% initial DMARD combination and 9% initial infliximab groups	Multivariable logistic regression, entering variables with significance on univariable analysis (plus age, gender, BMI, smoking, symptom duration, SJC, DAS44, HAQ and treatment group) using backwards step-wise selection (retention if p≤0.10) (continuous variables categorised using tertiles): • SHS erosion score ≥4 (OR 4, 95% CI 2-9), RF or ACPA-positivity (OR 2, 95% CI 1-6), both positive (OR 4, 95% CI 2-9), CRP ≥35mg/dL (OR 5, 95% CI 2-10), initial combination DMARD vs monotherapy (OR 0.1, 95% CI 0.1-0.4), initial infliximab vs monotherapy (OR 0.1, 95% CI 0.1-0.3).	(Visser et al., 2010)

BeSt (contd.)	2000-2002	497	508	• Disease duration <2yrs • SJC (of 66) ≥6 and TJC (of 68) ≥6, Either ESR ≥28 mm/hr or a VAS global health ≥20 mm	Sequential DMARD monotherapy; step-up to combination DMARD therapy; initial DMARD combination therapy including high dose prednisone; or initial MTX + Infliximab (single-blind)	HAQ ≥1 at 3 mths, rates not given	Multivariable logistic regression, entering variables with p<0.1 on univariable analysis (plus confounders, not specified) using backwards step-wise selection (retention if p≤0.10) (separate models constructed for variables with co-linearity or overlapping, with selection of final model with maximum Nagelkerke's' R^2) (continuous variables categorised using tertiles): • Treatment group; initial combination DMARD vs. monotherapy (OR 0.3, 95% CI 0.2–0.5) initial infliximab vs monotherapy (OR 0.4, 95% CI 0.2–0.6), HAQ; 2nd tertile (OR 2.6, 95% CI 1.6–4.2) 3rd tertile (OR 5.3, 95% CI 2.9–9.5) (vs lowest tertile HAQ<1.4), VAS pain; 2nd tertile (OR 2.2, 95% CI 1.3–3.8), 3rd tertile (OR 2.7, 95% CI 1.4–5.1) (vs lowest tertile VAS<40), RAI; 2nd tertile (OR 1.7, 95% CI 1.0–3.0), 3rd tertile (OR 2.7, 95% CI 1.5–4.7) (vs lowest tertile RAI<10).	(Dirven et al., 2012)
		508	508	As above	As above	Sustained drug-free remission at 5 yrs (DAS44<1.6 for ≥1 yr after cessation of DMARD/steroid) in 10%	Multivariable logistic regression, entering clinical, laboratory and radiographic variables with p<0.10 on univariable analysis, using backwards step-wise selection (retention if p≤0.10) (treatment group not significant predictor on univariable analysis, therefore not included in model): • Male gender (OR 2.4, 95% CI 1.3-4.5), symptom duration (wks) (OR 0.99, 95% CI 0.98-1.00), DAS44 (OR 0.6, 95% CI 0.4-0.9), ACPA-positivity (OR 0.2, 95% CI 0.1-0.4).	(van der Woude et al., 2012)
		508	508	As above	As above	Failure of initial treatment (DAS44-ESR>2.4)	Risk regression model with adjustment for sex, age, smoking, RF and baseline DAS44: • High BMI (≥25 vs. <25kg/m^2) (RR: 1.1, 95% CI 1.2-1.4). • BMI (continuous variable) (RR: 1.02, 95% CI 1.01-1.04). N.B. with stratification for treatment group, BMI (continuous variable) remained independently predictive of response to initial MTX monotherapy (groups 1 and 2). Linear mixed model demonstrated higher TJC and patient VAS in patients with high BMI over 1 yr	(Heimans et al., 2013)

BeSt (contd.)	2000-2002	186	508	As above, receiving initial MTX monotherapy, with blood samples for DNA analysis	Sequential DMARD monotherapy and step-up to combination DMARD groups received MTX 15mg x 3mths then escalated to 25-30mg weekly x 3 mths (if DAS44<2.4 at 3 mths)	DAS44-ESR ≥2.4 at 6 mths in 53%	Multivariable logistic regression, entering clinical and laboratory +/- genetic variables with p≤0.1 on univariable analysis, using backwards step-wise selection (retention if p≤0.10) (continuous variables categorised using quartiles) (RF-positivity fitted as interaction term with smoking) (separate models including and excluding genetic factors) • Female gender, RF-positivity in combination with smoking and DAS44 independent predictors (OR not given for non-genetic model).	(Wessels, van der Kooij et al. 2007
ASPIRE RCT	2000-2002	1004	1049	• Symptoms >3mths and <3yrs • SJ ≥10, TJC≥12 • 1 of: CRP >2mg/dL, RF- positivity, radiographic erosions	MTX + placebo; MTX + Infliximab 3mg/kg; or MTX + Infliximab 6mg/kg (double-blind)	Radiographic progression (change in SHS from baseline >0) at 1 yr in 61% (MTX alone) vs. 39% (MTX + Infliximab)	Multivariable logistic regression, entering pre-determined variables (age, gender, SJC44, TJC44, RF-positivity, CRP, ESR, baseline SHS), separate models for MTX alone and MTX + infliximab groups: • MTX alone: SJC44 (OR 1.04, 95% CI 1.01-1.07), ESR (OR 1.02, 95% CI 1.01-1.03). • MTX + Infliximab: age (OR 1.02, 95% CI 1.01-1.04), SHS (OR 0.99, 95% CI 0.97-1.00).	(Smolen et al., 2006)
		Not given	1049	As above	As above	Rapid radiographic progression (change in SHS from baseline ≥5) at 1 yr in 23% (MTX alone) vs. 8% (MTX + Infliximab)	Multivariable logistic regression, entering all variables identified using univariable analysis (SJC28, RF titre, ESR, CRP) and treatment group (separate models constructed for ESR and CRP due to co-linearity) (continuous variables categorised using tertiles). Matrix risk model developed with the following variables: • CRP (<0.6, 0.6–3 or >3 mg/dl) or ESR (<21, 21–50 or >50 mm/h), SJC28 (<10, 10–17 or >17) and RF (<80, 80–200 or >200 U/ml), treatment (MTX vs MTX+ infliximab)	(Vastesaeger et al., 2009)
RCT (Japan, multicentre)	Not reported	55	Not reported	• Symptoms <2 yrs • TJC (of 48) ≥6, SJC (of 46) ≥3, CRP ⩾1.0mg/dl or ESR ⩾ 30mm/hr	MTX 8 mg/week, bucillamine 200 mg/day, or MTX + bucillamine (double-blind) alternative DMARDs in non-responders after 24 wks or after adverse events	Radiographic progression (change in SHS from baseline) at 2 yrs	Univariable linear regression, baseline variables: • SJC (coefficient 0.3, p<0.05), CRP (coefficient 0.3, p<0.05), DAS28-CRP (coefficient 0.4, p<0.01) (95% CIs not given) Multiple linear regression using step-wise procedure, (variables considered were ACR core measures at baseline and over follow-up, RF and ACPA-positivity and baseline SHS), method not further specified. 2 final models reported include the following independent predictors: • Baseline SHS and 12 wk SJC, CRP and patient pain VAS. • Baseline SHS and mean SJC and CRP over follow-up (assessed every 3 mths).	(Ichikawa et al., 2010)

HOPEFUL (Japan, multicentre)	2009-2010	Not clear	334	• Disease duration ≤2 yrs • SJC≥8, TJC≥10, ESR≥28mm/hr or CRP≥10mg/l • RF positive or ≥radiographic erosion	MTX (6-8mg/wk) + placebo or Adalimumab + MTX	Clinical remission (DAS28<2.6) at 6 mths (proportions of patients achieving not reported).	Multivariable logistic regression, entering all variables identified using univariable analysis(p<0.1): • MTX alone: Female (OR 0.3, 95% CI 0.1-0.8), HAQ-DI (OR 0.4, 95% CI 0.2-1.0), physician VAS disease activity (OR 1.0, 95% CI 0.9-1.0). • Adalimumab +MTX: ACPA positive (OR 0.3, 95% CI 0.1-0.9), DAS28 (OR 0.5, 95% CI 0.3-0.9), HAQ-DI (OR 0.3, 95% CI 0.1-0.7), radiographic erosion (OR 0.1, 95% CI 0.01-1.0).	(Takeuchi et al., 2014)
						No radiographic progression (change in SHS from baseline ≤0.5) at 6 mths in 57/161 (35%) (MTX alone) vs. 106/171 (62%) (adalimumab + MTX).	Multivariable logistic regression, as above: • MTX alone: CRP>3mg/l (OR 3.1, 95% CI 1.1-8.7), physician VAS disease activity (OR 0.98, 95% CI 0.96-0.99). • Adalimumab +MTX: CRP per mg/dl (OR 0.8, 95% CI 0.7-0.9), SJC (OR 0.9, 95% CI 0.8-1.0), physician VAS disease activity (OR 0.98, 95% CI 0.96-1.00), SHS (OR 0.99, 95% CI 0.97-1.00).	

FIN-RACo: Finnish Rheumatoid Arthritis Combination Therapy Trial, COBRA: Combinatietherapie Bij Reumatoide Artritis, CAMERA: Computer Assisted Management in Early Rheumatoid Arthritis, CIMESTRA: Ciclosporin, Methotrexate and Steroids in Rheumatoid Arthritis, BeSt: Behandelstrategieën voor Reumatoide Artritis [treatment strategies for rheumatoid arthritis], DNA: deoxyribonucleic acid, ASPIRE: Active controlled Study of Patients receiving Infliximab for treatment of Rheumatoid arthritis of Early onset.

2.3 Ultrasound Imaging in the Assessment of Patients with Inflammatory Arthritis

Musculoskeletal ultrasound offers a means of imaging which is safe (not involving exposure to ionising radiation or contrast), relatively inexpensive and quick in comparison to other imaging modalities such as MRI or computed tomography (CT). It may be performed in real time in clinic. Two-dimensional, grey scale (GS) images enable the assessment of synovitis (through the detection of joint effusion and synovial hypertrophy), tenosynovitis, tendon damage and bone erosion.

Synovitis and tenosynovitis may also be measured via the detection of abnormal blood flow within microvessels in the synovium and tenosynovium, using methods based on the Doppler effect. Colour Doppler provides an image in which colour represents the difference in the frequency between transmitted ultrasound waves and those reflected back from moving blood cells. This is determined by the speed and direction of cells (Terslev et al., 2008). Whereas for images obtained using power Doppler, colour represents the amplitude of waves reflected back with a shift in frequency which is not dependent on the velocity of blood flow. Power Doppler activity (PD) is therefore more widely used in the assessment of the low-flow present in synovial microvessels (Wakefield et al., 2003).

The use of ultrasound in clinical practice is increasing. Studies illustrating its potential value in real-life include a cross-sectional study of 46 patients with established RA; treatment decisions were altered after ultrasound (hands and wrists) in seven (15%) patients (Ceponis et al., 2014). Of note, patients with suspected fibromyalgia were excluded. In a retrospective study of patients with RA undergoing ultrasound for disease activity assessment within routine practice, the treatment decision was influenced by ultrasound results in 31/60 (52%) patients (Agrawal et al., 2009). Of course, by nature of the design of this latter study, ultrasound was conducted in these patients as it was deemed to be of clinical use.

2.3.1 Methods of Reporting

The Outcome Measures in Rheumatology (OMERACT) group have provided standardised definitions of pathology visible on ultrasound, based on expert consensus (Wakefield et al., 2005):

- Synovial effusion: abnormal intra-articular material which is compressible and usually anechoic/hypoechoic compared to subdermal fat (PD is absent).
- Synovial hypertrophy: abnormal intra-articular material which is not compressible, is usually hypoechoic in comparison to subdermal fat and may be observed with/without PD.
- Tenosynovitis: anechoic/hypoechoic thickened tissue, seen with/without fluid within the tendon sheath and in two perpendicular planes (with/without PD).
- Tendon damage: an internal and/or peripheral focal tendon defect (i.e. absence of fibres) in the region enclosed by tendon sheath, seen in two perpendicular planes (Bruyn et al., 2014).
- Cortical erosion: an intra-articular discontinuity of the bone surface visible in two perpendicular planes.

- *At the Joint Level*

Synovitis, tenosynovitis, tendon damage and erosive damage at the joint level may be reported using dichotomous outcomes (present or absent), semi-quantitative scales or quantitative methods. Reporting methods vary across studies, particularly for tenosynovitis (Alcalde et al., 2012). Most studies have defined or adopted semi-quantitative scales (Table 8), with GS synovitis commonly defined by combined assessment of synovial effusion and hypertrophy (as these processes usually occur together in pathological synovitis). Recently, the EULAR-OMERACT semi-quantitative global score for synovitis, combining both the GS appearance of synovial hypertrophy and PD assessments, has been developed using an expert consensus-based approach (D'Agostino et al., 2017).

Quantitative measures include the depth of synovium for GS synovitis (Schmidt et al., 2004; Scheel, A. K. et al., 2005), the number or proportion of pixels affected by colour Doppler or PD on digital image analysis (Walther et al., 2001; Terslev et al., 2008) and diameter of erosions (Zayat et al., 2015). Good correlations have been observed between semi-quantitative and quantitative methods of assessments of both GS (Scheel, A. K. et al., 2005) and PD synovitis (Walther et al., 2001).

Table 8. Semi-quantitative methods of scoring pathology on ultrasound.

Research group	Ultrasound parameter	Grading
Szkudlarek et al	GS hypertrophy	0: none, 1: minimal synovial thickening (filling the angle between the periarticular bones, without bulging over the line linking tops of the bones), 2: synovial thickening bulging over the line linking tops of the periarticular bones but without extension along the bone diaphysis, 3: synovial thickening bulging over the line linking tops of the periarticular bones, with extension to at least one of the bone diaphyses (Szkudlarek, M. et al., 2003). Later publications include grade 4: extension to both diaphyses (Szkudlarek et al., 2004; Szkudlarek et al., 2006).
	GS effusion	0: none, 1: minimal amount of joint effusion, 2: moderate amount of joint effusion (without distension of the joint capsule), 3: extensive amount of joint effusion (with distension of the joint capsule) (Szkudlarek, M. et al., 2003).
Leeds score	GS hypertrophy	0: none, 1: mild, flat thickening, 2: moderate thickening, 3: marked thickening (Karim et al., 2004; Brown et al., 2006).
Newman et al	PD synovitis	0: no or minimal hyperaemia, 1: mild hyperaemia, 2: moderate hyperaemia, 3: marked hyperaemia (Newman et al., 1996).
EULAR/ OMERACT	GS hypertrophy	0: no hypertrophy independently of presence of effusion, 1: minimal; hypertrophy with or without effusion up to level of horizontal line connecting bone surfaces, 2: moderate; hypertrophy with or without effusion extending beyond joint line but with upper surface concave (curved downwards) or hypertrophy extending beyond joint line but with upper surface flat, 3: severe; hypertrophy with or without effusion extending beyond joint line but with upper surface convex (curved upwards) (D'Agostino et al., 2017).
	PD synovitis	0: none, 1: minimal; three single PD spots or up to one confluent spot and two single spots or up to two confluent spots, 2: moderate; greater than grade 1 but <50% PD signals in the total GS, 3: severe; PD affecting >50% of the background GS (D'Agostino et al., 2017).
	GS hypertrophy and PD synovitis combined	0: normal; no hypertrophy or PD, 1: minimal; GS=grade 1 and PD≤grade 1 2: moderate; GS=grade 2 and PD≤grade 2 or GS=grade 1 and PD=grade 2, 3: severe; GS=grade 3 and PD≤grade 3 or GS=grade 1 or 2 and PD=grade 3 (D'Agostino et al., 2017).
	GS tenosynovitis	In longitudinal and transverse planes… 0: normal, 1: minimal, 2: moderate, 3: severe (Naredo et al., 2013a).

EULAR/ OMERACT (contd.)	PD tenosynovitis	Visible in 2 perpendicular planes and excluding normal feeding vessels… 0: no signal, 1: peritendinous focal signal within the widened synovial sheath (i.e. signals in only one area of the widened sheath), 2: peritendinous multifocal signal within the widened synovial sheath (i.e. signals in more than one area of the widened sheath), 3: peritendinous diffuse signal within the widened synovial sheath (i.e. signals filling most of the widened sheath). In the presence of abnormal intratendinous signal (visible in 2 perpendicular planes and excluding normal feeding vessels) in addition to grade 1 or 2 peritendinous PD signal, increase grade by one point (Naredo et al., 2013a).
OMERACT	Tendon damage	In longitudinal and transverse planes… 0: normal, 1: minimal, 2: moderate, 3: severe (Bruyn et al., 2014).
Szkudlarek et al	Erosion	0: regular bone surface, 1: irregularity of the bone surface without formation of a defect seen in 2 planes, 2: formation of a defect in the surface of the bone seen in 2 planes, 3: bone defect creating extensive bone destruction (Szkudlarek, M. et al., 2003).
Wakefield et al	Erosion (cortical break seen in 2 planes)	Small: diameter <2mm, Moderate: diameter 2–4 mm, Large: diameter >4 mm (Wakefield et al., 2000).
Zayat et al	Erosion (cortical break seen in 2 planes)	0: none, 1: erosions covering less than one third, 2: erosions covering between one- and two-thirds, 3: erosions covering more than two-thirds of the bone surface (Zayat et al., 2015).

- *At the Patient Level*

The appropriate selection of joints and tendons to assess for an accurate depiction of disease activity and damage in an individual patient depends on a number of factors. These include the frequency of joint involvement (Iagnocco et al., 2008) as well as the sensitivity and specificity of ultrasound findings at various joint sites in IA (Backhaus et al., 2009). Integral within this is the accessibility of specific joints for imaging with ultrasound (Szkudlarek, M. et al., 2003; Iagnocco et al., 2008). Ultimately, the choice of joints to examine is dependent on the intended use of ultrasound. High sensitivity of an extensive joint assessment may be appropriate for use within a trial setting or for classification/prognostic assessment at the outset of treatment. In contrast, for monitoring of patients on treatment in clinical practice, examination of a reduced number of joints seems more feasible.

Previous studies have largely reported joint counts of the number of joints affected by GS and/or PD synovitis, in addition to total scores for GS and/or PD calculated by summation of the respective semi-quantitative scores at individual joints (Mandl et al., 2011). Work is currently underway to establish the optimal selection of joints to score using the EULAR-OMERACT combined score to facilitate the monitoring of RA activity and improve comparability across studies in the future (Terslev et al., 2017b). The performance of global ultrasound scores (calculated from examinations of multiple joints), in addition to ultrasound assessments at the level of individual joints, are discussed below.

2.3.2 Effectiveness of Ultrasound According to the OMERACT Filter

Ultrasound enables evaluation of joints and peri-articular structures based on GS appearance and PD in multiple planes, in real time. It is already widely used in clinical practice in the assessment of patients with IA, being relatively affordable and less time-consuming than other imaging methods (D'Agostino et al., 2009). Hence, it has face validity, content validity and feasibility. Other aspects of effectiveness of ultrasound as a tool in the assessment of early IA are discussed below, according to the criteria outlined within the OMERACT filter (Table 9) (Boers et al., 2014).

Table 9. The requirements of an effective measurement tool: definitions of terms within the OMERACT filter.

Truth	Face Validity	The theoretic plausibility of a measurement tool for its intended use.
	Content Validity	The completeness of a tool to reflect the entirety of the concept it is intending to measure and the necessity for inclusion of all the components within the measurement tool (i.e. do all its aspects contribute uniquely to the overall measure).
	Construct Validity	Agreement with other measures which are theoretically related and lack of agreement with those which are not.
	Criterion Validity	Agreement with an ideal or 'gold' standard. This includes: • Concurrent validity: agreement with a 'gold' standard assessment conducted simultaneously with the proposed new measurement tool. • Predictive validity: agreement with a 'gold' standard assessment carried out in the future, i.e. ability of a tool to predict a future state.
Discrimination	Includes the ability of a tool to differentiate between health and disease, as well as between disease severity states (including reliability and responsiveness).	
	Reliability	The ability of a tool to detect severity states with consistency. For example, between equipment or between observers (inter-observer) and by the same observer over time (intra-observer).
	Responsiveness	The ability to detect differences in severity over time, e.g. for the purposes of monitoring response to treatment.
Feasibility	Practicality of using the measurement tool, including involved time and financial costs.	

2.3.2.1 Synovitis

- *Synovitis: Construct Validity*

The most objective measure of active synovitis available real-time in clinic is presumed to be joint swelling on clinical examination, relative to other methods such as joint tenderness. However, clinically it may be difficult to distinguish active synovitis from other physical signs of swelling such as tenosynovitis, soft tissue oedema and osteophytes (Wakefield et al., 2004; Salaffi et al., 2008). Furthermore, subclinical synovitis may be detectable by ultrasound in the absence of overt clinical swelling. This has been confirmed in patients with early IA prior to treatment (Wakefield et al., 2004; Funck-Brentano et al., 2009), early RA (Szkudlarek et al.,

2004; Salaffi et al., 2008) and established RA (Szkudlarek, M. et al., 2003; Szkudlarek et al., 2004; Ceponis et al., 2014; Kawashiri et al., 2014a).

In comparison to synovitis detected by MRI as the reference standard, GS synovitis has been shown to offer higher sensitivity and slightly lower specificity in comparison to clinical examination. Amongst 40 patients with RA (20 of whom had been diagnosed within the preceding two years) and 20 controls, the sensitivity and specificity of low-grade GS synovitis at the MCPs (≥grade 1) was 70% and 78%, respectively (versus 40% and 85% for clinical swelling and/or tenderness) (Szkudlarek et al., 2006). For the MTPs, the sensitivity and specificity of GS synovitis was 87% and 74%, respectively (versus 43% and 89%, respectively, for clinical examination) (Szkudlarek et al., 2004).

Higher levels of GS and PD synovitis (both defined as ≥grade 2) have been shown to be highly sensitive and specific for MRI osteitis in DMARD-naïve patients with suspected early RA (Damjanov et al., 2012; Kawashiri et al., 2014b). Sensitivity and specificity for GS synovitis was 100% and 84% at the MCPs and 93% and 94% at the wrists, respectively. Sensitivity and specificity for PD synovitis were 96% and 91% at the MCPs and 83% and 90% at the wrists, respectively. Good correlations were observed between the respective semi-quantitative ultrasound scores and MRI osteitis scores ($p<0.001$).

Concerning summative GS and PD synovitis scores calculated from assessments of multiple joints, construct validity has been evaluated by assessing their concordance with clinical and laboratory measures of disease activity in patients with RA (Mandl et al., 2011). Significant correlations have been observed with composite clinical measures (mainly DAS28) (Hameed et al., 2008; Naredo et al., 2008b; Balsa et al., 2010; Perricone et al., 2012) and inflammatory markers (Hameed et al., 2008; Scirè et al., 2009; Dougados et al., 2010; Perricone et al., 2012). The selection of joints in such studies ranged from extensive assessments of 44 joints (Scirè et al., 2009) to examinations of the hands and wrists alone (Hameed et al., 2008). Scores of PD synovitis and those including large joints appear to show greater concordance with inflammatory markers than either GS synovitis scores (Hameed et al., 2008) or assessments restricted to small joints

(Ozgocmen et al., 2004; Mandl et al., 2011), although these conclusions are largely based on studies conducted in patients with established RA.

A systematic review concluded simplified assessments of either twelve (wrists, MCPs2-3, knees, ankles and elbows) (Naredo et al., 2008b) or seven joints (unilateral wrist, MCPs2-3, PIPs2-3 and MTP2 and 5) (Backhaus et al., 2009) provided good validity (Mandl et al., 2011). Significant correlations have been demonstrated between DAS28 and GS and PD scores for both the 12-joint and 7-joint sets in patients with established RA commencing TNF inhibitor therapy (Naredo et al., 2008b) and a mixed cohort of patients with IA commencing or receiving a change in DMARD or TNF inhibitor therapy (Backhaus et al., 2009). These standardised 12- and 7-joint assessments also demonstrate good correlation with more extensive ultrasound assessments in other cohorts of patients with active RA (Naredo, E et al., 2005; Hammer, H.B. and Kvien, T.K., 2011).

- *Synovitis: Concurrent Validity*

Grey scale synovitis (≥grade 1) has been compared to the macroscopic appearance of synovitis at arthroscopy in 60 patients undergoing the procedure for the investigation and/or treatment of knee pain (including 16 patients with RA) (Karim et al., 2004). Grey scale synovitis was identified in 107/119 compartments with visible synovitis and 14/56 compartments with a normal appearance (sensitivity 90% and specificity 75%).

Comparisons have also been made to the microscopic appearance of synovium in patients undergoing surgery. Strong and statistically significant correlation has been observed between the semi-quantitative assessment of PD and the histological appearance of vascularity in knee (Walther et al., 2001) and hip (Walther et al., 2002) synovium. Amongst 14 patients with RA in clinical remission (1981 ACR remission), undergoing procedures at various sites (including the knees, hips, wrists, shoulders, elbows and tendon sheaths), weak positive (but not statistically significant correlation) was observed between GS hypertrophy (graded 0-3) and synovial hyperplasia, and between PD (graded 0-3) and vascularity on histology (Anandarajah et al., 2014). Of note, these studies included patients with primary and secondary osteoarthritis. In addition, ex-vivo histological vascularity is arguably not an ideal gold standard, as PD represents more than simply the number and size

of vessels, but also the degree of perfusion in a living system. This is supported by the rapid resolution of PD which may be observed with steroid treatment within one (Strunk, Strube et al. 2006) or two weeks (Larché et al., 2010), or even a few days (Newman et al., 1996).

Some studies have employed more comprehensive histological scores for synovitis. Amongst patients undergoing knee replacement (15 patients with RA and 5 patients with osteoarthritis), significant correlation ($p<0.05$) was demonstrated between both GS and PD semi-quantitative scores and a combined histological score (encompassing inflammatory cell infiltrate, synovial thickness and vascularity) (Takase et al., 2012). Data from 20 knee joint replacements (including 10 patients with RA) demonstrated PD in 9/9 knees with pannus (defined as synovial proliferation with evidence of invasive destruction of bone and/or cartilage on histological examination), but also 5/11 knees without pannus. Of the latter, four demonstrated some evidence of synovitis (effusion and/or synovial proliferation during surgery and above average number of vessels per synovial area on histological inspection). Furthermore, PD in four of these patients was scored as grade 1 only, such that sensitivity and specificity of PD≥grade 2 (moderate or intense perfusion) for the detection of pannus was 89% and 91%, respectively (Schmidt et al., 2000).

Arguably, more pertinent to use of ultrasound in patients with early IA who may lack large joint involvement, data have also been obtained from percutaneous synovial biopsy of joints including the wrists and smaller joints. In 44 patients with inflammatory conditions, data obtained from synovial biopsy of various sites (mainly the knees or wrists but also small joints, bursae and tendon sheaths) demonstrated a weak positive (but not statistically significant) correlation between GS effusion, GS hypertrophy and PD (semi-quantitative scales) and a comprehensive histological score for synovitis (Koski et al., 2006a). In 29 patients with RA, ultrasound and biopsy of 58 wrists, 15 MCPs and 8 PIPs revealed a significant correlation between colour Doppler activity and comprehensive synovitis scores and densities of immunohistochemical staining using T cell, macrophage and vessel markers (Andersen et al., 2014). These studies included patients with a variety of disease durations. This is pertinent given that in very early RA PD may be absent from joints demonstrating histological evidence of inflammation (Koski,

2012) and GS change may be observed with chronic synovial thickening/fibrosis in patients with established RA.

Limited data are available from DMARD-naïve patients with early RA (Vreju et al., 2011). Synovial biopsies of the knee were obtained from 35 patients with symptoms for less than one year). Significant correlation was observed between PD assessments (graded 0-3) and immunohistochemical staining for expression of vascular endothelial growth factor.

- *Synovitis: Predictive Validity*
    - **Predicting Joint Damage in Patients with Early IA**

Support for the validity of ultrasound synovitis as representative of true, active synovitis is provided by data from longitudinal studies demonstrating its association with radiographic damage over time. Such studies have been conducted in DMARD-naïve patients with early IA (the ESPOIR cohort) (Funck-Brentano et al., 2013) and patients with early RA who are exclusively DMARD-naïve (Naredo et al., 2007; Macchioni et al., 2013) or may have recently commenced DMARDs (Pascual-Ramos et al., 2009; Fukae et al., 2010; Bøyesen et al., 2011).

In the ESPOIR study, the presence of any PD and total PD score (MCPs2-5 and MTP5, bilaterally) appeared to predict radiographic progression over one year on multivariable analysis (see Table 4) (Funck-Brentano et al., 2013). A major limitation was that no adjustment was made for existing radiographic damage at baseline. In a subgroup analysis of joints without radiographic erosions at baseline, ultrasound synovitis did not appear to be an independent predictor on multivariable analysis, whilst the predictive value of existing ultrasound erosions at baseline was suggested ($p=0.052$ for the association with new radiographic erosion). The low number of joints developing erosion (n=26 of 1091 joints) and the overlapping nature of some of the predictor variables in these models limit the conclusions that may be drawn.

In DMARD-naïve RA patients (fulfilling 1987 ACR criteria) ultrasound synovitis has been associated with progression in SHS over one year at both the level of single MCP joints (Macchioni et al., 2013) and the patient level (Naredo et al., 2007). At

MCPs, the following variables demonstrated significance in a conditional logistic regression model for the prediction of progression: presence of x-ray erosion at baseline (odds ratio [OR] 4.4, 95% CI 1.7-11), GS synovitis (≥grade 2) at baseline (OR 3.6, 95% CI 1.3-10) and PD synovitis (≥grade 2) on at least two occasions over one year (at 0, 6 and/or 12 months, OR 8.3, 95% CI 1.8-39) (Macchioni et al., 2013). No significant relationship was identified between clinical signs (swelling or tenderness) and radiographic progression in this small study in which progression of erosive disease was observed in only 17/240 joints. This is despite the relatively severe phenotype of these patients; inclusion criteria included DAS28>4 and raised inflammatory markers, 12 (50%) patients had radiographic erosions at baseline and disease duration ranged up to almost ten years. At the patient level, total GS and PD scores (28-joint assessments), the number of swollen joints and DAS28 scores over time (area under the curve calculations over one year) have been significantly associated with change in total SHS over one year ($p<0.05$) (Naredo et al., 2007). The correlation appeared strongest with ultrasound synovitis; regression coefficients 0.61 for GS score and 0.59 for PD score, in comparison to 0.46 for swollen joint count (SJC28) and 0.40 for DAS28. Again, this was a small study (n=42). Methods were restricted to univariable analyses and confidence intervals were not reported.

Validity of GS synovitis in predicting progression of erosive damage observed on MRI (increase in OMERACT RA MRI score) has been evaluated in the wrists of patients with early RA (symptoms up to one year, the majority were receiving DMARDs at baseline) (Bøyesen et al., 2011). Age, gender and clinical/laboratory/US/MRI variables with significance ($p<0.25$) on univariable analysis were entered into a multivariable model using a backwards step-wise approach. The number of areas in the wrist at which GS synovitis was present (radio-carpal joint, radial extensor tendons, dorsal midline extensor tendons, ulnar extensor tendons and flexor tendons) was an independent predictor of progression (OR 2.0, 95% CI 1.1-3.5), alongside MRI-measured bone marrow oedema (OR 1.3, 95% CI 1.0-1.6) and male gender (OR 4.4, 95% CI 1.1-18).

Two further studies have reported predictive validity of quantitative assessments of ultrasound synovitis. In Mexico, GS score was the sum of the measurements for the maximum depth of synovitis across all joints in the dominant hand and severity of PD was the sum of the measurements for the maximum depth of synovitis in

PD-positive joints (Pascual-Ramos et al., 2009). It was not clear that standardised views/probe positions were used and measurements of maximum depth may not be representative of the whole joint due to their variable shape. Other deficiencies included the outcome measure, presence of radiographic erosion, which was determined by consensus of between a radiologist and rheumatologist not blinded to patient data or chronology and variation in the duration of follow-up. In the final model, risk of erosion (at final follow-up, one to two years) was significantly associated with baseline PD score (HR 1.3, 95% CI 1.1-1.5) and the number of 1987 ACR criteria fulfilled (HR 2.3, 95% CI 1.1-5.0). In Japan, significant correlation between the number of colour pixels present, at the level of individual MCP and PIP joints, and Genant-modified Sharp score over 20 weeks has been demonstrated amongst 19 patients; however, analyses were restricted to univariable linear regression (Fukae et al., 2010). Trends were observed between semi-quantitative PD assessments (grading 0-3) and progression at the level of individual joints but these were not statistically significant. In MCP joints with PD at baseline, improvement in the number of colour pixels over eight weeks (as a proportion of the baseline number) showed a significant inverse correlation with progression at the individual joints.

- **Predicting Joint Damage in Patients with Established, Active RA**

Studies have been conducted in patients with various levels of disease activity and treatment regimens (Reynolds et al., 2009; Ogishima et al., 2014) as well as in a slightly more homogeneous groups of patients such as those with active disease requiring step-up or switch to an alternative biologic therapy (Taylor et al., 2004; Naredo et al., 2008a; Fukae et al., 2011; Dougados et al., 2013). The majority have examined radiographic progression by use of validated scoring methods including the SHS (Taylor et al., 2004; Naredo et al., 2008a) and Genant-modified Sharp score (Fukae et al., 2011) or alternative assessments of erosion and joint space narrowing (Dougados et al., 2013; Ogishima et al., 2014). Reynolds et al. have examined the predictors of progression of ultrasound erosive damage (Reynolds et al., 2009).

In an observational study of 59 patients requiring a TNF-inhibitor for RA, with at least six swollen joints, generalised estimated equation modelling was used to investigate any association between ultrasound synovitis and radiographic

progression at two years at the level of individual joints (Dougados et al., 2013). Worsening of radiographic erosion and/or joint space narrowing, as judged by a blinded assessor who was aware of the chronology of films, occurred in 9% of 1888 joints (wrists, MCPs, PIPs and MTPs). With adjustment for age, gender, disease duration, tender joint count (TJC), SJC, erythrocyte sedimentation rate (ESR), joint site and baseline x-ray damage score, either physician-judged definite clinical synovitis (OR 1.6, 95% CI 1.1-2.4), GS≥grade 1 (OR 1.6, 95% CI 1.1-2.4), GS≥grade 2 (OR 1.6, 95% CI 1.1-2.5) or PD≥grade 1 (OR 1.8, 95% CI 1.2-2.7) were significantly associated with the combined outcome of worsening of erosion and/or joint space narrowing. Sub-analyses of this study demonstrated the relevance of both subclinical GS≥grade 1 and PD≥grade 1. Amongst joints with normal clinical findings, worsening of erosion and/or joint space narrowing was observed in 11% of 420 joints with any GS present versus 4% of 675 joints without GS (OR 2.2, 95% CI 1.2-4.0) and 16% of 132 joints with PD present versus 5% of 963 joints lacking any PD (OR 3.5, 95% CI 1.8-7.0).

Further observational data suggests the relevance of subclinical PD to the risk of future joint damage (Ogishima et al., 2014). Amongst a heterogeneous group of 30 patients (approximately half of patients were receiving biologics and approximately one third were in clinical remission), wrists, MCPs1-5 and PIPs2-5 were scanned by ultrasound; 450 joints had normal clinical and ultrasound findings, 120 joints had clinical swelling and/or tenderness and 30 joints had subclinical PD (≥grade 1). Across these joint groups, progression of erosion was observed in 1/450 (0.2%), 2/120 (2%) and 1/30 (3%) joints, respectively. Progression of joint space narrowing was observed in 3/450 (0.7%), 6/120 (5%) and 1/30 (3%) joints, respectively. No statistical testing was performed for these infrequently occurring outcomes.

In one of the largest studies to date, ultrasound assessments of 28 joints were available for 278 patients receiving TNF-inhibitor therapies in clinic (Naredo et al., 2008a). Measures of GS and PD (number of joints affected and the sum scores of grading 0-3 at individual joints) were not independently predictive of change in SHS at one year on multiple linear regression analyses. In a second model considering time-integrated variables (area under the curve calculations for measures over one year), the number of joints with PD (coefficient 0.002, $p<0.05$), RF titre (0.0005, $p<0.05$) and ESR (0.0004, $p<0.05$) were significantly associated with progression. The lack of significance of baseline scores in this study may be related to the

efficacy of TNF-inhibitors in preventing joint damage. Indeed, on analysis of a small randomised-controlled trial of infliximab versus placebo (24 patients with inadequate response to methotrexate), total GS and PD scores for MCPs at baseline were significantly associated with change in SHS at one year, on univariable analysis, only amongst the placebo group (Taylor et al., 2004). Predictive validity of change in PD over time, in patients receiving biologics, is supported by a small observational study (Fukae et al., 2011). A 70% improvement in the number of colour pixels at MCPs and PIPs by week 8 was significantly associated with lack of progression at week 20 in 10 patients commencing adalimumab and 15 patients commencing tocilizumab.

Finally, a study examining predictors of progression in ultrasound erosion score did not detect any significant association between clinical variables or GS or PD scores on univariable analyses (Reynolds et al., 2009). Only baseline ultrasound erosion score was associated with progression (discussed further in section 2.3.2.3, below).

- **Predicting Radiographic Progression and Disease Flare in Early IA and RA Patients Achieving Clinical Remission**

The association between PD and radiographic progression is also apparent amongst DMARD-treated RA patients achieving clinical remission or low disease activity (Brown et al., 2008; Foltz et al., 2012; Raffeiner et al., 2017). Furthermore, the prevalence of PD is independently predictive of future clinical relapse in patients continuing therapy (Scirè et al., 2009; Foltz et al., 2012; Saleem et al., 2012) and those tapering or discontinuing biologic therapies (Iwamoto et al., 2014; Naredo et al., 2015).

In patients achieving remission according to physician judgement, radiographic progression over the subsequent one year of follow-up (determined by change in total Genant score) occurred in 17/90 patients (Brown et al., 2008). Total PD score (sum of PD scores, grades 0-3, at the wrist and MCPs2-5 of the dominant hand) was significantly associated with progression (OR 1.36, 95% CI 1.02-1.81), whereas associations with clinical measures of disease activity did not reach clinical significance. In the subset of joints lacking any swelling, tenderness or pain, presence of PD predicted progression at the individual joint level (OR 8.8, 95% CI

1.5-50), despite the low rate of progression which was observed (approximately 2% of 378 joints).

Amongst patients achieving DAS28 remission for at least six months with treatment with TNF-inhibitor, several PD variables were identified as predictors of progression in total SHS after one year (occurring in 17/121 [14%] patients) on univariable analysis (Raffeiner et al., 2017). Novel findings in this study included the potential importance of the location of PD: the presence of PD observed in contact with bone was associated with radiographic progression, with a risk ratio of 3.5 (95% CI 2.5-4.9), in comparison to PD without bone contact which showed no association with this outcome. Multivariable modelling which was conducted only considered PD variables and did not include adjustment for relevant factors such as baseline SHS or clinical joint swelling. Interestingly, radiographic progression was observed at different locations to the joints at which PD was observed. The authors suggest the lack of sensitivity of x-ray and the ability of TNF-inhibitor therapy to prevent joint damage as potential explanations.

Amongst patients achieving stable low disease activity (DAS44<2.4 at consecutive assessments two months apart), only PD parameters were significantly associated with radiographic progression (change in SHS) and relapse over one year on multivariable logistic regression analysis (Foltz et al., 2012). Demographic, clinical, radiographic, ultrasound and MRI parameters, with significance on univariable analyses at the $p<0.20$ level, were entered using a forwards, step-wise procedure. Total PD score (sum of grades 0-3, at the wrists, MCPs2-3, MCP5, MTPs2-3 and MTP5) was associated with progression (occurring in 9/80 patients); OR 1.4 (95% CI 1.1-1.9). The number of joints with PD was associated with relapse (defined by DAS44>2.4 and/or increase in DMARD/steroid therapy, occurring in 26/81 patients); OR 6.3 (95% CI 2.0-20). Results for other variables were not significant and not reported.

Predictors of flare have also been investigated for patients achieving clinical remission, according to the impression of their treating physician (Saleem et al., 2012), or defined by DAS44 (Peluso et al., 2011). Multivariable analyses confirmed presence of PD (within the wrist and MCPs of the dominant hand) and physical function (HAQ) predicted the need for treatment escalation, independently of

whether patients fulfilled any of the standardised criteria for clinical remission (Saleem et al., 2012). In patients achieving sustained DAS44 remission, presence of PD (within the wrists, MCPs2-3 and PIPs2-3) was associated with flare (DAS44≥1.6): flare occurred in 7/34 (20%) and 28/60 (47%) of patients with absence or presence of PD, respectively (p=0.01). However, only early disease, and not ultrasound characteristics, appeared to be associated with absence of flare on multivariable analysis. Statistical methods were not fully described and the cohort was mixed, including patients with early (n=48, two-thirds receiving methotrexate monotherapy and one third receiving a TNF-inhibitor) and established RA (n=46, all receiving a TNF-inhibitor).

In the only study exclusive to patients with early IA, 106 patients with early morning stiffness and at least three swollen joints or positive MCP/MTP squeeze test were followed for two years (Scirè et al., 2009). Protocol dictated initial methotrexate or hydroxychloroquine, with switch to methotrexate, increase in methotrexate dose and ultimately addition of TNF-inhibitor therapy according to a target of DAS44<2.4. Sustained DAS44 remission was achieved in 43 patients at or after one year, of whom 14 relapsed (DAS44≥1.6) within six months. The presence of any PD (≥grade 1 within 44 joints) was independently predictive of relapse (OR 13, 95%CI 1.6-104) in a model including the following variables: SJC>1, DAS44>1.1, abnormal GS in more than one joint (Schmidt et al., 2004) and steroid treatment (p≥0.05 for these variables).

Concerning the prediction of relapse in patients achieving DAS28 remission on biologic therapy, presence of PD has been associated with flare on univariable (Iwamoto et al., 2014) and multivariable analyses (Naredo et al., 2015) with biologic tapering (Naredo et al., 2015) or cessation (Iwamoto et al., 2014). Amongst 40 patients stopping biologic therapy, 16 (40%) patients relapsed (DAS28>3.2 with treatment escalation) within six months (Iwamoto et al., 2014). Total GS score≥14 or total PD score≥3 (sum of 0-3 grading at 40 joints) optimally differentiated those relapsing and were significantly associated with this outcome, whereas clinical disease activity greater than the cut-point identified for DAS28 was not significantly associated with flare. No independent predictors of relapse were identified on multivariable analysis in this small sample. The larger study revealed a rate of failure of biologic dose reduction (DAS28 and/or SDAI non-remission with increase in treatment) of 36/77 (47%) over one year (Naredo et al., 2015). This was

significantly more likely in patients with detectable PD (within 36 joints or reduced joint sets of 20 or 12 joints), with adjustment for the presence of a higher DAS28 (DAS28≥2.2).

- **Predicting Disease Persistence and/or Progression in DMARD-naïve Patients with Early IA**

In patients with new-onset clinical synovitis, studies investigating the ability of ultrasound to predict subsequent diagnosis of RA (defined according to 1987 ACR criteria) are summarised in Tables 3 and 5 (Salaffi et al., 2010; Filer et al., 2011). In Birmingham, of 58 patients with very early IA (at least one swollen joint with symptoms for up to three months), 29 (50%) fulfilled 1987 ACR RA criteria by 18 months (Filer et al., 2011). Of note 21% of patients fulfilled 1987 ACR RA criteria at baseline. Assessments of GS at the wrists and MCPs, and PD assessments at the MCPs and MTPs, were predictive of 1987 ACR RA, independently of the Leiden prediction score (van der Helm-vanMil et al., 2007). The total PD score (sum of PD scores, graded 0-3, at individual joints) calculated for 10 joints (wrists, MCPs2-3 and MTPs2-3) combined with the Leiden score was superior in the prediction of 1987 ACR RA in comparison to the Leiden score alone (area under the curve 0.96 versus 0.90, $p<0.05$).

A similar rate of progression to fulfil 1987 ACR RA criteria was observed amongst patients with very early UA (not fulfilling 1987 ACR criteria, with at least one swollen joint with symptoms for up to 16 weeks): 62/149 (42%) progressed after a mean duration of follow-up of 12 months (range 11-14 months) (Salaffi et al., 2010). The number of joints with GS≥grade 1 and PD≥grade 2 predicted progression, independently of other clinical parameters such as inflammatory markers and early morning stiffness. However other clinical assessments (for example swollen or tender joint counts) were not considered in the model.

- **Predicting Disease Persistence and/or Progression in DMARD-naïve Patients with Inflammatory Symptoms +/- Joint Swelling**

Studies have also been conducted in more heterogeneous patient groups, not restricted to patients with clinical joint swelling (Ozgul et al., 2009; Freeston et al.,

2010; Kawashiri et al., 2013; Nakagomi et al., 2013; Pratt et al., 2013; Minowa et al., 2016). In the earliest study, 33/51 (65%) patients with early morning stiffness of at least 30 minutes for up to one year (excluding patients fulfilling 1987 ACR RA criteria or with x-ray erosions) progressed to fulfil 1987 ACR RA criteria over two years (Ozgul et al., 2009). Superior agreement was demonstrated between progression and the symmetrical appearance of GS changes on extensive ultrasound examination in comparison to the agreement with symmetrical appearance of synovitis on Technetium^{99} bone scanning (kappa values 0.6 and 0.2, respectively). The prognostic value of clinical or other ultrasound parameters was not assessed.

In a cohort of 50 patients presenting with early morning stiffness in the hands for at least one hour and symptoms for up to 12 weeks, all patients with positivity for RF and/or ACPA demonstrated persistence of IA (physician diagnosis) at one year (Freeston et al., 2010). In patients who were seronegative, predictive utility of ultrasound was demonstrated in the proportion of patients with at least one of the following features: joint swelling, abnormal CRP or x-ray erosion. In this group, the presence of GS=grade 3, PD≥grade 1 and ultrasound erosion in the wrists or MCPs raised the post-test probability of persistent IA from 2-30% to 50-94%, whilst if none of these features were present it reduced to 0-5% (diagnostic uncertainty remained in patients with one or two of these ultrasound features).

The value of including ultrasound findings in the context of the 2010 ACR/EULAR RA criteria has been assessed in patients with suspected RA in predicting the need for DMARDs (Kawashiri et al., 2013) or methotrexate in particular (Nakagomi et al., 2013; Minowa et al., 2016). In a study restricted to univariable analyses, the presence of PD≥grade 2 in any of the wrists, MCPs and PIPs appeared to demonstrate the greatest accuracy (amongst various clinical, laboratory and imaging variables) to predict the need for DMARDs within three months; sensitivity and specificity were 81% and 94%, respectively, versus 60% and 88% for the clinical fulfilment of 2010 criteria (Kawashiri et al., 2013). Multivariable analysis of real-life data, from a retrospective study of ultrasounds conducted in the course of managing patients with no firm diagnosis and arthralgia (Minowa et al., 2016), demonstrated the presence of at least one wrist, MCP or PIP joint with GS=grade 3 (OR 3.6, 95% CI 1.1-14) or with PD≥grade 2 (OR 2.8, 95% CI 1.6-15) were significantly associated with commencement of methotrexate for a physician

impression of RA after at least six months, independently of fulfilment of 2010 ACR/EULAR RA criteria (OR 4.7, 95% CI 0.9-20). However, treatment was commenced in the knowledge of ultrasound findings.

In the most comprehensive study, ultrasound of 38 joints was used to determine fulfilment of 2010 criteria at baseline at two-steps (Nakagomi et al., 2013). Firstly, by substituting the requirement for clinical swelling in at least one joint, with ultrasound synovitis in at least one joint, then by determining joint involvement (score 0-5 points) by ultrasound synovitis. Two definitions for ultrasound synovitis were considered: GS≥grade 1, and a more stringent definition of GS≥grade 2 and/or PD≥grade 1. Fulfilment of 2010 criteria using ultrasound better differentiated patients requiring methotrexate from those who did not. The area under the receiver operating characteristic curve (AUC) was greatest for the latter definition of ultrasound synovitis, although confidence intervals overlapped: AUC was 0.84 (95% CI 0.74-0.90), 0.87 (95% CI 0.80-0.94) and 0.89 (95% CI 0.83-0.95) for fulfilment of 2010 criteria with joint involvement determined clinically, by GS≥grade 1 and GS≥grade2/PD≥grade1, respectively. Multivariable logistic regression was used to determine the value of ultrasound findings at individual joint sites in predicting methotrexate use. Presence of various grades of GS and PD at individual joints, with $p<0.05$ on univariable analysis, were entered along with the 2010 criteria score (score 0-10, determined clinically), using a forwards step-wise approach. Presence of GS≥grade 1 and PD≥grade 2 at the wrist predicted methotrexate use independently of fulfilment of 2010 criteria. Inclusion of both GS and PD at any one joint site within a single model indicates a degree of uncertainty in these results, due to the overlapping nature of these variables.

In the largest study available, 389 unselected patients presenting with arthralgia in Newcastle were followed for at least one year (Pratt et al., 2013). Ten patients with persistent UA at the end of follow-up (not fulfilling 1987 ACR criteria) were excluded. At baseline, 18% of patients had a working diagnosis of RA, 36% had a working diagnosis of osteoarthritis or non-inflammatory arthralgia and 54% of patients had no swollen joints. Persistent IA (physician diagnosis) was observed in 162/379 (43%) patients, at a median duration of follow-up of 27 months. Predictors of persistent IA were determined by multivariable logistic regression (backwards step-wise method, retaining demographic/clinical/laboratory/ultrasound variables with significance at $p<0.1$). The presence of GS≥grade 1 in at least three joints (of

MCPs2-4, PIPs2-4 and MTPs1-2) was independently predictive of persistence (OR 4.9, 95% CI 2.3-10) in addition to the following clinical characteristics: age, symptom duration, presence of joint swelling, CRP, ESR and ACPA-positivity. However, the AUC was comparable for a model constructed by the same method but excluding ultrasound variables. In a subgroup analysis of 91 patients with UA (not fulfilling 1987 RA criteria) at baseline, AUCs for models constructed with and without the consideration of ultrasound variables were also comparable.

- **Predicting Development of Arthritis in Patients With Joint Symptoms in the Absence of Swelling**

Ultrasound measures of synovitis have been associated with the development of IA in cohorts of seropositive (van de Stadt et al., 2010; Rakieh et al., 2015) and seronegative (Zufferey et al., 2017) patients with joint symptoms alone. Amongst seropositive (for RF and/or ACPA) patients with arthralgia, 45/192 (23%) developed at least one swollen joint over a median follow-up of 26 months (range 6-54 months) (van de Stadt et al., 2010). At the joint level, the presence of GS≥grade 2 and PD≥grade 1 (tender/painful joints and adjacent joints within MCPs, PIPs and MTPs) were significantly associated with development of swelling in that joint (78/1823 joints developed swelling). However, the predictive value of clinical variables, such as tenderness, was not evaluated, and the trend for an association between ultrasound variables and the development of arthritis at the patient level was not statistically significant. Amongst ACPA-positive patients with new-onset musculoskeletal symptoms, the presence of PD (≥grade 1 in at least one joint of the wrists, MCPs and PIPs) was significantly associated with the development of at least one swollen and tender joint on multivariable analysis (independently of the presence of small joint tenderness, early morning stiffness, high ACPA and/or RF titre, and presence of the shared epitope) (Rakieh et al., 2015). Rate of progression was higher in this cohort (50/100 progressed over a median follow-up of 20 months), although only 50% had small joint tenderness at baseline. Analysis was conducted by entering variables with significance (HR≥1.5) on univariable analysis. Grey scale synovitis was not reported.

As expected, a lower rate of progression has been observed amongst seronegative patients with polyarthralgia: IA developed in 9/80 (11%) patients, seven of whom fulfilled 2010 ACR/EULAR RA criteria, over a mean follow-up of 18 months

(Zufferey et al., 2017). Only five patients displayed PD on the baseline ultrasound assessment of elbows, wrists, MCPs2-5, PIPs2-5 and knees; however, GS synovitis (the total score considered as a continuous variable or presence of significant GS defined by either total score greater than eight, or presence of GS≥grade 2 in at least two joints) was independently associated with progression to RA or IA (in a multivariate logistic regression model with age, gender, abnormal CRP, duration of follow-up and anti-nuclear antibody [ANA] positivity).

- **Predicting Response to Treatment**

Limited data is available in DMARD-naïve patients with UA (not fulfilling 2010 ACR/EULAR RA criteria) at baseline, suggesting baseline PD is predictive of response to a treatment to target strategy (Table 5) (Sakellariou et al., 2014). Measures of PD were significantly associated with DAS28 remission within one year, but whilst adjustment was made for some relevant confounders (age, gender and treatment), others, such as clinical disease activity and serology, did not appear to be included in the same model.

The ability of PD to predict continuation of the same TNF-inhibitor therapy after one year (as a proxy for clinical response to treatment) has been evaluated (Ellegaard et al., 2011). Of 162 patients with established RA commencing TNF-inhibitors, complete data was available for 109 patients, of whom 78 were continuing on the same therapy at one year. Doppler activity of a target joint (selected as a joint with greatest Doppler activity at baseline, with preference for a wrist joint) was assessed by colour fraction (percentage of colour pixels). This was the only variable of several clinical, laboratory and treatment parameters assessed, to be significantly associated with treatment persistence (standardised mean difference 0.5, p=0.01). Although this outcome is not wholly representative of response (8 patients stopped therapy due to side-effects), it is a pragmatic measure of response in patients with established RA in clinical practice, in whom DAS and other clinical response measures may not be truly reflective of inflammatory disease activity. For example, joint damage may be expected to contribute to joint pain.

- *Synovitis: Discrimination*
    - **Differentiation from Normal**

The discriminative validity of ultrasound synovitis has been evaluated using GS imaging and with Doppler in a number of studies (Table 10). Small, early studies reported a low rate of GS change in healthy individuals (Hau et al., 1999; Hameed et al., 2008) and did not identify Doppler activity in healthy volunteers (Hau et al., 1999). However, with increased sensitivity of machines used in more recent studies, low-grade GS changes are now accepted as a relatively common finding in small joints of healthy individuals (Ellegaard et al., 2007; Keen et al., 2008; Millot et al., 2011; Kitchen and Kane, 2015). In addition, Doppler activity may be observed within the synovium of asymptomatic controls (Terslev et al., 2004; Hameed et al., 2008; Keen et al., 2008; Rosenberg et al., 2009; Millot et al., 2011; Carotti et al., 2012; Witt et al., 2013; Zufferey et al., 2014; Kitchen and Kane, 2015; Padovano et al., 2016).

Table 10. Prevalence of GS effusion/hypertrophy and Doppler activity observed on ultrasound examination in healthy subjects.

Reference	n	Method of recruitment	Age (yrs)	Joints examined	Prevalence of GS and/or Doppler activity
GS synovitis in wrists, hands and feet					
(Wiell et al., 2007)	5	Not fully reported (exclusions: history/signs of joint disease)	Median 63, range 35-71	MCP2-5, PIP2-5, DIP2-5, MTP1-5 (Bilateral)	GS (effusion and/or hypertrophy)≥grade 2 in 3% of MCPs and PIPs, and 34% of MTPs.
(Szkudlarek et al., 2006)	20	Not reported	Median 52, range 27-79	MCPs 2-5, PIPs 2-5 (Unilateral)	GS (effusion and/or hypertrophy)≥grade 2 in 5 (3%) MCP/PIP joints.
(Szkudlarek et al., 2004)	20	Not reported	Median 52, range 25-78	MTPs 1-5 (Unilateral)	GS (effusion and/or hypertrophy)≥grade 2 in at least 1 MTP in 50% subjects. Most frequent at MTP1 (7/20 [35%] first MTPs and 15/80 [19%] MTP2-5 joints).
(Witt et al., 2013)	30	Age- and gender-matched to patients with early RA (exclusions: arthralgia, joint disease)	Mean 52 (SD 17)	Wrists, MCPs, PIPs, MTPs (Bilateral)	GS (effusion and/or hypertrophy)=grade 1 in 15% of joints. Prevalence of higher GS grades not reported.

Colour Doppler in wrists and hands					
(Terslev et al., 2004)	27	Medical staff members and staff relatives (exclusions: arthritis, trauma, use of hands in sports/labour, arthralgia)	Mean 45, range 18-93	Wrist, MCP1-5, PIP1-5 (Unilateral)	Colour Doppler in 26 (9%) joints. Most frequent at wrist (15 [56%] wrists).
(Carotti et al., 2012)	43	Volunteers (age- and gender-matched to patients with symptomatic osteoarthritis)	Mean 55, SD 11	Wrist, MCP2-3, PIP2-3 (Bilateral)	Colour Doppler in 45 (10%) joints. Most frequent at wrist (39 [86%] wrist joints).

GS and PD synovitis in wrists and hands					
(Rosenberg et al., 2009).	46	Medical students (exclusions: arthralgia, hand use in sports, trauma, IA)	Mean 26 (age>40 excluded)	PIP2-5, DIP2-5 (Bilateral)	GS effusion in 100/368 PIPs. No PD observed.
(Keen et al., 2008)	19	Musculoskeletal clinic patients without hand pain. Included patients with tender joints and/or recent low-grade trauma.	Median 58, IQR 51-71	CMC1, MCP1-5, PIP1-5, DIP2-5 (Bilateral)	GS (effusion and/or hypertrophy)≥grade 1 in 64 [34%] MCPs (grade 1 in 53 [28%]) and 62 [33%] of PIPs. PD≥grade 1 in 4% of MCPs and 2% of PIPs. N.B. Osteophytes in 11% of MCPs and 33% of PIPs.
(Hameed et al., 2008)	25	Not fully reported (exclusions: history/signs of joint disease)	Mean 45, range 24-62	MCPs (Bilateral)	GS (hypertrophy)=grade 1 in 2 (8%) subjects (in 3 MCPs). No higher GS grades observed. PD≥grade 1 in 8 (32%) subjects (in 13 [5%] of all MCPs). Grade 1 in each. N.B. Both subjects with GS and 4/8 subjects with PD engaging in manual labour.
GS and PD synovitis in wrists, hands and feet					
(Millot et al., 2011)	127	Hospital staff and patients with sciatica, age- and gender-matched to early IA patients in ESPOIR	Mean 50	MCP2,5 and MTP5 (Bilateral)	GS (hypertrophy)≥grade 2 in 12 (9%) subjects (in 14/1016 [1%] MCPs, in none of MTP5 joints). PD in 5 (4%) of subjects (1 MCP in each, PD was universally absent at MTP5).
(Padovano et al., 2016)	207	Staff, students, relatives of patients and other volunteers (exclusions: osteoarthritis, trauma, arthralgia)	Mean 36, range 18-74	Wrists, MCPs, PIPs, MTPs (Bilateral)	GS effusion≥grade 1 alone in 95 (46%) subjects. GS hypertrophy≥grade 1 (with/without either effusion or PD) in 87 (42%) subjects. GS effusion and/or hypertrophy≥grade 2 only observed at MTPs. PD≥grade 1 in 44/6621 (<1%) joints. Most frequent in wrists (6 [1%] of wrists) and MTP1 joints (31 [7%] MTP1 joints).

GS and PD in wrists, hands, feet and large joints					
(Zufferey et al., 2014)	38	Gender-matched to patients with established RA (age-matching was unsuccessful)	Median 47	Elbow, wrist, MCP2-5, PIP2-5, knee (Bilateral)	GS (effusion and/or hypertrophy)≥grade 2 in 26% subjects (in at least 2 joints in 8% subjects). Total GS score>8/66 in 10% subjects. PD in 2 (5%) subjects (grade 1 in 1 joint in each).
(Kitchen and Kane, 2015)	30	Volunteers (exclusions: history of arthritis, heavy manual labour, trauma)	Mean 39, range 22-63	Shoulder, elbow, wrist, MCPs, PIPs, knees, ankles, MTPs (Bilateral)	GS (effusion and/or hypertrophy)≥grade 2 in 3% of MCPs and PIPs, 2% of wrists, 32% of MTP1 joints and 6% of MTP2-5 joints . GS infrequent in larger joints (excepting grade 1 in the knee). PD≥grade 1 in 121 (10%) joints. Most frequent in wrists (25 [42%] of wrists) and MTP1 joints (17 [28%] MTP1 joints). PD≥grade 2 in 13 joints (wrists and MTP1 joints only).

These studies varied in their methods of recruitment. Factors such as occupation (Hameed et al., 2008), as well as age and gender of controls are of relevance. Studies demonstrate a significant association between age and presence and/or severity of GS changes (Ellegaard et al., 2007; Kitchen and Kane, 2015; Padovano et al., 2016) and statistically significantly higher total GS scores in men versus women (Kitchen and Kane, 2015). Asymptomatic osteoarthritis may not fully explain this observation, as osteophytes have been observed infrequently on ultrasound when reported in these studies (5/332 joints) (Ellegaard et al., 2007).

In the small joints of the hands, small effusions are relatively prevalent and particularly visible on the volar/palmer aspect of joints (Boutry et al., 2004; Scheel, A. K. et al., 2005; Rosenberg et al., 2009). The size of effusions appears to differ significantly between controls and patients with RA (Scheel, A. K. et al., 2005). In a study of 102 staff, students and authors' friends, Schmidt et al. reported measurements for the GS appearance of effusion/hypertrophy which may be considered within the limits of normality (lying within 2 standard deviations of the mean) (Schmidt et al., 2004). The normal depth of GS change was greater at the MTPs in comparison to the small joints of the hands: normal limits were ≤3.5mm at MTP1 and ≤3.1mm at MTP2 in comparison to ≤1.9mm at MCP2 and ≤1.6mm at PIP2. Increased prevalence and volume of GS change at the MTPs, particularly MTP1, in comparison to other small joints has been confirmed by other groups. (Szkudlarek et al., 2004; Szkudlarek et al., 2006; Wiell et al., 2007; Padovano et al., 2016).

A cut-off level, at which ultrasound findings of GS and PD may be considered of pathological significance, is desirable (Terslev et al., 2017a). Grade 1 GS changes, as defined by Szkudlarek et al. (Szkudlarek, M. et al., 2003), have been considered to be physiological by several investigators (Szkudlarek et al., 2004; Szkudlarek et al., 2006; Ellegaard et al., 2007; Wiell et al., 2007; Witt et al., 2013; Zufferey et al., 2014). The EULAR-OMERACT combined score for synovitis has been restricted to synovial hypertrophy, given the frequent occurance of visible effusion in healthy joints (Terslev et al., 2017b). The clinical relevance of grade 1 GS synovitis is also questionable, given the significantly lower rate of swelling, tenderness and PD which has been observed in association with grade 1 GS synovitis in comparison to GS≥grade 2 (Witt et al., 2013). However, no comparison was made to joints lacking any GS synovitis (grade 0) in this study. Power Doppler appears to be a less

frequent finding, and if present has generally been observed at a low level, except in the wrists and first MTPs (Kitchen and Kane, 2015; Padovano et al., 2016).

- **Differentiation from Osteoarthritis**

Although not considered to be an inflammatory arthritis in the same way as RA and other aggressive arthropathies, sensitive imaging techniques including ultrasound and MRI have confirmed that synovial inflammation is involved in the pathology of osteoarthritis. This is an important consideration in view of the high prevalence of osteoarthritis and its frequent coexistence with inflammatory arthritis. In Leeds, ultrasound of the hands was conducted in 36 patients with symptomatic hand osteoarthritis (patients with suspected IA were excluded) (Keen et al., 2008). Considering the joints frequently affected by RA, GS synovitis was observed at PIPs2-5 in 126/287 (44%) joints and at MCPs2-5 in 72/288 (25%) joints. Power Doppler was observed in 23 (8%) and 12 (4%) joints at these sites, respectively. Notably, this included low-grade changes of grade 1 GS. Prevalence of GS restricted to grades which may be considered pathological was not presented. A higher rate of GS change ($p<0.001$) and PD synovitis ($p=0.002$) was observed in the most painful joints (one joint selected per subject, from all MCP, PIP, DIP and first CMC joints) in comparison to the other joints examined.

In a further study of 78 patients with hand osteoarthritis, GS≥grade 1 was observed in at least one joint in 73 (94%) patients and PD≥grade 1 was observed in 33 (42%) patients on ultrasound examination of 30 joints including several not included in assessments of RA (CMC1, MCPs1-5, PIPs1-5 and DIPs2-5 bilaterally) (Mathiessen et al., 2016). The distribution of joints affected was not reported. Of 1078 joints with definite evidence of radiographic osteoarthritis (Kellgren-Lawrence grade≥2), GS=grade 1 was demonstrated in 16%, GS≥grade 2 was demonstrated in 12% and PD≥grade 1 was demonstrated in only 5%. Interestingly, presence of GS (even grade 1 changes) and PD synovitis were significantly associated with radiographic progression over 4-5 years with adjustment for age, gender, BMI, follow-up time and presence of radiographic erosive osteoarthritis (although not for baseline radiographic change or clinical joint swelling).

The prevalence of positive US findings in the hands of patients with hand OA has also been evaluated in comparison to patients with RA, in a real-life cohort study

(Hussain et al., 2017). Scans of 73 patients with hand OA and 224 patients with established RA, conducted in the course of their clinical management (for example, to aid in diagnosis or to exclude ongoing disease activity in patients with known RA), were analysed retrospectively. The proportion of patients with synovitis, determined by GS or PD, was greater for patients with RA vs OA: 57% vs 40% of patients displayed GS=grade 1 in at least one joint (rates were 43% vs 31% for grade 3 GS) and 46% vs 8% of patients displayed PD≥grade 1 in at least one joint. Of note, the patients with OA were significantly older and had fewer swollen joints than patients with RA.

- *Synovitis: Reliability*

A notorious limitation of ultrasound is that it is operator dependant. Findings are dependent on the scanning technique, but also rely on operator experience in the interpretation of images, particularly in differentiating physiological from pathological findings. A systemic literature review of the inter-observer and intra-observer reliability of ultrasound to detect synovitis illustrates great variation across study methods (Cheung et al., 2010).

The majority of studies assessing inter-observer reliability for the acquisition and interpretation of ultrasound images have done so between two observers within single-centres. Reliability exercises, undertaken by the OMERACT ultrasound task force, have addressed this, including a number of experienced operators from several European countries (D'Agostino et al., 2005; Scheel, A K et al., 2005; Naredo et al., 2006; Bruyn et al., 2009; D'Agostino et al., 2017; Terslev et al., 2017b). As may be expected, agreement in the interpretation of still images was generally superior to agreement in the acquisition and interpretation of real-time examination of patients (D'Agostino et al., 2005). Rating of PD appears reliable, with at least good levels of agreement determined by kappa (kappa >0.6) generally reported (D'Agostino et al., 2005; Bruyn et al., 2009). However, inter-observer agreement for GS synovitis suggests less reliability in this measure (D'Agostino et al., 2005; Scheel, A K et al., 2005; Bruyn et al., 2009). Unfamiliarity of the experts with the machines used in these studies may have contributed to poor agreement, but the difficulty in differentiating active synovitis from inactive fibrous synovial thickening (Mandl et al., 2011) or from the appearance of GS in healthy joints (Schmidt et al., 2004; Scheel, A. K. et al., 2005) is appreciated. Initial studies to test

the reliability of the EULAR-OMERACT scoring systems for GS hypertrophy, PD synovitis and synovitis combining the two measures, have generally demonstrated moderate to good intra- and inter-reliability across a variety of joints (Terslev et al., 2017b; Ventura-Ríos et al., 2017). Reliability was improved with use of the EULAR-OMERACT standardised scanning technique; grading synovitis from images obtained in the midline of the dorsal aspect of the joint, with joint positioning as instructed according to joint site (Terslev et al., 2017b).

Interpretation of PD may be less dependent on the experience of the observer (Koski et al., 2006b). Reliability of PD measurements are, however, still dependant on several aspects of scanning technique (Koski et al., 2006b), including: pressure applied to the joint with the transducer (Wakefield et al., 2003; Joshua et al., 2005), movement of the patient or transducer which produces artefacts (Wakefield et al., 2003; Torp-Pedersen and Terslev, 2008), temperature (Strunk et al., 2006; Ellegaard et al., 2009) and joint position (Lee et al., 2009; Zayat et al., 2012).

Reliability may also be affected by differences in machine characteristics such as image resolution. However, a study conducted by the same OMERACT ultrasound task force using six different machines concluded these differences were not a major contributory factor to the variance observed in the reporting of GS and PD at MCP joints amongst 11 experts. This accounted for an estimated 1-6% of the variance, in comparison to 21-55% of variance attributable to differences in operator-dependant techniques and interpretation (D'Agostino et al., 2008).

Reliability of ultrasound should be considered in the context of other measures of active synovitis available real-time in clinic, i.e. clinical joint swelling. This is also dependent on the examiner and their level of experience. Intra- and inter-observer agreement of 28-joint swollen joint counts have been shown to vary between poor/fair and good (Marhadour et al., 2010), i.e. not even the most experienced physicians in this study (experience of at least 5 years) demonstrated excellent kappa values for reproducibility. Furthermore, outwith these 28 joints, MTP joint examination may be particularly unreliable (Naredo, E et al., 2005; Salaffi et al., 2008; Damjanov et al., 2012).

- *Synovitis: Responsiveness*

Power Doppler synovitis appears to be sensitive to change, with reductions in PD being observable within two weeks of steroid administration (Newman et al., 1996; Strunk et al., 2006; Larché et al., 2010). In patients with established RA, synovial thickening detected on GS imaging may be chronic and represent fibrous change rather than active synovial inflammation. As such, it may be difficult to distinguish between GS hypertrophy representative of synovitis (as defined by OMERACT as usually hypoechoic thickening) and inactive thickening (echoic or hyperechoic), hence GS may be less responsive to change. Despite this, good responsiveness has been observed in both total GS and PD synovitis scores, including the 7-joint (Backhaus et al., 2009) and 12-joint assessments (Naredo et al., 2008b) mentioned above (Hammer et al., 2010; Mandl et al., 2011).

Recently, the EULAR-OMERACT combined synovitis score has been tested in patients receiving abatacept (D'Agostino, M.-A. et al., 2016). Improvement in the sum score for MCP2-5 joints bilaterally was observed as early as week one. Responsiveness for the sum score for 44 joints was similar to sum scores for various reduced joint sets including the aforementioned 12-joint assessment and bilateral examination of the 7-joint assessment.

2.3.2.2 Tendon Abnormalities

A systematic review identified 24 studies assessing the construct validity of ultrasound assessment of tendon abnormalities (Alcalde et al., 2012). The majority investigated the agreement between tenosynovitis and clinical and/or MRI assessment. Results generally suggested superior sensitivity of ultrasound in comparison to clinical examination. In a relatively large study of patients with early, DMARD-naïve RA (n=50), sensitivity and specificity of ultrasound for the detection of tenosynovitis (reported as present/absent) were 44% and 99% in the flexor tendons and 15% and 98% in the extensor tendons of the fingers at the level of the MCP joints, with reference to MRI as the gold standard (Wakefield et al., 2007). Only two studies were identified which addressed criterion validity. One addressed concurrent validity, assessing finger extensor tendon damage (partial tendon tears) in patients with RA, rather than inflammatory changes, against surgical inspection as the gold standard (Swen et al., 2000). The other, concerning predictive validity, assessed global inflammatory disease activity on ultrasound, of which assessment

of tendons was a small component (findings of this study are discussed above in section 2.3.2.1) (Naredo et al., 2008a).

Since the time of this review, few other studies have emerged. Data from patients with early RA (fulfilling 1987 ACR RA criteria) enrolled in an observational study between 2002 and 2004 (Haavardsholm et al., 2008) were analysed by Lillegraven et al. (Lillegraven et al., 2011). Progression in erosive disease at one year, determined by MRI at the dominant wrist (change from baseline in MRI RAMRIS erosion score of ≥1 unit), was demonstrated in 39/60 patients with complete data. Multivariable logistic regression (entering variables with $p<0.20$ on univariable analysis, using a backwards step-wise procedure) revealed the presence of extensor carpi ulnaris GS tenosynovitis independently predicted progression (OR 7.2, 95% CI 1.6-33) in a final model which also included MRI RAMRIS bone oedema score at the wrist, age and gender.

In the multicentre, observational STARTER study, cross-sectional analysis of baseline data suggested US-detectable tenosynovitis is independently associated with recent symptoms of flare in patients achieving clinical remission (Bellis et al., 2016). Amongst 427 patients with established RA in remission (defined by any one of various definitions including DAS28 and expert rheumatologist opinion), multivariate logistic regression (adjusting for age, gender, disease duration, remission duration, treatment and ACPA status) demonstrated an association between the presence of PD tenosynovitis (PD≥grade 1 on bilateral ultrasound assessment of wrist and finger tendons) was associated with a flare score ≥3 (patient questionnaire designed to identify symptoms of flare within the preceding three months). The presence of GS or PD synovitis (≥grade 1 in at least one MCP or PIP) or GS tenosynovitis was not significantly associated with this measure. The presence of PD tenosynovitis, particularly of the extensor carpi ulnaris tendon, also appears to be predictive of RA (fulfilment of 1987 ACR criteria) amongst patients with swelling of at least one joint, with symptoms for up to three months (Sahbudin et al., 2015). However, methods were limited to univariable analyses.

Available studies assessing inter-observer agreement for ultrasound-detected tenosynovitis, between more than two sonographers, suggest fair to moderate levels of agreement (Scheel, A K et al., 2005; Bruyn et al., 2009; Ohrndorf et al.,

2012; Naredo et al., 2013a). Reported kappa values vary between 0.2 for GS tenosynovitis (Bruyn et al., 2009) and 0.6 for PD tenosynovitis (Bruyn et al., 2009; Naredo et al., 2013a). Responsiveness of tenosynovitis detected by ultrasound has been confirmed in patients commencing biologic therapies (Backhaus et al., 2009; Hammer, H. and Kvien, T., 2011; Vlad et al., 2015) as well as in a small number of patients commencing or receiving a change in DMARD therapy (Backhaus et al., 2009).

2.3.2.3 Erosions

- *Erosions: Construct Validity*

Bone erosions are a defining feature of RA, with evidence of radiographic erosions being included in both the 1987 ACR and 2010 ACR/EULAR classification criteria for RA. Studies conducted in patients with early (Wakefield et al., 2000; Szkudlarek et al., 2004; Szkudlarek et al., 2006; Bajaj et al., 2007) and established RA (Wakefield et al., 2000; Klocke et al., 2001; Szkudlarek et al., 2004; Szkudlarek et al., 2006) demonstrate the majority of erosions detected by conventional radiography are indeed detectable by ultrasound. X-ray erosions undetected by ultrasound are perhaps more likely to be those occurring at sites which are more difficult to visualise by ultrasound, such as MCP4, the ulnar aspect of MCP2 (Wakefield et al., 2000) and medial aspect of MTP5 (Klocke et al., 2001). Moreover, these studies and others demonstrate it is possible to detect more erosive abnormalities on ultrasound than are visible on x-ray in early (Wakefield et al., 2000; Szkudlarek et al., 2004; Szkudlarek et al., 2006; Bajaj et al., 2007) and established RA (Wakefield et al., 2000; Klocke et al., 2001; Weidekamm et al., 2003; Szkudlarek et al., 2004; Scheel et al., 2006; Szkudlarek et al., 2006). Reports of the prevalence of ultrasound erosions in early, treatment-naïve IA (including patients with UA) suggest a three-fold higher prevalence of erosions may be detected by ultrasound, in comparison to x-ray (Funck-Brentano et al., 2009; Sheane et al., 2009). However, ultrasound in these studies was limited to a small number of joints: examination of MTP5 only in 30 patients with a mean duration of symptoms of 15 months (a proportion of whom had previous DMARD exposure) (Sheane et al., 2009) and bilateral ultrasound examination of MCP2, MCP5 and MTP5 in the ESPOIR study (Funck-Brentano et al., 2009).

Interestingly, RA patients lacking any swollen or tender joints with subclinical PD (either PD≥grade 1 or ≥grade 2 in any wrist, MCP or PIP) were significantly more likely to demonstrate erosions on ultrasound, in comparison to patients without PD, in a cross-sectional, univariable analysis (radiographic erosions were not assessed) (Kawashiri et al., 2014a). Joints with PD may also be more likely to display ultrasound erosion in patients with sustained low disease activity (DAS28<3.2) on biologic therapy for RA; erosion was observed on ultrasound in 10/31 wrist/finger joints with PD, in comparison to 7/607 joints without PD in a further Japanese cross-sectional, univariable analysis (Kawashiri et al., 2017).

- *Erosions: Concurrent Validity*

Concurrent validity of ultrasound in the detection of erosions in RA has been demonstrated in a recent systematic literature review (Szkudlarek et al., 2016). Good correlations are observed between erosions detected with ultrasound and those detected by MRI (Wakefield et al., 2000; Szkudlarek, M. et al., 2003; Magnani et al., 2004; Szkudlarek et al., 2004; Szkudlarek et al., 2006; Rahmani et al., 2010; Szkudlarek et al., 2016) or CT (Dohn et al., 2006; Finzel et al., 2011; Szkudlarek et al., 2016) as gold standards. Vascular bone channels (particularly at the palmar aspect of MCPs) and pseudo-erosions created by osteophytes have been identified as potential reasons for false-positive results for erosion detected on ultrasound, in comparison to micro-CT (Finzel et al., 2011). Good correlation between the number of erosions detectable by ultrasound and the true number of erosions has also been demonstrated using an experimental bovine model (Koski et al., 2010).

- *Erosions: Predictive Validity*

Limited evidence for the predictive validity of ultrasound erosions is available. In an early prospective study of 12 patients with established RA with no evidence of radiographic erosions, ultrasound erosions were observed in nine out of a total of 96 joints examined by ultrasound (unilateral MCPs2-5 and PIPs2-5) (Scheel et al., 2006). After seven years, x-ray erosion had developed in 2/9 (22%) of joints with ultrasound erosions versus 23/87 (26%) of joints without ultrasound erosion. The low sensitivity of these baseline ultrasound assessments, performed in 1996, may not be relevant to modern-day ultrasound scanning. Analysis of the ESPOIR study demonstrated the presence of ultrasound erosion at baseline (although only assessed in MCP2, MCP5 and MTP5) was associated with presence of

radiographic erosion within the hands and/or feet at two years (Funck-Brentano, Gandjbakhch et al. 2013). However, baseline radiographic erosions were not considered within the multivariable model (27% of patients displayed radiographic changes typical of RA at baseline). When subgroup analysis was carried out in patients with no radiographic erosions at baseline (n=93), the association of ultrasound erosions at baseline and radiographic erosion at two years was no longer significant, although the low number of patients with this outcome (n=13, 14%) should be borne in mind. Subgroup analysis was also conducted at the joint level: radiographic erosion at one year was observed in 26 of 1091 joints without radiographic erosion at baseline. With adjustment for age, DAS28, CRP, ESR, RF-positivity, ACPA-positivity, steroid/DMARD/biologic use and ultrasound parameters including total GS and PD scores, CRP and RF-positivity were independent predictors of erosion at one year. There was a trend towards an association with the presence of ultrasound erosion at baseline (p=0.052) suggesting larger studies are desirable.

A Japanese study suggested that in patients with RA, achieving low disease activity (DAS28<3.2), the presence of ultrasound erosions is a risk factor for failure of biologic drug cessation (treatment escalation within the following year) (Kawashiri et al., 2017). The presence of ultrasound erosion in any wrist, MCP or PIP was significantly associated with treatment escalation (occurring in 19/40 patients); OR 8.4 (95% CI 1.8-53), adjusted for gender and SDAI at biologic initiation. This model was constructed by entering variables with potential significance (p<0.2) on univariable analysis; other ultrasound variables, including GS and PD synovitis were considered, however univariable results for radiographic erosions were not reported.

Other evaluations of the predictive validity of ultrasound erosion have been restricted to univariable analyses. In the Birmingham very early IA cohort, the presence of any ultrasound erosion at the wrists, MCPs, PIPs or MTPs demonstrated 38% sensitivity and 93% specificity for the fulfilment of 1987 ACR RA criteria over 18 months (Filer et al., 2011). In patients with early inflammatory symptoms presenting in Leeds, 53% sensitivity and 73% specificity was demonstrated for the presence of any ultrasound erosion at the wrists or MCPs in the determination of persistence of IA at one year (defined according to a physician diagnosis) (Freeston et al., 2010). In one of the aforementioned Japanese cohorts

of patients with suspected RA, any ultrasound erosion detected in the wrists, MCPs and PIPs, was only 20% sensitive but 100% specific for the use of DMARDs within the following three months (Kawashiri et al., 2013). In Newcastle, ultrasound erosions at MCPs2-4, PIPs2-4 and MTPs1-2 were considered as a potential variable for inclusion in a prediction model of persistent IA (physician diagnosis or diagnosis of RA according to fulfilment of 1987 ACR criteria), however this variable was not identified as discriminatory and was therefore not included in the final reported model (Pratt et al., 2013).

One study has aimed to assess the predictive value of ultrasound (including severity of ultrasound erosion at baseline, as well as measures of ultrasound synovitis) at the individual joint level, in predicting progression in ultrasound erosive disease as an outcome measure (Reynolds et al., 2009). In each of 40 patients with established RA (fulfilling 1987 ACR RA criteria), a target joint was selected for ultrasound examination in order to provide 10 joints in each of the following categories: clinically swollen and tender joints, swollen but not tender joints, tender but not swollen joints and joints without clinical swelling or tenderness. However, a significant number of patients were excluded from the analysis: 2 died, 4 declined follow-up and 9 had a baseline ultrasound erosion score of 3 and therefore could not demonstrate progression. Ultrasound erosion was scored on a 0-3 grade (0=no erosion, 1=erosion<2mm, 2=erosion>2mm or >2 erosions<2mm, 3=large/diffuse/regional joint destruction) at baseline and follow-up (mean 26, range 24-32 months). Progression was defined by a worsening in grade from baseline. Progression was observed in 12/25 patients (2 receiving NSAIDs alone, 6 receiving DMARDs and 4 patients receiving TNF-inhibitors). Baseline ultrasound erosion score was the only ultrasound variable significantly associated with progression on univariable analysis (p=0.05).

- *Erosions: Discrimination*

The appearance of erosion on ultrasound may be observed in healthy individuals, perhaps as a result of normal variation in bone profile or artefacts (Szkudlarek et al., 2012). Table 11 displays the prevalence of erosion-like change which has been observed in various control groups. Erosive change may also be reflective of aging or degenerative processes. Indeed, the study by Zayat et al. demonstrated an increase in the number of erosive joints with age, although this was amongst their entire cohort including patients with RA, psoriatic arthritis, gout and osteoarthritis as well as healthy controls (Zayat et al., 2015).

This study by Zayat et al. included several comparator groups, including 60 patients with osteoarthritis (which excluded patients with knee or hip osteoarthritis alone). A high prevalence of ultrasound erosion was observed in patients with osteoarthritis: at least one erosive joint was found in 42 (70%) and large erosion (diameter≥2.5mm) was found in 11 (18%) patients. The most frequently affected joint sites were similar to controls; 18 (30%) of patients displayed erosion at the wrist (radius) and 13 (22%) displayed erosion at the proximal aspect of MTP1. This compares to a rate of any erosion of 64/70 (91%) observed in RA patients in this study, and a rate of any large erosion (≥2.5mm diameter) of 48/70 (69%). The most frequently involved joint site in RA was the proximal aspect of MTP5. In calculating the sensitivity and specificity for joint erosion detectable at individual joint sites for the discrimination of RA (versus all other comparator groups), the best combination was demonstrated at this site (sensitivity 69%, specificity 85%).

Whilst the size of erosions also appeared to be relatively discriminatory for RA (sensitivity and specificity for the presence of at least one large erosion ≥2.5mm diameter were 69% and 68%, respectively), the majority of RA patients had established disease (n=42) and healthy controls were excluded from this analysis (Zayat et al., 2015). Subgroup analysis suggested that erosions were smaller amongst the early RA patients (n=28) in comparison to those with established RA. The study by Millot et al. also indicated that size of erosions is not sufficient to differentiate findings in normal individuals from those with early IA (Millot, Clavel et al. 2011).

Table 11. Prevalence of erosion-like change observed on ultrasound examination in healthy subjects.

Reference	n	Method of recruitment	Age (yrs)	Joints examined	Prevalence of US Erosion
(Padovano et al., 2016)	207	Staff, students, relatives of patients and other volunteers (exclusions: osteoarthritis, trauma, recent arthralgia)	Mean 36, range 18-74	Wrists, MCPs, PIPs, MTPs (Bilateral)	4/6621 joints (all MTP1).
(Zayat et al., 2015)	60	Across 2 sites (Leeds and Copenhagen)	Mean 40, range 23-73	Wrist, MCP2,3,5, PIP2-3, MTP1,5 (Bilateral)	20 (33%) of subjects. Most frequent at wrist (radius) (12 [20%] subjects) and MTP1 (6 [10%] subjects). Only 1 subject with erosion ≥2.5mm diameter.
(Millot, Clavel et al. 2011)	127	Hospital staff and patients with sciatica, age- and gender-matched to early IA patients in ESPOIR	Mean 50	MCP2,5 and MTP5 (Bilateral)	14 (11%) of subjects (1 erosive joint in each; MTP5 in 8, MCP2 in 5 and MCP5 in 1 subject). Only 3 subjects with erosion >2mm diameter. No erosion observed in association with GS or PD signal in the same joint.
(Wiell et al., 2007)	5	Not reported	Median 63, range 35-71	MCP2-5, PIP2-5, DIP2-5, MTP1-5 (Bilateral)	9 erosive joints in an unknown number of subjects; 5 PIPs, 3 MTPs and 1 MCP.
(Terslev et al., 2004; Terslev et al., 2008)	27	Staff and staff family members	Mean 45, range 18-93	Wrist, CMC1, MCP1-5, PIP1-5 (Unilateral)	Erosions in 3 CMCs only.

(Bajaj et al., 2007)	5	Not reported	Mean 45	MCP2,5, most swollen PIP (one per hand), MTP5 (Bilateral)	No erosions (although defined as size >2mm diameter).
(Szkudlarek et al., 2006)	20	Not reported	Median 52, range 27-79	MCPs 2-5, PIPs 2-5 (Unilateral)	No erosions.
(Szkudlarek et al., 2004)	20	Not reported	Median 52, range 25-78	MTPs 1-5 (Unilateral)	2 (10%) subjects. Occurring in MTP1 (2 subjects) and MTP5 (1 subject).

- *Erosions: Reliability*

Several studies have addressed the reliability of US between two operators (Wakefield et al., 2000; Szkudlarek, M. et al., 2003; Scheel, A K et al., 2005; Naredo et al., 2006; Wiell et al., 2007; Millot et al., 2011). Levels of agreement for the presence of erosion on ultrasound, denoted by kappa, have ranged between 0.5 (moderate) (Wiell et al., 2007) and 0.9 (excellent) (Millot et al., 2011). The former was observed at the PIP joints amongst six patients with psoriatic arthritis, one patient with RA and one control; in this same study, good to excellent agreement was observed at other sites (MCPs, DIPs and MTPs). In Mexico, ultrasound examination of MCP2 and the ulnar head, revealed poor inter-observer agreement for erosions amongst five operators (Chávez-López et al., 2013). Insufficient time to perform an adequately thorough examination (ten minutes to examine the wrist, MCPs2-3 and PIPs2-3 for synovitis, tenosynovitis and erosion) and poor familiarity with the equipment were cited as potential contributory factors to the poor agreement. When considering all of these studies, the prevalence of erosions (which has not always been reported) should be considered as kappa estimates are susceptible to prevalence bias. The kappa statistic represents the agreement which exceeds the expected level of agreement arising by chance; therefore, at the extremes of prevalence (very rare or ubiquitous findings) values may be misleadingly low.

In reliability exercises undertaken by OMERACT, including a large number of sonographers from across Europe, respectable rates of inter-observer agreement for ultrasound-detected erosions and cortical abnormalities were reported (Scheel, A K et al., 2005; Naredo et al., 2006; Bruyn et al., 2015). In the earliest study, four patients with positive ultrasound findings (using agreement of at least 10/14 operators as the reference standard) volunteered: ultrasound erosions were present at the humeral head in a patient with RA, MCP2 in a patient with remitting seronegative symmetrical synovitis with pitting oedema, the knee in a patient with gout and the talonavicular joint in a patient with reactive arthritis (Scheel, A K et al., 2005). Agreement for the presence of erosion was observed in 14/14, 13/14, 11/14 and 12/14 operators, respectively. In a later exercise, wrist and hand ultrasound was conducted in six patients with RA, and ankle and foot ultrasound was conducted in a further three patients with RA, two patients with SpA and one patient with osteoarthritis (Naredo et al., 2006). Erosions were detectable at CMC1, MCP2, PIP2, talonavicular, MTP1 and MTP5 joints; kappa values for agreement for cortical

abnormalities were 0.6 at each region amongst 23 operators. Limitations of these studies included the small number of joints examined (Scheel, A K et al., 2005) and the method of reporting cortical abnormalities which grouped erosive findings together with osteophytes (Naredo et al., 2006).

- *Erosions: Responsiveness*

A small number of studies have reported change in ultrasound erosive damage over time. In one of the earliest prospective studies, ultrasound of MCPs2-5 and PIPs2-5 (unilaterally) in 16 patients with established RA demonstrated erosions in 12/128 (9%) joints in 1996 and 62/128 (49%) joints seven years later, in 2003 (Scheel et al., 2006). However, advancement in the sensitivity of ultrasound technology may have accounted for at least some of this difference as a different machine was used at follow-up.

Concerning patients with early disease, of 58 patients with early RA (1987 ACR criteria with disease duration less than one year) development of new ultrasound erosions at the distal ulna was observed in 11/58 (19%) patients over one year (Hammer et al., 2009). In a more extensive examination of 11 joints (unilateral MCPs1-5, PIPs1-5 and the wrist), 46 patients with early RA (fulfilling 1987 ACR RA criteria, within two years of diagnosis) were studied (Hoving et al., 2004). The number of patients with ultrasound erosions increased from 14/46 (30%) to 19/46 (41%) over six months. No statistical testing was performed and this study was also conducted relatively early (1999-2003).

A small number of studies have assessed responsiveness of various scoring systems for erosions, although without much consistency of scoring methods (Szkudlarek et al., 2016). At the level of a single MCP or PIP joint, Reynolds et al. observed progression in ultrasound erosion score (grade 0-3 according to erosion size) from baseline to follow-up (range 24-32 months) in 12/25 patients with RA (6 were receiving DMARDs, 4 receiving TNF-inhibitors and 2 receiving NSAIDs only) (Reynolds et al., 2009). In 120 patients with RA initiating or receiving a change in DMARD therapy, no change in the number of ultrasound erosions across six joints (unilateral MCPs2-3, PIPs2-3 and MTP2,5) was observed between baseline and 6 month follow-up examinations (mean 2.6 erosions at both time-points) (Backhaus et al., 2009). Of note, the majority of patients (59%) were treated with TNF-inhibitors.

A semi-quantitative score for ultrasound erosions (according to their size) has also been shown to improve amongst 38 patients with established RA starting or receiving a change in DMARD/biologic therapy (53% receiving biologics): the mean total score (for 13 joints of the clinically most affected hand and foot) improved from 21.5 to 18.1 after one year (p=0.046) (Ohrndorf et al., 2014).

2.3.3 Summary

This evidence supports ultrasound as a valid tool to define the phenotype of patients with IA and assess disease activity in patients receiving treatment. It offers supplementary information to clinical and radiographic evaluations. Studies suggest the predictive value of ultrasound, however further research is needed to determine the prognostic value of ultrasound-detected synovitis and erosions, particularly in early IA in the context of the new 2010 ACR/EULAR RA criteria.

Assessment of synovitis (and possibly joint damage) by ultrasound is now recommended by experts within European guidelines for the confirmation of early IA (Colebatch et al., 2013; Combe et al., 2017). Nevertheless, with the increasing use of ultrasound as an aid in diagnosing and directing treatment decisions it is critically important to be aware its limitations. These include its operator-dependant nature and the existence of ultrasound abnormalities in normal or osteoarthritic joints, such as low-grade synovitis or erosive-like change.

The choice of joints to include in an ultrasound examination is contingent on its intended purpose. An assessment to determine future prognosis in a patient with early UA may include more joints than if assessing disease activity in a patient already receiving treatment or as an outcome in a clinical trial. A more extensive joint examination may be expected to be more sensitive, albeit with a potential trade-off in specificity and reliability. Ultrasound within research should be replicable and conducted in such a way that results are interpretable and generalisable to the target population. In this setting, therefore, standardised ultrasound of a core set of joints may be appropriate versus a clinical setting in which ultrasound may be directed according to clinical history and restricted to examination of just the hands, or hands and feet, for example. Feasibility, especially in this latter setting, is another key consideration.

The definition for abnormality at the joint level may also depend on the clinical situation. For example, GS synovitis may be a useful measure of disease activity in treatment-naïve early IA (bearing in mind that a small volume of low-grade GS synovitis may be observed in normal individuals), whilst in later disease it may be difficult to differentiate active synovitis from inactive fibrous synovial thickening using GS appearance alone, in which circumstance PD may be more informative. Indeed, GS synovitis has been shown to correlate with disease duration in patients with established RA (Saleem et al., 2009).

2.4 Strategies for Management

2.4.1 Rheumatoid Arthritis

2.4.1.1 The Therapeutic Window of Opportunity in Early RA

The key principle in the management of patients with RA is that inflammatory disease activity over time leads to cumulative joint destruction. In addition, inadequately supressed inflammation contributes to an increased risk of comorbidities related to chronic inflammatory diseases such as cardiovascular disease and lymphoma. It has been shown that joint damage occurs early in the disease process. Indeed, prospective data from biannual hand and feet radiographs has demonstrated the rate of progression of joint damage to be significantly greater in the first year, in comparison to the second and third years, from diagnosis (van der Heijde et al., 1995).

It follows that early effective treatment offers favourable long-term outcomes, through limiting the burden of inflammation over time. This has been a prevailing concept in management since the 1990s (Quinn et al., 2001) and is supported by comparisons of patients receiving early and delayed DMARD therapy in both a non-randomised (Lard et al., 2001; Nell et al., 2004) and randomised (van der Heide et al., 1996) manner. Further evidence is available from several observational cohorts and randomised-controlled studies in early IA in which symptom duration at baseline has been consistently identified as an independent predictor of poor outcome (see Tables 3-5) (Bosello et al., 2011; Lukas et al., 2011; Söderlin and Bergman, 2011; Gremese et al., 2013).

Over and above the quantitative reduction in inflammation that may be afforded by DMARD therapy, a window of opportunity may exist in very early disease in which pathogenic mechanisms are not yet fully evolved and may be more readily modifiable with therapy. The early initiation of DMARD therapy positively impacts on the aggressive and persistent nature of the disease in the future, with meta-analyses demonstrating lower rates of future radiographic progression (Finckh et al., 2006) and higher rates of DMARD-free remission (van Nies et al., 2014). More recently, in patients receiving TNF-inhibitors as first-line therapy in randomised controlled trials, the importance of early initiation of such therapy in

order to achieve optimal remission rates (Emery, P. et al., 2010) and sustained remission after TNF-inhibitor cessation (Saleem et al., 2010) has also been demonstrated.

Recently, pivotal results from an analysis of RA patients receiving DMARDs in observational cohorts (Leiden EAC and ESPOIR) have demonstrated a non-linear relationship between a patient's symptom duration at their first visit to a rheumatologist and achievement of DMARD-free remission (van Nies et al., 2015). This is fundamental to the concept of a therapeutic window of opportunity in early disease. In this combined cohort, symptoms for up to 19 weeks prior to the first visit provided the optimal combination of sensitivity and specificity for discriminating the ability to achieve DMARD-free remission in the future. The timing of the window of opportunity is likely to vary according to disease characteristics, with studies suggesting it may be narrower in patients with ACPA-positive disease (van Nies et al., 2015) and even narrower or non-existent in patients who continue to smoke (Söderlin and Bergman, 2011).

An underlying hypothesis is that, within this critical phase in early disease, immunosuppressive therapy may enable full reversal of immunopathogenic abnormalities and hence reduce the propensity for disease mechanisms to become chronic (Raza, 2010). It has been postulated that this window, in which disease mechanisms may be distinct from those in established disease, may exist very early in the disease process. A distinct cytokine profile has been observed in the synovial fluid of patients with early IA (symptoms <12 weeks) who later fulfilled 1987 ACR RA criteria, in comparison to patients with established RA (Raza et al., 2005b). Synovial tissue immunohistochemical analysis has also demonstrated features apparently unique to patients with very early IA (symptoms <6 weeks) destined to later fulfil the 1987 ACR RA criteria (Singh et al., 2004). Whereas the histological appearance of synovium from patients with RA already fulfilling 1987 ACR RA criteria, within one year of onset of joint swelling, has been found to be similar to that observed in later disease (Tak et al., 1997).

These studies highlight the importance of early identification of IA and prompt commencement of therapy. Connotations for the various definitions of symptom or disease duration within studies of patients with early IA (i.e. time from onset of

symptoms, joint swelling or fulfilment of classification criteria) are also an area of on-going discussion (Raza et al., 2012).

2.4.1.2 Treatment Strategies: Synthetic DMARDs

- *Initial Combination Synthetic DMARD Therapy versus DMARD Monotherapy*

The COBRA study was the first to demonstrate the benefit of initial combination DMARD therapy (sulfasalazine, methotrexate and high dose prednisolone) over DMARD monotherapy (sulfasalazine) (Boers et al., 1997). The high steroid doses administered in the combination treatment arm may have contributed significantly to the results. The FIN-RACo study also demonstrated superior clinical outcomes in patients randomised to combination therapy (sulfasalazine, methotrexate, hydroxychloroquine and low-dose prednisolone) versus initial sulfasalazine (Möttönen et al., 1999). This study was more realistic in allowing patients with persistent disease activity in the sulfasalazine monotherapy arm to receive additional steroid therapy and switch treatment to methotrexate, and subsequently to alternative DMARDs. In the CIMESTRA study, methotrexate plus ciclosporin was compared to methotrexate and placebo (Hetland et al., 2006). Patients in both arms also received frequent assessment and intra-articular steroid treatment for swollen joints (at 0, 2, 4, 6 and 8 weeks, then 4-weekly intervals). Patients receiving initial combination therapy achieved higher ACR20 response rates at one year (the primary end-point) in comparison to those receiving methotrexate monotherapy; 85% versus 68%, respectively (p=0.02).

- *Treatment-to-Target Strategies*

Several studies support initial DMARD therapy, either as monotherapy or in combination with other DMARDs, with adjustment in therapy according to a pre-defined target of clinical remission or at least a low disease activity state. These include treatment regimens restricted to synthetic DMARDs only (Grigor et al., 2004; Proudman, Susanna M. et al., 2007; Verstappen et al., 2007; Saunders et al., 2008; Knevel et al., 2010; den Uyl et al., 2014; Verschueren et al., 2017), as well as studies designed with protocolled escalation to biologic therapies (Soubrier et al., 2009; van Vollenhoven et al.; Goekoop-Ruiterman et al., 2010; Knevel et al., 2010; Soubrier et al., 2011; Moreland et al., 2012; de Jong et al., 2014; Hørslev-Petersen et al., 2014; Nam et al., 2014a; Scott et al., 2014; Smolen, Josef S. et al., 2014;

Heimans et al., 2016). The latest evidence-based guidelines, first published in 2010 by EULAR, recommend this approach (Smolen et al., 2010; Smolen, Josef S et al., 2014; Singh et al., 2016; Smolen et al., 2016; Smolen et al., 2017).

For example, in the TICORA study, tight control of disease proved advantageous over routine treatment (Grigor et al., 2004). Intensive management involved monthly assessment and step-up to combination DMARD therapy according to a target of low disease activity, in comparison to three-monthly monitoring without use of a formal measure of disease activity. At 18 months, clinical remission (DAS44-ESR<1.6) was achieved in 65% of the intensive therapy group, compared to only 16% of the routine treatment group (although the intensive group also received greater steroid doses).

Initial intensive combination therapy, based on the COBRA regimen, has also been compared to initial DMARD monotherapy (either methotrexate, sulfasalazine, hydroxychloroquine or azathioprine) with change in therapy according to a target of DAS28 remission (Verschueren et al., 2008). However, this was a pragmatic study based on daily practice. Allocation to either initial combination or monotherapy was based on physician judgement, as was initial choice of DMARD monotherapy and subsequent treatment adjustments. In a further open-label study, randomisation to treatment groups and a protocol for escalation was employed (den Uyl et al., 2014). Patients were randomised to ‘COBRA’ (methotrexate, sulfasalazine and prednisolone tapering from 60mg daily) or ‘COBRA-light’ (methotrexate escalating to 25mg weekly, over approximately two months, in combination with prednisolone tapering from 30mg daily) regimens. At three months, methotrexate treatment was escalated according to a target of remission (DAS44<1.6): an increase in oral dose in ‘COBRA’-treated patients or switch to subcutaneous administration in ‘COBRA-light’ patients. Non-inferiority for the primary outcome (change from baseline DAS44 at six months) between the regimens was suggested. However, the confidence interval for the estimated difference between the groups included 0.5, the pre-defined clinically relevant difference suggesting non-inferiority, and the low starting dose of methotrexate in the original COBRA regimen may be of significance.

The CareRA trial concluded that initial methotrexate monotherapy with prednisolone (30mg daily, reducing to stop over nine months) with addition of leflunomide after 16 weeks in the instance of DAS28≥3.2, was as effective as initial combination DMARD therapy; either the COBRA regimen (including prednisolone 60mg, tapering over 9 months) or methotrexate and leflunomide (in combination with 30mg prednisolone daily, tapering over 9 months) (Verschueren et al., 2015; Verschueren et al., 2017). However, a greater number of patients in the initial methotrexate monotherapy arm received intra-muscular and/or intra-articular steroids and both the high cumulative dose of prednisolone and the escalation to a combination of methotrexate and leflunomide may not be ideal for routine clinical use due to their side-effect profiles.

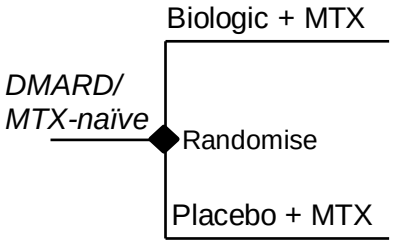
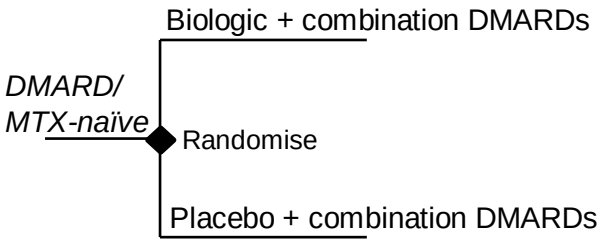
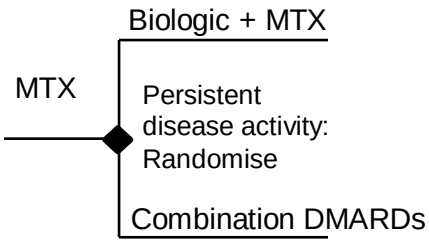
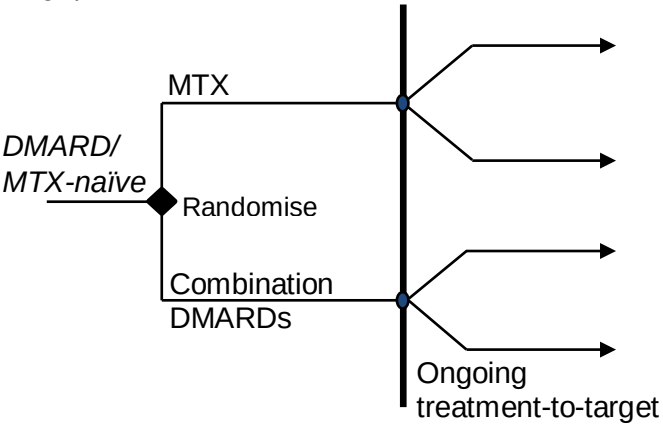
2.4.1.3 Treatment Strategies: The Role of Biologic Therapy

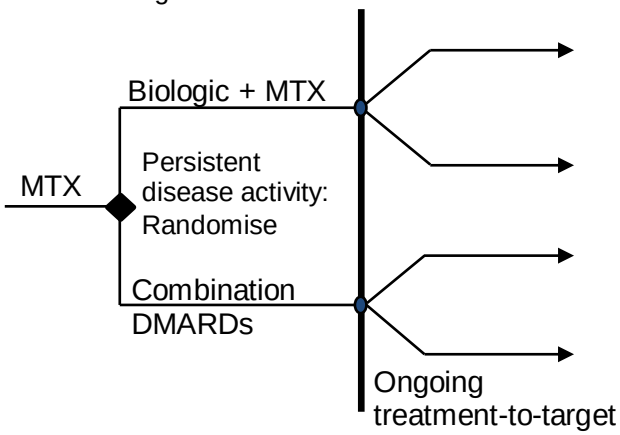
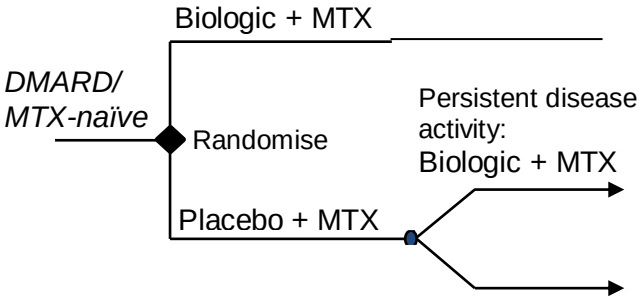
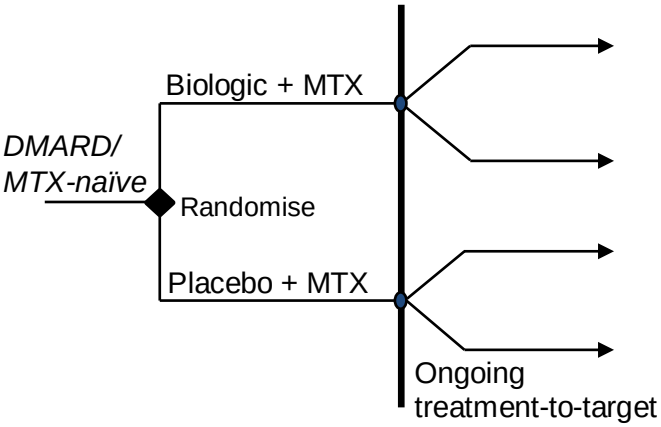
TICORA and other pragmatic studies demonstrate that clinical remission is a realistic goal but it is not always achievable with synthetic DMARD therapy alone; indeed rates of remission are often quite low (Proudman, S. M. et al., 2007; Verstappen et al., 2007; Saunders et al., 2008). In patients failing to achieve remission in this way, biologic therapy may be indicated. TNF-inhibitor therapies were initially introduced, followed by rituximab and subsequently abatacept and tocilizumab, all licensed for use in these patients. In the UK, the National Institute for Health and Care Excellence (NICE) currently recommends biologic therapies in the instance of failure of two synthetic DMARDs (including methotrexate) and in the presence of high disease activity (DAS28>5.1).

The DREAM study offers some insight into efficacy of a treatment-to-target regimen, with escalation to biologic therapy in patients with persistent disease activity, within a clinical setting (Vermeer et al., 2011). It was a single arm, open-label, pragmatic study of patients with early RA (defined by physician impression, 82% of patients were fulfilling 1987 ACR criteria at baseline). Patients were treated with initial methotrexate, with subsequent steps of addition of sulfasalazine and switch of sulfasalazine to adalimumab in the instance of DAS28≥3.2 at or after six months. The rate of DAS28 remission at one year, 58%, was still less than ideal. Evidence of the efficacy of treatment-to-target management in a UK clinical setting, with potential barriers to adherence to treatment-to-target guidelines such as NICE restrictions for the use of biologics, is currently limited.

There is an argument for the earlier introduction of biologic therapy, particularly in patients with poor prognostic factors, owing to the therapeutic window of opportunity in early disease and the superior efficacy of biologics in comparison to methotrexate therapy (St Clair et al., 2004; Breedveld et al., 2006; Emery et al., 2008; Emery et al., 2009) (Table 13). However, evidence for the early initiation of biologic therapy versus initial use of synthetic DMARDs with ongoing management within a treatment-to-target regimen, or initial combination synthetic DMARD therapy, is less conclusive. The evidence for these treatment strategies, in patients with either early or DMARD/methotrexate-naïve RA, is reviewed here. Randomised studies are grouped according to the categories described in Table 12.

Table 12. Summary of randomised studies assessing treatment strategies including biologic therapies in DMARD/MTX-naïve patients.

Treatment Regimen and Simplified Schematic of Study Design	Study Examples
Fixed Treatment Regimens	
1. Biologic (+/- MTX) *versus* MTX monotherapy 	See Table 13
2. Biologic + combination DMARDs *versus* combination DMARDs 	NEO-RACo
Step-up regimens: first-line DMARD regimens with step-up in therapy (including delayed biologic therapy) according to a disease activity target	
3. MTX monotherapy with escalation to delayed biologic *versus* MTX monotherapy with escalation to combination DMARDs 	SWEFOT
4. MTX monotherapy with ongoing treatment-to-target (including escalation to delayed biologic) *versus* combination DMARDs with ongoing treatment-to-target (including escalation to delayed biologic) 	tREACH Extension of COBRA vs. COBRA-light study

5. MTX monotherapy with escalation to delayed biologic *versus* MTX monotherapy with escalation to combination DMARDs, followed by later escalation to biologic  	IMPROVED
Step-up regimens: first-line biologic therapy versus first-line DMARD regimens with step-up in therapy according to a disease activity target	
6. Biologic (+ MTX) *versus* MTX monotherapy with escalation to delayed biologic  	OPTIMA HOPEFUL
7. Biologic (+ MTX) with ongoing treatment-to-target including switch to alternative biologic *versus* MTX monotherapy with ongoing treatment-to-target including delayed biologic  	U-Act-Early IDEA Similar examples: • GUEPARD (open-label, i.e. no placebo) • OPERA (escalation to combination DMARDs, i.e. no delayed biologic in patients randomised to initial MTX monotherapy)
8. Studies with multiple treatment arms (see text for descriptions of studies)	BeSt TEAR

Fixed treatment regimens

1. First-line biologic (+/- methotrexate) *versus* first-line methotrexate monotherapy

Double-blind randomised controlled trials of biologic therapies in patients with early RA are summarised in Table 13. Early trials were largely conducted in patients with indicators of severe, progressive disease, such as high disease activity, RF-positivity and radiographic erosions. With accumulating evidence of the safety and efficacy of these therapies, and the importance of the achievement of remission to optimise long-term outcomes in patients with early RA, later studies have been conducted in patients with lower disease activity at baseline (Emery et al., 2008; Emery et al., 2009). Increasingly ambitious primary outcomes have been set including clinical remission, first assessed in the COMET study (Emery et al., 2008). The majority of trials excluded patients with significant prior exposure to methotrexate, whilst several more recent studies excluded patients receiving any prior DMARDs.

The HIT-HARD study was recently conducted with the intention of assessing the efficacy of a short duration of biologic therapy, with a primary outcome several months after biologic withdrawal (Detert et al., 2013). Although the difference in the primary outcome was not statistically significant (see Table 13), significant differences were observed between the groups in secondary outcomes. These included clinical responses whilst receiving the study treatments at six months, and radiographic outcomes after treatment withdrawal at one year. Results of follow-up studies of a number of the randomised trials described in Table 13 are also available. These include a follow-up of patients receiving initial infliximab and methotrexate versus methotrexate and placebo (Quinn, M. A. et al., 2005): eight years on, 40% of patients initially treated with infliximab were still in remission, in comparison to none of the controls (Bejarano et al., 2010). The impact of tapering and stopping biologic and/or synthetic DMARDs has also been reviewed in open-label and single-blind studies including treatment-to-target/step-up treatment arms and initial combination synthetic DMARD therapy arms (discussed below).

Table 13. Efficacy of biologic therapy in early RA patients (fulfilling 1987 ACR RA criteria, unless otherwise stated as fulfilling 2010 ACR/EULAR criteria) in double-blind randomised controlled trials. Controls were treated with methotrexate. Only groups treated with the dose currently approved for clinical practice are presented.

Drug and Study	Inclusion Criteria			Primary/Co-primary endpoints	Results: Primary outcome(s) in active treatment group (dose used in clinical practice) vs. controls***
	Disease Activity	Disease Duration*/ Previous DMARD Exposure**	Other Prognostic Factors		
Etanercept monotherapy, Enbrel ERA (Bathon et al., 2000)	SJC ≥10, TJC ≥12, EMS≥45min, ESR≥28mm/hr CRP≥20mg/l.	≤3 yrs/ MTX-naïve	RF+ or ≥3 x-ray erosions.	Clinical response over 6 mths (area under the curve for ACR-N up to 6 mths). Mean change in SHS from baseline at 12 mths.	Significantly greater area under the curve for ACR-N ($p<0.05$). Mean change in SHS 1.0 vs. 1.6 ($p=0.11$).
Etanercept with MTX, COMET (Emery et al., 2008)	DAS28≥3.2, ESR ≥28mm/hr or CRP≥20mg/l.	≤2 yrs/ MTX-naïve	-	Clinical remission at 52 wks (DAS28-CRP<2.6). Change in SHS from baseline to wk 52.	DAS28 remission in 50% vs. 28% ($p<0.0001$) (mITT based on 528 of 542 patients randomised). Change in SHS 0.3 (95% CI -0.1 to 0.7) vs. 2.4 (95% CI 1.5-3.4) (mITT based on 476 of 542 patients randomised).
Infliximab with MTX, ASPIRE (St Clair et al., 2004)	SJC ≥10, TJC ≥12.	≤3 yrs (persistent synovitis)/ MTX-naïve	≥1 of: RF+, ≥1 x-ray erosion, CRP ≥20mg/l.	Clinical response over 54 wks (area under the curve for ACR-N up to wk 54). Change in SHS (baseline to wk 54).	Median ACR-N 39% vs. 26% ($p<0.001$). Mean (SD) change in SHS 0.4 (5.8) vs. 3.7 (9.6) ($p<0.001$). Both outcomes mITT based on 1004 of 1049 patients randomised.
Infliximab with MTX (Quinn, M. A. et al., 2005)	MCP joint involvement.	<1 yr (symptoms)/ DMARD-naïve	PISA≥3.	MRI synovitis (measured at MCP2-5 of the dominant hand) at wk 14.	Reduction in median total synovitis score from 5.5 to 3.4 vs. 6.2 to 5.9 ($p<0.05$).

Infliximab with MTX (Durez et al., 2007)	SJC ≥6, TJC ≥8.	<1 yr/ MTX-naïve (and excluded patients who had received >2 previous DMARDs)	-	Change from baseline in MRI sores for synovitis, bone marrow oedema and erosion (assessed using semi-quantitative methods at wrists, MCP2-5 and MTP1-5, bilaterally) at wk 18 and wk 52.	Median (IQR) change in score from baseline (mITT based on 26 of 29 patients randomised): Wk 18: synovitis: -7(8) vs. -1(2) (p<0.001) oedema: -5.5(15) vs. -2(7) (p=0.03) erosion: 1 (2) vs. 1 (2) (p=NS). Wk 52: synovitis: -10.5(11) vs. -4.5(9)(p=0.02) oedema: -9(20) vs. -2(6) (p=NS) erosion: 1 (3) vs. 1 (6) (p=NS).
Adalimumab with MTX and Adalimumab monotherapy, PREMIER (Breedveld et al., 2006)	SJC ≥8, TJC ≥10, ESR ≥28mm/hr or CRP≥15mg/l.	<3 yrs/ MTX-naïve (and excluded patients who had received >2 other DMARDs)	RF+ or ≥1 x-ray erosion.	ACR50 at 1 yr. Mean change in SHS from baseline at 1 yr.	Adalimumab in combination with MTX superior to adalimumab monotherapy or MTX alone: ACR50 in 62% vs. 41% (adalimumab monotherapy) and 46% (MTX monotherapy) (p<0.001 combination therapy vs. either monotherapy group). Mean change in SHS 1.3 vs. 3.0 (adalimumab monotherapy) and 5.7 (MTX monotherapy) (p≤0.002 combination therapy vs. either monotherapy group).
Adalimumab with MTX (Bejarano et al., 2008)	None specified (mean DAS28 6).	<2 yrs (symptoms)/ MTX-naïve	Self-reported RA-related work impairment.	Job loss/imminent job loss at/after wk 16 (defined as failure to achieve ACR20 and either WIS score deterioration or persistent high WIS score).	12/75 vs 20/73 (p=0.092) (data for all withdrawals imputed as no job loss in this ITT analysis, greater withdrawals observed in controls due to high disease activity).
Adalimumab with MTX (MTX 4-8mg/wk consistent with local practice in Japan), HOPEFUL (Takeuchi et al., 2014)	SJC≥8, TJC≥10, ESR ≥28mm/hr or CRP≥15mg/l.	<2 yrs/ MTX-naïve/LEF-naïve (excluded patients who had received >2 DMARDs)	RF+ or ≥1 x-ray erosion	Mean change in SHS at wk 26.	Mean change 2.3 vs. 4.3 (p<0.001) (mITT based on 232 of 234 patients randomised).

Adalimumab with MTX, HIT-HARD (adalimumab stopped at 24 wks) (Detert et al., 2013)	SJC≥6, TJC≥6, EMS≥30min, ESR ≥28mm/hr or CRP≥10mg/l.	<1 yr/ DMARD-naïve	-	DAS28 at wk 48.	Mean DAS28 (SD): 3.2 (1.4) vs. 3.4 (1.6). Difference between the groups 0.21 (95% CI -0.3 to 0.7, p=0.41).
Golimumab with MTX, GO-BEFORE (Emery et al., 2009)	SJC ≥4, TJC ≥4.	≥3 mths (no upper limit, mean 3.5 yrs vs. 2.9 yrs in controls)/ MTX-naïve	≥2 of: 1) ESR ≥28mm/hr or CRP≥15mg/l, 2) EMS≥30 min, 3) ≥1 erosion on x-ray or MRI, 4) RF+ or ACPA+.	ACR50 at 24 wks.	40% vs. 29% (p=0.038).
Certolizumab with MTX, C-EARLY (Emery et al., 2017)	SJC≥4 (of 28), TJC≥4 (of 28), DAS28>3.2, ESR ≥28mm/hr or CRP≥10mg/l.	≤1 yr/ DMARD-naïve	RF+ or ACPA+. Fulfilling 2010 ACR/EULAR RA criteria.	Sustained remission at 1 yr (DAS28<2.6 at wks 40 and 52).	29% vs. 15% (p<0.001) (mITT based on 868 of 879 patients randomised).
Certolizumab with MTX, C-OPERA (Atsumi et al., 2016)	DAS28≥3.2.	≤1 yr (persistent symptoms)/ MTX-naïve/ LEF-naïve	ACPA+ (≥3xULN) and either RF+ or radiographic erosions. Fulfilling 2010 RA criteria.	Mean change from baseline in SHS at 1 yr.	Mean (SD) change in SHS 0.4 (2.7) vs. 1.6 (4.9) (p<0.001) (mITT based on 315 of 319 patients randomised).

Rituximab every 24 wks with MTX, IMAGE (Tak et al., 2011)	SJC ≥8, TJC ≥8, CRP≥10mg/l.	≤4 yrs/ MTX-naïve	RF+ or ≥1 x-ray erosion.	Mean change in Genant-modified total Sharp Score at 52 wks.	Mean change in radiographic score 0.4 vs. 1.1 (p<0.001) (mITT based on 473 of 503 patients randomised).
Abatacept with MTX (Westhovens et al., 2009)	SJC ≥10, TJC≥12, CRP≥4.5mg/l.	≤2 yrs/ MTX-naïve	RF+ or ACPA+, and ≥1 x-ray erosion.	DAS28 remission at 1 year Mean change in Genant-modified total Sharp score from baseline at 1 yr.	Remission in 41% vs. 23% (p<0.001). Mean change in radiographic score 0.6 vs. 1.1 (p=0.04).
Tocilizumab with MTX and Tocilizumab monotherapy, FUNCTION (Burmester et al., 2016)	SJC≥4, TJC≥6, DAS28>3.2, ESR ≥28mm/hr or CRP≥10mg/l.	<1 yr/ MTX-naïve	RF+ or ACPA+ or ≥1 x-ray erosion. Fulfilling 1987 ACR or 2010 RA criteria.	Clinical remission (DAS28<2.6) at wk 24.	Remission in 45% (tocilizumab with MTX) vs. 39% (tocilizumab monotherapy) and 15% (MTX controls) (p<0.0001 for comparisons of either tocilizumab group vs. controls).
Tocilizumab with MTX and Tocilizumab monotherapy (addition of HCQ if DAS28≥2.6 or SJC[of 28]>4 with maximum MTX), U-Act-Early (Bijlsma et al., 2016)	DAS28≥2.6.	≤1yr/ DMARD-naïve	Fulfilling 1987 ACR or 2010 ACR/EULAR RA criteria.	Sustained clinical remission (DAS28<2·6 and SJC[of 28]≤4 for ≥24) on initial treatment regimen (duration varied according to treatment arm and response).	Sustained remission in 86% (tocilizumab with MTX) vs. 84% (tocilizumab monotherapy) and 44% (MTX controls) (p<0.0001 for comparisons of either tocilizumab group vs. controls).

*Time since diagnosis, unless otherwise stated, **Studies excluded patients receiving previous biologics, ***Statistical analyses based on all randomised patients receiving ≥1 dose of study medication, unless otherwise stated as modified-intention-to-treat (mITT) analysis.
MTX: methotrexate, ACR-N: mean American College of Rheumatology response, EMS: early morning stiffness duration, ERA: Early Rheumatoid Arthritis, COMET: combination of methotrexate and etanercept in early rheumatoid arthritis, ASPIRE: Active-controlled Study of Patients receiving Infliximab for the treatment of Rheumatoid arthritis of Early onset, PISA: Persistent Inflammatory Symmetrical Arthritis score (scoring 1 point for each of the following: RF-positivity, possession of the shared epitope (HLA–DR1/DR4/DR10), CRP>20 mg/L, female sex, Health Assessment Questionnaire raw score>4, or 2 points for HAQ raw score >11), NS: not significant, ACR20/50: American College of Rheumatology response criteria improvements of 20% or 50%, respectively, WIS: Work Instability Scale, LEF: leflunomide, HIT-HARD: High Induction Therapy with Anti-Rheumatic Drugs, GO-BEFORE: Golimumab Before Employing methotrexate as the First-line Option in the treatment of Rheumatoid arthritis of Early onset, C-OPERA: Certolizumab-Optimal Prevention of joint damage for Early RA, ULN: upper limit of normal, HCQ: hydroxychloroquine.

2. First-line biologic + combination DMARDs *versus* first-line combination DMARDs

The NEORACo study offered early aggressive treatment in the form of initial combination therapy of methotrexate, sulfasalazine, hydroxychloroquine, prednisolone and randomisation to either infliximab or placebo (Leirisalo-Repo et al., 2013). Intra-articular steroid was also administered to swollen joints. In the instance of inefficacy or intolerance to synthetic DMARDs, these were switched to alternatives. If ACR50 response was not achieved after six months (at two consecutive visits) patients were considered non-responders (in statistical analyses) and treatment was unrestricted to enable alternative biologic therapy (occurring in 3 of the 99 patients randomised). The primary end-point was remission at two years (SJC66=0, TJC68=0 and at least 3 of: early morning stiffness<15min, no fatigue, no joint pain and normal ESR). This was achieved in 66% of patients randomised to infliximab and 53% of patients randomised to placebo (p=0.2). However, the groups differed significantly in analyses of secondary outcomes, with infliximab offering superior rates of sustained remission and radiographic outcomes in comparison to placebo. Rates of sustained remission (at every visit between 6 and 24 months) were 26% and 10% (p=0.04), mean changes in total SHS from baseline to two years were 0.2 and 1.4 (p=0.006), and rates of absence of radiographic progression were 80% and 53% (p=0.006), respectively. With these intensive regimens nine serious adverse events occurred in seven (7%) patients. The rate of adverse events or serious adverse events was similar between the two treatment groups.

Step-up regimens: first-line DMARD regimens with step-up in therapy (including delayed biologic therapy) according to a disease activity target

3. First-line methotrexate monotherapy with escalation to delayed biologic *versus* first-line methotrexate monotherapy with escalation to combination DMARDs

The SWEFOT study demonstrated that, subsequent to failure of three months' initial treatment with methotrexate monotherapy (DAS28>3.2), single-step escalation to addition of infliximab (3mg/kg 8-weekly, increasing to 6-weekly in the instance of insufficient response) is superior to addition of sulfasalazine and hydroxychloroquine (van Vollenhoven et al., 2009b). The primary end-point was EULAR good response at one year in randomised patients (with reference to

disease activity at the point of randomisation). Of 487 patients enrolled, 145 (30%) achieved DAS28≤3.2 after three months of methotrexate, and 258 patients were randomised and included in the intention to treat analysis. A EULAR good response at one year was achieved in 50/128 (39%) patients receiving infliximab and 32/130 (25%) of patients receiving synthetic DMARDs (p=0.02). The open-label study design and lack of permissible treatment escalations (other than a moderate dose increase in sulfasalazine from 2g to 3g daily) in patients with a poor response to combination therapy, who in clinical practice may be eligible for biologic therapy according to NICE criteria, are significant limitations of this study. It demonstrates that a clinically significant proportion of patients may achieve good responses to methotrexate monotherapy and combination synthetic DMARD therapy. However, rates of remission (the treatment goal of today) have only been reported in the group of patients who continued on initial methotrexate monotherapy, and ongoing radiographic damage has been observed in these patients (Rezaei et al., 2012).

4. First-line methotrexate monotherapy with ongoing treatment-to-target (including escalation to delayed biologic) *versus* first-line combination DMARDs with ongoing treatment-to-target (including escalation to delayed biologic)

Results of a single-blind study, tREACH, are available (de Jong et al., 2014; Kuijper et al., 2016). Patients with either RA or UA (arthritis affecting at least one joint), with symptoms lasting for less than one year, were grouped according to their risk of persistent arthritis as defined by Visser et al. (Visser et al., 2002). Those at high risk of developing a persistent arthritis were randomised to either triple synthetic DMARD therapy (methotrexate, sulfasalazine and hydroxychloroquine) or methotrexate monotherapy, with both groups receiving initial corticosteroid bridging therapy; 95% and 98% of patients in these groups fulfilled 2010 RA criteria at baseline. Disease activity was assessed every three months, with escalation of treatment according to achievement of a target of DAS44 low disease activity, as follows: step-up to methotrexate plus etanercept, followed by switch of etanercept to adalimumab and subsequently abatacept, as required. In the instance of a patient achieving sustained DAS44 remission (at two consecutive visits), therapy was tapered. Over the course of the first year, superior disease control was observed in patients randomised to initial triple therapy; the primary outcome AUC for DAS44 was generally lower in these patients by an estimated difference of 2.4 (95% CI 0.0-4.8, p=0.0497). A trend was also observed in favour of initial triple

DMARD therapy in physical function over one year, as measured by the AUC for HAQ, with secondary analysis adjusting for baseline characteristics (RF, ACPA and baseline HAQ) demonstrating a significant difference between the groups. However, the superior suppression of disease activity observed with triple therapy did not appear to translate into superior radiographic outcomes. No statistically significant difference was detected between the groups in the proportion of patients with radiographic progression at one year: rates were 24% and 23% in patients randomised to triple DMARD and methotrexate monotherapy, respectively. As may be expected, a greater proportion of patients in the methotrexate monotherapy arm required biologic therapy over this year (43% in comparison to 26% in the comparator triple therapy DMARD arm, p=0.01) which may account for the similar radiographic outcomes. Aspects of this study to consider include the proportion of patients who were either demonstrating a degree of response to methotrexate monotherapy, and/or had favourable prognostic factors, prior to step-up to etanercept at three months (16 of the 36 patients with DAS44≥2.4), in whom escalation to triple DMARD therapy may have been considered a more appropriate treatment escalation. Likewise, the DAS44 low disease activity target after three months of biologic therapy may have necessitated switch in biologic in patients who were demonstrating a clinical response, which is not entirely reflective of clinical practice. Interestingly, a greater proportion of patients failed their first biologic in the methotrexate monotherapy arm (16%) in comparison to the triple DMARD therapy arm (6%, p=0.03).

Subsequent to the initial six month phase of open-label ‘COBRA’ versus ‘COBRA-light’ therapy (see above, section 2.4.1.2), in which methotrexate therapy was altered at three months according to a target of remission (DAS44<1.6), etanercept was added at six months (or nine months in patients responding at six months with subsequent disease flare) according to the same target (ter Wee et al., 2015). At one year, rates of remission (DAS44<1.6) were similar between the groups (38% versus 31%, respectively, p=0.2). Fewer patients receiving the ‘COBRA’ regimen than receiving the ‘COBRA-light’ regimen required the addition of etanercept per protocol (59% versus 75%, p=0.03). However, a significant number of the patients requiring etanercept per protocol (n=108) did not receive it (41 [38%] of these patients), and the proportion starting etanercept of those requiring it was less in the ‘COBRA’ group (p=0.04), implying a degree of uncertainty in the results.

5. First-line methotrexate monotherapy with escalation to delayed biologic *versus* first-line methotrexate monotherapy with escalation to combination DMARDs, followed by later escalation to biologic

The IMPROVED study investigated the efficacy of initial methotrexate in combination with prednisolone, followed by a treatment-to-target regimen in patients with early IA (Heimans et al., 2016). Inclusion criteria included either fulfilment of 2010 ACR/EULAR RA criteria with symptoms lasting for up to two years, or the presence at least one swollen joint and one other painful joint clinically suspected as due to early RA (the majority, approximately 80%, fulfilled 2010 RA criteria at baseline). Patients with DAS44≥1.6 after four months of methotrexate and tapering prednisolone were randomised (with single-blinding) to triple synthetic DMARD therapy or methotrexate plus adalimumab (40mg fortnightly). Treatment was escalated according to a target of DAS44 remission to methotrexate plus adalimumab 40mg fortnightly or methotrexate plus adalimumab 40mg weekly, respectively. A tapering regimen was employed for patients achieving remission.

Of 610 patients enrolled, 387 (63%) achieved DAS44 remission at four months and 161 patients were randomised according to protocol. Fewer patients randomised to combination synthetic DMARD therapy achieved the primary outcome, DAS44 remission at one year, in comparison to those randomised to adalimumab: rates were 21/83 (25%) versus 32/78 (41%), respectively ($p<0.05$). Limitations include the potentially, relatively short duration of adalimumab therapy; four months in patients randomised to triple synthetic DMARD therapy requiring treatment escalation at eight months, and patients randomised to adalimumab and tapering therapy at eight months due to the achievement of remission. In addition, the maximum dose of adalimumab is not currently approved for use in clinical practice, being associated with higher cost and dose-dependent side-effects such as infection. At two years (with treatment allocated according to the physician in non-responders to maximum-dose adalimumab), rates of DAS44 remission and drug-free DAS44 remission were similar between the groups: 27% versus 31% ($p=0.76$) and 7% and 9% ($p=0.73$), respectively (Heimans et al., 2016). No differences in radiographic outcomes were detected. However, the groups did appear to differ in the rate of achievement of more stringent remission criteria, with 2% versus 18% of patients, respectively, achieving 2011 ACR/EULAR Boolean remission at two years.

In all of these studies, it may be argued that the early window of opportunity, to gain the maximum benefits from biologic therapy in the patients with the most resistant disease, has been missed. Insight into whether this may be to the long-term detriment of such patients is provided by strategy trials comparing first-line use of biologic therapies with relevant comparator regimens, including treatment-to-target regimens and initial combination synthetic DMARD regimens (discussed below).

Step-up regimens: first-line biologic therapy versus first-line DMARD regimens with step-up in therapy according to a disease activity target

6. First-line biologic (+ methotrexate) *versus* first-line methotrexate monotherapy with escalation to delayed biologic

In OPTIMA, patients were randomised to initial adalimumab plus methotrexate or placebo plus methotrexate, with addition of adalimumab after six months in patients with DAS28CRP≥3.2 (Smolen, Josef S. et al., 2014). The study was designed with a combined primary end-point of DAS28CRP<3.2 and radiographic non-progression at 18 months in the group of patients who had achieved sustained DAS28CRP<3.2 at six months, and were, therefore, continuing their initial regimen of adalimumab and methotrexate or methotrexate monotherapy. Post-hoc analyses provided data demonstrating that similar clinical outcomes (rates of ACR response and remission) were observed six months after commencement of adalimumab in both patients receiving adalimumab from the outset and patients requiring addition of adalimumab due to persistent disease activity at six months.

In patients requiring escalation to adalimumab, the six month delay to treatment escalation may not be considered comparable to a tight-control treatment-to-target regimen by today's standards, in which additional corticosteroids and DMARDs may be considered. In addition, radiographic outcomes in this group may be expected to be inferior, as illustrated in analyses of the open-label extension study to the initial randomised, double-blind, controlled trial, HOPEFUL (see Table 13) (Takeuchi et al., 2014). After completing the initial six month phase of this trial, all patients were eligible to receive open-label adalimumab and methotrexate (Yamanaka et al., 2014). Although clinical disease activity (DAS28) amongst patients initially randomised to adalimumab and placebo groups appeared to converge after approximately eight weeks of open-label adalimumab, and remission outcomes at one year were similar between the groups, radiographic progression was greatest

amongst patients receiving initial methotrexate and placebo (mean change in SHS from baseline was 3.3 versus 2.6, p<0.001).

7. First-line biologic (+ methotrexate) with ongoing treatment-to-target including switch to alternative biologic *versus* first-line methotrexate monotherapy with ongoing treatment-to-target including delayed biologic

In an open-label study, GUEPARD, patients were randomised to initial adalimumab plus methotrexate or methotrexate monotherapy with the following treatment adjustments every three months: if DAS28≥3.2 adalimumab added (or dose increased in patients already receiving adalimumab); if DAS28≥3.2 despite increased dose of adalimumab switched to etanercept and subsequently to leflunomide. Cessation of adalimumab was indicated in the instance of DAS28<3.2 after at least three months of adalimumab treatment. Despite a superior rate of early remission (DAS28<2.6 at 12 weeks) in patients receiving initial adalimumab versus initial methotrexate monotherapy (36% vs 13%, p=0.02), there was a trend towards an inferior rate of remission at one year (39% vs 59%, p=0.2). In part, this may be explained by administration of an insufficient duration of adalimumab therapy in patients demonstrating a good response early.

The U-Act-Early study offers further insight, with randomisation of patients to initial regimens of tocilizumab plus methotrexate, tocilizumab monotherapy and methotrexate monotherapy, all with or without later addition of hydroxychloroquine in patients not achieving remission (DAS28<2.6 and SJC[of 28]≤4) (Bijlsma et al., 2016). Three months after the addition of hydroxychloroquine, patients who were not achieving remission switched to tocilizumab plus methotrexate, or tocilizumab was switched to a TNF-inhibitor in patients already receiving combination therapy. Primary outcomes were rates of sustained remission (DAS28<2.6 and SJC[of 28]≤4 for 24 weeks) achieved with the initial treatment regimens (see Table 13) and over the entire two year study. Over two years, initial tocilizumab appeared superior to initial methotrexate monotherapy, with 86%, 88% and 77% of patients achieving sustained remission in the respective treatment groups (p=0.06 for initial combination therapy versus methotrexate alone, and p=0.04 for initial tocilizumab monotherapy versus methotrexate alone). Therapy was tapered and stopped in patients achieving sustained remission. Sustained drug-free remission was observed in 35%, 27% and 11% of patients, respectively (p<0.001 for initial

combination therapy versus methotrexate alone, and p=0.003 for initial tocilizumab monotherapy versus methotrexate alone). No significant differences were detected in the secondary outcomes of clinical response and physical function at two years; however, radiographic progression was significantly lowest in patients receiving initial tocilizumab. A major strength of this study was the double-blinding of tocilizumab and methotrexate. Drawbacks include the relatively slow escalation of methotrexate (commenced at 10mg weekly and slowly increased to 30mg over 20 weeks if remission was not achieved), followed by addition of a relatively mild DMARD, hydroxychloroquine, and a lag-time of three months to assess its effect prior to further escalation. The methotrexate monotherapy arm may therefore be considered sub-standard relative to current daily practice.

The OPERA and IDEA studies are two further double-blind randomised trials which included what may be considered as more intensive treatment regimens, with protocolled administration of steroid as well as escalation of DMARD therapy according to disease activity targets. The OPERA study compared initial adalimumab plus methotrexate to placebo plus methotrexate, with concomitant intra-articular triamcinolone (in up to four swollen joints, up to a maximum total dose of 160mg; up to fortnightly for the first three months, then monthly) (Hørslev-Petersen et al., 2014). Sulfasalazine and hydroxychloroquine were added in both groups in patients with DAS28CRP≥3.2 and at least one swollen joint at three months, or in patients requiring at least 160mg intra-articular triamcinolone monthly for three consecutive months up to six months. At or after six months, patients with DAS28CRP≥3.2 were treated as non-responders and could receive open-label biologic therapy. There was no significant difference in the primary end-point, DAS28CRP<3.2 at 12 months, although patients receiving initial adalimumab were significantly more likely to achieve DAS28 remission (achieved in 74% versus 49% of patients receiving initial methotrexate monotherapy, p<0.001) and demonstrated greater improvements in physical function and quality of life measures.

In IDEA patients were randomised to receive either methotrexate plus infliximab or methotrexate plus one dose of 250mg intravenous methylprednisolone followed by placebo infusions (Nam et al., 2014a). Patients in both arms were treated with a total of 120mg methylprednisolone (intramuscularly and/or intra-articular) according to a target of DAS44<2.4, initially every six-eight weeks for the first six months, then

three-monthly. After six months, treatment was unblinded and therapy was escalated according to the same treatment target and a protocolled regimen including increased infliximab dose in patients already receiving this or addition of sulfasalazine and hydroxychloroquine followed by switch to methotrexate and leflunomide in patients receiving initial methotrexate with intravenous methylprednisolone. During the unblinded phase, biologic therapies were permitted according to NICE criteria. Although the rate of early remission (at week six) was superior with initial infliximab therapy, no significant differences were apparent between the treatment groups at one year in either the mean change in SHS (the primary end-point) or rate of DAS44 remission. In a sub-group of patients undergoing ultrasound examination of 22 joints (bilateral wrists, MCPs2-3, PIPs2-3 and MTPs1-5) at week 50, evidence of ongoing synovitis (GS≥grade 2 and PD≥grade 1 in at least one joint) was apparent in a lower proportion of patients receiving infliximab plus methotrexate first-line versus methylprednisolone plus methotrexate (41% versus 79%, p=0.001).

8. Studies with multiple treatment arms

The randomised, double-blind trial, TEAR, compared four treatment regimens in methotrexate-naïve patients (Moreland et al., 2012). Two groups received initial methotrexate monotherapy with a planned step-up in treatment at six months if DAS28ESR≥3.2; to triple synthetic DMARD therapy in one group (‘ST’), and methotrexate and etanercept in the other (‘SE’). The remaining two groups received first-line combination therapy; either initial triple synthetic DMARD therapy (‘IT’) or initial etanercept and methotrexate therapy (‘IE’) without any step-up in their treatment. No significant differences were observed across all four groups for the various outcomes; mean DAS28 score between years one and two, levels of ACR response at year two and radiographic progression between baseline and year two. However, there was an indication that initial etanercept and methotrexate, followed by initial methotrexate with step-up to etanercept if required, may be slightly favourable to other treatment regimens. No radiographic progression (change in SHS score≤0.5) was observed in 79%, 71%, 68% and 65% patients across the groups IE, SE, ST and IT, respectively (p=0.33 across all groups, p=0.02 for IE and SE groups combined versus ST and IT groups combined). A similar trend was observed in ACR70 response rate at two years; 18% of patients in IE and SE groups combined, versus 11% of patients in the ST and IT groups combined, achieved this superior level of clinical response (p=0.01). Limitations include the

six-month interval between commencing therapy and escalation of therapy in the relevant step-up treatment groups, as well as the analysis which did not assess differences between individual treatment groups of interest; i.e. between the step-up groups, or between initial etanercept and initial combination synthetic DMARD therapy.

The BeSt study, a randomised, single-blind trial, compared four treatment strategies in early RA: sequential DMARD monotherapy; initial methotrexate with step-up to combination DMARD therapy; initial combination synthetic DMARD therapy (methotrexate and sulfasalazine) with high dose corticosteroid; and initial infliximab and methotrexate (Goekoop-Ruiterman et al., 2007). In all groups, treatment was switched every three months in the instance of DAS44≥2.4 according to a protocol which varied across the groups. More rapid clinical improvement was achieved in patients randomised to initial combination of synthetic DMARDs or infliximab with methotrexate, with less progression of joint damage seen on radiographs. Of note, the protocol for patients randomised to initial methotrexate with step-up to combination DMARD therapy, was relatively unaggressive in comparison to more recent trials: escalation steps, occurring as frequently as every three months if required according to disease activity, were addition of sulfasalazine, addition of hydroxychloroquine, then addition of prednisolone and only later switching to methotrexate and infliximab if the combination of these four medications failed. Switch to biologic therapy, if required, therefore occurred significantly later in these patients in comparison to patients randomised to the initial combination DMARD therapy arm (switching to methotrexate and ciclosporin with prednisolone, followed by switching to methotrexate and infliximab). Of note, after failure of infliximab (3mg/kg every eight weeks) and methotrexate to achieve DAS44<2.4 after three months, infliximab dose was increased (in steps up to a maximum of 10mg/kg every eight weeks) followed by switching to alternative synthetic DMARDs (i.e. no alternative biologic therapies were permitted within the protocol) which is not entirely reflective of current clinical practice. In cases where disease remained effectively suppressed, drug therapies (preferentially corticosteroids and infliximab in the first instance) were tapered and withdrawn. This was most successful in the group initially treated with infliximab: 53% of patients were on just one drug for disease control at the end of the two-year study (compared to 31-36% in other groups).

2.4.1.4 Treatment Strategies: Summary

Presently, European and American guidelines recommend the use of DMARD monotherapy (with a preference for methotrexate) as first-line therapy, with consideration for concomitant glucocorticoids in the short-term (Singh et al., 2016; Smolen et al., 2017). Biologic therapies are recommended (preferably in combination with methotrexate) if a pre-defined target for treatment is not achieved with either the first-line DMARD regimen (in patients with poor prognostic factors) or after failure of additional synthetic DMARDs (preferably used in combination with methotrexate) (Singh et al., 2016; Smolen et al., 2017). The American (ACR) recommendations are a recent update from their previous guidance suggesting a TNF-inhibitor combined with methotrexate could be used first-line as an alternative to synthetic DMARD therapy in patients with poor prognostic factors (Singh et al., 2012).

Indeed, there is an argument for the early introduction of biologic therapy, particularly in patients with poor prognostic factors, owing to the therapeutic window of opportunity in early disease and the superior efficacy of biologics in comparison to methotrexate therapy (St Clair et al., 2004; Breedveld et al., 2006; Emery et al., 2008; Emery et al., 2009) (Table 13). However, evidence for early initiation of biologic therapy versus combination synthetic DMARD therapy, or an aggressive step-up treatment-to-target regimen, is less conclusive. Several studies report similar clinical outcomes at one or two years between these treatment groups (Goekoop-Ruiterman et al., 2007; Moreland et al., 2012; Leirisalo-Repo et al., 2013), although results for their secondary outcomes and the long-term follow-up of these patients have often indicated certain advantages to using biologic therapies either first-line or very early within a treatment-to-target regimen. Superior disease control in the early stages of the disease may afford greater protection against joint damage (Moreland et al., 2012; Leirisalo-Repo et al., 2013; Bijlsma et al., 2016) and physical disability (Hørslev-Petersen et al., 2014), a greater reduction in subclinical synovitis (Nam et al., 2014a) and improved rates of sustained remission (Leirisalo-Repo et al., 2013) and biologic- or DMARD-free remission (Quinn, M. A. et al., 2005; Goekoop-Ruiterman et al., 2007; Bejarano et al., 2010; Saleem et al., 2010; Bijlsma et al., 2016).

Hence, it is perceivable that early, short-term use of biologics may be cost-effective, potentially offsetting the need for long-term treatment with several, sequential biologic therapies in the most resistant patients (de Jong et al., 2014). This remains controversial and further studies are ongoing (Dumitru et al., 2016).

2.4.1.5 Defining the Target for Treatment

The EULAR guidelines recommend remission as the target for treatment (Smolen et al., 2010; Smolen et al., 2016). Clinical remission (by various definitions) is associated with improved cardiovascular disease risk markers (Provan et al., 2011) and long-term outcomes, in comparison to even low disease activity, across several studies (Radner et al., 2010; van Tuyl et al., 2010). Guidelines define remission as the 'absence of signs and symptoms of significant inflammatory disease activity'. They advise the use of composite measures, incorporating clinical assessments of swelling and tenderness, to monitor disease activity (Smolen et al., 2010; Smolen et al., 2016; Smolen et al., 2017).

Many validated measures are available for this purpose. Since the publication of the original disease activity score, DAS44 (van der Heijde et al., 1990), alternative measures have been developed which are easier to incorporate into clinical practice. The modified disease activity score, DAS28, has been validated in the assessment of disease activity in RA for use in clinical trials (Prevoo et al., 1993; Smolen et al., 1995), and can be used reliably by assessors with varying levels of experience in clinical practice (Walsh et al., 2008). The simplified disease activity index (SDAI) is even easier to calculate by adding variables (SJC28, TJC28, CRP, physician global and patient global visual analogue scale [VAS] assessments) rather than using the more complicated DAS formulae (Smolen et al., 2003). The SDAI correlates with DAS28 as well as patients' physical function (HAQ score) (Smolen et al., 2003; Aletaha et al., 2005).

There are pitfalls in the use of composite scores of which clinicians should be aware of. Clinical assessments included in simplified scores, such as DAS28 and SDAI, do not include the feet, although disease activity at this site is represented to an extent within the included global assessments (for example, patient general health VAS) (Landewé et al., 2006). The DAS28, in particular, has been criticised

as high TJC and small changes in ESR at low levels (<20mm/hr) may disproportionately affect the score (Gardiner et al., 2005). Such a composite index has limitations in accurately reflecting synovitis; in particular, the complex interrelationship between an individual's pain perception on subjective components including TJC and patient VAS is well-recognised (Ton et al., 2012; Cordingley et al., 2014). The presence of comorbidities may also exaggerate disease activity by affecting the patient general health assessment, although the patient global disease activity assessment may be used an alternative, within the DAS score (www.das-score.nl, 2011). In early disease especially, disease activity may also be underestimated due to the insensitivity of the clinical assessment or the lack of elevation in inflammatory markers in peripheral blood, despite true joint synovitis. Furthermore, the cut-off for DAS28 remission (DAS28<2.6) allows for the presence of clinically significant joint swelling (Mäkinen et al., 2005).

With multiple measures of disease activity available, to facilitate the comparison of results across clinical studies, a provisional ACR/EULAR definition of remission for use in clinical trials was recently published (Felson et al., 2011) and has since been validated using observational study data in patients with early RA (Zhang et al., 2012). In development of the criteria (Felson et al., 2011), and their validation using data from the ESPOIR cohort (Zhang et al., 2012), it was apparent that that SDAI and CDAI remission performed better than DAS28 remission in predicting a good outcome (stable state in radiographic joint damage and HAQ score). The use of either of two stringent definitions for remission in clinical trials was proposed, SDAI remission or a definition developed using a Boolean-approach: a score of one or less in TJC, SJC (out of 28 joints assessed by DAS28 plus feet and ankles), patient global VAS (0-10 cm) and CRP (mg/dL).

However, in unselected patients in clinical practice, these measures may be too stringent for their universal application. In an observational study, patients with established RA achieving SDAI and Boolean remission actually demonstrated significantly superior physical functioning in comparison to controls who were age- and gender-matched (Thiele et al., 2013). Additionally, these patients were less likely to have comorbidities, including degenerative joint disease, than those achieving DAS28 remission but missing SDAI or Boolean remission. In cross-sectional analyses of two large observational RA cohorts, 2011 ACR/EULAR

remission was observed in up to 10% of patients, however, long-term remission was rare (Shahouri et al., 2011). The patient global VAS was found to be the best predictor of fulfilment of both SDAI and Boolean remission, and variability in this assessment was identified as a major reason for non-remission in patients previously fulfilling the criteria, possibly related to the poor reliability of this measure (Lassere et al., 2001). Furthermore, heterogeneity was observed amongst physician assessments, particularly the SJC and physician global VAS.

Limitations in the universal application of remission criteria are acknowledged within the clinical guidelines, accepting the importance of physician judgement of remission in reaching decisions on future treatment, and acceptability of a target of low disease activity in specific patients, such as those with established disease. In essence, all of these measures rely on clinical assessments that may not be entirely accurate in delineating the true absence of inflammatory disease activity.

The inability of clinical criteria to accurately reflect a true absence of inflammatory disease activity is illustrated by studies demonstrating progression of radiographic damage in patients achieving persistent remission by these standards (Molenaar et al., 2004). Ultrasound imaging is also able to identify subclinical synovitis in patients achieving clinical remission, which has been shown to have prognostic implications (section 2.3.2.1). Several groups have reported the frequency of ongoing PD in patients with established RA across various definitions of remission including DAS28 (Brown et al., 2006; Saleem et al., 2009; Balsa et al., 2010; Saleem et al., 2011; Montecucco et al., 2012; Naredo et al., 2013b; Geng et al., 2014; Harman et al., 2014; Iwamoto et al., 2014; Zufferey et al., 2014; Naredo et al., 2015; Vlad et al., 2015; Bellis et al., 2016; Vreju et al., 2016; Raffeiner et al., 2017), DAS44 (Peluso et al., 2011; Foltz et al., 2012) and 2011 ACR/EULAR Boolean-defined remission (Saleem et al., 2011; Geng et al., 2014; Harman et al., 2014; Zufferey et al., 2014; Vlad et al., 2015; Bellis et al., 2016). These studies have included ultrasound assessments limited to the hands (Brown et al., 2006; Ozgocmen et al., 2008; Saleem et al., 2009; Peluso et al., 2011; Saleem et al., 2011; Montecucco et al., 2012; Gärtner et al., 2013; Geng et al., 2014; Harman et al., 2014; Vlad et al., 2015; Bellis et al., 2016; Vreju et al., 2016) or have involved more extensive joint assessments (Balsa et al., 2010; Foltz et al., 2012; Naredo et al., 2013b; Iwamoto et al., 2014; Zufferey et al., 2014; Naredo et al., 2015; Raffeiner et al., 2017).

Cross-sectional analysis of patients with RA achieving a stringent definition of remission (SDAI≤3.3 and absence of swollen and tender joints of 66- and 68-joint examinations respectively) has confirmed the existence of subclinical PD in the absence of any physical evidence of synovitis (Kawashiri et al., 2014a). The presence of PD≥grade 1 or ≥grade 2 in any wrist, MCP or PIP joint was detected in 17/29 (59%) and 9/29 (31%) patients, respectively.

Evidence for the persistence of ultrasound synovitis in patients achieving clinical remission in early disease is more limited. In patients with early RA (fulfilling 1987 ACR RA criteria at one year after starting treatment), responding to methotrexate, the rates of achievement of absence of PD were 50/72 (69%), 43/56 (77%), 25/28 (89%) and 21/22 (95%), for patients achieving DAS44, DAS28, SDAI and Boolean remission, respectively (Sakellariou, Garifallia et al., 2013). The exclusion of patients with more severe or resistant disease, who had required addition of a TNF-inhibitor in the first year of treatment, and the restricted ultrasound assessment (MCPs and wrists) were limitations of this study. A further analysis, using a 44-joint ultrasound assessment in this cohort, demonstrated absence of PD in only 41% of 43 patients achieving sustained DAS44 remission (DAS44<1.6 at two visits three months apart) (Scirè et al., 2009). A similar level of disparity between sustained DAS44 remission (DAS44<1.6 for 6 months) and absence of PD on ultrasound was observed in another cohort (Peluso et al., 2011). Power Doppler activity in any of 10 joints (wrists, MCPs2-3 and PIPs2-3, bilaterally) was observed in 42% of 48 early RA patients. In addition, PD was observed in 14% of 27 patients achieving the stringent 1981 ACR remission criteria (Pinals et al., 1981).

Data are now beginning to emerge with respect to targeting ultrasound evidence of synovitis in the treatment of RA. Data from a randomised trial are available in patients with early IA (either RA or UA with ACPA-positivity and at least three swollen joints, i.e. the majority of patients were likely to have fulfilled 2010 RA criteria) (Dale et al., 2016). Patients were randomised to two groups, differing in the treatment target used to guide their treatment escalations (occurring at a maximum frequency of every three months); either DAS28 low disease activity (n=58) or a total PD joint count≤1 (PD of any grade affecting ≤1of 14 joints [wrists, MCPs2-3, PIPs2-3, MTP2 and MTP5 joints]) with ultrasound conducted in the presence of

DAS28<3.2 or SJC≤1 swollen joints (treatment escalated on clinical grounds if DAS28>5.1 or DAS28≥3.2 with SJC≥2) (n=53). Treatment was methotrexate monotherapy, escalating to triple synthetic DMARD therapy, followed by triple DMARD therapy with etanercept (occurring at nine months or later). No significant differences were observed in the co-primary endpoints in patients completing the 18-month study (101 of 111 patients randomised), including mean change from baseline in DAS44 and progression in MRI erosive damage in the dominant hand. However, a significantly higher rate of DAS44 remission was observed in patients managed with ultrasound (66%, versus 43% in patients managed clinically, p=0.03). In the ultrasound arm, of 271 visits at which patients were achieving DAS28 remission, PD was demonstrated in more than one joint at 66 (24%) visits.

The ARCTIC study had a similar design, randomising patients with early RA (fulfilling 2010 RA criteria, with symptoms of joint swelling for up to two years) to clinically-directed and ultrasound-targeted treatment groups (Haavardsholm et al., 2016). The ultrasound assessments were more extensive, comprising assessments of GS and PD (graded 0-3) at 32 joints. Treatment was escalated up to every two months, unless response since the last treatment change was observed or the treatment target was reached. In the ultrasound-targeted group response was defined by improvement in DAS44≥1.2, reduction in total ultrasound score (sum of GS and PD scores)≥20% and current DAS44>2.4, or improvement in DAS44≥0.6, reduction in total ultrasound score (sum of GS and PD scores)≥10% and current DAS44≤2.4. The target was DAS44 remission (DAS44<1.6) with no swollen joints and no PD detectable in any joint. In the clinically-directed treatment group, the same definitions were used, except with exclusion of the ultrasound components. Swollen joints, and joints with PD in the ultrasound-targeted arm, were also injected with corticosteroid. Other differences from the TASER study included potentially earlier addition of a TNF-inhibitor (protocolled as early as four months in patients with high disease activity and poor prognostic factors), the protocolled increase in dose/frequency of TNF-inhibitor and later switch to alternative biologics in non-responders. No significant difference was observed between the groups in the primary outcome, sustained remission (DAS44<1.6, no swollen joints and no radiographic progression between 16 and 24 months). However, there was a trend towards less radiographic progression over two years in patients receiving ultrasound-targeted treatment (median [IQR] change in SHS from baseline 1.0 [0-2.5], versus 1.5 [0.5-3.0] in patients receiving clinically-directed care alone,

p=0.05). As may be expected, significantly less PD was also observed in these patients, with potential implications for longer-term outcomes: 75% of patients in the ultrasound-targeted arm demonstrated ultrasound remission (total PD score=0), versus 62% of patients in the clinically-directed treatment arm (p=0.02).

Other limitations of these studies include the incomplete blinding of ultrasound assessments, inclusion of DAS44 in combined primary endpoints (which was also used either directly or related to measures used [DAS28 in TASER study] in directing treatment decisions), and the potential rate of protocol deviations (reported as 19% in ARCTIC and not reported in TASER) (D'Agostino et al., 2017). The limitations of current therapies to achieve a complete and universal absence of inflammatory activity must also be borne in mind. The indications for when treatment should be escalated in view of combined clinical and ultrasound targets were also arguably quite complicated, in comparison to clinical practice in which an ultrasound may be conducted when the clinician perceives a difference between their impression and DAS.

The TURA (Targeted Ultrasound in RA) and REVECHO studies are currently recruiting patients with RA in stable low disease activity or remission states. They aim to evaluate the effect of treating subclinical ultrasound-detected synovitis (in addition to clinical signs of active disease), in comparison to targeting clinical evidence of disease activity alone on patient outcomes such as loss of remission and radiographic progression (Bruyn et al., 2015).

Issues of face validity of the clinical composite measures as indicators of remission, which have previously been raised in established RA, therefore appear to be pertinent to early RA and the currently recommended treatment strategy of targeting clinical remission. Due to the limitations of studies in early RA identified here, further data are needed to evaluate the potential use of the 2011 ACR/EULAR remission criteria and ultrasound assessments within the treatment-to-target management of patients with RA in clinical practice.

2.4.2 Undifferentiated Arthritis

Patients with UA may also require treatment to alleviate the symptoms and functional impairment associated with active synovitis. The impact of UA on patient function (Jansen et al., 2002; Krabben et al., 2012), work impairment (Marzo-Ortega et al., 2007) and unemployment due to the illness (Marcos et al., 2011) has previously been shown to be comparable to that of RA in longitudinal (Jansen et al., 2002; Krabben et al., 2012) and cross-sectional studies (Marzo-Ortega et al., 2007; Marcos et al., 2011). Furthermore, loss of bone mineral density (Haugeberg et al., 2006) and radiographic progression (van Aken et al., 2006) have been demonstrated in patients with early UA. Albeit acknowledging these studies largely defined UA as non-fulfilment of the 1987 ACR criteria.

Extending the RA treatment paradigm, highlighting the systemic as well as local joint-related consequences of the inadequate control of inflammation (including cardiovascular morbidity), adds further justification to intervening in UA. Based largely on expert opinion and RA studies, EULAR guidelines for the treatment of early IA recommend that if a definitive diagnosis cannot be reached, DMARD therapy (ideally methotrexate) should be initiated as early as possible in patients at risk of persistent arthritis (Combe et al., 2007; Combe et al., 2017).

2.4.2.1 Longitudinal Observational Studies

Over the last 20 years, treatment of patients with UA has varied within and between observational early IA cohorts, with practices evolving considerably over this time. Bias introduced through the non-random assignment of treatment (confounding by indication) is inherent within these studies, although statistical modelling can help to minimise this. Propensity modelling takes account of a single treatment decision/pathway per patient (Bukhari et al., 2003; Lukas et al., 2011; Escalas et al., 2012), whilst marginal structural modelling may be used to weight results according to the probability of receiving various treatments over time (Farragher et al., 2010).

Efficacy of early methotrexate was recently assessed in the ESPOIR cohort which included a proportion of patients with UA (77% of patients fulfilled 2010 RA criteria at baseline) (Gaujoux-Viala et al., 2012). Patients receiving at least three months of

methotrexate within the first six months (n=313) were compared to those receiving any other treatments within the same time frame (including less than three months of methotrexate, but excluding patients receiving sulfasalazine, leflunomide or TNF inhibitors due to their known efficacy in preventing structural damage) (n=384). After adjustment for propensity score, there was no significant difference between the groups in DAS28 or HAQ at six months, but significantly less radiological progression at one year was observed amongst patients receiving methotrexate. However, 29% of patients had stopped methotrexate prior to one year, 10% of patients initially commenced methotrexate in combination with other DMARDs and the proportion of patients escalating treatment to combination therapy over follow-up was not reported.

Efficacy of immediate versus delayed treatment has been addressed in analyses of patients followed in the ESPOIR and NOAR cohorts. In ESPOIR, after adjustment for propensity score (based on the probability of receiving treatment over the initial six months), statistically less radiographic progression over 12 months was observed in patients who received DMARDs (excluding hydroxychloroquine alone) within three months of diagnosis compared to those who did not (Lukas et al., 2011). Sub-analysing patients grouped according to propensity score quintile revealed a significant superiority of early treatment only amongst patients in the 4^{th} and 5^{th} quintiles. Therefore, this study does not fully answer the question as to whether it may be acceptable to delay DMARD therapy in a subset of patients with UA, likely lying in the lower quintiles. In NOAR, delay to DMARD and/or steroid treatment from symptom onset appeared to adversely affect long-term radiographic outcomes (Bukhari et al., 2003). In comparison to patients never treated, progression in Larsen score over five years was 1.1 times (95% CI 0.8-1.7) greater in patients commencing DMARDs and/or steroids within six months, compared to 1.6 times (95% CI 1.0-2.6) and 1.5 times (95% CI 1.0-2.2) for patients first treated between six and 12 months and after 12 months, respectively. In these studies, the influence of treatment changes over time was not accounted for which could have been considerable considering the time-points of the outcome assessments.

Using marginal structural modelling, NOAR data suggests that ACPA-negative patients may benefit more than ACPA-positive patients from early treatment (Farragher et al., 2010). The mean difference in change in HAQ at five years

between patients treated with DMARDs and/or steroids within six months of symptom onset and those never treated was calculated for each group: -0.31 (95% CI -0.53 to -0.09) for ACPA-negative patients versus -0.14 (95% CI -0.52 to 0.24) for ACPA-positive patients. However, numbers in some groups were small (only 22 ACPA-positive patients were never treated) and confidence intervals were overlapping. Treatment profiles in this cohort (initial sulfasalazine in 57% and methotrexate in only 5%) and the higher incidence of self-limiting disease amongst seronegative patients must also be borne in mind.

A multivariable model, with adjustment for propensity score and confounders for prognosis, was employed in ESPOIR to determine efficacy of initial methotrexate and a treatment-to-target strategy (Combe et al., 2007; Escalas et al., 2012). Patients in whom treatment deviated from this strategy (77% of patients) were at increased risk of developing at least one new radiographic erosion at one year (OR 2.0, 95% CI 1.1-3.6), and functional impairment (HAQ≥1.0) at two years (OR 2.4, 95% CI 1.2-4.7). Of note, propensity score by quintile was associated with disability ($p<0.0001$) but not with radiographic progression ($p=0.75$).

2.4.2.2 Pragmatic, Open-label and Single-blind Studies

A selection of prospective cohort studies have utilised protocols to maintain treatment homogeneity (see Tables 3-5). In cohorts excluding patients with RA (fulfilling 1987 ACR criteria), or restricting patients to those less likely to fulfil RA criteria (such as oligoarthritis), NSAIDs and/or steroids have been assessed prior to addition of DMARDs (Green et al., 1999; Green et al., 2001; Quinn et al., 2003; El Miedany et al., 2008). In others, initial methotrexate (Kudo-Tanaka et al., 2015) and treatment-to-target strategies (Heimans et al., 2016) have been employed.

Methotrexate versus no DMARD therapy has been evaluated (NSAIDs and corticosteroids ≤10mg prednisolone daily were permitted in both groups) (Kudo-Tanaka et al., 2015). Patients with ACPA-positive UA (not fulfilling 1987 ACR RA criteria) were assigned to treatment group according to the treating physician's judgement. The proportion of patients fulfilling 2010 RA criteria was not reported. The rate of progression to fulfilment of 1987 ACR RA criteria over one year was significantly lower in the methotrexate group (17% of 29 patients) than in patients

never receiving DMARDs (79% of 19 patients); the HR, adjusted for potential confounders, including fulfilment of the 2010 RA criteria, was 0.03 (95% CI 0.003-0.25, p=0.001).

In the IMPROVED study, patients with early RA (fulfilling 2010 RA criteria, results discussed previously in section 2.4.1.3) and UA (at least one swollen joint and one other painful joint, clinically suspected as due to early RA) were treated with four months of methotrexate and tapering prednisolone followed by a treatment-to-target strategy including the addition to adalimumab if required (Heimans et al., 2016). In patients with UA at baseline, the primary outcomes of DAS44 remission and drug-free remission at two years were achieved in 64/122 (52%) and 41/122 (34%) patients, respectively. Patients with RA achieved a similar rate of DAS44 remission (p=0.25), but lower rate of drug-free remission (19%, p<0.001). In addition, post-hoc analysis did not demonstrate any statistical difference in the rate of early remission (DAS44<1.6) after four months of treatment with methotrexate and prednisolone (Wevers-de Boer, K. V. C. et al., 2012).

The single-blinded STREAM study, compared conventional care to initial methotrexate with addition of adalimumab according to a target of DAS44<1.6 (van Eijk et al., 2012). Patients were required to have between two and five swollen joints and a SHS score less than five (one-third and two-thirds of patients fulfilled 1987 and 2010 RA criteria respectively at baseline). Less progression of radiographic damage was demonstrated in patients in the treat-to-target arm although this was not statistically significant. Of relevance was the significantly greater steroid exposure in patients receiving conventional treatment.

An open-label study of abatacept has been conducted in twenty patients with early IA (symptomatic synovitis of at least two joints and PD in at least one wrist/MCP2-5/PIP2-5/knee, with a maximum symptom duration of 18 months) (Buch et al., 2017). All but one patient was ACPA-negative, and less than half of patients (n=9) fulfilled 2010 RA criteria, at baseline. Only 2/20 patients achieved the primary outcome: DAS44 remission at six months, a maximum of one swollen joint for at least three consecutive months and no radiographic progression over one year. However, reductions in disease activity were reported: mean (SD) DAS44 reduced from 2.66 (0.77) at baseline to 1.78 (0.95) at one year, and median (IQR) PD score

(sum of PD graded 0-3 at 20 joints) reduced from 10 (4-23) at baseline to 3 (0-5) at one year. Of note, two patients required additional DMARD therapy (permitted at the discretion of the physician in patients with persistent arthritis).

2.4.2.3 Randomised Double-blind Placebo-Controlled Trials

Trials in early IA patients with limited joint involvement, have demonstrated steroid may have a short-term effect on disease activity (Machold et al., 2010) and delay the need for DMARD therapy (Verstappen et al., 2010), but not greatly alter the long-term course of the disease. The double-blind PROMPT study demonstrated short-term methotrexate may also delay but not prevent the development of RA (defined by 1987 ACR criteria) in patients fulfilling the ACR 1958 criteria for probable RA at baseline (van Dongen et al., 2007). Escalation of methotrexate was relatively slow (15mg weekly, increasing in 5mg intervals to 25mg every three months if DAS44>2.4).

Trials of biologics have been conducted in patients with early IA with poor prognostic factors. Eligibility criteria and baseline characteristics in these studies indicate a proportion of subjects would fulfil 2010 ACR/EULAR RA criteria, but a diagnosis of RA was not required for inclusion. For example, in ADJUST, 50% of patients had erosions at baseline. A trial of infliximab was terminated early due to poor outcome in all patients (only 2/10 infliximab- and 1/7 placebo-treated patients achieved remission at week 26) (Saleem et al., 2008). In the ADJUST trial, ACPA-positive patients meeting between one and three of the 1987 ACR RA criteria, with synovitis of at least two joints, were randomised to receive abatacept or placebo for six months (Emery, P et al., 2010). The primary end-point, fulfilment of 1987 ACR criteria after one year (six months after abatacept discontinuation) occurred in fewer patients receiving abatacept (46% versus 67% of controls), but this difference was not statistically significant. The AVERT study randomised patients with at least two synovitic joints, DAS28≥3.2 and ACPA-positivity to abatacept plus methotrexate or methotrexate alone (Emery et al., 2015). The primary end-point, DAS28 remission at one year, was achieved in 61% of 115 patients receiving abatacept and methotrexate versus 45% of 115 patients receiving methotrexate alone (p=0.01). Amongst patients achieving DAS28<3.2 at one year, in whom all treatment was withdrawn, 18/73 (25%) versus 9/53 (17%) of patients, respectively, remained in drug-free remission after a further six months. In

EMPIRE, inclusion criteria were presence of at least one swollen and one tender joint and either RF, ACPA or shared epitope positivity (Nam et al., 2014b). No significant difference was observed in the primary endpoint, the absence of swollen and tender joints at one year, in patients randomised to etanercept plus methotrexate or methotrexate alone, although DAS28 remission was achieved earlier in patients receiving etanercept. With the exception of AVERT and EMPIRE, biologics were used without methotrexate.

2.4.2.4 Response to Methotrexate in Patients with Seropositive versus Seronegative IA

Subgroup analyses of a number of these studies suggest a possible differential response to methotrexate according to serological status. In IMPROVED, after four months of treatment with methotrexate, remission was achieved less often in ACPA-negative patients with RA (51%) compared to patients with UA (62%) and ACPA-positive patients with RA (66%), p=0.006 (Wevers-de Boer, K. V. C. et al., 2012). One may have expected patients with UA to achieve a higher rate of remission; their baseline characteristics were generally more favourable, although they had comparable symptom duration and radiographic damage at baseline (erosions were present in 9%). It is possible that the remission rate was falsely high in the RA group accepting that some patients are overclassified by the 2010 RA criteria; however, the rate of remission in patients fulfilling 1987 ACR RA criteria was also similar to the rate observed in patients with UA. Multivariable analysis identified ACPA-positivity amongst independent predictors for remission after four months (OR 1.6, 95% CI 1.1-2.3), although the result was not significant in a second model including the baseline numbers of affected small and large joints (OR 1.4, 95% CI 1.0-2.1). At one year, after four months of initial methotrexate monotherapy followed by a treatment-to-target regimen, similar proportions of patients achieved remission regardless of their UA/RA classification or ACPA status. This implies response to methotrexate may be slower in patients who are ACPA-negative, or that methotrexate may be less effective.

Subgroup analysis of the PROMPT study demonstrated that methotrexate significantly delayed progression to RA, in comparison to placebo, only amongst ACPA-positive patients (van Dongen et al., 2007). A post hoc analysis of the EMPIRE study detected a more rapid response to treatment (methotrexate +/-

etanercept) in ACPA-positive patients; significantly greater improvements in DAS28 were noted at two weeks and six months (with adjustment for treatment group and baseline DAS28), whilst no statistically significant differences were observed at three months or one year (Nam et al., 2014b). However, this analysis was restricted to the subset of patients in whom ACPA status was known at baseline and the authors acknowledged that the number of patients with ACPA-negative IA was small (15 patients receiving methotrexate and etanercept and 10 patients receiving methotrexate plus placebo).

These data have implications for the management of patients with IA in clinical practice. Not only is serology useful in the stratification of future disease severity, but it may also be relevant to directing therapies according to the likelihood of response to therapies, potentially including methotrexate.

2.4.3 Realising the Need for Early Intervention in Clinical Practice

The realisation of early treatment is dependent on several factors: a patient promptly seeking medical attention after symptom onset (stage i), rapid referral from primary care to a rheumatologist (stage ii), punctual assessment by a rheumatologist (stage iii), and timely initiation of DMARDs after their first assessment (stage iv).

2.4.3.1 Time to First Assessment by a Rheumatologist: Stages (i) to (iii)

Studies conducted in Europe have demonstrated average times between symptom onset and first assessment by a rheumatologist (stages i to iii) of between four and nine months, with only 10-40% of patients being assessed within 12 weeks (Kumar et al., 2007; Kiely et al., 2009; www.nao.org.uk, 2009; van der Linden et al., 2010; Raza et al., 2011). These studies have suggested delays at stages (i) and (ii), in particular, are a major hindrance to the early assessment of patients with new-onset IA.

In the UK, half of patients diagnosed with RA appear to delay seeking help from their general practitioner (GP) (stage i) for at least three months after the onset of symptoms, a finding which seems to have been constant over time

(www.nao.org.uk, 2009; van der Linden et al., 2010). Delays arising at the level of the GP (stage ii) may also be relevant (Sandhu et al., 2008), with up to half of patients in the UK attending their GP several times before being referred to a specialist and subsequently being diagnosed with RA (www.nao.org.uk, 2009). Delays at this level of primary care also appear to be the principal factor precluding early rheumatologist assessment in other healthcare systems (van der Linden et al., 2010; Jamal et al., 2011; Raza et al., 2011).

Numerous studies have investigated the causes for delays at stages (i) (Stack et al., 2012; van Nies et al., 2013a) and (ii) (Suter et al., 2006; Spies-Dorgelo et al., 2009). Recurring themes include a lack of awareness of IA, its seriousness and the importance of early treatment. Strategies to increase public and GP awareness of the importance of early treatment in IA are therefore warranted (Villeneuve et al., 2013). Recent measures include the introduction of national guidelines recommending urgent referral in individuals with suspected IA with specific indicators of disease (www.nice.org.uk, 2009).

In secondary care, triage systems and EACs aim to minimise the time between referral and assessment by a rheumatologist (stage iii) (Govoni et al., 2013; Villeneuve et al., 2013). The majority of studies evaluating triage systems and EACs have demonstrated their efficacy in reducing the time lag between referral and first assessment by a rheumatologist, in comparison to patients referred via conventional routes (Govoni et al., 2013; van Nies et al., 2013b). Further strategies to minimise delay include the recent introduction of payments to secondary care by the Department of Health in the UK, for meeting a three-week target for assessment of patients with suspected early IA by a rheumatologist after their referral (www.gov.uk, 2013).

2.4.3.2 Time from First Assessment to Treatment: Stage (iv)

Previous studies demonstrate that delays at this stage may be inversely associated with the number of swollen joints (Jamal et al., 2011; De Cock et al., 2013). This is reasonable considering there may be less diagnostic uncertainty in patients with greater disease activity. Other relevant factors include concomitant musculoskeletal conditions (Tavares et al., 2012) and socio-economic factors (Hernandez-Garcia et

al., 2000). In an American study, socio-economic status was associated with delays at the level of the rheumatologist, although the time of diagnosis and treatment was determined by patient interview after the events which may have been affected by recall bias (Molina et al., 2015).

In the UK, the Department of Health have introduced payments to secondary care for the initiation of DMARD treatment within six weeks of referral (www.gov.uk, 2013). Furthermore, the recent development of the 2010 ACR/EULAR RA classification criteria now provide a guide to rheumatologists for the identification of patients who are likely to benefit from methotrexate, which may help in reducing time between first rheumatologic assessment and DMARD initiation (Aletaha, D. et al., 2010).

2.5 Summary

This literature review has identified several concepts relevant to the management of patients with IA. These include the ability to stratify patients for risk of persistent and aggressive disease on the basis of their clinical phenotype. The most compelling characteristics associated with poor prognosis are now incorporated in the 2010 ACR/EULAR RA classification criteria, providing a tool for the early identification of patients with unexplained clinical synovitis who are likely to benefit from methotrexate (i.e. patients who are at risk of persistent or erosive disease). It must be borne in mind that they were developed for use in disease classification in clinical trials, rather than as diagnostic criteria for use in clinical practice. Although their sensitivity in predicting severe and/or persistent IA has proved superior to the pre-existing 1987 ACR RA criteria, they are not fully sensitive or specific when applied in early IA cohorts (see Table 2). Therefore, a means of identifying patients with UA (not fulfilling 2010 RA criteria) who may also benefit from early treatment is needed, as well as a method for stratifying patients who fulfil the criteria in order to avoid over treating a subset of these patients (Combe et al., 2017).

The body of evidence supporting the ultrasound assessment of synovitis as a valid and effective tool in the assessment of IA has been presented. Its prognostic value in DMARD-naïve patients with early IA has previously been evaluated. Limitations

in these studies have been noted. In the ESPOIR cohort, PD appeared to predict radiographic progression, although baseline radiographic damage was not accounted for in the analysis (Funck-Brentano et al., 2013). In addition, low rates of radiographic progression may be expected with modern-day treatment strategies. Therefore radiographic progression is arguably not the only measure of outcome which should be considered. Studies investigating the ability of ultrasound synovitis to predict future disease progression in early IA have employed the 1987 ACR RA criteria as their measure of outcome (Salaffi et al., 2010; Filer et al., 2011). Studies addressing the potential added prognostic value of ultrasound to predict disease persistence and/or progression, over and above the new 2010 ACR/EULAR criteria, are lacking. Even less is understood regarding the prevalence and predictive validity of ultrasound erosions in early IA. The ongoing need to better define the diagnostic and prognostic value of ultrasound has recently been promoted by experts (Combe et al., 2017).

Determining the predictors of response to treatment is another significant area of interest. A window of opportunity is recognised in early disease in which effective treatment permits the attainment of optimal outcomes in the future. Hence, avoiding delays through the use of personalised medicine, directing therapy according to the likelihood of response, is an objective for future research (Smolen et al., 2017). In particular, efficacy of methotrexate according to serological status, and in patients with UA is one matter which needs to be clarified further.

In terms of treatment for patients with RA, advantages of early, tight control of inflammation are now widely accepted. Clinical disease activity measures, including various composite scores, can be used to direct treatment with the aim of achieving clinical remission. Superior outcomes, in both the short- and long-term, can be achieved with this approach versus non-target driven treatment. However, studies demonstrate subclinical ultrasound synovitis may persist in patients achieving even the most stringently defined clinical remission states. In established RA, these findings appear to be associated with future disease flare and radiographic progression. This research raises the question as to whether superior outcomes may be achievable with the use of ultrasound to direct therapy, in addition to clinical assessments (Combe et al., 2017).

Chapter 3 : **Hypothesis, Aims and Objectives**

3.1 Hypothesis

The clinical and imaging phenotype of a patient's disease at diagnosis is predictive of their future disease course. Ultrasound may provide additional prognostic information over the 2010 ACR/EULAR RA criteria and other clinical and laboratory characteristics of disease.

3.2 Aims

The overarching aims are to determine the clinical and imaging phenotype, management and outcomes of patients with early IA in a clinical practice setting and identify strategies for improvement in their care. This includes risk stratifying patients according to disease progression and future severity in the context of the new 2010 ACR/EULAR criteria, determining their response to treatment and evaluating the utility of ultrasound within the treatment-to-target management of RA.

3.3 Objectives

In subsequent chapters, the following objectives are addressed:

Chapter 5: To audit the performance of the Leeds EAC. This includes determining the phenotype of all-comers to the clinic, the efficacy of triage of referrals to the clinic and any delays in the assessment and treatment of patients presenting with IA, against national standards.

Chapter 6: To describe the clinical and imaging phenotypes of patients presenting to the Leeds EAC with new-onset, DMARD-naïve IA (specifically patients with UA and RA, classified according to the 2010 ACR/EULAR RA criteria). Specific objectives were to determine:

- The proportion of patients with UA or RA whose disease may be reclassified with consideration of ultrasound evidence of synovitis in the application of the 2010 criteria.
- Whether reclassification with the use of ultrasound is more discriminating for the presence of erosions at diagnosis than application of the classification criteria using clinical findings alone.

Chapter 7: To determine the one year outcomes, and predictors of outcome, for patients attending the Leeds EAC with new-onset, DMARD-naïve IA (specifically patients with UA and RA classified according to the 2010 ACR/EULAR RA criteria).

In order to investigate the efficacy of, and predictors of response to, particular intervention strategies in patients with early IA, subsequent chapters focus on subgroups of patients receiving specific treatment in the clinic:

Chapter 8: To determine clinical response to methotrexate in patients with new-onset, DMARD-naive IA in clinical practice. In particular, to establish whether there is any difference in response according to serological status or fulfilment of the 2010 ACR/EULAR RA classification criteria.

Chapter 9: In patients with early RA managed according to the EULAR treat-to-target guidelines, to assess how the paradigm for targeting clinical remission translates into clinical practice, particularly in relation to ultrasound imaging. Specific objectives were to evaluate:

- Adherence to the EULAR treat-to-target guidelines and identify potential barriers to adherence in clinical practice.
- The rates of DAS28 remission, DAS44 remission, 2011 ACR/EULAR Boolean remission and imaging remission.
- Agreement between these clinical remission states and imaging remission.
- Predictors of achievement of these clinical and imaging remission outcomes.

Chapter 4 : **Methods**

4.1 Patients

4.1.1 Early Arthritis Clinic Audit

A clinical audit was conducted in all new-comers to the Leeds EAC. This clinic includes patients referred from primary and secondary care. Referrals are triaged by rheumatologists, with preference for rapid assessment in the EAC in the instance of possible new-onset IA. Clinical notes were obtained for 100 patients consecutively attending this EAC for the first time on or after January 9th 2012. They were reviewed retrospectively. Results of laboratory tests and imaging, performed as clinically indicated, were recorded from the clinical results server. All recorded data was anonymised.

4.1.2 Prospective Observational Inflammatory Arthritis Cohort Study

Between 2010 and 2014, patients attending the Leeds EAC with suspected new-onset IA were invited to participate in a pragmatic, prospective, observational study. Inclusion criteria were age at least 18 years, provision of informed consent and likely new-onset IA, defined by a consultant rheumatologist impression of new IA with current or recent history of any of the following: (i) symptoms of IA (including early morning stiffness of at least one hour), (ii) clinical signs of IA such as joint swelling, or (iii) imaging evidence of IA including synovitis, erosion or tenosynovitis. The study was approved by the Leeds West Regional Ethics Committee. Data was recorded at the time of assessment using electronic case report forms.

In order to obtain informed consent, eligible patients were provided with written information about the study at their first EAC consultation. They returned to give written consent (and to collect baseline data) at the next opportunity after 24 hours. In patients receiving DMARDs or significant corticosteroids prior to consent (i.e. prior to or at the first EAC visit, when it was deemed unethical to delay treatment), baseline data was obtained retrospectively from clinical notes (as permitted within the study protocol). Significant corticosteroid was defined as at least 120mg

methylprednisolone intramuscularly or intra-articularly (or equivalent triamcinolone or oral prednisolone dose) within the preceding three months.

The following patients were selected from this cohort for this research: patients with current or history of clinical swelling of at least one joint (as documented by a rheumatologist), UA or RA (defined by the 2010 ACR/EULAR RA criteria) at baseline, and patients enrolling in the study between June 2010 and September 2012. The 2010 criteria were applied cumulatively from symptom onset as per their intended use (Aletaha, D. et al., 2010). Joint involvement within the criteria was primarily determined by clinical findings (swelling and/or tenderness). Radiographic change sufficient for a diagnosis of RA was defined using the published definition (van der Heijde et al., 2013).

4.2 Clinical Assessments

4.2.1 Baseline characteristics

In the prospective observational study, general characteristics recorded at baseline were age, gender, BMI, smoking status (current or previous history of smoking), presence of comorbidity (including hypertension, hypercholesterolaemia, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, asthma, chronic obstructive airways disease, diabetes, peptic ulcer disease, chronic kidney disease, chronic liver disease, epilepsy, demyelination, depression, thyroid dysfunction, cancer) and current or previous history of osteoarthritis (defined by diagnosis by a rheumatologist, with symptoms and signs consistent with osteoarthritis).

Baseline variables relevant to the clinical phenotype of IA were:

- Symptom duration: rheumatologist judgement of duration of inflammatory symptoms relevant to the current presentation of IA, obtained through patient consultation.
- Presence of features of SpA (defined within the Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis: inflammatory back pain, enthesopathy, uveitis, dactylitis,

psoriasis [skin and/or nail], inflammatory bowel disease, family history, HLA-B27 positive, sacroiliitis on imaging) (Rudwaleit et al., 2009).

- Joint involvement according to four categories: (i) palindromic arthritis (no swollen joints at baseline, with no steroid exposure within three months, but documented history of swollen joints determined by a rheumatologist), (ii) monoarthritis (1 swollen joint), (iii) oligoarthritis (2-4 swollen joints) and (iv) polyarthritis (>4 swollen joints).
- Symmetrical joint swelling (as defined within the 1987 ACR RA criteria).
- Duration of early morning stiffness.
- RF status.
- ACPA status.
- Disease activity; recorded using examination of 28 and 44 joints for swelling (SJC28 and SJC44, respectively), and 28 and 53 joints for tenderness (TJC28, TJC53 and Ritchie Articular Index [RAI]) by rheumatologists and rheumatology nurse specialists, patient Visual Analogue Scale assessment of Disease Activity (VASDA) and CRP. Composite scores, calculated using these variables, were DAS28-CRP and DAS44-CRP.
- Physical function; recorded using the HAQ score.

4.2.2 Follow-up assessments

Over the following 12 months, data were collected prospectively every three months (or as clinically indicated). This included assessments of disease activity as performed at baseline and the HAQ score.

4.3 Imaging Assessments

4.3.1 X-ray

Posteroanterior radiographs of the hands and feet were performed at baseline. Musculoskeletal radiologists reported the presence and location of erosions. Erosive disease on x-ray was defined as the presence of any radiographic erosion within the hands and feet, as well as according to 1987 ACR and 2010 ACR/EULAR definitions, i.e. radiographic changes typical of rheumatoid arthritis on hand and wrist radiographs (Arnett et al., 1988) and erosion in at least three

separate joints amongst the PIP, MCP, wrist and MTP joints (van der Heijde et al., 2013), respectively.

4.3.2 Ultrasound

Ultrasound examinations of 26 joints (elbows, wrists, second and third metacarpophalangeal [MCP2-3] and proximal interphalangeal [PIP2-3] joints, knees, ankles and first to fifth metatarsophalangeal [MTP1-5] joints) were performed at baseline and 12 months. Scans were conducted in a clinical out-patient setting by either a rheumatologist (n=7) or ultrasonographer (n=2) who were blinded to clinical details. All sonographers had undergone independent calibration training with an experienced EULAR teacher and consultant rheumatologist. The same machine (GE E9) was used, employing either a 15-6 or 18-8 MHz linear array transducer as appropriate for the size of joint.

The joints were selected on the basis of the frequency of ultrasound involvement previously reported at these sites in RA (Naredo, E. et al., 2005). A reduced joint assessment, in comparison to the number of joints assessed clinically, was conducted in order to optimise feasibility; each ultrasound examination required up to 30 minutes of time.

Due to the number of patients in the study, the availability of clinicians and the availability of only one ultrasound machine, it was not always possible to perform clinical assessments on the same day as ultrasound assessments. Assessments were generally undertaken within the same week. Any treatment changes were made after both clinical and ultrasound examinations.

4.3.3 Synovitis

Scoring of GS and PD synovitis was performed according to a standard operating procedure, showing probe positions and scoring scenarios utilising the semi-quantitative EULAR/OMERACT scoring system (Table 8, section 2.3.1). Each joint was graded 0-3 for severity of GS synovitis and 0-3 for PD. At the joint level, significant ultrasound synovitis was defined as the appearance GS≥grade 2 and/or PD≥grade 1, i.e. excluding GS=grade 1 changes which may be observed in healthy

controls (Kitchen and Kane, 2015). At the patient level, global ultrasound measures of synovitis were the number of joints displaying significant synovitis and the total GS and PD scores (the sum of the GS and PD semi-quantitative scores, respectively, in all 26 joints giving a maximum total score of 78 for each).

Ultrasound evidence of synovitis was used to reclassify patients as UA_{US} or RA_{US} with consideration of ultrasound evidence of significant synovitis in the determination of joint involvement within the 2010 ACR/EULAR RA criteria (Aletaha, D. et al., 2010). It was also used to define 'active' erosion as the co-existence of significant ultrasound synovitis and erosion within the same joint.

4.3.4 Erosions

Eighteen of the small joints examined (wrists, MCPs2-3, PIPs2-3 and MTPs2-5) were assessed for the presence of erosion, defined as a cortical break observable in two planes. The first MTP was excluded due to the low specificity of ultrasound erosions previously observed at this site (Zayat et al., 2015). Erosive disease at the patient level was defined as the presence of at least one erosion within these 18 joints.

4.4 Intervention

All patients were reviewed and managed by consultant rheumatologists in an out-patient clinical setting, following EULAR treatment-to-target guidelines for the management of RA when clinically appropriate (Smolen et al., 2010; Smolen, Josef S et al., 2014). Treatment escalation to biologic DMARD was in accordance with National Institute of Health and Care Excellence (NICE) technology appraisals, stipulating at least high disease activity (DAS28>5.1) after failure of at least two DMARDs (including methotrexate). Current therapies (DMARDs and/or corticosteroids) and change in therapy from the previous assessment were recorded at each visit.

The target for treatment was defined as DAS28-CRP remission (DAS28-CRP<2.6). This was selected due to the familiarity of clinicians with its use in the management

of IA in an out-patient setting, prior to publication of the 2011 ACR/EULAR remission criteria. The use of CRP, rather than ESR, was selected due to the dependency of ESR on age and gender (Crowson et al., 2009). The DAS28-CRP has been validated as a measure of disease activity in RA for use in clinical trials (Prevoo et al., 1993; Smolen et al., 1995) and can be used by assessors with varying levels of experience in clinical practice (Walsh et al., 2008). As this definition of remission may allow persistence of clinical evidence of disease activity, including joint swelling (Mäkinen et al., 2005), the clinician impression of disease remission also factored in treatment decisions, as did other considerations such as comorbidity, in accordance with guidelines (Smolen et al., 2010).

4.5 Outcomes

4.5.1 Clinical

In the prospective observational study, clinical outcomes were; (i) the requirement for methotrexate within 12 months, and (ii) persistence of IA at 12 months (defined as presence of clinically swollen joints at one year and/or use of DMARD or corticosteroid within the preceding three months, and the absence of an alternative diagnosis, other than UA or RA). In the subset of patients with UA at baseline, progression to fulfilment of 2010 ACR/EULAR RA criteria within 12 months was also reported. In patients fulfilling 2010 RA criteria at baseline, requirement for triple DMARD (methotrexate, sulfasalazine and hydroxychloroquine) or biologic therapy within 12 months was reported.

These outcomes were selected on the basis of their use in previous research and their clinical relevance. Initiation of treatment, within the context of clinical guidelines, was likely to have been related to baseline characteristics perceived to be related to poor prognosis (including baseline disease activity and characteristics previously discussed, see section 2.2), as well as disease activity during follow-up. This includes ultrasound findings, as treating clinicians were not blinded to ultrasound results. However, the use of methotrexate was employed as an outcome measure given that this was considered by experts to be reflective of patients at risk of developing persistent and/or erosive arthritis that would currently be considered to be RA, in the development of the 2010 ACR/EULAR RA criteria.

Disease activity outcomes were not considered appropriate in the exploration of prediction of outcome in the main cohort (all patients with UA or RA) due to heterogeneity of patient and treatment-related factors. Instead, the outcomes persistence of IA, progression to RA in patients with UA, and need for triple DMARD or biologic therapy in patients with RA, were judged to be easier to interpret and less ambiguous. Disease activity outcomes were considered in analyses of subgroups of patients receiving a particular treatment or treatment strategy (first-line treatment with methotrexate in Chapter 8 and a treatment-to-target strategy in RA in Chapter 9, see sections 8.3 and 9.3).

4.5.2 Imaging

Imaging outcomes included the presence of new ultrasound erosion at 12 months at the patient and the joint level. New ultrasound erosion was defined as ultrasound erosion detectable in any joint (of the 18 examined for erosions) previously lacking ultrasound or x-ray erosion at baseline. New ultrasound erosion was selected over radiographic outcomes due to the expected low rate of radiographic progression.

In patients managed according to treatment-to-target guidelines (Chapter 9) imaging remission was defined as absence of PD on ultrasound examination of 26 joints at 12 months.

4.6 Statistics

Characteristics were described using frequencies for categorical variables and means and standard deviations for continuous variables following a normal distribution. For non-parametric data median values and interquartile ranges were calculated.

4.6.1 Missing data

In the analyses of the main clinical outcomes, data from last assessments were carried forward for patients with missing clinical data at 12 months. A patient's status at their last assessment was felt to be relevant to the main 12 month clinical outcomes, including the requirement for methotrexate and disease persistence,

especially considering the intention that the cohort would include patients with mild, potentially self-limiting disease in whom ongoing follow-up may not be clinically indicated. Other methods of imputation were not considered appropriate due to the frequency of missing data which occurred with the pragmatic design of the study. In the instance of lack of any clinical follow-up data within 12 months, patients were excluded. In the analyses of imaging outcomes, patients with missing imaging data were excluded.

To determine any difference between patients included in analyses and those excluded due to missing data, the following tests were performed: Chi-squared tests (or Fisher's exact tests when appropriate according to expected numbers) for categorical variables, t-tests for continuous variables following a normal distribution (either before or after log transformation, using Shapiro-Wilks test to assess normality), and Mann-Whitney-U tests for non-parametric variables.

Other statistical methods specific to individual chapters are discussed under the relevant chapter headings.

Chapter 5 : **A Clinical Audit of all First-Time Attendees to the Leeds Early Arthritis Clinic.**

5.1 Introduction

The concept of a window of opportunity in which appropriate treatment initiation affords maximal benefits in the treatment of IA has steered early IA research and management since the 1990s (Quinn et al., 2001; Sokka et al., 2007; Kiely et al., 2009; van der Linden et al., 2010) (see section 2.4.1.1). Current guidelines based on evidence and expert opinion recommend specialist assessment by a rheumatologist and commencement of DMARD therapy as early as possible (ideally within 3 months of symptom onset (www.nice.org.uk, 2009)) in patients with RA (Smolen et al., 2017) and patients with UA at risk of persistent or erosive disease (Combe et al., 2017).

Over the last decade there has been improvement in the early assessment and diagnosis of patients with RA (Sørensen and Hetland, 2015), although recent data suggests the target to initiate DMARD therapy within three months of the onset of symptoms remains unmet for the majority of patients (Raza et al., 2011; De Cock et al., 2013; van Nies et al., 2013b; Sørensen and Hetland, 2015). Early treatment initiation is reliant on several factors (see section 2.4.3): a patient seeking medical attention after symptom onset (stage i), prompt referral from primary care to a rheumatologist (stage ii), punctual assessment by a rheumatologist (stage iii), and timely initiation of DMARDs after their assessment (stage iv).

Strategies for reducing delays at the level of primary care (stage ii) include UK guidelines recommending urgent referral in individuals with suspected IA with specific with indicators (www.nice.org.uk, 2009). In secondary care, triage systems and EACs aim to minimise the time between referral and assessment by a rheumatologist (stage iii) (Govoni et al., 2013; Villeneuve et al., 2013). In 2013, the Department of Health introduced payments to secondary care for meeting the following standards of best practice: assessment of patients with suspected early IA by a rheumatologist within three weeks of referral and initiation of DMARD

treatment within six weeks of referral (www.gov.uk, 2013). Furthermore, the recent development of the 2010 ACR/EULAR RA classification criteria now provide a guide to rheumatologists in the identification of patients who are likely to benefit from methotrexate, which may help in reducing time between first rheumatologic assessment and DMARD initiation (stage iv) (Aletaha, D. et al., 2010).

Studies evaluating triage systems and EACs have mostly demonstrated their efficacy in reducing the time between referral and first assessment by a rheumatologist, in comparison to patients referred via conventional routes (Govoni et al., 2013; van Nies et al., 2013b). Intuitively, this may reduce delays in time to treatment. Only a limited number of studies have investigated this directly and the majority were conducted prior to the availability of the 2010 ACR/EULAR RA classification criteria (Jamal et al., 2011; Govoni et al., 2013). Previous studies describing the characteristics of patients attending EACs have generally excluded patients lacking confirmed arthritis (van Nies et al., 2013b) or joint swelling (Marcos et al., 2011).

An audit of the Leeds EAC was conducted, prior to the introduction of the 2013 Department of Health standards for best practice, to identify any areas requiring improvement in order to meet these targets. The characteristics of all patients attending the clinic were of interest, regardless of whether arthritis was confirmed, in order to inform triage procedures in the future.

5.2 Aims and Objectives

- To evaluate the phenotypes of patients attending a large EAC.
- To determine the efficacy of triage of referrals to the clinic and assess whether national standards for best practice (early specialist assessment and DMARD initiation in patients with UA and RA) have been achieved.
- To identify reasons for any delays in the assessment and treatment of patients with IA in order to inform future practice.

5.3 Methods

A clinical audit was conducted in first-time attendees to the Leeds EAC (see section 4.1.1).

5.3.1 Triage

Written letters from GPs or other referring clinicians (for example in the instance of patients first presenting to the accident and emergency department) formed the basis of referral to the EAC. Rheumatologists used the information provided within referral letters to allocate urgent and more routine EAC appointments according to the possibility of new-onset IA. Patients with other reasons for rheumatology referral could be triaged to alternative clinics.

5.3.2 Assessments

Referral information was retrospectively reviewed for the presence of the NICE indicators for urgent referral. These were documentation of suspected synovitis, joint swelling or arthritis with any of the following: involvement of the small joints of the hands or feet, involvement of more than one joint or duration of symptoms of three months or longer at the time of referral.

Clinical, laboratory and imaging assessments conducted at the first EAC visit (performed on the basis of clinical need) were recorded. A clinical pro forma was used in the EAC to aid patient assessments, including prompts for clinical examination of 66 joints for swelling and 68 joints for tenderness. In the instance of suspected IA, the duration of symptoms was defined as duration of inflammatory symptoms. Capacity for simultaneous ultrasound examination was available during the clinic, conducted by a rheumatologist with experience in musculoskeletal ultrasound. Musculoskeletal radiologists read the X-rays.

A patient's primary diagnosis at the first EAC visit was determined by the impression of a consultant rheumatologist and the 2010 ACR/EULAR RA classification criteria when applicable (i.e. in the presence of at least one clinically swollen joint not explicable by a non-RA diagnosis). For patients in whom more

than one differential diagnosis was documented for the rheumatologist's impression, the primary diagnosis was defined as that which was documented foremost in the correspondence to the GP. The rheumatologist's impression of IA was categorised according to the primary diagnosis and rheumatologist's examination as: non-IA (non-IA primary diagnosis), possible IA (rheumatologist's impression of possible IA in the absence of current joint swelling, i.e. a history compatible with IA) and confirmed IA (primary diagnosis of IA in the presence of at least one clinically swollen joint).

5.3.3 Outcomes

Efficacy of triage was evaluated by calculating the time between referral and first EAC assessment and the proportion of patients who met the national standard for assessment by a rheumatologist within three weeks of referral. Other outcomes included change in diagnosis from the primary diagnosis over the following 12 months.

Outcomes in patients with UA and RA were DMARD initiation over 12 months and achievement of national targets for early DMARD commencement: within six weeks of referral (www.gov.uk, 2013) and three months of symptom onset (www.nice.org.uk, 2009). Areas for service improvement were explored by calculating the length of delays occurring at stages (i) to (iv), described above, and identifying reasons for delays arising after rheumatologic assessment (stage iv) through retrospective review of clinical notes.

5.3.4 Statistics

Descriptive statistics were used to illustrate the clinical phenotypes of patients, grouped according to the prevalent primary diagnoses. To evaluate the triage process, the times between referral and first EAC assessment were compared for patients with and without any of the NICE indicators for urgent assessment identifiable from their referral letters (www.nice.org.uk, 2009) and according to the impression of IA at first EAC assessment. To evaluate the reliability of referral information, presence of the NICE indicators for urgent assessment within referral letters was also compared according to the impression of IA. Mann-Whitney U and Chi-square tests (or Fisher's exact test, as appropriate for numbers of expected

values) were used to compare patients with and without the presence or absence of NICE indicators for urgent referral. Kruskal-Wallis and Chi-square tests were used to compare patients across the three IA categories.

5.4 Results

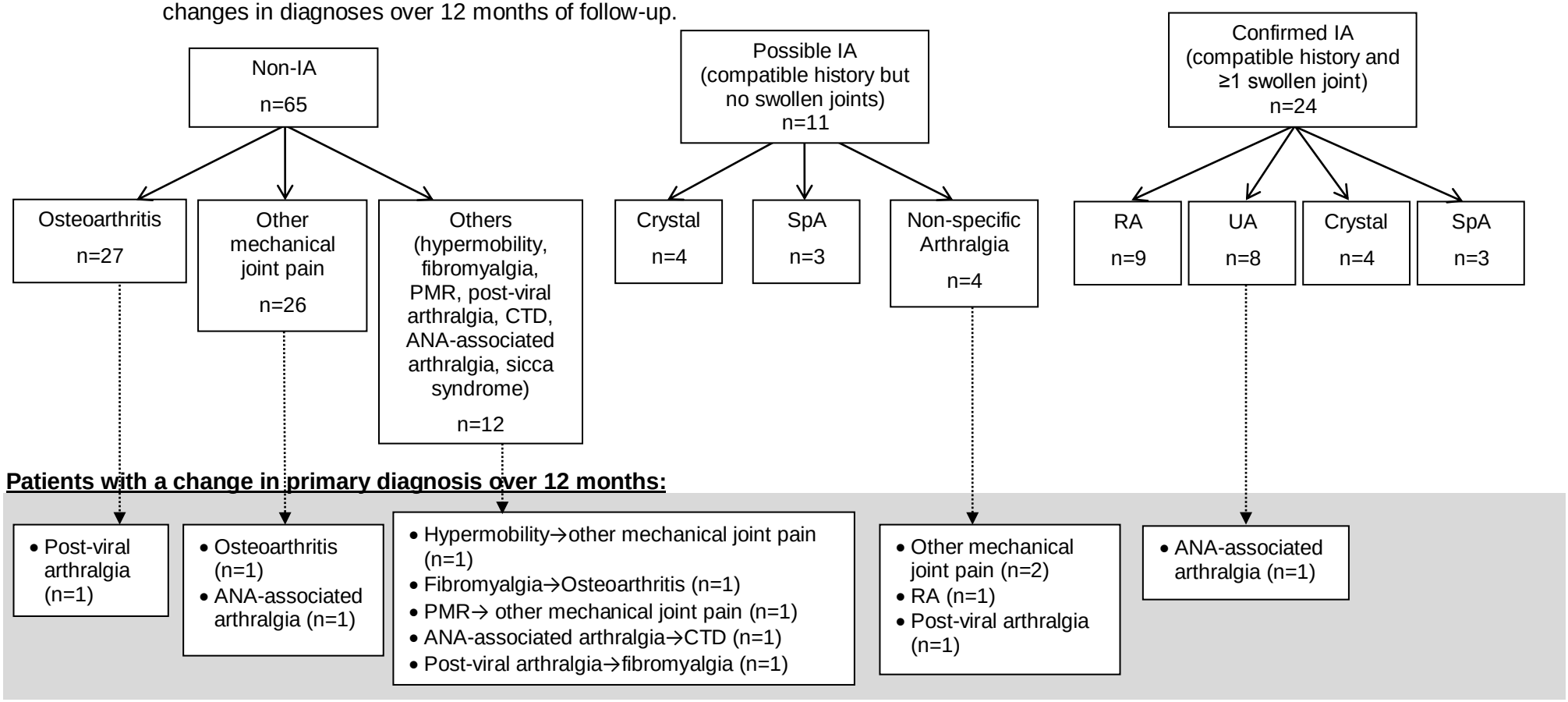
Clinical notes were reviewed for 105 patients consecutively attending the EAC between 9th January and 6th February 2012. Five patients were excluded from the audit due to the presence of established IA, having been re-referred after loss to follow-up after a previous diagnosis of IA under the care of a rheumatologist.

5.4.1 Clinical phenotypes

Of 100 patients attending the EAC for the first time, 24 cases of IA were confirmed in 24 patients (Figure 1). The majority of patients (65%) had non-IA primary diagnoses including: osteoarthritis (n=27), other mechanical joint pain (n=26), hypermobility (n=3), fibromyalgia (n=2), polymyalgia rheumatica (n=2), post-viral arthralgia (n=2), connective tissue disease, ANA-associated arthralgia and sicca syndrome (each n=1).

Diagnoses of confirmed IA were RA (n=9), UA (n=8), crystal arthropathy (n=4) and SpA (psoriatic arthritis in 2 patients and undifferentiated SpA in 1 patient). In a further 11 patients the rheumatologist's opinion was of possible IA, although no current clinical joint swelling was found (i.e. patients with histories compatible with IA). The primary suspected diagnoses for these patients were: crystal arthropathy (n=4), non-specific arthralgia (n=4) and SpA (psoriatic arthritis, reactive arthritis and inflammatory bowel disease-associated SpA in 1 patient each).

Figure 1. Prevalence of non-inflammatory and inflammatory arthritis primary diagnoses amongst one hundred all-comers to the EAC and changes in diagnoses over 12 months of follow-up.



PMR: polymyalgia rheumatic, CTD: connective tissue disease, ANA: anti-nuclear antibody.

The characteristics of all patients at their first EAC assessment and patients with the main primary diagnoses (osteoarthritis, other mechanical joint pain, RA, UA, crystal arthropathy and SpA) are displayed in Table 14 and Figure 2. Although no statistical tests were carried out due to the small size of the diagnostic groups, the following trends were observed in the phenotypes of patients:

- Age appeared highest in patients with osteoarthritis, RA and crystal arthropathy (mean age>50 years).
- There was a predominance of females amongst patients diagnosed with osteoarthritis and other mechanical joint pain. There was a predominance of males amongst patients with crystal arthropathy and SpA.
- Symptom duration was longest in patients with osteoarthritis and other mechanical joint pain (eight patients reporting symptoms for more than five years). Symptom duration was generally shortest amongst patients with crystal arthropathy; excluding patients with a prior GP diagnosis of gout (n=3), the maximum reported symptom duration was one month.
- Most patients reported less than 30 minutes of early morning stiffness except for those with likely RA or SpA.
- At least one feature of SpA was reported in approximately a quarter of patients. As expected, these were more prevalent in patients diagnosed with SpA. Three or more features of SpA were reported in three patients with SpA, whilst no more than two features of SpA were reported amongst other patients. Features of SpA that were exclusively reported in patients with SpA were dactylitis, abnormal sacroiliac joints on imaging and HLAB27 positivity.
- There was a predominance of symptoms affecting the upper limbs. Exceptions were patients with crystal arthropathy, in whom the lower limbs more commonly affected, and patients with UA or SpA, in whom symptoms in the upper and lower limbs were reported with approximately similar frequency.
- Joint involvement was greatest in patients with RA; of whom, most had oligoarthritis and one third of had polyarthritis. The majority of patients with UA had monoarthritis, whilst half of patients with crystal arthropathy or SpA had no clinically detectable joint swelling.
- Raised CRP (>10mg/dL) was more frequently observed in patients with RA, UA, crystal arthropathy and SpA, in comparison to patients with

osteoarthritis or other mechanical joint pain. Levels were generally highest amongst patients with SpA.

- Testing for RF was performed in most patients (90% of the total audit sample). Rheumatoid factor was detected in two-thirds of patients with RA and approximately 20% of patients with osteoarthritis, other mechanical joint pain, crystal arthropathy and SpA. All patients with UA were RF-negative.
- Positivity for ACPA was only detected in patients with RA and one patient with non-specific arthralgia who was diagnosed with RA within the following 12 months.
- Radiographs of the hands and feet were complete in one third of patients, in whom erosions were detected in four (2 patients with RA, 1 patient with UA and 1 patient with psoriatic arthritis). Only one patient fulfilled the 2010 ACR/EULAR definition for erosive RA (van der Heijde et al., 2013).

Other investigations included a symptom-directed ultrasound in 11 patients. Power Doppler synovitis was detected in patients with RA (n=3) and UA (n=2). Grey scale synovitis alone was demonstrated in a further patient with UA and a patient with other mechanical joint pain. Bursitis alone was found in three further patients with other mechanical joint pain. In the final patient undergoing ultrasound (diagnosed with UA) no abnormalities were recorded.

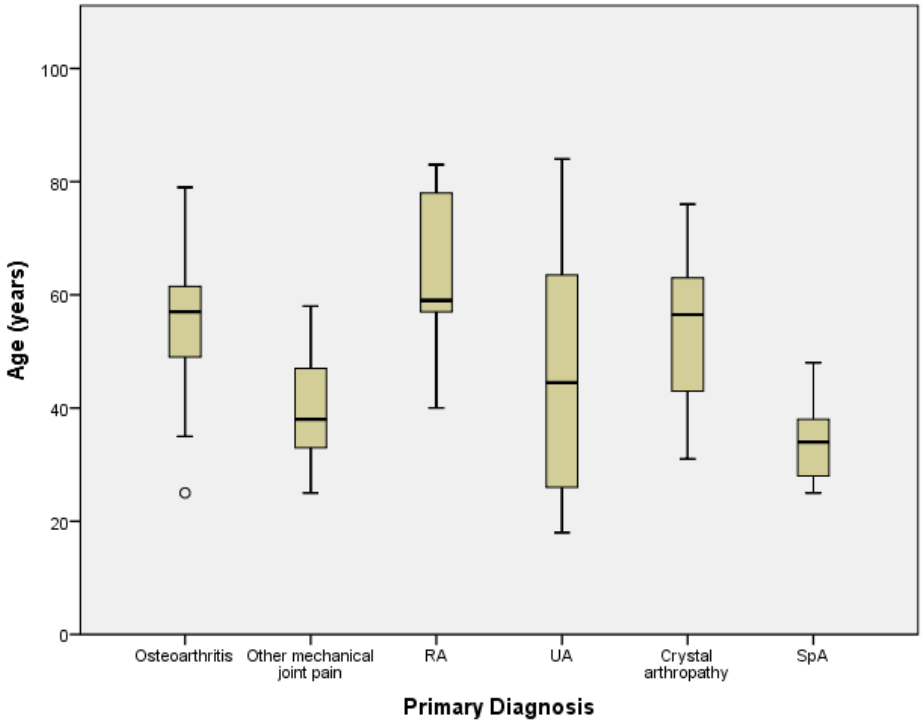
Table 14. Characteristics of one hundred all-comers to the EAC.
Characteristics are summarised for the total group and sub-groups classified according to the most prevalent primary diagnoses.
Values are median (IQR) and number of patients (percentage of patients), unless otherwise stated.

	All patients n=100	**Osteoarthritis n=27**	**Other mechanical n=26**	**RA n=9**	**UA n=8**	**Crystal arthropathy n=8**	**SpA[a] n=6**
Age, mean (SD)	48 (16)	56 (12)	40 (10)	63 (15)	46 (23)	54 (15)	35 (8)
Female	67 (67%)	23 (85%)	21 (81%)	4 (44%)	6 (75%)	0	1 (17%)
Symptom duration, months	8 (3-36)[e]	11 (3-36)[g]	12 (6-36)[g]	8 (4-15)	6 (2-24)	2 (1-36)	6 (1-29)
Early morning stiffness, minutes	0 (13-56)[f]	0 (13-30)[g]	4 (0-30)	60 (34-60)[g]	10 (0-120)[g]	0 (0-18)	60 (0-75)
≥1 feature of SpA[b]	24 (24%)	5 (19%)	1 (4%)	2 (22%)	2 (25%)	0	5 (83%)
Symptom distribution: Predominantly upper limb	44 (44%)	16 (59%)	10 (38%)	5 (56%)	4 (50%)	1 (13%)	1 (17%)
Predominantly lower limb	23 (23%)	4 (15%)	3 (12%)	1 (11%)	3 (38%)	6 (75%)	2 (33%)
Upper & lower limb affected equally	29 (29%)	7 (26%)	11 (42%)	3 (33%)	1 (13%)	1 (13%)	2 (33%)
Predominantly axial	3 (3%)	0	2 (8%)	0	0	0	1 (17%)
No joint symptoms	1 (1%)	0	0	0	0	0	0
Joint involvement[c]: 1 M/L[d]	6 (6%)	0	1 (4%)	0	3 (38%)	2 (25%)	1 (17%)
2-10 M/L	2 (2%)	0	0	0	1 (13%)	0	0
1-3 S	6 (6%)	0	0	2 (22%)	2 (25%)	1 (13%)	1 (17%)
4-10 S	8 (8%)	2 (7%)	0	3 (33%)	2 (25%)	0	1 (17%)
>10 joints (at least 1 S)	5 (5%)	0	0	4 (44%)	0	1 (13%)	0
Pattern of joint swelling: No swollen joints	74 (74%)	25 (93%)	26 (100%)	0	0	4 (50%)	3 (50%)
Monoarthritis (SJC=1)	10 (10%)	0	0	1 (11%)	6 (75%)	2 (25%)	1 (17%)
Oligoarthritis (SJC=2-4)	10 (10%)	2 (7%)	0	5 (56%)	1 (13%)	1 (13%)	1 (17%)
Polyarthritis (SJC>4)	6 (6%)	0	0	3 (33%)	1 (13%)	1 (13%)	1 (17%)
TJC68	1 (0-8)	0 (0-8)	1 (0-4)	7 (4-13)	2 (0-4)	1 (0-1)	1 (0-4)
CRP, mg/dL	0 (0-11)	0 (0-1)	0 (0-8)	10 (0-18)	5 (0-100)	4 (0-22)	37 (9-101)
RF-positivity, number positive/number tested	19/90	5/26	4/22	6/9	0/8	1/5	1/5
ACPA-positivity, number positive/number tested	5/78	0/19	0/18	4/9	0/8	0/4	0/5
Radiographic erosions, number of patients with erosion/number with complete hand and feet x-rays	4/33	0/9	0/5	2/6	1/2	0/3	1/3

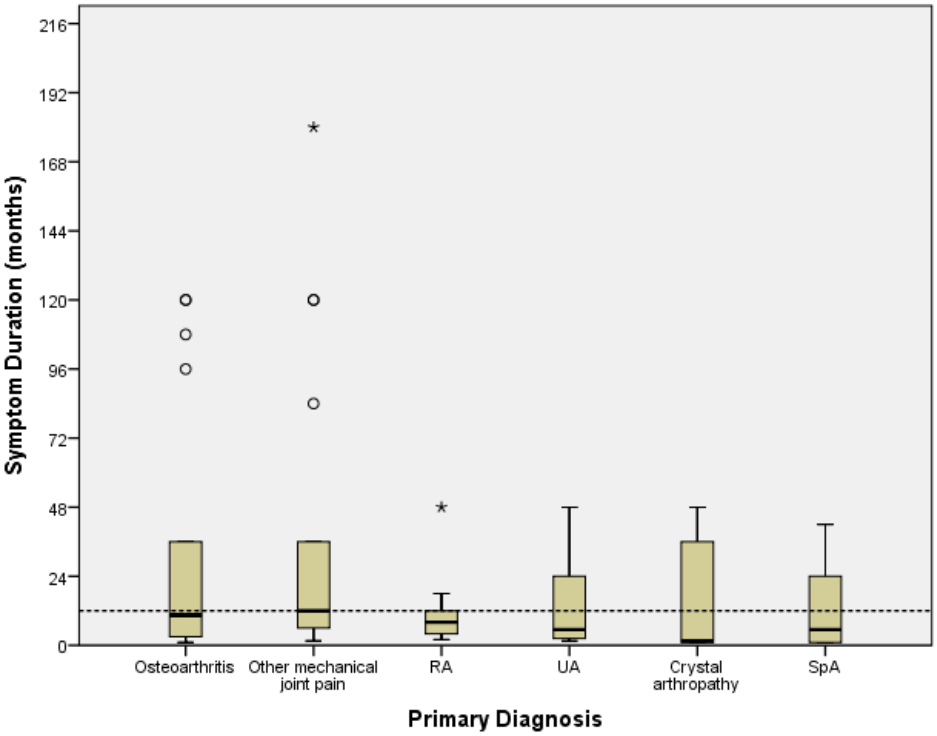
M/L: medium-sized or large joint, L: large joint, S: small joint (according to definitions employed in the 2010 ACR/EULAR RA criteria).
[a]Includes primary diagnoses of psoriatic arthritis in 3 patients and reactive arthritis, inflammatory bowel disease-associated SpA and undifferentiated SpA in 1 patient each.
[b]As defined within Assessment of Spondyloarthritis (ASAS) criteria: inflammatory back pain, enthesopathy, uveitis, dactylitis, psoriasis (skin and/or nail), inflammatory bowel disease, family history, HLA-B27 positive, sacroiliitis on imaging.
[c]As defined within 2010 ACR/EULAR RA criteria
[d]Or involvement of joints not included in 2010 criteria
[e-g]Excludes missing data in [e]3, [f]4 and [g]1 patients.

Figure 2. Characteristics at first EAC assessment in patients grouped according to the prevalent primary diagnoses. Boxplots of: A) age, B) symptom duration, C) duration of early morning stiffness, D) number of tender joints and E) CRP.

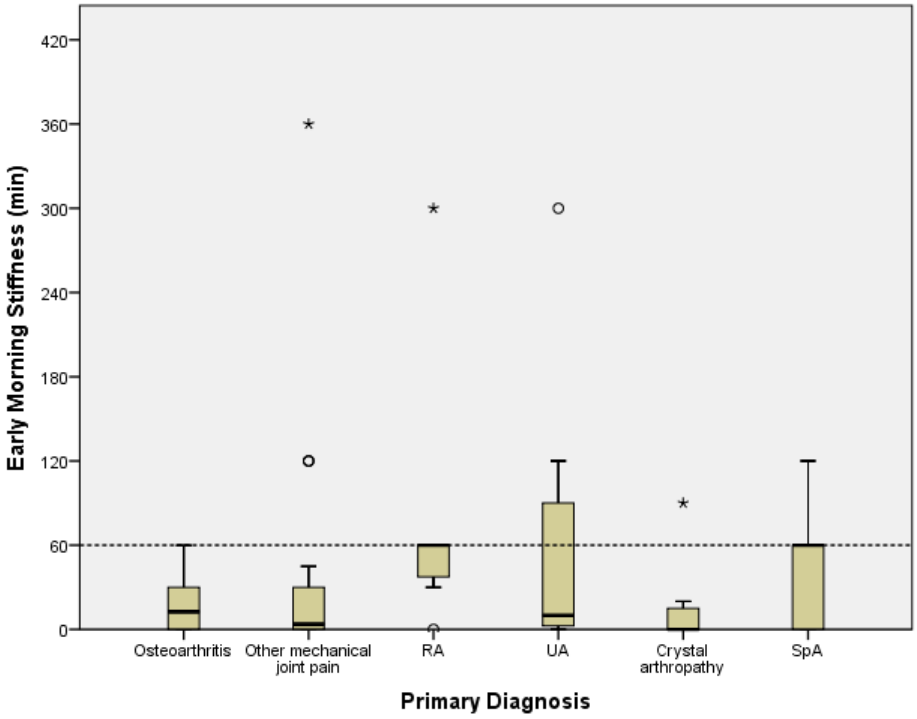
A) Age at first EAC assessment according to primary diagnosis.



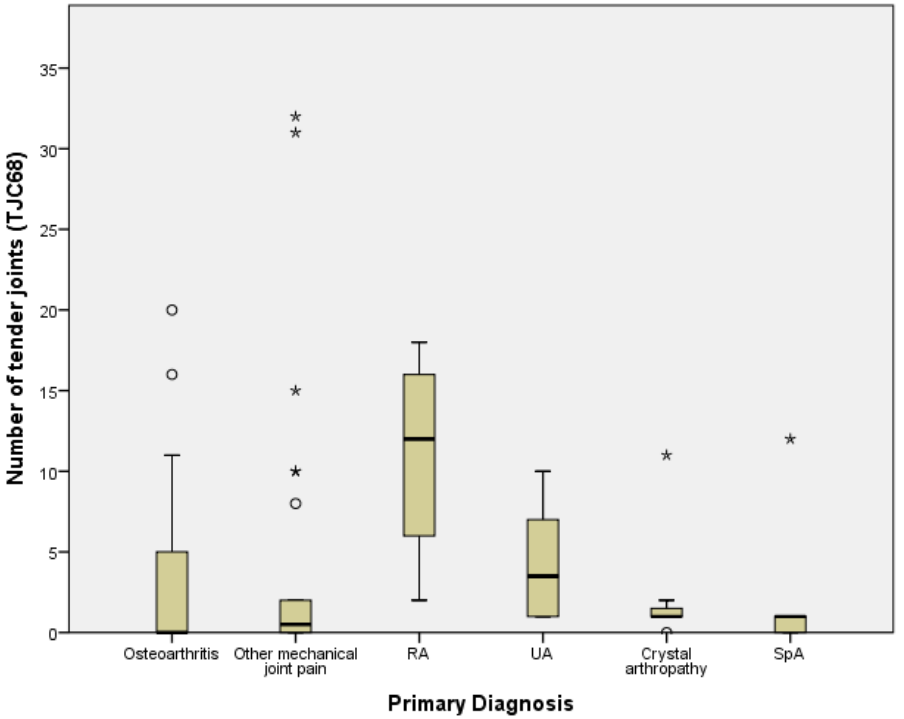
B) Symptom duration at first EAC assessment according to primary diagnosis.



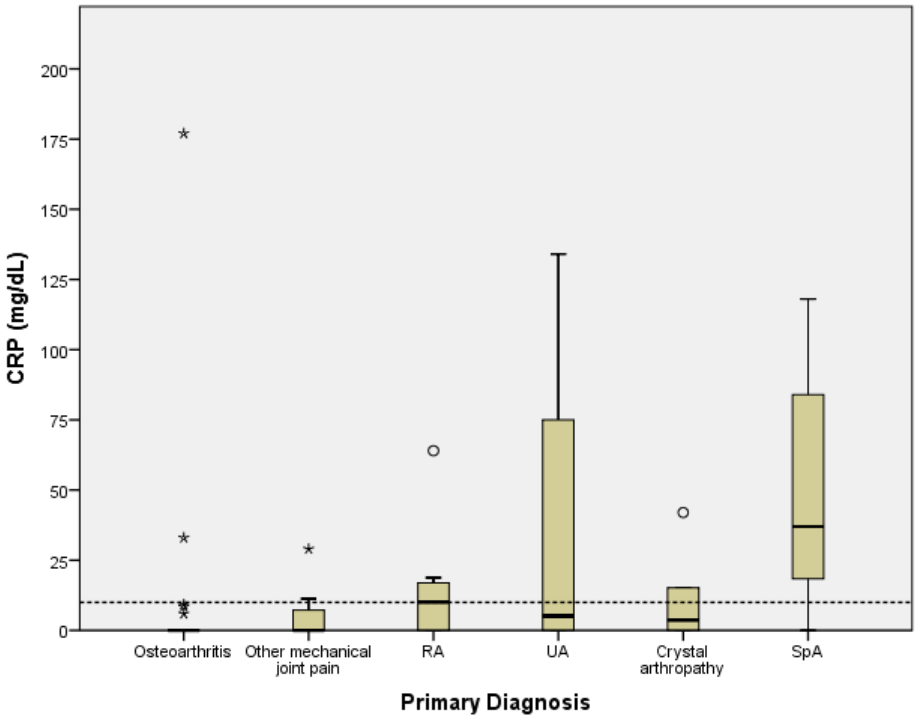
C) Duration of early morning stiffness at first EAC assessment according to primary diagnosis.



D) Number of tender joints at first EAC assessment according to primary diagnosis.



E) Value of CRP at first EAC assessment according to primary diagnosis.



5.4.2 Efficacy of triage

The majority of patients were referred by their GP (84/95 [88%] patients in whom the source of the referral was known). Date of referral was available in 93 patients; amongst these patients, the median (IQR) time between initial referral and first EAC assessment was 3 (2-5) weeks and the target for assessment within three weeks of referral was met in 55/93 (59%) patients. Three patients did not attend the first EAC appointment which was allocated to them. After exclusion of these patients, the maximum delay between initial referral and first EAC assessment was 10 weeks.

Further referral details were available in 86 patients. Documentation of at least one NICE indicator for urgent assessment was identifiable from referral information in 38 (44%) of these patients. Presence of at least one NICE indicator differed significantly across the IA categories: identified in 16/23 (70%), 2/9 (22%) and 20/54 (37%) patients with confirmed IA, possible IA and non-IA, respectively ($p=0.01$). The difference was not significant between patients with possible IA and non-IA ($p=0.5$), but significant between patients with confirmed IA and non-IA ($p=0.01$).

Presence of at least one NICE indicator within referral information was not associated with time to assessment. The median (IQR) time from referral to assessment was 3 (2-5) weeks in both patients with and without documentation of at least one indicator ($p=0.7$) (Table 15).

In the subset of patients with a primary diagnosis of RA or UA, at least one NICE indicator was identifiable in 6/8 (75%) and 7/8 (89%) with referral information available, respectively. There was variation in the indication for urgent referral. As may be expected due to the weighting of small joint involvement within the RA criteria, involvement of the small joints of the hands or feet and involvement of more than one joint were more prevalent in patients with RA (both documented in all six patients) in comparison to patients with UA (both documented in three patients). Duration of symptoms of at least three months at the time of referral was documented in with 3 (38%) patients with RA and 6 (75%) patients with UA.

Table 15. Referral information for one hundred all-comers to the EAC.
Patients grouped according to the presence of NICE indicators for urgent assessment and impression of IA. Values are number of patients (percentage of patients with complete data), unless otherwise stated.

	Presence of NICE indicator for urgent assessment within referral information			**Impression of IA at first EAC assessment**						
	None n=48	**At least 1 n=38**	**p**	**Non-IA n=65**	Missing Values	**Possible IA[a] n=11**	Missing Values	**Confirmed IA[b] n=24**	Missing Values	**p**
Source of referral: Primary care Secondary care	41 (85%) 7 (15%)	35 (92%) 3 (8%)	0.5	54(90%) 6(10%)	5	7(64%) 4(36%)	-	23(96%) 1(4%)	-	NA
Presence of NICE indicators for urgent assessment identifiable within referral letters: Suspected synovitis with…										
• Involvement of the small joints of hands/feet	-	27 (71%)	-	15(28%)	11	1(11%)	2	11(48%)	1	0.1
• Involvement of ≥1 joint		21 (55%)		10(19%)		1(11%)		10(43%)		0.04
• ≥3 months symptom duration at time of referral		21 (55%)		10(19%)		1(11%)		10(43%)		0.04
• At least 1 of the above		100%		20(37%)		2(22%)		16(70%)		0.01
Time between initial referral and first EAC assessment: median (IQR), weeks achieving ≤3 week target	3 (2-5) 29 (60%)	3 (2-5) 21 (55%)	0.7 0.6	3 (2-4) 38(64%)	6	3 (3-5) 6(55%)	1	4 (2-6) 11(48%)	1	0.5 0.4

NA: not assessed (>20% of cells with expected number <5, therefore not appropriate to perform Chi-square test).
[a]Possible IA defined as a primary impression of possible IA without current clinical joint swelling (i.e. history compatible with IA) at first EAC assessment.
[b]Confirmed IA defined as a primary diagnosis of IA and presence of at least one clinically swollen joint at first EAC assessment.

5.4.3 Management

5.4.3.1 Corticosteroids

Corticosteroids were prescribed for a total of 32 patients at the first EAC assessment: 23 patients received 120mg methylprednisolone (intramuscular and/or intra-articular), 7 patients received ≤120mg methylprednisolone and 2 patients were prescribed oral prednisolone (including 1 patient with polymyalgia rheumatica). The frequency with which any corticosteroids were administered across the prevalent primary diagnoses were: 7/27 (26%) patients with osteoarthritis, 2/26 (8%) patients with other mechanical joint pain, 4/9 (44%) patients with RA, 5/8 (63%) patients with UA, 4/8 (50%) patients with crystal arthropathy, and 4/6 (66%) patients with SpA.

Of note, 10 patients received treatment with corticosteroids prior to their first EAC assessment. They included patients with possible IA (crystal arthropathy [n=3], non-specific arthralgia [n=1]) and confirmed IA (RA and UA [each n=1]).

5.4.3.2 DMARDs

Fifteen patients were treated with DMARDs, either at their first EAC assessments or within the subsequent 12 months. The frequency of DMARD use in patients with a primary diagnosis of UA and RA is shown in Table 16. One patient with an initial primary diagnosis of UA, subsequently diagnosed with ANA-associated arthralgia and treated with hydroxychloroquine, was excluded. Other primary diagnoses in patients receiving DMARDs were psoriatic arthritis (n=2 receiving methotrexate), non-specific arthralgia (n=1, subsequently diagnosed as RA, receiving sulfasalazine), osteoarthritis and ANA-associated arthralgia (each n=1, receiving hydroxychloroquine).

5.4.4 Change in diagnosis over 12 months

Approximately one third of patients were discharged with a definitive diagnosis at their first EAC visit (n=29), one third were discharged within 12 months (n=37) and one third remained under follow-up at 12 months (n=34). The median (IQR) length of follow-up in patients discharged after their first EAC visit, but before 12 months, was 21 (11-29) weeks. In patients with at least one follow-up assessment, a change in diagnosis was observed in thirteen (Figure 1), including four patients with

non-specific arthralgia at their first EAC assessments who were subsequently diagnosed with mechanical joint pain (n=2), ANA-associated arthralgia (n=1) and RA (1 patient with ACPA-positivity who had received oral prednisolone from their GP prior to their first EAC assessment). No patients with a non-IA diagnosis at their first presentation were subsequently diagnosed with IA and only one patient with confirmed IA (unilateral knee swelling at their first EAC assessment, classifiable as monoarthritic UA) received a revised diagnosis of non-IA (ANA-associated arthralgia).

5.4.5 DMARD initiation in patients with UA and RA

One patient with a primary diagnosis of UA was excluded from the following analysis due revision of their diagnosis to ANA-associated arthralgia during follow-up. Of the remaining 16 patients with a consistent diagnosis of UA or RA from their first assessment, 9 (56%) commenced DMARDs within 12 months: 2/7 (29%) patients with UA and 7/9 (78%) patients with RA (Table 16). Patients who did not commence DMARDs experienced resolution of synovitis, either with (n=4) or without corticosteroids (n=1), or did not attend any follow-up (n=2). These patients were all seronegative for RF and ACPA and the majority presented with monoarthritis at their first assessment.

National standards for early DMARD commencement were achieved in two patients: one with UA commencing hydroxychloroquine within six weeks of referral and three months of symptom onset and one with RA commencing methotrexate within six weeks of referral. Time delays occurring at stages (i) to (iv) and factors contributing to delays at the level of the rheumatologist, identifiable from clinical notes, are shown in Table 16. Unfortunately it was not possible to establish when patients first sought medical attention from medical records, therefore the time between symptom onset and referral (stages i and ii combined) was reported. The commonest reason identified for delay at stage (iv) was consideration of therapy within a clinical trial, relevant in 4/7 (57%) patients with RA commencing DMARDs.

Table 16. Management and one year outcomes of patients diagnosed with UA or RA from their first EAC assessment.

Values are number of patients (%) and median (IQR) or actual values where number in the sample was small (n=2).

	UA (n=7)	RA (n=9)
Outcomes over 12 months:		
Commencement of DMARD therapy	2 (29%)	7 (78%)
Self-limiting/resolution with corticosteroids	3 (42%)[a]	2 (22%)[b]
Not attending any follow-up	2 (29%)[c]	0
First-line DMARD: Methotrexate	1 (14%)	6 (66%)
Hydroxychloroquine	1 (14%)[d]	0
Azathioprine	0	1 (11%)[e]
None	5 (71%)	2 (22%)
In patients commencing DMARD therapy:	(n=2)	(n=7)
Length of delays in DMARD initiation:		
• Stages (i) and (ii), time between symptom onset and referral, weeks	11, 203	29 (12-46)
• Stage (iii), time between referral and first EAC assessment, weeks	1, 5	6 (2-6)
• Stage (iv), time between first EAC assessment and DMARD initiation, weeks	0, 12	8 (4-27)
Total Rheumatologist Delay, stages (iii) and (iv):		
Time between referral and DMARD initiation:		
actual values or median (IQR), weeks	2, 18	14 (8-33)
achieving ≤6 week target	1 (50%)	1 (14%)
Total Delay, stages (i) to (iv):		
Time between symptom onset and DMARD initiation:		
actual values or median (IQR), weeks	13, 221	43 (28-80)
achieving ≤3 month target	1 (50%)	0
Factors contributing to delays at stage (iv):		
Diagnostic uncertainty	1	1
Contraindications to DMARDs	0	2[e,f]
Considering biologic clinical trial	0	4

[a]Synovitis resolved with a single dose of methylprednisolone in 3 patients (2 patients remaining under follow-up at 12 months and 1 patient discharged at 9 months). Clinical presentations in these patients were monoarthritis of the knee, monoarthritis of the midtarsal joint and polyarthritis affecting the wrists and MTPs.
[b]Synovitis resolved with a single dose of methylprednisolone in a patient, initially presenting with oligoarthritis of the hands/wrists, who remained under follow-up at 12 months. Synovitis resolved in a further patient without corticosteroids, initially presenting with monoarthritis of the knee, who was discharged at 9 months.
[c]Clinical presentations in these patients were monoarthritis of the knee and monoarthritis of the ankle.
[d-e]Contraindications to methotrexate occurring in one patient case each, including [d]deranged liver function tests and [e]abnormal chest-x-ray (interstitial lung disease later confirmed on CT).
[f]Abnormal chest-x-ray (pleural granuloma later confirmed on CT).

5.5 Discussion

This audit provides insight into the function of an EAC within a large rheumatology centre. It reports clinical characteristics of all-comers, including patients diagnosed with non-IA who formed the majority of patients referred to the clinic. Previous studies have largely excluded patients lacking joint swelling as determined by a rheumatologist (Govoni et al., 2013). Limited data are available from an Austrian rapid access clinic, demonstrating a diagnosis of degenerative joint pain in a quarter of patients referred, with discharge after initial assessment being possible in 43%, similar to the Leeds audit (Pflugbeil et al., 2009).

New-onset RA was detected in 10% of patients in this audit. With the Leeds EAC serving a secondary-care population of 800,000, receiving approximately 1000 referrals annually, this incidence of RA is consistent with rates reported across northern Europe (Guillemin et al., 1994; Söderlin et al., 2002; Savolainen et al., 2003; Pedersen et al., 2009; Humphreys et al., 2013).

At the time of this audit, room for improvement in order to meet the national standards for the timely commencement of DMARDs was identified. Symptom duration at first assessment in patients with IA was significant, consistent with previous studies (Kumar et al., 2007; Kiely et al., 2009; www.nao.org.uk, 2009; van der Linden et al., 2010; Raza et al., 2011) (see section 2.4.3). In line with these studies, the delay between symptom onset and referral to rheumatology contributed most to the total delay in DMARD initiation in patients with UA and RA, and, in the main, precluded achievement of the NICE recommendations for commencement of DMARDs within three months of symptom onset (www.nice.org.uk, 2009). Unfortunately, methods employed in this audit did not allow discrimination between delays arising at stages (i) or (ii), or the reasons for such.

Significant delays were observed at the level of the rheumatologist; between referral and the first EAC assessment (stage iii) and between the first EAC assessment and DMARD initiation (stage iv). With respect to stage (iii), almost half of patients were assessed later than the three week national standard for timely assessment which was due to be introduced (www.gov.uk, 2013). This included patients who were identified as having possible and confirmed IA, and those with a

primary diagnosis of UA or RA. Whilst the NICE indicators appear to be of use in the triage of patients with suspected IA, being observed more frequently in referral information for patients with confirmed IA, this audit suggests that they may not be the only factors used to prompt allocation of urgent EAC appointments. There was no association between the identification of NICE indicators within referral information and the time to assessment. This is justifiable as they were not universally present in referral information in patients with IA. Other expected differences in the characteristics of patients with the main non-IA and IA diagnoses, confirmed in this audit (such as early morning stiffness lasting over 30 min and abnormal CRP in patients with IA), may also have value in a triage process and may inform future procedures for allocating urgent appointments.

Although delay in DMARD initiation was noted at the level of the rheumatologist (stage iv), approximately half of patients with UA or RA were treated with intramuscular corticosteroid (120mg methylprednisolone) at their first assessment. The use of bridging corticosteroid therapy is standard practice in the management of early RA (Smolen et al., 2017) and there may be an argument for withholding DMARD therapy with a trial of corticosteroid in patients with IA with favourable prognostic factors. Audit data supports this, given that no ongoing synovitis or DMARD use was observed in a significant number of patients with UA or RA at their last visit within the subsequent 12 months. Delays in DMARD initiation may also be justifiable on clinical grounds, for example due to the need for further investigations in cases of diagnostic uncertainty or apparent contraindications to DMARDs. The necessity to provide patients with time to consider all options for treatment (including clinical trials) also appeared to be a factor in the delay. Since this audit, provision of appropriate study information to all patients potentially eligible for clinical trials is now recommended at their first assessment.

Limitations of this audit include its generalisability to other centres, including smaller district general hospitals. The method of sampling may have introduced bias in the range and frequency of clinical characteristics and diagnoses observed, due to seasonal variations in disease aetiology and/or symptoms (Iikuni et al., 2007). The reduced availability of clinic appointments over the Christmas period (clinics were not operating over two bank holidays) may also have contributed to delays in assessment. As noted by other groups, symptom onset may be subject to recall

bias (De Cock et al., 2013). Bias may also be present in the reasons identified for delay to DMARD initiation after rheumatology assessment; some factors, such as lack of follow-up appointments, may not have been obvious from retrospective review of clinical notes. Conclusions are limited by grouping patients into broad diagnostic categories, particularly 'other mechanical joint pains' which included complaints ranging from mild, localised complaints (e.g. epicondylitis) to widespread pains (e.g. with muscle deconditioning). Furthermore, patients with suspected new-onset SpA or connective tissue disease with associated IA may have been triaged to specific SpA and connective tissue disease clinics, respectively.

In order to optimise outcomes for patients with early IA, strategies to improve their earlier assessment, both prior to and after referral, are required. The use of a referral pro forma in primary care, to include the NICE clinical indicators for urgent referral as well as other relevant factors such as CRP and early morning stiffness, may assist in creating a more efficient triage system. Earlier recognition of eligibility for treatment within a clinical trial may also streamline the commencement of treatment. Although the 2010 ACR/EULAR RA criteria may be a useful guide in assessing the need for DMARDs in daily practice, they were developed for use as classification criteria in clinical trials (as opposed to diagnostic criteria) and are not entirely sensitive or specific (Sakellariou, G. et al., 2013; Radner et al., 2014), as suggested by this audit. It is problematic to draw conclusions in patients with UA and RA, defined according to these criteria, in this audit due to their small numbers. Further data are needed in order to describe the phenotype and assess outcomes in patients classified with prospective application of these criteria.

Chapter 6 : **What are the Clinical and Imaging Phenotypes of Patients with New-Onset UA and RA, Defined According to the 2010 ACR/EULAR Criteria?**

Does inclusion of ultrasound synovitis within the criteria improve the differentiation of patients with erosive disease?

6.1 Introduction

With awareness of the importance of early, aggressive treatment in the management of RA, the need for sensitive, accurate diagnostic tools has become paramount. Defining features of RA include small joint synovitis and bone erosions; however, existing methods for their detection (clinical examination and radiography, respectively) have limitations. Clinical examination is known to be poorly reproducible and may be inaccurate (Wakefield et al., 2004; Salaffi et al., 2008; Marhadour et al., 2010), and radiography is poorly sensitive for the detection of erosions, particularly in early disease (van der Heijde et al., 2013). Ultrasound is becoming increasingly used in clinical practice as a sensitive measure of synovitis and erosion, in determining the phenotype of patients with early IA (Colebatch et al., 2013; Combe et al., 2017).

Review of the literature has identified a number of questions pertinent to understanding the clinical and imaging phenotype of early IA, which remain to be answered, particularly in the context of the new 2010 ACR/EULAR RA criteria. It has been proposed that the addition of ultrasound, in the assessment of joint involvement, may improve the accuracy of the criteria (Nakagomi et al., 2013). However this study used an extensive 38-joint count which may not be feasible in clinical practice and included patients lacking clinical evidence of synovitis (in whom the criteria are not intended for). The 2010 ACR/EULAR RA criteria include the optional use of ultrasound in the determination of joint involvement, although a definition for ultrasound synovitis is not given (Aletaha, D. et al., 2010).

Whilst ultrasound assessment of inflammation has been recommended by experts in the diagnosis of IA in clinical practice (Combe et al., 2017), the majority of ultrasound studies have been conducted prior to development of the 2010 RA criteria or in heterogeneous groups of early IA patients (including UA, RA and other diagnoses). Less is understood regarding the validity of ultrasound assessment of erosions (Colebatch et al., 2013). Reports of the prevalence of ultrasound erosions in early, treatment-naïve IA (including patients with UA) are limited to studies of a small number of joints (Funck-Brentano et al., 2009; Sheane et al., 2009). It has been suggested that erosion observed in association with ultrasound synovitis (GS and/or PD) may be specific to IA (Millot et al., 2011).

A greater understanding is required of clinical and imaging phenotypes of patients with early UA and RA, classified using the 2010 RA criteria. Knowledge of the prevalence, distribution and agreement between clinical and ultrasound synovitis, as well as x-ray and ultrasound erosions and 'active' erosions (erosion observed in association with ultrasound synovitis), is needed in such patients. This will help to establish the optimal use of ultrasound in the classification of IA and guide future research in determining its prognostic value. In particular, it is important to determine whether inclusion of ultrasound synovitis within the 2010 RA criteria improves the accuracy of disease classification.

6.2 Aims and Objectives

- To describe the clinical and imaging phenotypes of patients with new-onset, DMARD-naïve IA (specifically UA and RA, classified according to the 2010 ACR/EULAR RA criteria).
- To evaluate the prevalence, distribution and concordance between clinical and ultrasound synovitis, and erosions and 'active' erosions (associated with ultrasound synovitis) detectable by radiography and ultrasound.
- To assess the proportion of patients with UA or RA whose disease may be reclassified with consideration of ultrasound evidence of synovitis in the application of the 2010 RA criteria.
- To determine whether reclassification with the use of ultrasound is more discriminating for the presence of erosions at diagnosis than application of the classification criteria using clinical findings alone.

6.3 Methods

A prospective, observational study was conducted in patients with new-onset, DMARD-naïve UA and RA, presenting to the Leeds EAC between June 2010 and September 2012 (see Chapter 4). Baseline data from this study was analysed. Additional exclusion criteria for these analyses were: incomplete clinical, ultrasound and x-ray data at baseline and change of initial diagnosis to an alternative non-RA diagnosis within 12 months of follow-up.

6.3.1 Assessments

Baseline assessments were recorded as per sections 4.2 and 4.3. Patients were primarily classified as RA or UA according to whether they fulfilled the 2010 ACR/EULAR RA criteria, or not, using clinical findings alone to determine their score for joint involvement.

Subsequently, the criteria were applied in the following two ways; (i) considering both clinical and ultrasound findings of significant synovitis, and (ii) ultrasound findings of significant synovitis alone, in the determination of joint involvement. Therefore, a joint was considered involved in the presence of; (i) clinical swelling and/or tenderness and/or GS≥grade 2 and/or PD≥grade 1 (see section 4.3.3 for further details regarding the definition of ultrasound synovitis), or (ii) on the basis of GS≥grade 2 and/or PD≥grade 1 only. Therefore, ultrasound of 24 joints (first MTPs being excluded as per 2010 RA criteria) enabled the categorisation of patients on the basis of:

(i) Clinical and ultrasound findings of synovitis;
    - Patients with UA reclassified as RA in the instance of sufficient clinical and subclinical synovitis ($UA \rightarrow RA_{clinical+US}$). Alternatively, their disease remained classified as UA ($UA \rightarrow UA_{clinical+US}$).

(ii) Ultrasound findings of synovitis alone;
    - Patients with UA reclassified as RA in the instance of sufficient subclinical synovitis ($UA \rightarrow RA_{US}$). Alternatively, their disease remained classifiable as UA ($UA \rightarrow UA_{US}$).

- Patients with RA reclassified as UA in the instance insufficient ultrasound synovitis ($RA \rightarrow UA_{US}$). Alternatively, their disease remained classified as RA ($RA \rightarrow RA_{US}$).

6.3.2 Statistics

Characteristics were compared between patients with UA and RA. Differences were evaluated using Chi-Squared or Fisher's exact tests for categorical variables (as appropriate for numbers of expected values), and t-tests for continuous variables following a normal distribution (Shapiro-Wilks test was utilised to assess for normality). For non-parametric data, Mann-Whitney-U testing was performed.

Descriptive summary statistics were used to analyse the concordance between clinical and ultrasound-detected synovitis, and x-ray and ultrasound-detected erosions. Other tests for agreement, such as kappa statistics, were not performed due to the variation in the prevalence of ultrasound findings according to joint site.

The ability of the 2010 ACR/EULAR RA criteria to discriminate patients with evidence of erosive disease at baseline (presence of any x-ray or ultrasound erosion) was determined by comparing the rates of erosive disease between: (i) patients with UA who were reclassified, using ultrasound findings in addition to clinical findings, as RA ($UA \rightarrow RA_{clinical+US}$) and patients with UA whose disease remained classified as UA ($UA \rightarrow UA_{clinical+US}$), and (ii) patients with RA who were reclassified, using ultrasound findings alone, as UA ($RA \rightarrow UA_{US}$) and patients with RA whose disease remained classified as RA ($RA \rightarrow RA_{US}$).

6.4 Results

6.4.1 Patients

During the study period, 1946 patients were referred to the Leeds EAC; 441 patients, with suspected new-onset IA, were screened for inclusion in the study. In total, 333 were DMARD-naïve with new-onset UA or RA (Figure 3). Fifteen patients received an alternative diagnosis (other than UA or RA) over 12 months of follow-up and were therefore excluded. Of the remaining patients, clinical and imaging joint

assessments were complete for 235 patients at baseline; 38 were diagnosed with UA and 197 fulfilled 2010 ACR/EULAR RA classification criteria (with joint involvement determined by clinical examination). Differences between included patients (n=235) and those excluded due to incomplete data (n=83) were statistically significant ($p<0.05$) for age, clinical joint involvement (as defined within 2010 ACR/EULAR RA criteria) and swollen joint counts. These were all greater in included patients (Table 17).

Figure 3. Disposition of patients registered in the longitudinal prospective observational study and included in the analysis of clinical and imaging phenotype.

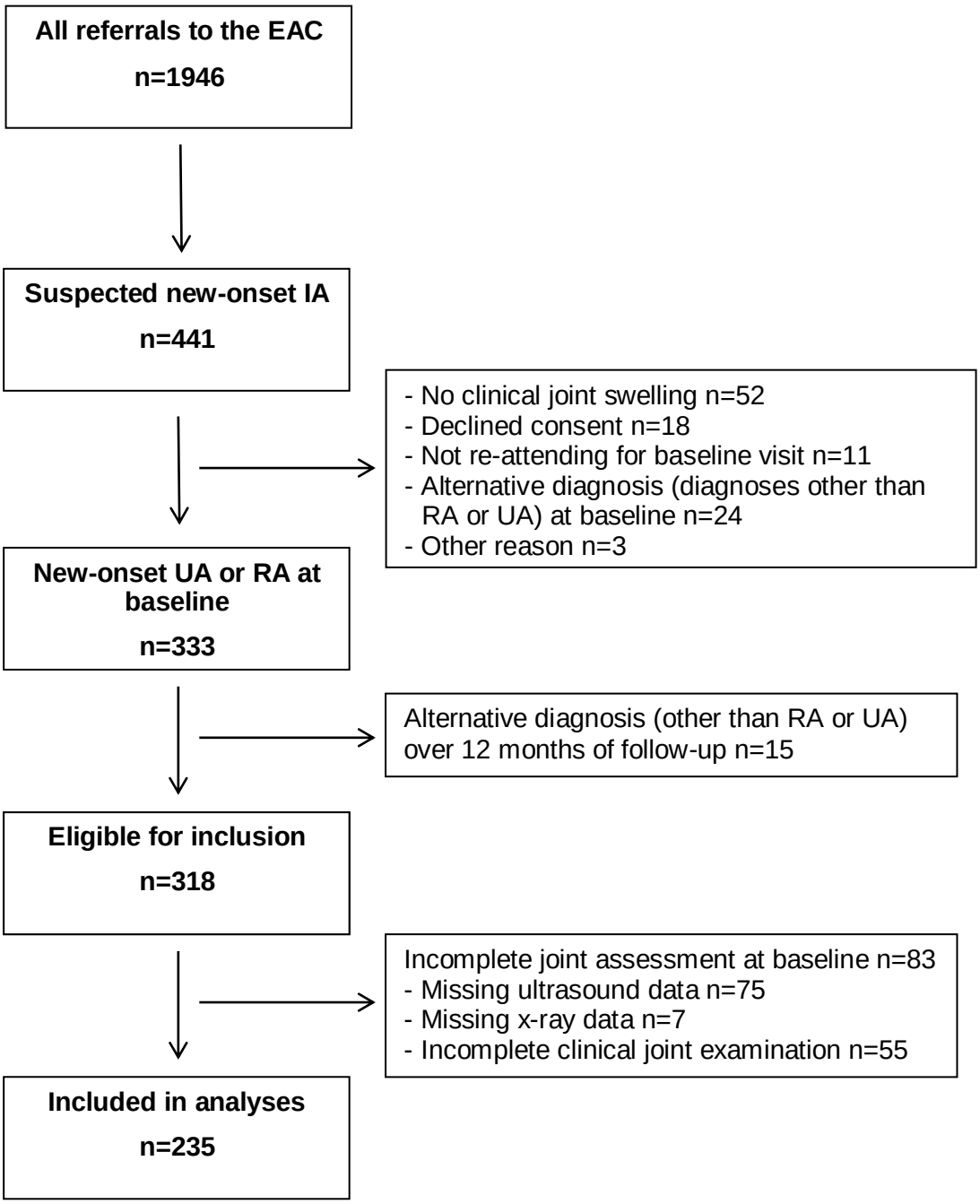


Table 17. Baseline characteristics of all patients with new-onset UA and RA included in the analysis of clinical and imaging phenotype, and those excluded due to incomplete data.

Values are median (IQR) or n (%) unless otherwise stated.

	Included in analyses		**Excluded due to incomplete data**		**p**
	(n=235)	Missing Values	**(n=83)**	Missing Values	
Age, mean (SD)	55 (14)	-	51 (15)	-	**0.03**
Female	163 (69%)	-	64 (77%)	-	0.2
BMI, mean (SD)	28 (5)	23	29 (6)	18	0.1
Symptom duration, months	7 (4-13)	-	8 (4-16)	-	0.7
Current/previous smoker	134 (57%)	-	52 (64%)	2	0.3
Number of comorbidities: 1 2 3 ≥4	71 (30%) 50 (21%) 26 (11%) 11 (5%)	-	17 (20%) 12 (14%) 9 (11%) 9 (11%)	-	0.5
History/current evidence of coexistent osteoarthritis	81 (34%)	-	27 (33%)	-	0.7
≥1 feature of SpA	26 (11%)	-	7 (8%)	-	0.5
Clinical joint involvement: 1M/L 2-10 M/L 1-3 S 4-10 S >10 (at least 1 S)	2 (1%) 3 (1%) 36 (15%) 82 (35%) 112 (48%)	-	1 (1%) 1 (1%) 20 (24%) 33 (40%) 28 (34%)	-	**0.02**
Pattern of joint swelling: Palindromic arthritis Monoarthritis (SJC=1) Oligoarthritis (SJC=2-4) Polyarthritis (SJC>4)	 1 (<1%) 28 (12%) 83 (35%) 123 (52%)	-	 1 (1%) 13 (16%) 35 (43%) 33 (40%)	1	0.06
Symmetrical joint swelling	150 (64%)	-	50 (60%)	-	0.6
RF positive	139 (59%)	-	47 (57%)	-	0.7
ACPA positive	138 (59%)	-	50 (60%)	-	0.8
Fulfilment of RA classification criteria (clinically): 1987 ACR RA 2010 ACR/EULAR RA	134 (57%) 197 (84%)	-	44 (53%) 64 (77%)	- -	0.5 0.2
Early Morning Stiffness ≥60 min	165 (70%)	-	65 (78%)	-	0.2
TJC28	7 (3-14)	-	6 (3-10)	2	0.2
SJC28	4 (2-8)	-	4 (1-6)	2	**0.04**
RAI	6 (4-10)	-	4 (2-9)	55	0.07
SJC44	5 (3-9)	-	3 (2-5)	55	**0.006**
CRP, mg/L	13 (0-34)	-	12 (0-27)	-	0.5
Patient VASDA, mm	50 (25-69)	48	50 (26-81)	53	0.7
DAS28-CRP	4.5(3.6-5.5)	48	4.5(3.4-5.2)	53	0.6
DAS44-CRP	2.9(2.3-3.5)	48	2.8(1.7-3.5)	63	0.4
HAQ	1.0(0.4-1.6)	40	0.8(0.3-1.8)	54	0.8
Ultrasound of 26 joints: Number of joints GS≥grade 1 Number of joints GS≥grade 2 Total GS score Number of joints PD≥grade 1 Total PD score	 10 (7-14) 5 (2-9) 16 (9-25) 2 (0-4) 3 (0-6)	-	NR	75	NR
Ultrasound erosion (in PIP2-3, MCP2-3, wrists or MTP2-4)	91 (39%)	-	NR	75	NR
Radiographic erosion in the hands and feet: Any 1987 ACR definition 2010 ACR/EULAR definition	34 (14%) 21 (9%) 15 (6%)	-	14 (18%) 11 (14%) 5 (7%)	7	0.4 0.1 1.0

M/L: medium-sized or large joint, L: large joint, S: small joint (according to definitions employed in the 2010 ACR/EULAR RA criteria).

6.4.2 Baseline characteristics of patients with UA and RA

Baseline characteristics are shown in Table 18. In line with the weighting of joint involvement and serology within the 2010 ACR/EULAR RA criteria, patients with RA had more extensive joint involvement (evidenced by greater clinical, laboratory and ultrasound measures of disease activity) and only a minority of patients with UA were seropositive for ACPA and/or RF. Patients with UA were also significantly younger and demonstrated lower rates of smoking, comorbidity and osteoarthritis. Features of SpA were more frequently recorded in patients with UA: at least one feature was documented in one quarter of patients with UA, in comparison to 9% of patients with RA (p=0.02).

Four patients who did not fulfil 2010 ACR/EULAR RA criteria fulfilled the 1987 ACR RA criteria, at baseline. In comparing patients fulfilling either of the 2010 or 1987 criteria (n=201) to patients fulfilling neither criteria (n=34), differences were observed between these groups for the same variables, with the exception of the number of comorbidities and evidence of osteoarthritis which were no longer significant.

Table 18. Comparison of baseline characteristics between patients with UA and RA (defined according to fulfilment of 2010 ACR/EULAR RA criteria, with joint involvement determined by clinical swelling and/or tenderness).

Values are median (IQR) or n (%) unless otherwise stated.

	UA		RA		p
	(n=38)	Missing Values	(n=197)	Missing Values	
Age, mean (SD)	44 (15)	-	57 (13)	-	**<0.001**
Female	26 (68%)	-	137 (70%)	-	0.9
BMI, mean (SD)	27 (6)	4	28 (5)	19	0.9
Symptom duration, months	10 (3-19)	-	7 (4-13)	-	0.2
Current/previous smoker	15 (39%)	-	119 (60%)	-	**0.02**
Number of comorbidities: 1 2 3 ≥4	14 (37%) 3 (8%) 4 (11%) 0	-	57 (29%) 47 (24%) 22 (11%) 11 (6%)	-	**0.02**
History/current evidence of coexistent osteoarthritis	7 (18%)	-	74 (38%)	-	**0.02**
≥1 feature of SpA	9 (24%)	-	17 (9%)	-	**0.02**
Clinical joint involvement: 1M/L 2-10 M/L 1-3 S 4-10 S >10 (at least 1 S)	2 (5%) 2 (5%) 15 (39%) 19 (50%) 0	-	0 1 (1%) 21 (11%) 63 (32%) 112 (57%)	-	**<0.001**
Pattern of joint swelling: Palindromic arthritis Monoarthritis (SJC=1) Oligoarthritis (SJC=2-4) Polyarthritis (SJC>4)	 0 11 (29%) 18 (47%) 9 (24%)	-	 1 (1%) 17 (9%) 65 (33%) 114 (58%)	-	**<0.001**
Symmetrical joint swelling	13 (34%)	-	137 (70%)	-	**<0.001**
RF positive	2 (5%)	-	137 (70%)	-	**<0.001**
ACPA positive	3 (8%)	-	135 (69%)	-	**<0.001**
Fulfilment of 1987 ACR RA classification criteria	4 (11%)	-	130 (66%)	-	**<0.001**
Early Morning Stiffness ≥60 min	17 (45%)	-	148 (75%)	-	**<0.001**
TJC28	4 (2-6)	-	8 (4-14)	-	**<0.001**
SJC28	2 (1-4)	-	5 (3-9)	-	**<0.001**
RAI	4 (2-6)	-	8 (4-10)	-	**<0.001**
SJC44	2 (1-4)	-	5 (3-10)	-	**<0.001**
CRP, mg/L	7 (0-22)	-	14 (0-38)	-	**0.03**
Patient VASDA, mm	45 (25-68)	8	50 (26-71)	40	**0.03**
DAS28-CRP	3.8(3.0-4.5)	8	4.8(3.7-5.7)	40	**<0.001**
DAS44-CRP	2.4(1.7-2.9)	8	3.1(2.4-3.7)	40	**<0.001**
HAQ	0.3(0.1-0.9)	6	1.1(0.5-1.6)	34	**<0.001**
Ultrasound of 26 joints: Number of joints GS≥grade 1 Number of joints GS≥grade 2 Total GS score Number of joints PD≥grade 1 Total PD score	 7 (4-10) 2 (1-5) 10 (5-17) 1 (0-1) 1 (0-2)	-	 11 (7-14) 6 (3-9) 18 (11-26) 2 (0-4) 3 (0-8)	-	 **<0.001** **<0.001** **<0.001** **<0.001** **<0.001**
Ultrasound erosion (in PIP2-3, MCP2-3, wrists or MTP2-4)	4 (11%)	-	87 (44%)	-	**<0.001**
Radiographic erosion in the hands and feet: Any 1987 ACR definition 2010 ACR/EULAR definition	 3 (8%) 1 (3%) -	-	 31 (16%) 20 (10%) 15 (8%)	-	 0.2 0.2 0.1

6.4.3 Inflammation

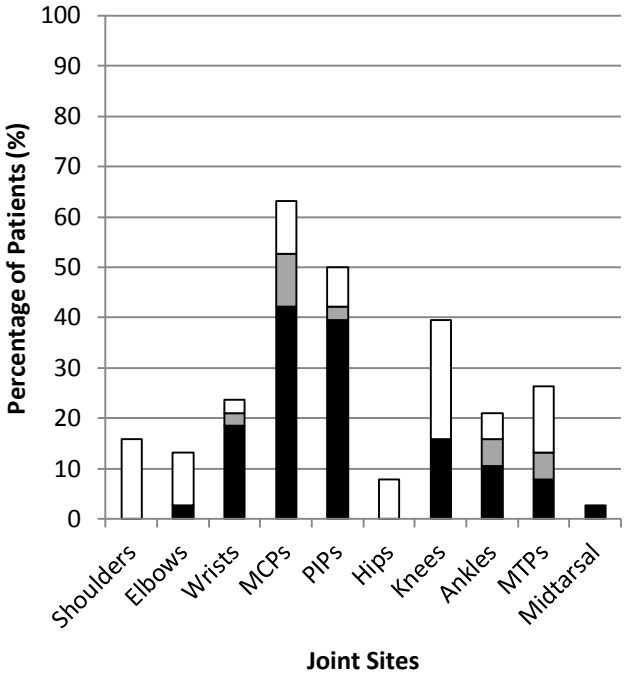
6.4.3.1 Clinical synovitis

Figure 4 illustrates the frequency of joint involvement determined by clinical examination (swelling and/or tenderness) in patients with UA and RA. There was predominance for clinical involvement of the small joints in the hands in both groups. Clinical swelling was detected in at least one MCP or PIP joint in 26/38 (68%) patients with UA and 173/197 (88%) patients with RA (p=0.001). A further four (11%) patients with UA and 13 (7%) patients with RA had tenderness without swelling of at least one of these joints.

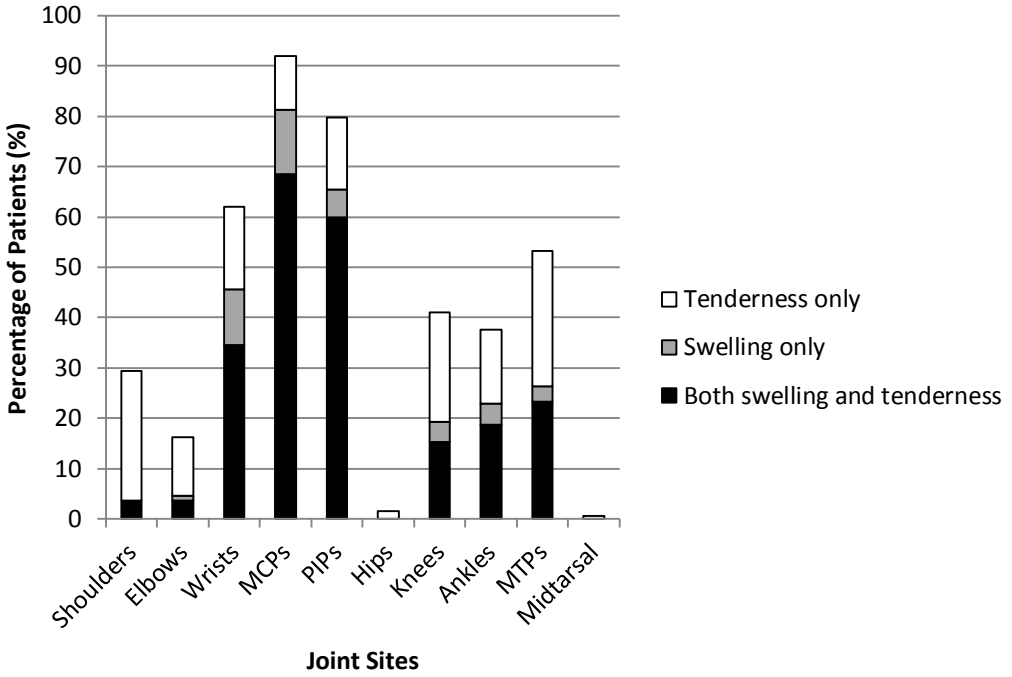
In patients lacking any swelling of the small joints of the hands, swelling was most frequently detected at the following sites: wrists (4/12 patients with UA and 17/24 patients with RA), knees (4/12 patients with UA and 5/24 patients with RA), MTPs (2/12 patients with UA and 4/24 patients with RA), ankles (2/12 patients with UA and 3/24 patients with RA), elbows (1 patient with UA) and shoulders (1 patient with RA). Joint swelling was less frequently symmetrical in patients with UA (34%) in comparison to patients with RA (70%, p<0.001), although this may be expected due to the greater number of swollen joints present in the latter group.

Figure 4. Percentage of patients with clinical swelling and/or tenderness detected in at least one joint per joint site, in patients with A) UA and B) RA.

A) Clinical Findings in Patients with UA at baseline.



B) Clinical Findings in Patients with RA at baseline.



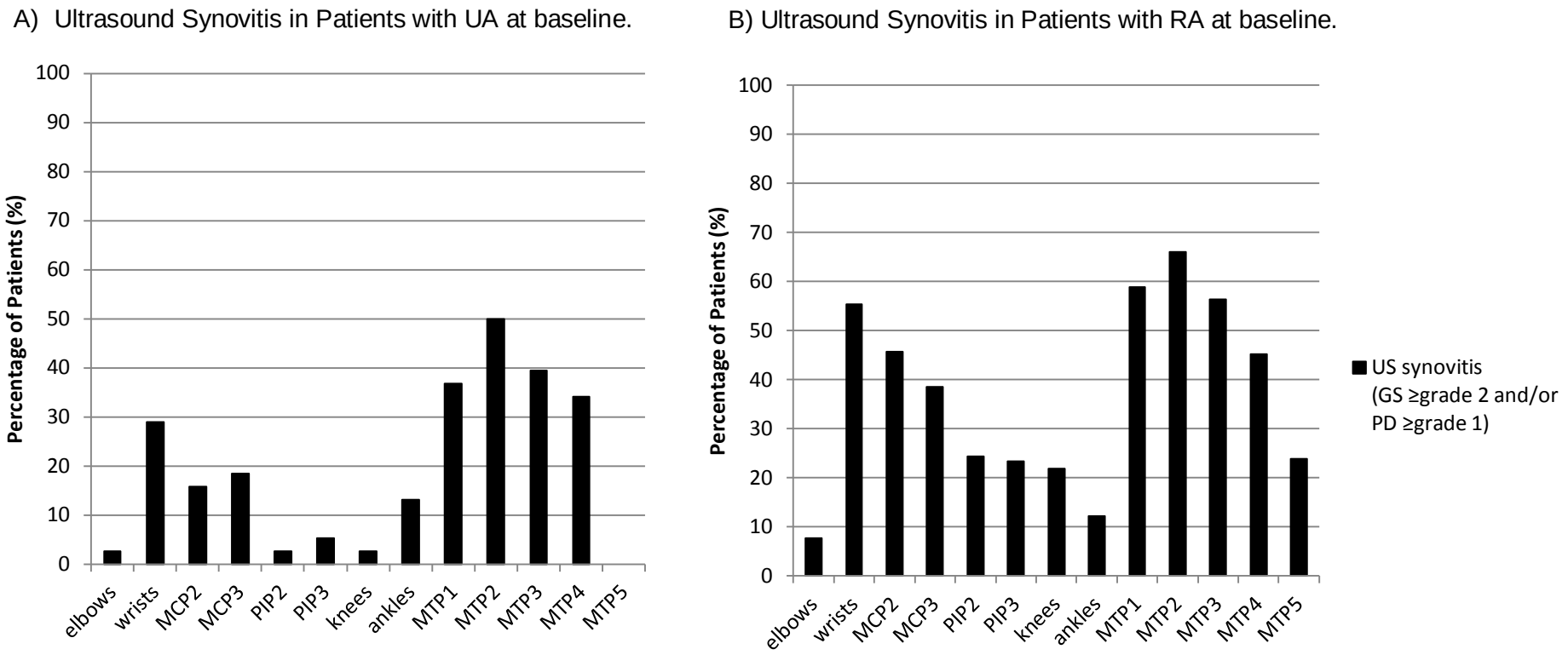
6.4.3.2 Synovitis detected by ultrasound

The majority of patients demonstrated significant ultrasound synovitis (GS≥grade 2 and/or PD≥grade 1) within the 26 joints examined. This was present in at least one of the 26 joints in 32/38 (84%) patients with UA and 184/197 (93%) patients with RA. A further three (8%) patients with UA and 12 (6%) patients with RA demonstrated GS=grade 1 only.

The location of ultrasound synovitis was similar between patients with UA and RA (Figures 5 and 6). There was preponderance for the presence of ultrasound synovitis at the MTPs, wrists and MCPs in both groups. The proportion of patients in which ultrasound synovitis was detected in at least one of these joints, in patients with UA and RA, respectively, was as follows: MTP2 (50% and 66%), MTP1 (37% and 59%), MTP3 (39% and 56%), MTP4 (34% and 45%), wrists (29% and 55%), MCP2 (16% and 46%) and MCP3 (18% and 39%). Ultrasound synovitis at MTP5 was observed exclusively in patients with RA.

Ultrasound synovitis was symmetrical (significant synovitis observed bilaterally in at least one joint site, i.e. bilateral involvement of the elbows, wrists, MCPs, PIPs, knees, ankles or MTPs) in 18 (47%) of patients with UA and 153 (78%) of patients with RA. A number of patients had symmetry at the MTPs alone (10 [26%] patients with UA and 49 [25%] patients with RA), whilst eight (21%) of patients with UA and 104 (53%) of patients with RA demonstrated symmetry in at least one other joint site.

Figure 5. Percentage of patients with ultrasound (US) synovitis (GS≥grade 2 and/or PD≥grade 1) affecting at least one joint on bilateral ultrasound examination in patients with A) UA and B) RA.

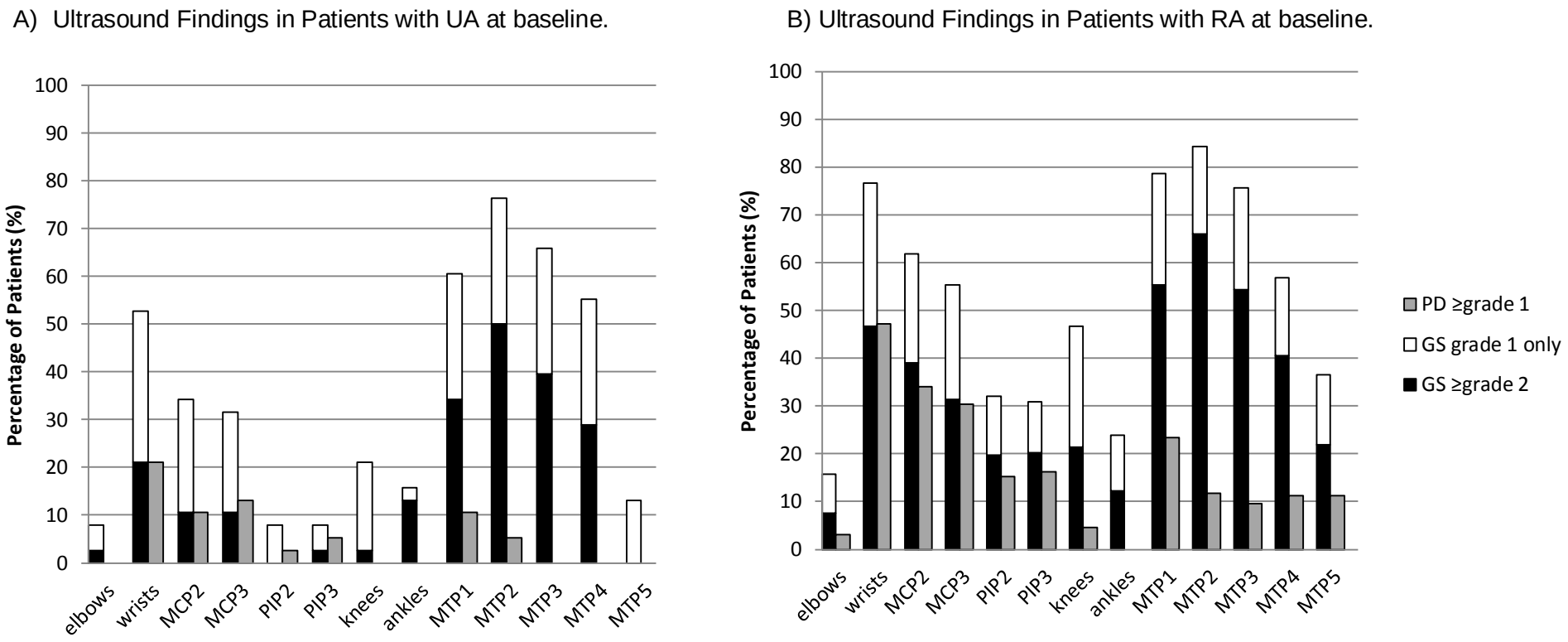


Power Doppler was most frequently observed in association with significant GS synovitis (Table 19). The distributions of GS and PD findings are depicted in Figure 6. The frequency of GS synovitis was the major contributing factor to the high prevalence of ultrasound synovitis observed at MTPs2-4. In contrast, the prevalence of PD was approximately similar to the prevalence of GS synovitis at the wrists and MCPs2-3, at the patient level. Power Doppler was most commonly observed at the wrists, MCPs2-3 and MTP1.

Table 19. Relationship between GS and PD synovitis, at the joint level (n=6110 joints).

		PD Activity	
		Absent (grade 0)	Present (≥grade 1)
GS Synovitis	Absent (grade 0)	3708	6
	Grade 1 only	897	128
	Significant (≥grade 2)	897	474

Figure 6. Percentage of patients with GS and PD affecting at least one joint on bilateral ultrasound examination in patients with A) UA and B) RA.



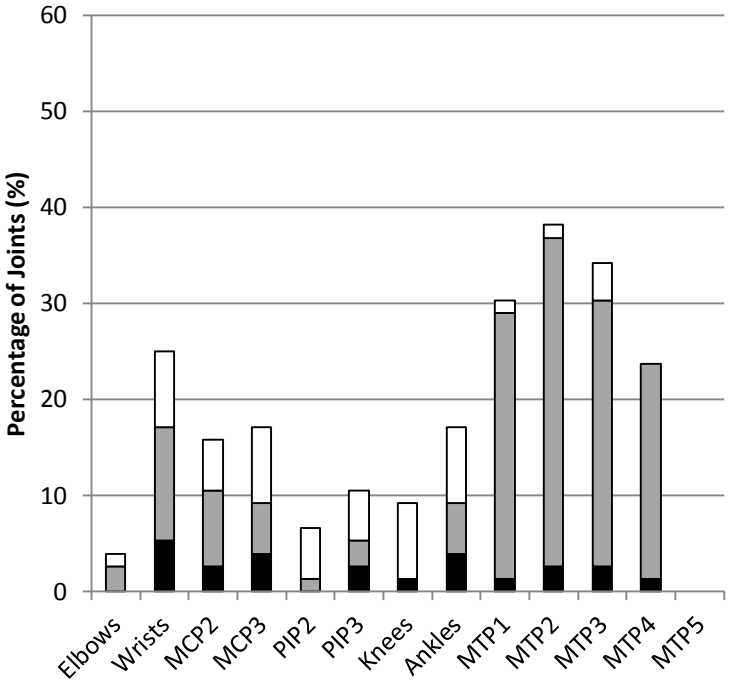
6.4.3.3 Concordance between clinical and ultrasound examination for the detection of synovitis

Of 6110 joints examined both clinically and by ultrasound, 913 were clinically swollen. Of these swollen joints, significant ultrasound synovitis was demonstrated in 439 (48%) joints. Grade 1 GS changes without PD were observed in a further 113 (12%) joints. Amongst non-swollen joints (n=5197), significant ultrasound synovitis was detected in 1066 (21%) joints. Tenderness on clinical examination was detected in only 259/1066 (24%) of these joints.

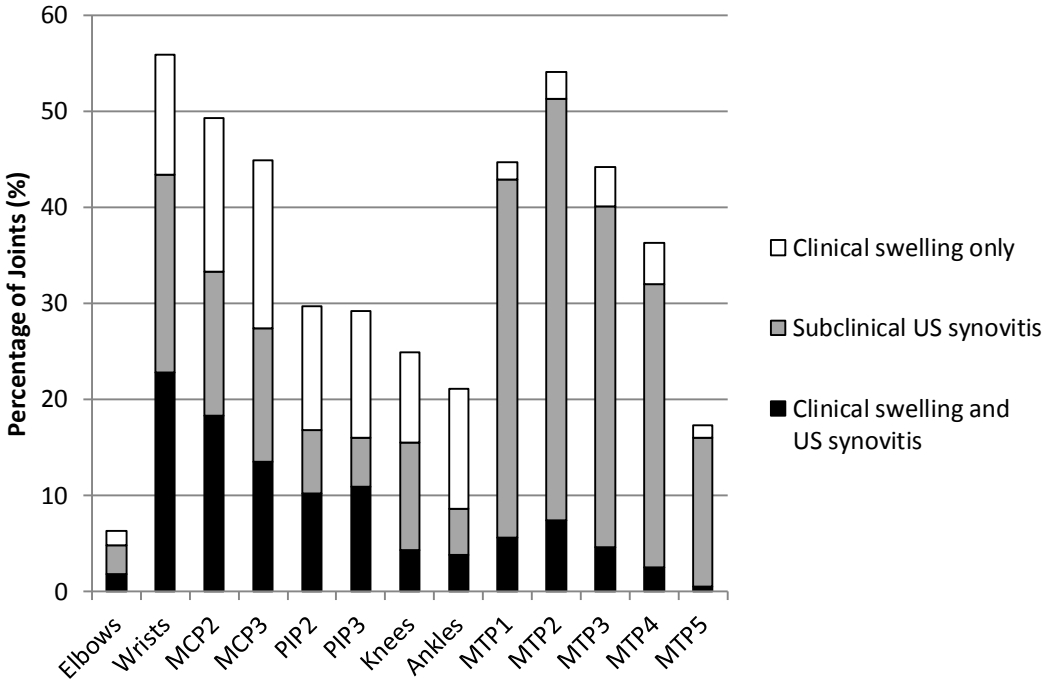
At the patient level, subclinical synovitis (GS≥grade2 and/or PD≥grade1 in the absence of clinical swelling) was observed in at least one joint in 28/38 (74%) patients with UA and 177/197 (90%) patients with RA (p=0.006). The median (IQR) number of joints with subclinical synovitis was 2 (0-4) and 5 (2-7) in patients with UA and RA, respectively (p=0.001). The distribution of subclinical synovitis in patients with UA and RA was similar (Figure 7); subclinical synovitis was most prevalent at the MTP joints, followed by the wrists.

Figure 7. Frequency of synovitis detectable by clinical examination (swelling) and ultrasound (GS≥grade 2 and/or PD≥grade 1), at the joint level, in patients with A) UA and B) RA.

A) Clinical and Ultrasound Findings in Patients with UA.



B) Clinical and Ultrasound Findings in Patients with RA.



6.4.4 Erosions

6.4.4.1 Radiography

Erosions were detected on x-ray in three (8%) and 31 (16%) patients with UA and RA, respectively. Fifteen (8%) patients with RA had erosive disease to constitute classification as erosive RA according to the EULAR definition (van der Heijde et al., 2013); all fifteen also fulfilled the 2010 ACR/EULAR RA classification criteria regardless of x-ray findings, in line with the intended high specificity for this definition (van der Heijde et al., 2013). The commonest sites for erosions detectable by x-ray were: the wrists (n=16), MTP5 (n=13), MTP2 (n=8), MTP3 (n=7) and MCP2-3 (n=6).

In joints of the hands and feet examined exclusively by radiography, erosions were observed at MTP1 (n=3), MCP4 (n=2), MCP5 (n=2), PIP4 (n=2), MCP1 and PIP5 (each n=1). Of note, all patients with x-ray erosions in joints of the hands and feet examined exclusively by radiography also displayed x-ray erosions in joints evaluated by both methods, except for a single patient with UA with bilateral x-ray erosions at MTP1 only.

6.4.4.2 Ultrasound

Ultrasound of 18 joints (wrists, MCPs2-3 and MTPs2-5) detected at least one erosion in four (11%) and 87 (44%) patients with UA and RA, respectively. Only one patient with UA and 20 (10%) patients with RA demonstrated ultrasound erosions in at least three joints included in the EULAR definition of erosive RA. Erosions detectable by ultrasound were most frequently observed at MTP5 (n=48), MCP2 (n=32), wrists (n=22) and MCP3 (n=12), see Figure 8.

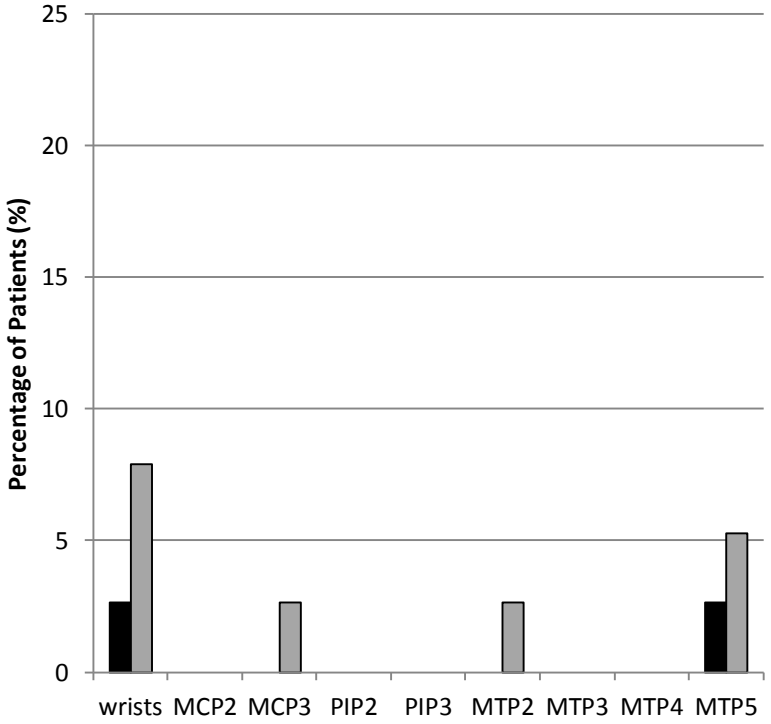
6.4.4.3 Concordance between radiography and ultrasound for the detection of erosion

Of 4230 joints evaluated for erosions by both radiography and ultrasound, erosions were detected exclusively by radiography in 54 (1.3%) joints, exclusively by ultrasound in 215 (5%) joints and by both modalities in 39 (0.9%) joints. Erosions were demonstrated in a greater number of joints with ultrasound than with x-ray at all sites examined with exception of MTPs2-4 (Figure 8).

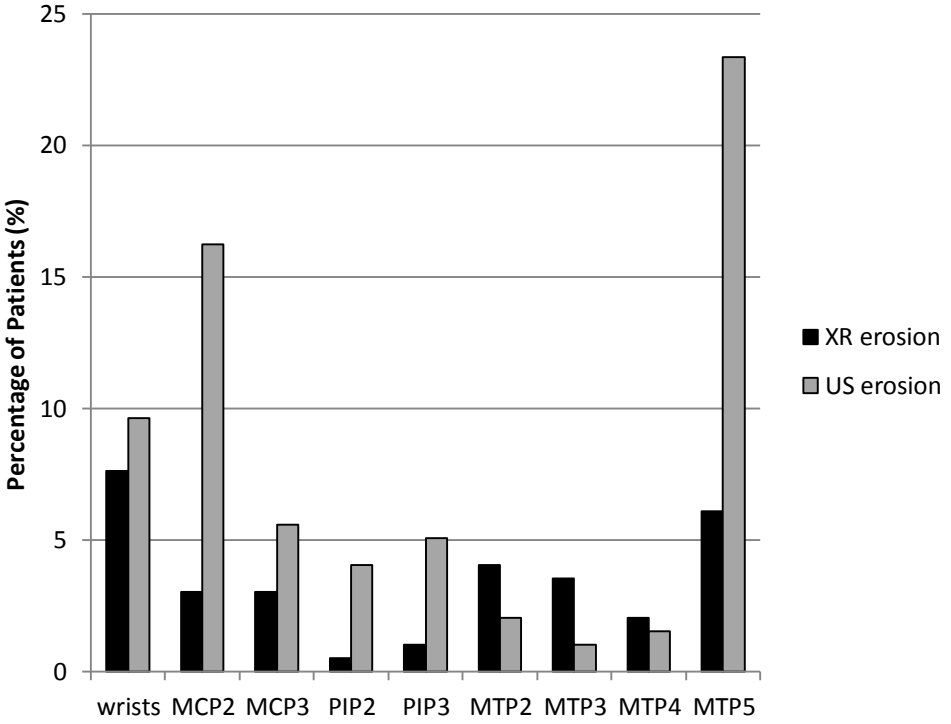
At the patient level, amongst patients with UA, erosive disease was demonstrated by radiography alone in one (3%) patient, ultrasound alone in two (5%) patients and both modalities in a further two (5%) patients. Amongst patients with RA, erosive disease was detected by radiography alone in five patients (3%), ultrasound alone in 61 (31%) patients and both imaging methods in 26 (13%) patients.

Figure 8. Percentage of patients with erosion detected by x-ray and/or ultrasound in at least one joint on bilateral imaging (at sites examined by both modalities), in patients with A) UA and B) RA.

A) Distribution of Erosions in Patients with UA at baseline.



B) Distribution of Erosions in Patients with RA at baseline.



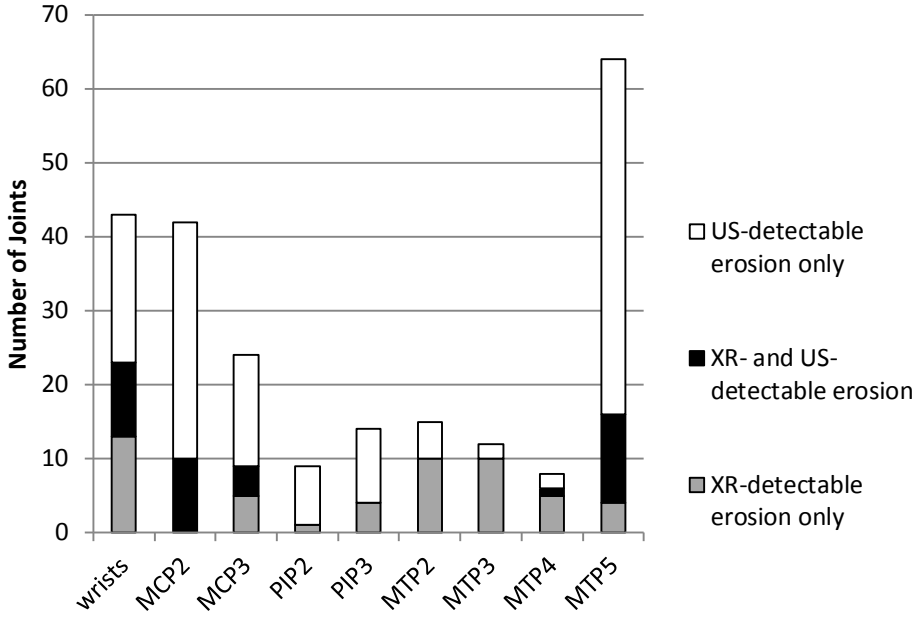
6.4.5 'Active' Erosions

At the patient level, amongst patients with erosive disease visible on x-ray, ultrasound synovitis (GS≥grade 2 and/or PD≥grade 1) was observed in association with at least one radiographically-defined erosive joint in 27/34 (79%) patients (2/3 patients with UA and 25/31 patients with RA). In patients with ultrasound-detected erosive disease, concomitant ultrasound synovitis was observed in at least one ultrasound-defined erosive joint in 61/91 (67%) (4/4 patients with UA and 57/87 patients with RA).

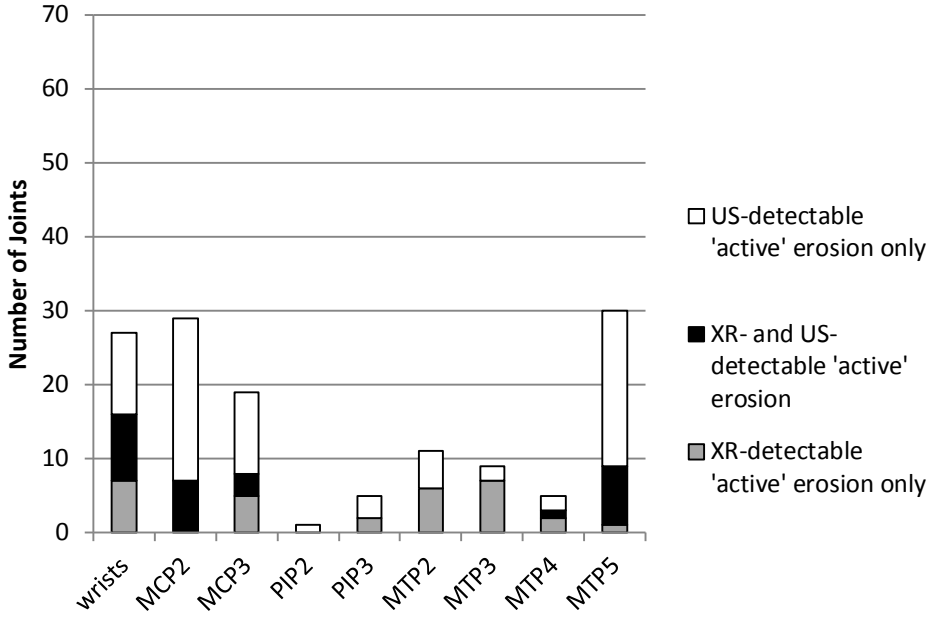
At the joint level, ultrasound synovitis was evident in 30/52 (58%) joints with erosions detected by radiography alone, 78/142 (55%) joints with erosions detected by ultrasound alone, and 28/37 (76%) with erosions detectable by both methods. The distribution of erosions observed in association with concomitant ultrasound synovitis was similar to the distribution of joints affected by any erosion (Figure 9), with exception of PIP2-3s and MTP5, which were proportionately more frequently affected by erosion without associated ultrasound synovitis.

Figure 9. Number of joints with erosions detectable by x-ray and/or ultrasound, in all patients with UA and RA: A) any erosion and B) 'active' erosion, i.e. erosion detected by x-ray or ultrasound with ultrasound synovitis (GS≥grade 2 and/or PD≥grade 1) in the same joint.

A) Distribution of Erosion in All Patients with IA.



B) Distribution of 'Active' Erosions in All Patients with IA.



6.4.6 Reclassification of IA with use of ultrasound in the application of the 2010 ACR/EULAR RA criteria

Of 38 patients with UA, defined according to the 2010 ACR/EULAR RA criteria with joint involvement determined by clinical examination alone, consideration of ultrasound synovitis changed disease classification to RA in four (11%) patients (joint involvement defined by clinical swelling and/or tenderness and/or ultrasound synovitis, $UA \rightarrow RA_{clinical\ +US}$). Only one patient also demonstrated sufficient ultrasound synovitis on ultrasound examination of 24 joints (excluding MTP1 as stipulated by the criteria) to fulfil criteria with joint involvement determined solely by ultrasound synovitis irrespective of clinical findings ($UA \rightarrow RA_{US}$).

Forty-seven (24%) patients with RA (fulfilling the 2010 criteria on the basis of clinical examination) did not demonstrate sufficient ultrasound synovitis within the relevant 24 joints examined by ultrasound, to fulfil the criteria with joint involvement determined by ultrasound alone (reclassified as $RA \rightarrow UA_{US}$).

6.4.7 Performance of the 2010 ACR/EULAR RA criteria to discriminate patients with erosive disease at baseline, with joint involvement determined clinically or by ultrasound

Of the four patients with UA whose disease was reclassified as $UA \rightarrow RA_{clinical+US}$, x-ray erosions were observed in one patient (25%); erosions were observed at both wrists. Ultrasound erosions were also only observed in this one patient; it was in this patient that ultrasound erosions were detected in at least three joints included in the EULAR definition of erosive RA.

Amongst patients for whom the diagnosis of UA did not change ($UA \rightarrow UA_{clinical+US}$, n=34), erosions were detected by x-ray in two (6%) patients and by ultrasound in three (9%) patients, all of whom had less than three erosive joints detectable by either method. No statistically significant difference was identified in the rate of x-ray or ultrasound erosion between patients with $UA \rightarrow RA_{clinical+US}$ and $UA \rightarrow UA_{clinical+US}$ ($p=0.3$ and $p=0.4$ for comparisons in the rate of x-ray and ultrasound erosions, respectively).

In the singular patient with UA (determined clinically) demonstrating sufficient ultrasound synovitis to fulfil criteria with joint involvement determined solely by ultrasound synovitis, irrespective of the findings of clinical examination ($UA \rightarrow RA_{US}$), no erosions were observed by either x-ray or ultrasound. No statistical tests were conducted due to low numbers (n=1) in this group.

Amongst the majority of patients with RA in whom classification of IA did not change ($RA \rightarrow RA_{US}$), erosions were detected on x-ray in 27/150 (18%) and by ultrasound in 73/150 (49%) patients. Erosions were less frequent amongst the 47 patients reclassified as UA ($RA \rightarrow UA_{US}$); erosions were detected by x-ray in 4/47 (9%) and ultrasound in 14/47 (30%) patients (p=0.1 and p=0.02 for comparisons in the rates of x-ray and ultrasound erosion between patients with $RA \rightarrow RA_{US}$ and $RA \rightarrow UA_{US}$, respectively).

6.5 Discussion

This study is the first to depict several aspects of the imaging phenotypes of patients with early UA and RA, defined according to the 2010 ACR/EULAR RA criteria, in a large, true inception cohort. It confirms the presence of significant levels of subclinical ultrasound synovitis and ultrasound erosion, and is the first description of the concept of 'active' erosion. Further analyses in subsequent chapters aim to determine the prognostic significance of these parameters.

Clinical characteristics of patients with UA in this study appear similar to those previously described in IA cohorts with retrospective application of the 2010 RA criteria, including the Leiden (Krabben et al., 2012; Krabben et al., 2013a), Birmingham (Cader et al., 2011; Krabben et al., 2013a) and Amsterdam (Britsemmer et al., 2011; Krabben et al., 2013a) EAC cohorts. Low rates of ACPA-positivity and slight female predominance were also reported in these studies (Britsemmer et al., 2011; Cader et al., 2011; Krabben et al., 2012; Krabben et al., 2013a). Whilst a similarly high frequency of small joint involvement in the hands has been observed in some cohorts (Cader et al., 2011; Krabben et al., 2012; Krabben et al., 2013a), others have demonstrated greater involvement of larger joints and the lower extremities (Britsemmer et al., 2011; Krabben et al., 2013a). Differences may be reflective of different inclusion criteria; for example, greater swollen joint

counts were observed the latter study which required the presence of at least two swollen joints. It should be noted that prior to the publication of the ACR/EULAR definition of erosive disease, which is sufficient to fulfil 2010 RA classification criteria (in the context of a compatible history) (van der Heijde et al., 2013), typical erosions have been defined inconsistently in the application of the criteria in these previous studies.

As expected, the burden of synovitis was significantly lower in patients with UA, in comparison to patients fulfilling 2010 RA criteria at presentation. Of note, the sites affected by synovitis (clinically and on ultrasound) appeared similar to patients with RA, within the limitations of the clinical and ultrasound examinations performed. There was predominance for small joint involvement in both groups; in particular, MCP and PIP involvement was prominent clinically and MTP involvement was predominant on ultrasound examination. However, the higher prevalence of SpA features in patients with UA suggests a possible difference in disease pathogenesis between these groups, at least in a subset of patients. In comparison to other early IA cohorts, a relatively low number of patients (n=15) progressed to non-RA diagnoses within one year (excluded from these analyses). Divergence in disease phenotypes may have become apparent with longer follow-up. It is also likely that additional patients with features of non-RA arthritides, such as SpA or connective tissue disease, were triaged and followed-up in specific SpA and connective tissue disease clinics, as discussed previously (section 5.5).

This study confirms the discordance between the clinical and ultrasound assessment of synovitis identified previously in patients with early IA (Wakefield et al., 2004; Salaffi et al., 2008; Funck-Brentano et al., 2009; Filer et al., 2011; Nakagomi et al., 2013). Of these studies, perhaps the most similar in terms of the included cohort was the ESPOIR study which reported a similar rate of ultrasound-detectable synovitis, occurring in 52% of clinically swollen joints and 26% of clinically non-swollen joints (Funck-Brentano et al., 2009). A high prevalence of subclinical synovitis was identified in our data (observed in at least one joint in three-quarters of patients with UA and 90% of patients with RA), consistent with rates of subclinical GS observed in an earlier UA study (Wakefield et al., 2004). Although their ultrasound assessment was restricted to ten joints per patient (MCPs2-5 and MTP5 bilaterally) and joints with GS=grade 1 alone were

included in their definition of ultrasound synovitis. The distribution of subclinical synovitis (MTPs most frequently affected, followed by wrists) is in accordance with other early IA cohorts reporting distribution of findings, in which wrists (Nakagomi et al., 2013) and MTPs followed by wrists (Filer et al., 2011) were similarly identified as the most affected sites. This is with exception of the low prevalence of subclinical synovitis observable at the large joints in our study in comparison to these two studies. Possible explanations again include the incorporation of GS=grade 1 within the definition of ultrasound synovitis (Filer et al., 2011; Nakagomi et al., 2013), as well as inclusion of non-RA patients and restriction to patients with symptoms less than three months (including crystal arthropathy and early seronegative spondyloarthropathy, for example) in the latter study (Filer et al., 2011).

This Leeds data also verifies the greater sensitivity of ultrasound for the detection of erosion in comparison to x-ray, previously reported in RA (Wakefield et al., 2000; Klocke et al., 2001; Szkudlarek, M. et al., 2003; Weidekamm et al., 2003; Szkudlarek et al., 2004; Scheel et al., 2006; Szkudlarek et al., 2006; Bajaj et al., 2007; Sheane et al., 2009). Ultrasound of 18 joints detected erosive disease in approximately three times the number of patients in whom erosive disease was detected by conventional radiography of the hands and feet, consistent with other studies in patients with early IA. Amongst patients with synovitis of at least one joint, ultrasound erosions at MTP5 were reported in 17/30 (57%) patients (versus presence of x-ray erosions in 23%), appreciating a proportion of patients had prior DMARD exposure and the mean duration of symptoms was 15 months (Sheane et al., 2009). In ESPOIR, on bilateral ultrasound examination of MCP2-5 and MTP5, ultrasound erosions were observed in 42/114 (37%) patients (versus x-ray erosions in 11% of patients, when read in the usual manner) (Funck-Brentano et al., 2009).

Our data demonstrate MTP5 as the commonest site for erosions identifiable by sonography, consistent with studies in patients with RA (Hulsmans et al., 2000; Klocke et al., 2001; Lopez-Ben et al., 2004; Szkudlarek et al., 2004; Funck-Brentano et al., 2009; Tămaş et al., 2014; Zayat et al., 2015). Indeed, a recent study including patients with polyarticular osteoarthritis and healthy controls, confirms erosions at MTP5 are relatively specific to patients with IA, in particular patients with RA (Zayat et al., 2015). A greater number of erosive joints were

observed with ultrasound in comparison to x-ray at all sites examined with exception of MTPs2-4, possibly explained by reduced ultrasound visualisation of these joints, consistent with previous studies (Szkudlarek et al., 2004).

Previous cross-sectional studies have reported an association between subclinical ultrasound synovitis and ultrasound erosion in patients with established RA on treatment (Kawashiri et al., 2014a; Vreju et al., 2016; Kawashiri et al., 2017). Data from ESPOIR suggests the concomitant finding of both synovitis and erosion on ultrasound may be specific to patients with IA, with this combination of findings being absent from joints of healthy controls (Millot et al., 2011). However, the concept of 'active' erosion, and the prevalence of such, has not previously been reported in patients with early, DMARD-naïve IA. In our study, the majority of erosive joints identified by ultrasound were 'active', i.e. associated with concomitant ultrasound synovitis. The proportion of ultrasound erosions associated with ultrasound synovitis was similar to the proportion of erosive joints detected by x-ray which were affected by concomitant ultrasound synovitis. This suggests the potential relevance of 'active' ultrasound erosions to disease assessment in early IA.

A small proportion of patients with UA (n=4, 11%) received a revised diagnosis with consideration of ultrasound synovitis, in addition to clinical findings, in determining the joint involvement score within the 2010 RA criteria. Amongst patients with RA, fulfilling the 2010 criteria clinically, fulfilment of the criteria using the standardised ultrasound of 24 joints alone to determine joint involvement score (irrespective of clinical findings) was associated with a higher rate of ultrasound erosion. A previous study addressing the use of ultrasound within the criteria (defining joint involvement as GS≥grade 2 and/or PD≥grade 1) reported reclassification of disease in 7/69 (10%) of patients with UA and 17/40 (43%) of patients with RA (as determined clinically) (Nakagomi et al., 2013). Differences in study methods included use of a more extensive 38-joint ultrasound examination, which may not always be feasible in clinical practice, and inclusion of patients without clinical joint swelling within their definition of UA.

This study highlights the challenges of data collection in a clinical practice setting, with a number of patients being excluded from the analysis due to incomplete data

(particularly ultrasound data). Patients excluded due to missing data were more likely to be younger, score less for clinical joint involvement within the 2010 criteria and have a lower burden of swollen joints. Results may therefore be skewed towards patients with more extensive disease. A potential explanation may be the non-attendance for ultrasound examination due to time pressures in younger patients (plausibly more likely to have work or childcare commitments) and the perceived importance of the examination (likely to be reduced in patients with less severe disease). Other limitations, inherent to the use of ultrasound, include the inability to differentiate low-grade changes of synovitis relevant to IA from changes associated with osteoarthritis, or even normal findings in healthy individuals. In particular, GS and PD findings at the first MTPs and PD at the wrists may be particularly unreliable, as evidenced by a recent study of 30 healthy controls: GS≥grade 2 was observed in 32% of the first MTPs (19/60 joints) and PD≥grade 1 or greater was observed in 28% (17/60) of the first MTPs and 42%(25/60) wrists (Kitchen and Kane, 2015). Other strengths and limitations of this study are detailed in the main discussion (Chapter 10).

Further research is needed to determine the predictive value of ultrasound findings in determining the future disease course. There is a need to assess the prognostic implications of several prevalent findings in patients with early IA which have been identified here, including: ultrasound-detectable synovitis, ultrasound erosions, ‘active’ ultrasound erosions and reclassification of IA with inclusion of ultrasound synovitis in the application of the 2010 ACR/EULAR RA criteria.

Chapter 7 : **One-Year Outcomes for Patients with New-Onset UA and RA, Defined According to the 2010 ACR/EULAR Criteria.**

What are the prognostic implications of ultrasound-detectable synovitis and erosions?

7.1 Introduction

A window of opportunity is recognised in early IA in which effective treatment permits the attainment of optimal outcomes (section 2.4). There is an ongoing need to establish effective biomarkers to predict disease persistence and response to treatment to avoid potentially detrimental delays in the initiation of effective treatment (Combe et al., 2017; Smolen et al., 2017).

The 2010 ACR/EULAR RA classification criteria were recently developed in order to provide a means of identifying patients with IA who are likely to benefit from methotrexate, early in their disease course (Aletaha, D. et al., 2010). Retrospective application of the 2010 RA criteria across several early IA cohorts has shown they offer greater sensitivity, in comparison to the 1987 ACR RA criteria, in discriminating patients for various RA outcomes (Table 2, section 2.1.3). Meta-analyses of such studies report pooled sensitivity and specificity of the order of 80% and 60% respectively for the identification of disease requiring DMARDs (Sakellariou, G. et al., 2013; Radner et al., 2014). This suggests a risk of misclassifying a proportion of patients with RA under the current criteria. In addition, there may be a proportion of patients with UA in whom early intervention may also be beneficial.

Furthermore, there is limited data concerning the natural history/progression of disease in patients with UA or RA (determined by 2010 RA criteria) in contemporary real-life cohorts. Hence, there is a need to determine modern-day disease outcomes for these patients, as well as methods for predicting which of these patients are likely to have persistent or progressive disease.

Ultrasound has been identified as a potential additional tool for determining which patients may benefit from early treatment. The prognostic value of ultrasound synovitis to predict radiographic joint damage has been demonstrated in patients with established RA with active disease commencing TNF-inhibitors (Dougados et al., 2013) as well as in patients in clinical remission (Brown et al., 2008) (section 2.3.2.1).

Studies investigating the prognostic value of ultrasound in the prediction of outcomes amongst patients with early IA are now beginning to emerge, suggesting the significance of GS synovitis (Freeston et al., 2010; Filer et al., 2011; Nakagomi et al., 2013; Pratt et al., 2013) and PD (Freeston et al., 2010; Salaffi et al., 2010; Filer et al., 2011; Kawashiri et al., 2013; Nakagomi et al., 2013). The outcomes studied have included persistence of disease (Freeston et al., 2010; Pratt et al., 2013), the requirement for DMARDs (Kawashiri et al., 2013) or methotrexate (Nakagomi et al., 2013), progression to fulfilment of 1987 ACR RA criteria (Salaffi et al., 2010; Filer et al., 2011) and radiographic progression (Funck-Brentano et al., 2013). However, these studies have largely been conducted in heterogeneous patient groups, including patients without any clinical evidence of joint swelling (Freeston et al., 2010; Kawashiri et al., 2013; Nakagomi et al., 2013; Pratt et al., 2013) and patients with various types of IA including those with non-RA diagnoses (Filer et al., 2011). Furthermore, outcomes such as disease progression to fulfilment of the1987 RA criteria and radiographic progression may be insufficiently sensitive in early disease (Banal et al., 2009). Other limitations of these existing studies have been discussed in section 2.3.2.1.

Evidence for the prognostic validity of ultrasound erosions, or the predictors of progression in ultrasound-detectable erosive damage, is especially lacking (section 2.3.2.3). To date, knowledge of the predictors of new ultrasound erosions is limited to a small study of single joint ultrasound in patients with established RA only (Reynolds et al., 2009).

In particular, the preceding Chapter (Chapter 6) described two characteristics of disease, discernible by ultrasound, which warrant further exploration in terms of

determining their prognostic significance. These include fulfilment of the 2010 ACR/EULAR RA classification criteria using ultrasound in the determination of joint involvement, and presence of 'active' ultrasound erosions.

7.2 Aims and Objectives

- To determine the one year outcomes of patients with new-onset, DMARD-naïve IA (specifically UA or RA, classified according to the 2010 ACR/EULAR RA criteria).
- To include the presence of severe and/or persistent IA, progression to RA in patients with UA, need for triple DMARD or biologic therapy in patients with RA and progression in ultrasound erosive change at one year.
- To determine the clinical and imaging features of disease which may be useful in predicting these outcomes, including the following features of disease measureable by ultrasound: fulfilment of the 2010 RA criteria with joint involvement determined by ultrasound, ultrasound erosions and 'active' erosions.

7.3 Methods

A prospective, observational study was conducted in patients with new-onset, UA and RA presenting to the Leeds EAC as previously described (Chapter 4).

7.3.1 Assessments

Clinical and imaging assessments were defined as per sections 4.2 and 4.3. Reclassification of patients using ultrasound synovitis alone to determine the score for joint involvement in the application of the 2010 ACR/EULAR RA criteria was ascertained as per section 6.3.1. The reclassification of UA patients according to fulfilment of the 2010 RA criteria considering both clinical and ultrasound signs of synovitis ($UA \rightarrow UA_{clinical+US}$ or $UA \rightarrow RA_{clinical+US}$) was not assessed here due to the small number of patients receiving a revised diagnosis by this approach in the total cohort (section 6.4.6).

7.3.2 Outcomes

These have been described in section 4.5.

7.3.3 Statistics

In order to assess the utility of clinical and imaging parameters in the prediction of clinical outcomes, univariable logistic regression analyses were conducted in patients grouped according to clinical fulfilment of the 2010 ACR/EULAR RA classification criteria. As follow-up imaging data was available in a smaller number of patients, analysis of imaging outcomes was conducted in all patients with IA (either UA or RA) at baseline (i.e. without grouping into UA and RA subgroups). The following baseline variables were selected due to their known or likely association with treatment choice, disease persistence and erosion progression:

- Age.
- Gender.
- Symptom duration.
- ACPA-positivity.
- Duration of early morning stiffness.
- Clinical disease activity variables: RAI, SJC44, CRP, patient VASDA and DAS44-CRP. These were selected over TJC28, SJC28 and DAS28-CRP due to their potential to be more reflective of disease activity in patients with UA and/or limited joint involvement.
- HAQ score.
- Ultrasound parameters (section 4.3):
    - total GS score,
    - total PD score,
    - number of joints with significant ultrasound synovitis (GS≥grade 2 and/or PD≥grade 1),
    - presence of any ultrasound erosion,
    - presence of any ‘active’ ultrasound erosion,
    - fulfilment of 2010 ACR/EULAR RA classification criteria, with joint involvement determined by ultrasound examination, assessed as a dichotomous variable (rather than criteria score) to reflect its intended use.
- Presence of any radiographic erosion.

Multivariable logistic regression analyses were conducted to assess whether ultrasound measures of synovitis (total GS score, total PD score and the number of joints with significant ultrasound synovitis) were associated with outcomes, with adjustment for the likely confounder clinical disease activity (as measured by SJC44 or DAS44-CRP). Further multivariable logistic regression analyses for outcomes at the patient level were not attempted, due to the inadequate number of patients in the outcome categories to enable inclusion of all relevant variables.

To determine the implications of clinical swelling and ultrasound synovitis on the development of ultrasound erosion at the joint level, conditional logistic regression (stratifying for patient case) was conducted in joints lacking evidence of either radiographic or ultrasound erosion at baseline. Two models were planned; firstly, considering the presence of any significant ultrasound synovitis (GS≥grade 2 and/or PD≥grade 1) and secondly, considering the presence of significant GS (≥grade 2) and PD (≥grade 1) as separate variables in order to assess the independent contribution of either finding to the prediction of new ultrasound erosion.

7.3.3.1 Missing data

Methods for handling missing data have been described previously (section 4.6.1). Patients with incomplete clinical, ultrasound and/or x-ray data at baseline and patients lacking any clinical follow-up data (no re-attendance within 12 months) were excluded. In the analyses of imaging outcomes, patients lacking ultrasound data at 12 months were excluded.

7.4 Results

7.4.1 Patients

Of 441 patients with suspected new-onset IA, screened for inclusion in the observational study, 333 patients were eligible for inclusion in these analyses (Figure 10). A further 95 patients were excluded due to incomplete clinical and imaging data at baseline and/or lack of any follow-up data.

Baseline characteristics are shown in Tables 20 and 21: 41 and 197 patients were classified as UA or RA according to 2010 RA criteria (with joint involvement score determined by clinical assessment). No significant differences were observed between all patients included in the analysis of clinical outcomes (n=238) and those excluded due to missing data (n=95). Whereas, patients included in the analysis of imaging outcomes (n=144) differed significantly ($p<0.05$) from those excluded due to missing data (n=189) in age (greater mean age was observed amongst included patients), measures of disease activity (incidence of significant early morning stiffness, RAI, DAS44-CRP, total GS score and number of joints with ultrasound synovitis were all lower in included patients) and HAQ score (lower in included patients) (Table 21).

Figure 10. Disposition of patients registered in the longitudinal prospective observational study and included in the analysis of clinical and imaging outcomes.

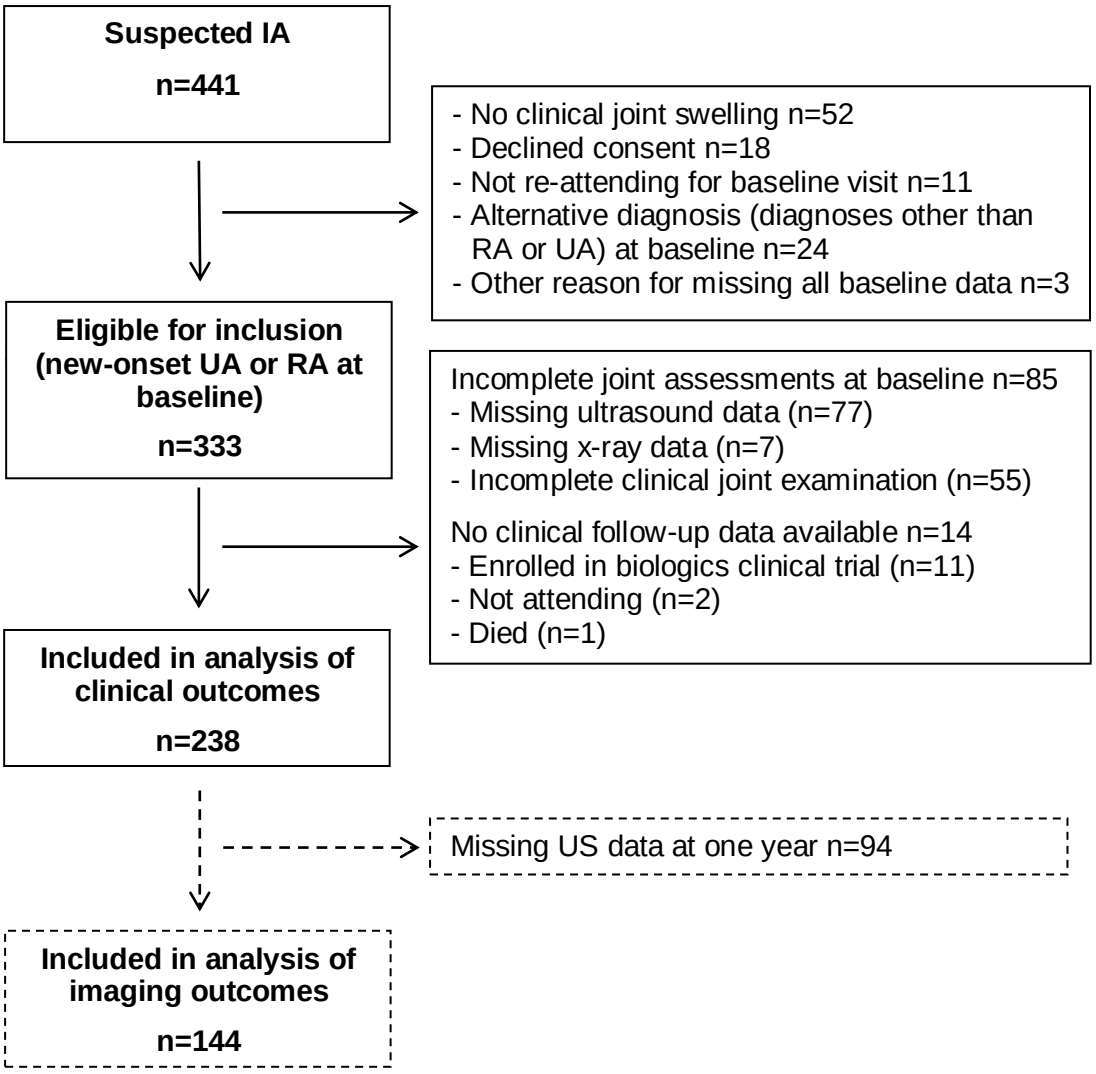


Table 20. Baseline characteristics of patients with new-onset UA and RA included in the analysis of clinical outcomes, and those excluded due to incomplete data.

Values are median (IQR) or n (%) unless otherwise stated.

	Included			**Excluded n=95**	**All Included vs. Excluded (p value)**
	UA n=41	**RA n=197**	**All n=238**		
Age, mean (SD)	45 (15)	56 (13)	54 (14)	52 (15)	0.1
Female	27 (66%)	136 (69%)	163 (68%)	72 (76%)	0.2
Symptom duration, months	9 (4-18)	7 (4-13)	7 (4-14)	8 (4-13)	0.9
ACPA positive	3 (7%)	131 (66%)	134 (56%)	57 (60%)	0.5
Fulfilment of 2010 ACR/EULAR RA criteria with joint involvement determined clinically	-	100%	197 (83%)	76 (80%)	0.6
Early Morning Stiffness ≥60 min	19 (46%)	147 (75%)	166 (70%)	72 (76%)	0.3
RAI SJC44	3 (2-6) 2 (1-5)	8 (4-10) 5 (3-10)	6 (3-10) 5 (2-8)	6 (3-11)[a] 3 (2-8)[a]	0.6 0.1
CRP, mg/L	6 (0-22)	14 (0-37)	13 (0-32)	12 (0-28)	0.7
Patient VASDA, mm	45 (25-68)[b]	53 (27-73)[c]	50 (26-71)[d]	49 (25-76)[e]	0.9
DAS44-CRP	2.3 (1.8-2.9)[b]	3.1 (2.4-3.7)[c]	2.9 (2.3-3.5)[d]	2.9 (1.9-3.7)[f]	0.4
HAQ	0.3 (0.1-0.9)[g]	1.1 (0.5-1.6)[h]	1.0 (0.4-1.6)[i]	1.0 (0.4-1.7)[j]	1.0
US of 26 joints: Total GS score	9 (5-17)	18 (11-26)	16 (9-25)	14 (12-23)[k]	1.0
Total PD score	1 (0-2)	3 (0-8)	2 (0-6)	1 (0-4)[k]	0.2
Number of joints GS≥2 and/or PD≥1	2 (1-6)	6 (3-10)	6 (2-9)	5 (4-8)[k]	0.9
Fulfilment of 2010 ACR/EULAR RA criteria with joint involvement determined by US findings (RA_{US})	1 (2%)	147 (75%)	148 (62%)	10 (56%)[k]	0.6
US erosion (PIP2-3, MCP2-3, wrists or MTP2-4)	4 (10%)	88 (45%)	92 (39%)	5 (28%)[k]	0.4
'Active' US erosion	4 (10%)	58 (29%)	62 (26%)	3 (17%)[k]	0.6
Radiographic erosion in the hands and feet	3 (7%)	31 (16%)	34 (14%)	14 (16%)[l]	0.7

Missing data in [a]55, [b]8, [c]40, [d]48, [e]54 [f]25, [g]6, [h]33, [i]39, j55, [k]77 and [l]7 cases: percentages are number of patients/number of patients with complete data.

Table 21. Baseline characteristics of all patients with new-onset UA and RA included in the analysis of imaging outcomes, and those excluded due to incomplete data.

Values are median (IQR) or n (%) unless otherwise stated.

	Analysis of imaging outcomes		
	Included n=144	**Excluded n=189**	**p**
Age, mean (SD)	**56 (14)**	**52 (14)**	**0.002**
Female	103 (72%)	132 (70%)	0.7
Symptom duration, months	7 (4-14)	7 (4-13)	0.4
ACPA positive	91 (63%)	100 (53%)	0.06
Fulfilment of 2010 ACR/EULAR RA criteria with joint involvement determined clinically	118 (82%)	155 (82%)	1.0
Early Morning Stiffness ≥60 min	**94 (65%)**	**144 (76%)**	**0.03**
RAI	**6 (3-10)**	**7 (4-11)[a]**	**0.04**
SJC44	4 (2-8)	5 (3-10)[a]	0.07
CRP, mg/L	11 (0-28)	13 (0-33)	0.3
Patient VASDA, mm	47 (25-69)[b]	55 (25-77)[c]	0.1
DAS44-CRP	**2.7 (2.2-3.3)[b]**	**3.1 (2.4-3.8)[d]**	**0.005**
HAQ	**0.9 (0.3-1.5)[e]**	**1.0 (0.5-1.6)[f]**	**0.04**
US of 26 joints: Total GS score	**14 (8-23)**	**18 (12-26)[c]**	**0.008**
Total PD score	2 (0-6)	3 (0-7)[c]	0.3
Number of joints GS≥2 and/or PD≥1	**5 (2-8)**	**6 (3-11)[c]**	**0.01**
Fulfilment of 2010 ACR/EULAR RA criteria with joint involvement determined by US (RA_{US})	89 (62%)	69 (62%)[c]	1.0
US erosion (PIP2-3, MCP2-3, wrists or MTP2-4)	51 (35%)	46 (41%)[c]	0.4
'Active' US erosion	31 (22%)	34 (30%)[c]	0.1
Radiographic erosion in the hands and feet	17 (12%)	31 (17%)[g]	0.2

Missing data in [a]55, [b]25, [c]77, [d]87, [h]39, [e]22, [f]72 and [g]7 cases: percentages are number of patients/number of patients with complete data.

7.4.2 Clinical outcomes at one year

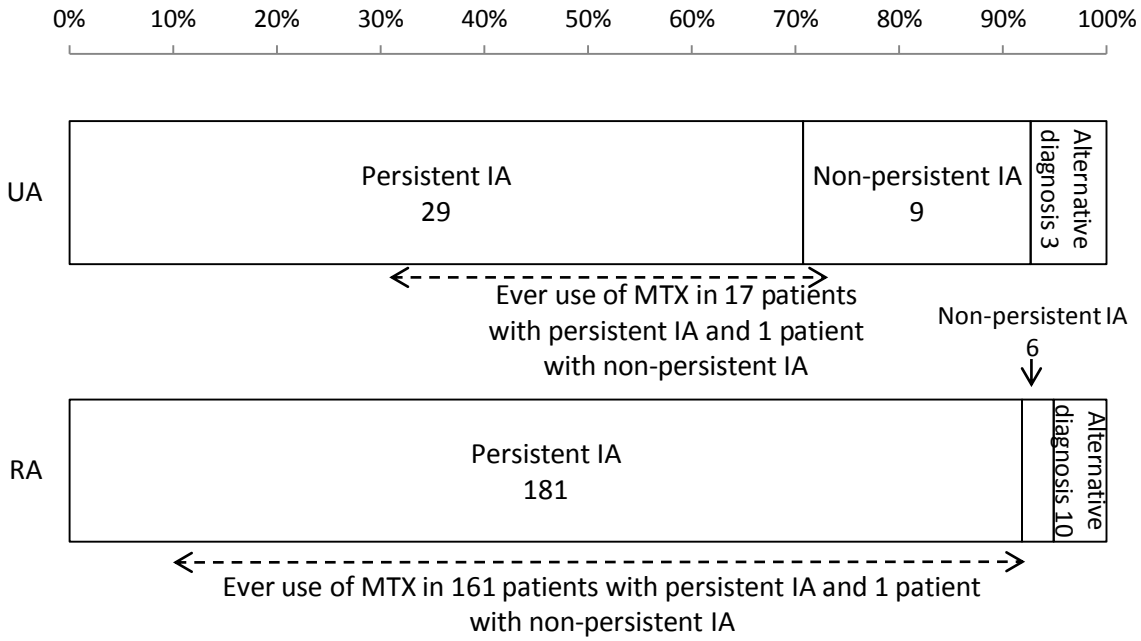
7.4.2.1 Methotrexate Initiation and Disease Persistence

Clinical data were available at one year in 202 patients, and were carried forward from last assessments in 36. Reasons for missing data at one year in the latter were: non-attendance (n=17), enrolment in biologics drug trials (n=10), moving out of the area (n=1), pregnancy (n=1), death (n=1) or unknown (n=6).

Outcomes are illustrated in Figure 11. Over one year, 18/41 (44%) patients with UA and 162/197 (82%) patients with RA, at baseline, ever received methotrexate. Persistent IA at one year was observed in 29 (71%) and 181 (92%) patients with UA and RA, respectively. This consisted of patients receiving DMARDs (24 [59%] patients with UA and 170 [86%] patients with RA), patients receiving recent or concurrent steroids without DMARD therapy (4 [10%] patients with UA and 11 [6%] patients with RA) and one patient with UA with swollen joints without concurrent use of DMARDs or recent steroid exposure. This latter patient had a history of palindromic PIP swelling, with two swollen, non-tender, PIP joints on clinical examination at one year.

Of the remaining patients, progression to an alternative diagnosis (diagnoses other than UA or RA) was observed in three (7%) patients with UA and ten (5%) patients with RA at baseline. The alternative diagnoses were: gout (n=3), inflammatory osteoarthritis (n=3), psoriatic arthritis (n=2), connective tissue disease (n=2), ANA-associated arthralgia (n=1) and other non-inflammatory joint pain (n=1). Non-persistent IA at one year (i.e. absence of swollen joints without DMARD or corticosteroid exposure within the preceding three months) was observed in nine patients with UA (22%); five patients never received DMARD or corticosteroid treatment, one patient had received methotrexate, one had received sulfasalazine and two patients had received corticosteroids alone over follow-up. Amongst patients with RA at baseline, six had non-persistent disease (3%); three never received DMARD/corticosteroid treatment, one received methotrexate and two received corticosteroids alone over follow-up.

Figure 11. Outcomes at one year in patients with UA and RA at baseline.



7.4.2.2 Progression to RA and Need for Triple DMARD or Biologic Therapy for the Treatment of RA

Of 41 patients with UA at baseline, nine (22%) progressed to fulfil 2010 RA criteria over one year. Five of these patients received methotrexate (commenced prior to progression in three and after progression in two). Of 197 patients with RA at baseline, 27 (14%) required escalation to triple DMARD therapy or received biologic therapy over the course of one year.

7.4.3 Predictors of Clinical Outcome

7.4.3.1 Undifferentiated Arthritis

Clinical variables which demonstrated statistically significant associations with outcome were patient VASDA, which associated with use of methotrexate, and RAI and functional disability (HAQ score) which were associated with progression to RA (Tables 22 and 23).

The requirement for methotrexate, persistence of IA and progression to RA were all significantly associated with total GS score (Tables 22 and 23). Progression to RA

was also associated with greater number of joints with significant ultrasound synovitis (GS≥grade 2 and/or PD≥grade 1). These ultrasound parameters remained significantly associated with outcome after adjustment for swollen joint count. Only the association between total GS score and disease persistence lost statistical significance after adjustment for DAS44-CRP.

All patients with x-ray erosions at baseline received methotrexate within one year and had persistent IA. All patients with ultrasound evidence of erosion had persistent IA at one year. Progression to RA did not occur in any of the three patients with ACPA-positivity at baseline, one of whom received methotrexate.

Table 22. Association between baseline characteristics and the requirement for methotrexate and persistence of IA at one year in patients with UA at baseline.
Values are median (IQR) or n (%) unless otherwise stated.

	Ever Received Methotrexate				**Persistent IA**			
	Yes n=18	**No n=23**	**OR (95%CI)**	**p**	**Yes n=29**	**No n=12**	**OR (95%CI)**	**p**
Age, mean (SD)	46 (14)	43 (16)	1.01 (0.97-1.05)	0.6	46 (16)	41 (13)	1.02 (0.97-1.07)	0.4
Female	12 (67%)	15 (65%)	1.07 (0.29-3.92)	0.9	19 (66%)	8 (67%)	0.95 (0.23-3.94)	0.9
Symptom duration, months	15 (5-26)	6 (3-14)	1.06 (0.99-1.13)	0.09	13 (4-23)	5 (3-10)	1.08 (0.99-1.18)	0.1
ACPA positive	1 (6%)	2 (9%)	0.62 (0.05-7.41)	0.7	3 (10%)	0	NA	NA
Early Morning Stiffness ≥60 min	7 (39%)	12 (52%)	0.58 (0.17-2.04)	0.4	13 (45%)	6 (50%)	0.81 (0.21-3.13)	0.8
RAI	4 (3-6)	3 (1-6)	1.14 (0.88-1.47)	0.3	4 (3-6)	3 (1-6)	1.23 (0.91-1.67)	0.2
SJC44	3 (1-4)	2 (1-5)	0.98 (0.75-1.28)	0.9	2 (1-4)	2 (1-8)	0.87 (0.66-1.16)	0.3
CRP, mg/L	9 (0-28)	6 (0-17)	1.01 (0.99-1.03)	0.3	7 (0-28)	3 (0-9)	1.04 (0.98-1.11)	0.2
Patient VASDA, mm	**64 (38-74)[a]**	**30 (17-60)[b]**	**1.03 (1.00-1.07)**	**0.04**	49 (26-71)[c]	26 (17-59)[c]	1.02 (0.98-1.05)	0.3
DAS44-CRP	2.2 (2.0-2.6)[a]	2.1 (1.5-2.7)[b]	1.90 (0.64-5.66)	0.2	2.2 (1.8-2.7)[c]	1.9 (1.6-2.5)[c]	2.21 (0.67-7.35)	0.2
HAQ	0.5 (0.1-0.9)[b]	0.3 (0.1-0.8)[b]	1.06 (0.30-3.78)	0.9	0.5 (0.0-0.9)[d]	0.3 (0.2-0.6)[c]	1.91 (0.33-11.0)	0.5
US synovitis: Total GS score (unadjusted)			**1.13 (1.02-1.26)**	**0.02**			**1.13 (1.00-1.27)**	**0.05**
Adjusted for SJC44	**12 (9-18)**	**7 (2-12)**	***1.14 (1.02-1.26)***	***0.02***	**11 (7-18)**	**6 (3-10)**	***1.14 (1.00-1.30)***	***0.04***
Adjusted for DAS44-CRP			***1.12 (1.01-1.25)***	***0.04***			*1.09 (0.96-1.23)*	*0.2*
Total PD score (unadjusted)			1.00 (0.69-1.46)	1.0			1.03 (0.68-1.56)	0.9
Adjusted for SJC44	0 (0-2)	1 (0-2)	*1.00 (0.69-1.46)*	*1.0*	0 (0-2)	1 (0-2)	*1.04 (0.69-1.59)*	*0.8*
Adjusted for DAS44-CRP			*1.03 (0.67-1.61)*	*0.9*			*0.94 (0.57-1.56)*	*0.8*
Number of joints GS≥2 and/or PD≥1 (unadjusted)			1.20 (0.98-1.47)	0.08			1.26 (0.95-1.67)	0.1
Adjusted for SJC44	3 (2-7)	1 (1-4)	*1.20 (0.98-1.48)*	*0.08*	3 (1-7)	1 (1-3)	*1.27 (0.95-1.70)*	*0.1*
Adjusted for DAS44-CRP			*1.23 (0.97-1.55)*	*0.09*			*1.17 (0.88-1.56)*	*0.3*
Fulfilment of 2010 ACR/EULAR RA criteria with joint involvement determined by US (RA_{US})	1 (6%)	0	NA	NA	1 (3%)	0	NA	NA
US erosion (PIP2-3, MCP2-3, wrists or MTP2-4)	2 (11%)	2 (9%)	1.31 (0.17-10.4)	0.8	4 (14%)	0	NA	NA
'Active' US erosion	2 (11%)	2 (9%)	1.31 (0.17-10.4)	0.8	4 (14%)	0	NA	NA
Radiographic erosion in the hands and feet	3 (17%)	0	NA	NA	3 (10%)	0	NA	NA

NA: logistic regression not performed. Missing data in [a]5, [b]3, [c]4 and [d]2 cases.

Table 23. Association between baseline characteristics and progression to RA in patients with UA at baseline. Values are median (IQR) or n (%) unless otherwise stated.

	Progression to RA			
	Yes n=9	**No n=32**	**OR (95%CI)**	**p**
Age, mean (SD)	42 (15)	44 (15)	1.02 (0.97-1.07)	0.5
Female	7 (78%)	20 (63%)	2.10 (0.37-11.8)	0.4
Symptom duration, months	12 (5-29)	9 (4-18)	1.00 (0.97-1.04)	0.8
ACPA positive	0	3 (9%)	NA	NA
Early Morning Stiffness ≥60 min	5 (56%)	14 (44%)	1.61 (0.36-7.12)	0.5
RAI	**6 (3-8)**	**3 (2-6)**	**1.43 (1.02-2.01)**	**0.04**
SJC44	4 (1-6)	2 (1-4)	1.16 (0.85-1.57)	0.3
CRP, mg/L	0 (0-10)	6 (0-22)	1.01 (0.99-1.03)	0.2
Patient VASDA, mm	59 (33-75)[a]	45 (23-64)[b]	1.02 (0.99-1.05)	0.3
DAS44-CRP	2.8 (2.1-3.1)[a]	2.2 (1.9-2.6)[b]	3.21 (0.78-13.2)	0.1
HAQ	**0.9 (0.1-1.3)**	**0.3 (0.1-0.8)[c]**	**6.26 (1.11-35.4)**	**0.04**
US synovitis: Total GS score (unadjusted)	**16 (12-19)**	**8 (4-12)**	**1.14 (1.02-1.27)**	**0.02**
Adjusted for SJC44			***1.14 (1.02-1.28)***	***0.02***
Adjusted for DAS44-CRP			***1.14 (1.01-1.29)***	***0.04***
Total PD score (unadjusted)	0 (0-1)	1 (0-2)	1.00 (0.64-1.57)	1.0
Adjusted for SJC44			*0.99 (0.63-1.55)*	*0.9*
Adjusted for DAS44-CRP			*0.94 (0.59-1.52)*	*0.8*
Number of joints GS≥2 and/or PD≥1 (unadjusted)	**7 (3-9)**	**1 (1-3)**	**1.33 (1.05-1.68)**	**0.02**
Adjusted for SJC44			***1.33 (1.05-1.70)***	***0.02***
Adjusted for DAS44-CRP			***1.36 (1.03-1.80)***	***0.03***
Fulfilment of 2010 ACR/EULAR RA criteria with joint involvement determined by US (RA_{US})	0	1 (3%)	NA	NA
US erosion (PIP2-3, MCP2-3, wrists or MTP2-4)	2 (22%)	2 (6%)	4.29 (0.51-35.9)	0.2
'Active' US erosion	2 (22%)	2 (6%)	4.29 (0.51-35.9)	0.2
Radiographic erosion in the hands and feet	2 (22%)	1 (3%)	8.86 (0.70-112)	0.09

NA: logistic regression not performed. Missing data in [a]1, [b]7 and [c]6 cases.

7.4.3.2 Rheumatoid Arthritis

In patients fulfilling 2010 RA criteria (with joint involvement determined clinically) at baseline, ACPA-positivity was associated with methotrexate use and persistent IA (Table 24). Both clinical (SJC44) and ultrasound evidence of synovitis (total PD) were significantly associated with methotrexate use. Total PD was associated with methotrexate use independently of SJC44 or DAS44-CRP. Two patients with x-ray detectable erosions never received methotrexate; one patient was treated with sulfasalazine and hydroxychloroquine, in whom methotrexate was contraindicated. In the other, joint swelling resolved after corticosteroid therapy.

Patients who demonstrated sufficient ultrasound synovitis to also fulfil the 2010 RA criteria with joint involvement determined solely by ultrasound examination were more likely to have received methotrexate and have persistent IA at one year.

The requirement for triple DMARD or biologic therapy within one year was associated with greater disease activity at baseline as indicated by several measures including: significant early morning stiffness, RAI, SJC44, CRP, DAS44-CRP, total GS score, total PD score and number of joints with significant ultrasound synovitis. In line with this, greater HAQ score, fulfilment of the 2010 RA criteria when defining joint involvement by significant ultrasound-detectable synovitis and higher incidence of ‘active’ erosion were also associated with this outcome (Table 25).

Table 24. Association between baseline characteristics and the requirement for methotrexate and persistence of IA at one year in patients with RA at baseline.
Values are median (IQR) or n (%) unless otherwise stated.

	Ever Received Methotrexate				**Persistent IA**			
	Yes n=162	**No n=35**	**OR (95%CI)**	**p**	**Yes n=181**	**No n=16**	**OR (95%CI)**	**p**
Age, mean (SD)	57 (13)	56 (16)	1.00 (0.97-1.03)	0.9	57 (13)	55 (17)	1.01 (0.97-1.05)	0.6
Female	115 (71%)	21 (60%)	1.63 (0.77-3.48)	0.2	128 (71%)	8 (50%)	2.42 (0.86-6.77)	0.09
Symptom duration, months	6 (4-13)	9 (6-17)	0.99 (0.97-1.01)	0.2	7 (4-13)	12 (6-20)	0.99 (0.97-1.02)	0.6
ACPA positive	**116 (72%)**	**15 (43%)**	**3.36 (1.59-7.13)**	**0.002**	**126 (70%)**	**5 (31%)**	**5.04 (1.67-15.2)**	**0.004**
Early Morning Stiffness ≥60 min	123 (76%)	24 (69%)	1.45 (0.65-3.22)	0.4	137 (76%)	10 (63%)	1.87 (0.64-5.43)	0.3
RAI	8 (4-11)	7 (4-9)	1.04 (0.96-1.12)	0.3	7 (4-10)	8 (2-12)	1.01 (0.92-1.12)	0.8
SJC44	**5 (3-11)**	**4 (2-7)**	**1.12 (1.02-1.23)**	**0.02**	5 (3-10)	4 (2-7)	1.08 (0.96-1.22)	0.2
CRP, mg/L	14 (0-39)	14 (0-27)	1.00 (0.99-1.01)	0.5	14 (0-39)	8 (0-18)	1.02 (0.99-1.04)	0.1
Patient VASDA, mm	54 (28-74)[a]	48 (18-72)[b]	1.01 (0.99-1.02)	0.3	53 (27-72)[c]	50 (22-75)[d]	1.01 (0.99-1.03)	0.5
DAS44-CRP	3.1 (2.5-3.7)[a]	2.8 (2.3-3.4)[b]	1.50 (0.95-2.36)	0.08	3.1 (2.5-3.7)[c]	2.7 (2.2-3.7)[d]	1.51 (0.84-2.72)	0.2
HAQ	1.1 (0.5-1.6)[e]	1 (0.4-1.7)[f]	1.07 (0.60-1.91)	0.8	1.1 (0.5-1.6)[g]	0.8 (0.4-1.3)[h]	1.79 (0.80-3.98)	0.2
US synovitis: Total GS score (unadjusted)	18 (11-26)	14 (7-24)	1.03 (0.99-1.07)	0.1	18 (11-26)	15 (7-20)	1.03 (0.98-1.08)	0.3
Adjusted for SJC44			*1.01 (0.97-1.05)*	*0.5*			*1.01 (0.96-1.07)*	*0.6*
Adjusted for DAS44-CRP			*1.38 (0.85-2.24)*	*0.2*			*1.41 (0.75-2.65)*	*0.3*
Total PD score (unadjusted)	**4 (0-9)**	**2 (0-3)**	**1.14 (1.03-1.26)**	**0.009**	3 (0-8)	2 (0-5)	1.07 (0.96-1.20)	0.2
Adjusted for SJC44			***1.12 (1.01-1.24)***	***0.03***			*1.06 (0.94-1.19)*	*0.4*
Adjusted for DAS44-CRP			***1.13 (1.01-1.26)***	***0.04***			*1.40 (0.74-2.61)*	*0.3*
Number of joints GS≥2 and/or PD≥1 (unadjusted)	6 (3-10)	5 (1-10)	1.07 (0.99-1.17)	0.1	6 (3-10)	5 (1-9)	1.06 (0.94-1.20)	0.3
Adjusted for SJC44			*1.04 (0.95-1.14)*	*0.4*			*1.06 (0.94-1.21)*	*0.3*
Adjusted for DAS44-CRP			*1.09 (0.98-1.22)*	*0.1*			*1.06 (0.93-1.22)*	*0.4*
Fulfilment of 2010 ACR/EULAR RA criteria with joint involvement determined by US (RA_{US})	**129 (80%)**	**18 (51%)**	**3.69 (1.72-7.94)**	**0.001**	**140 (77%)**	**7 (44%)**	**4.39 (1.54-12.5)**	**0.006**
US erosion (PIP2-3, MCP2-3, wrists or MTP2-4)	71 (44%)	17 (49%)	0.83 (0.40-1.72)	0.6	81 (45%)	7 (44%)	1.04 (0.37-2.92)	0.9
'Active' US erosion	50 (31%)	8 (23%)	1.51 (0.64-3.55)	0.3	55 (30%)	3 (19%)	1.89 (0.52-6.90)	0.3
Radiographic erosion in the hands and feet	29 (18%)	2 (6%)	3.60 (0.82-15.8)	0.09	29 (16%)	2 (13%)	1.34 (0.29-6.19)	0.7

Missing data in [a]31, [b]9, [c]38, [d]2, [e]26, [f]7, [g]32 and [h]1 cases.

Table 25. Association between baseline characteristics and the need for triple DMARD therapy or biologic therapy in patients with RA at baseline.

Values are median (IQR) or n (%) unless otherwise stated.

	Need for Triple DMARD Therapy or Biologic Therapy			
	Yes n=27	**No n=170**	**OR (95%CI)**	**p**
Age, mean (SD)	55 (13)	57 (13)	0.99 (0.96-1.02)	0.5
Female	21 (78%)	115 (68%)	1.67 (0.64-4.38)	0.3
Symptom duration, months	6 (4-13)	7 (4-14)	0.99 (0.95-1.03)	0.6
ACPA positive	22 (81%)	109 (64%)	2.46 (0.89-6.83)	0.08
Early Morning Stiffness ≥60 min	**25 (93%)**	**122 (72%)**	**4.92 (1.12-22.6)**	**0.04**
RAI	**10 (7-15)**	**7 (4-10)**	**1.12 (1.04-1.20)**	**0.002**
SJC44	**8 (4-16)**	**5 (3-9)**	**1.14 (1.06-1.23)**	**0.001**
CRP, mg/L	**29 (9-92)**	**13 (0-32)**	**1.01 (1.00-1.02)**	**0.01**
Patient VASDA, mm	**62 (47-94)[a]**	**50 (25-70)[b]**	**1.02 (1.00-1.04)**	**0.02**
DAS44-CRP	**3.7 (3.0-4.8)[a]**	**3.0 (2.4-3.5)[b]**	**2.44 (1.50-3.95)**	**<0.001**
HAQ	**1.6 (1.4-2.2)[c]**	**1.0 (0.4-1.5)[d]**	**3.91 (1.90-8.04)**	**<0.001**
US synovitis: Total GS score (unadjusted)	**26 (18-36)**	**16 (10-25)**	**1.07 (1.03-1.11)**	**<0.001**
Adjusted for SJC44			***1.05 (1.01-1.10)***	***0.01***
Adjusted for DAS44-CRP			***1.07 (1.02-1.13)***	***0.004***
Total PD score (unadjusted)	**7 (2-15)**	**3 (0-6)**	**1.09 (1.04-1.15)**	**0.001**
Adjusted for SJC44			*1.06 (1.00-1.12)*	*0.07*
Adjusted for DAS44-CRP			***1.08 (1.01-1.16)***	***0.03***
Number of joints GS≥2 and/or PD≥1 (unadjusted)	**10 (7-13)**	**6 (3-9)**	**1.18 (1.08-1.29)**	**<0.001**
Adjusted for SJC44			***1.13 (1.03-1.25)***	***0.009***
Adjusted for DAS44-CRP			***1.19 (1.06-1.33)***	***0.003***
Fulfilment of 2010 ACR/EULAR RA criteria with joint involvement determined by US (RA_{US})	**25 (93%)**	**122 (72%)**	**4.92 (1.12-21.6)**	**0.04**
US erosion (PIP2-3, MCP2-3, wrists or MTP2-4)	13 (48%)	75 (44%)	1.18 (0.52-2.65)	0.7
'Active' US erosion	**13 (48%)**	**45 (26%)**	**2.58 (1.13-5.90)**	**0.02**
Radiographic erosion in the hands and feet	6 (22%)	25 (15%)	1.66 (0.61-4.51)	0.3

NA: logistic regression not performed. Missing data in [a]4, [b]36, [c]3 and [d]30 cases.

7.4.4 Development of new ultrasound erosion at one year

Ultrasound data was available for 144 patients at one year. Development of new ultrasound erosion, in at least one joint of 18 joints examined for erosions, was observed in 4/26 (15%) patients classified as UA and 25/118 (21%) patients classified as RA, clinically, at baseline.

The majority of these patients developed new ultrasound erosion in only one joint (three patients with UA and 14 patients with RA). In patients with multiple new erosions, the number of joints with new erosions was as follows: 3 joints in one patient with UA, and 2 joints (n=9), 3 joints (n=1) and 4 joints (n=1) in patients with RA. At the joint level, this equated to a rate of development of ultrasound erosion, in joints lacking x-ray or ultrasound erosion at baseline, of 45/2469 (2%) joints. Additionally, new ultrasound erosions were observed in four joints with erosion previously visible on x-ray, but not ultrasound, at baseline; this occurred in four patients with RA, one of whom also demonstrated new ultrasound erosion in at least one other joint.

7.4.4.1 Predictors of new ultrasound erosion

- *At the patient level*

Baseline characteristics of patients with or without the development of new ultrasound erosion are shown in Table 26. A significant difference was observed in age only.

Table 26. Association between baseline characteristics and development of new ultrasound erosion at one year in patients with new-onset UA or RA.

Values are median (IQR) or n (%) unless otherwise stated.	New US Erosion			
	Yes n=29	No n=115	OR (95%CI)	p
Age, mean (SD)	**64 (14)**	**55 (13)**	**1.06 (1.02-1.09)**	**0.002**
Female	19 (66%)	84 (73%)	0.70 (0.29-1.67)	0.4
Symptom duration, months	8 (4-16)	7 (4-14)	0.99 (0.96-1.03)	0.7
ACPA positive	18 (62%)	73 (63%)	0.94 (0.41-2.18)	0.9
Fulfilment of 2010 ACR/EULAR RA criteria with joint involvement determined clinically	25 (86%)	93 (81%)	1.48 (0.47-4.68)	0.5
Early Morning Stiffness ≥60 min	22 (76%)	72 (63%)	1.88 (0.74-4.76)	0.2
RAI	5 (3-8)	6 (3-10)	0.96 (0.86-1.06)	0.4
SJC44	5 (3-9)	4 (2-7)	1.02 (0.94-1.12)	0.6
CRP, mg/L	15 (6-41)	10 (0-27)	1.00 (0.99-1.01)	0.9
Patient VASDA, mm	47 (27-66)[a]	48 (24-71)[b]	1.00 (0.98-1.02)	1.0
DAS44-CRP	2.6 (2.3-3.4)[a]	2.7 (2.0-3.3)[b]	1.12 (0.71-1.77)	0.6
HAQ	0.9 (0.2-1.6)[c]	0.9 (0.3-1.4)[d]	1.01 (0.52-1.94)	1.0
US synovitis: Total GS score (unadjusted)	15 (10-23)	13 (7-23)	1.01 (0.97-1.04)	0.8
Adjusted for SJC44			*1.02 (0.92-1.13)*	*0.7*
Adjusted for DAS44-CRP			*0.99 (0.95-1.04)*	*0.7*
Total PD score (unadjusted)	5 (1-8)	1 (0-6)	1.04 (0.98-1.11)	0.2
Adjusted for SJC44			*0.98 (0.88-1.09)*	*0.8*
Adjusted for DAS44-CRP			*1.04 (0.61-1.76)*	*0.6*
Number of joints GS≥2 and/or PD≥1 (unadjusted)	6 (3-9)	5 (2-8)	1.04 (0.95-1.13)	0.4
Adjusted for SJC44			*1.01 (0.91-1.11)*	*0.9*
Adjusted for DAS44-CRP			*1.10 (0.67-1.82)*	*0.7*
Fulfilment of 2010 ACR/EULAR RA criteria with joint involvement determined by US (RA_{US})	22 (76%)	67 (58%)	2.25 (0.89-5.69)	0.09
US erosion (PIP2-3, MCP2-3, wrists or MTP2-4)	10 (34%)	41 (36%)	0.95 (0.40-2.23)	0.9
'Active' US erosion	7 (24%)	24 (21%)	1.21 (0.46-3.16)	0.7
Radiographic erosion in the hands and feet	4 (14%)	13 (11%)	1.26 (0.38-4.18)	0.7

Missing data in [a]1, [b]24, [c]5 and [d]17 cases.

- *At the joint level*

Conditional logistic regression was possible using data from the 29 patients who developed ultrasound erosion in at least one joint. Amongst these patients, data from 499 joints lacking any evidence of erosion (either on x-ray or ultrasound) at baseline were used in the analysis (Table 27). New ultrasound erosions were observed in 41 (8%) joints. After stratifying for patient case, OR (95% CI) for the development of new ultrasound erosion in the presence of clinical swelling or significant ultrasound synovitis (GS≥grade 2 and/or PD≥grade 1) at baseline were 3.86 (1.80-8.30; p=0.006) and 1.90 (0.95-3.81; p=0.06), respectively. Considering the independent contributions of GS and PD (entering both variables in the models), PD predicted the development of new ultrasound erosion, independently of clinical swelling or GS; OR (95% CI) were 4.18 (1.59-11.0; p=0.004) for the presence of PD≥grade 1 and 1.72 (1.07-2.76; p=0.03) for PD score (grade 0-3).

Table 27. Association of baseline measures of clinical and ultrasound synovitis with development of new ultrasound erosion, in the subgroup of joints lacking ultrasound or x-ray erosion at baseline (multivariable conditional logistic regression analysis, n=499 joints).

Separate models were constructed to include: A) the presence of significant ultrasound synovitis (GS≥grade 2 and/or PD≥grade 1), B) the presence of significant GS (≥grade 2) and PD (≥grade 1) considered as separate categorical variables, and C) the GS and PD scores considered as continuous variables.

A) Association Between Ultrasound synovitis and New Erosion

Baseline Variable	OR (95% CI)	p
Presence of clinical swelling	**3.86 (1.80-8.30)**	**0.006**
Presence of significant US synovitis (GS≥grade 2 and/or PD≥grade 1)	2.03 (0.98-4.20)	0.06

B) Association Between GS and PD synovitis and New Erosion

Baseline Variable	OR (95% CI)	p
Presence of clinical swelling	**2.36 (1.04-5.38)**	**0.04**
Presence of GS≥grade 2	0.98 (0.41-2.34)	1.0
Presence of PD≥grade 1	**3.76 (1.40-10.1)**	**0.009**

C) Association Between Grade of GS and PD and New Erosion

Baseline Variable	OR (95% CI)	p
Presence of clinical swelling	**2.39 (1.03-5.55)**	**0.04**
GS score (grade 0-3)	1.02 (0.67-1.57)	0.9
PD score (grade 0-3)	**1.72 (1.07-2.76)**	**0.03**

7.5 Discussion

This is the first study to demonstrate the predictive validity of ultrasound in DMARD-naïve UA and RA patients, defined by the 2010 ACR/EULAR RA criteria and treated in a contemporary clinical practice setting. It is also the first to assess predictors of progression to fulfilment of 2010 RA criteria and new ultrasound erosions on standardised ultrasound examination of several joints.

Over half of patients with new-onset UA in this cohort had persistent disease. This is higher than that observed in patients with UA in earlier studies (Krabben et al., 2013a), possibly reflecting the definition used for persistent disease (includes DMARD and/or recent corticosteroid use) and an increased awareness of the benefits of early therapy. A significant rate of progression to 2010 RA was also observed, higher than that reported in a previous UK study in which 10% of patients with very recent-onset UA progressed (Cader et al., 2011). This could be explained by the exclusion of patients with symptom durations over three months in this very early cohort.

In patients with new-onset UA, greater GS synovitis was associated with the requirement for methotrexate, persistence of disease and progression to fulfilment of 2010 RA criteria. Progression to RA was also associated with a greater number of joints with significant ultrasound synovitis (GS≥grade 2 and/or PD≥grade 1). These associations remained statistically significant after adjustment for the burden of clinical synovitis. Power Doppler activity was infrequently observed in the 26-joint examination in this early UA cohort. When detected, it was not associated with outcome; the statistical power to detect a relationship being limited by the low levels of PD observed. Furthermore, only one patient with UA, not fulfilling RA criteria by clinical assessment, fulfilled the 2010 RA criteria with the use of standardised ultrasound assessment restricted to 26 joints (defining joint involvement by GS≥grade 2 and/or PD≥grade 1). Therefore, study of more extensive ultrasound assessments may be required to determine the most useful method for determining joint involvement by imaging within the 2010 RA criteria in this group.

The majority of patients clinically fulfilling the 2010 RA criteria in this cohort were treated with DMARD therapy (for the most part receiving methotrexate). This is in line with awareness of the benefits of early DMARD therapy in RA and knowledge of the 2010 criteria, which were applied prospectively in these patients. However, a small number of patients fulfilling the criteria demonstrated resolution of IA at one year or went on to receive alternative diagnoses. Total PD score (independent of clinical synovitis) was predictive of methotrexate initiation and fulfilment of the 2010 criteria on ultrasound (defining joint involvement by significant ultrasound synovitis) was predictive of both methotrexate initiation and persistent disease, in this high risk group. In addition, all ultrasound measures of synovitis (total GS, total PD, number of joints with significant ultrasound synovitis and fulfilment of the 2010 criteria on ultrasound) were associated with severe/refractory disease (defined by the need for triple DMARD or biologic therapy), independent of clinical measures of disease activity.

Two recent studies investigating the prognostic validity of ultrasound in early IA patients (with at least one swollen joint) are available. Rates of progression to fulfilment of 1987 RA over 12-18 months were 42-50% (Salaffi et al., 2010; Filer et al., 2011). Independent predictors of progression included global GS and PD measures across 38 joints (independent of the Leiden prediction score) (van der Helm-vanMil et al., 2007; Filer et al., 2011) and the number of joints with PD≥grade 2 in the hands and wrists (independent of serological status, inflammatory markers and presence of early morning stiffness>30 minutes) (Salaffi et al., 2010). Implications for clinical practice are not immediately clear; particularly given the number of joints examined in calculating a global score and the use of the Leiden score undertaken in the former study (generally not used routinely in clinical practice) and that no adjustment was made for clinical evidence of synovitis in the latter study. Importantly, both of these studies included both patients with UA and RA (defined by 2010 RA criteria), therefore the predictive value of such ultrasound parameters over the clinical application of the 2010 criteria was not clear from their results.

The study of imaging outcomes revealed a significant proportion of patients with new-onset UA and RA developed ultrasound erosion in joints previously lacking evidence of erosion at baseline. At the joint level, the association between new

ultrasound erosion and ultrasound synovitis (GS≥grade 2 and/or PD≥grade 1) did not reach significance with adjustment for the presence of clinical swelling. However, the presence of PD synovitis appeared to be a stronger predictor, being significantly associated with the development of ultrasound erosion independently of clinical swelling and GS synovitis.

This is consistent with previous studies suggesting PD synovitis is predictive of radiographic progression amongst patients with early IA (Funck-Brentano et al., 2013), early RA (Naredo et al., 2007; Pascual-Ramos et al., 2009; Fukae et al., 2010) and established RA (Taylor et al., 2004; Naredo et al., 2008a; Dougados et al., 2013). However, several of these studies have been limited to univariable analyses (Taylor et al., 2004; Naredo et al., 2007; Brown et al., 2008; Fukae et al., 2010), or have not adjusted for the burden of clinical synovitis within final prediction models (Naredo et al., 2008a; Foltz et al., 2012).

The most convincing evidence to date is provided by a study of 59 patients with active RA (at least six swollen joints) requiring initiation or change of TNF-inhibitor therapy (Dougados et al., 2013). Both GS and PD were independently associated with radiographic progression at the joint level. Multivariable analyses included assessment of clinical synovitis and other relevant factors such as age and global disease activity, although not serology. The only data available in patients with early IA (including patients with UA and early RA defined by 2010 criteria) are from the ESPOIR cohort (Funck-Brentano et al., 2013). This study demonstrated associations between radiographic progression over one year (increase in SHS erosion score from baseline) and both PD (at MCPs2-5 and/or MTP5) and presence of ultrasound erosion (at MCP2, MCP5 and/or MTP5), at baseline. Adjustment was made for several relevant baseline factors including DAS28, serology and steroid use, although not for baseline radiographic score. Amongst joints lacking radiographic erosion at baseline, no association was observed with ultrasound measures of synovitis and new radiographic erosion on adjusted analyses. There was a non-significant trend towards association with ultrasound erosion at baseline. This may be related to the smaller number of joints examined by ultrasound in this study, and/or the difficulties of assessing new radiographic erosions in patients with early IA treated according to modern-day standards: new x-ray erosions developed

in only in 26/1091 (2%) joints at one year and only 13/93 (14%) patients, lacking x-ray erosive disease at baseline, at two years.

The observational design of this study implies the results are generalisable to clinical practice; however, the results may be susceptible to confounding by indication bias. For example, presence of ultrasound synovitis (perceived by clinicians to be related to poor prognosis) may have affected the choice of treatment; greater ultrasound synovitis being expected to be associated with outcomes such as initiation of methotrexate and persistent IA (the definition of which includes DMARD use). However, the association of greater ultrasound synovitis with progression to RA and new ultrasound erosion supports the true prognostic validity of ultrasound; in patients with greater ultrasound synovitis DMARD use may be expected to be higher and therefore a lower rate of progression to RA or new ultrasound erosion may be predicted, rather than the higher rates that were observed. As noted in previous early arthritis inception cohorts, data (particularly baseline ultrasound parameters) were missing in a significant number of patients who were excluded from the analyses. However, comparing baseline characteristics between included and excluded patients for the main analysis of clinical outcomes did not identify any major differences between these groups. Differences observed between included and excluded patients for the analyses of imaging outcomes suggests that younger patients and those with greater disease activity at baseline were more likely to be excluded. This may be related to the proportion of patients who were subsequently referred to biologic DMARD clinical trials or received biologic DMARDs with follow-up in biologic-monitoring clinic in which standardised ultrasound did not form part of routine assessments. Excluding patients with greater disease activity suggests the rate of development of new ultrasound erosions in this analysis may be an under-estimate; however, age is known to be associated with an increased risk of joint erosion.

Bearing these limitations in mind, the results suggest the prognostic value of ultrasound in the management of patients with early IA. In particular, the degree of GS appears to be a sensitive indicator of disease progression in DMARD-naïve patients with UA, whilst PD appears to be predictive of the development of new ultrasound erosion.

Chapter 8 : **Use of Methotrexate in Patients with Early Inflammatory Arthritis in Clinical Practice.**

Does response differ according to fulfilment of 2010 ACR/EULAR RA classification criteria or ACPA status?

8.1 Introduction

Methotrexate is currently recommended as the first-line therapy in the management of RA (Smolen, Josef S et al., 2014). For patients with RA fulfilling 1987 ACR RA criteria, data from randomised controlled studies suggest up to one third of methotrexate-naïve patients with early disease achieve remission (defined by DAS28) with methotrexate monotherapy (Emery et al., 2008; Emery et al., 2009).

More recently, clinical trials using methotrexate have been conducted in patients with early IA, including patients with UA and RA defined by the 2010 RA criteria (section 2.4) (Wevers-de Boer, K. V. C. et al., 2012; de Jong et al., 2013; Nam et al., 2014b). With the recognition that patients with UA may develop persistent and progressive disease (albeit with a lower propensity than those who fulfil the RA criteria) (Cader et al., 2011; Krabben et al., 2012; Krabben et al., 2013a), the need to establish the efficacy of therapies, including methotrexate, in these patients has been identified (Emery, P et al., 2010; Wevers-de Boer et al., 2013). Furthermore, there is evidence that the use of methotrexate in clinical practice may be suboptimal (Gaujoux-Viala et al., 2012).

The variable response to methotrexate which is observed may be explained, at least in some part, by differences between patients in their disease pathogenesis. Amongst patients with RA, divergence in the pathogenic mechanisms of disease is becoming increasingly apparent between patients with seronegative and seropositive disease (section 2.1.1.2) (Hill et al., 2003; Huizinga et al., 2005; Irigoyen et al., 2005; Verpoort et al., 2005; van der Helm-van Mil et al., 2006; Sigurdsson et al., 2007; van Oosterhout et al., 2008; Ding et al., 2009; Cuthbert et al., 2010; Stahl et al., 2010; Law et al., 2012). Currently, data suggest methotrexate

may improve outcomes, including delaying disease progression, in patients with ACPA-positive UA (Emery et al., 2015), but be less effective or have a slower onset of action in ACPA-negative patients (van Dongen et al., 2007; Wevers-de Boer, K. V. C. et al., 2012; Nam et al., 2014b) (section 2.4.2.4). Further research is required to investigate this.

8.2 Aims and Objectives

To determine clinical response to methotrexate in patients with new-onset, DMARD-naive IA in clinical practice. In particular, to establish whether there is any difference in response according to serological status or fulfilment of the 2010 ACR/EULAR RA classification criteria.

8.3 Methods

A prospective, observational study was conducted in patients with new-onset UA and RA (Chapter 4). Additional criteria for inclusion in these analyses were the commencement of methotrexate monotherapy as a first-line DMARD regimen within three months of baseline, presence of at least low disease activity at baseline (defined by DAS28-CRP based on 3 variables SJC28, TJC28 and CRP [DAS28-CRP3v≥2.6]) and continued use of methotrexate monotherapy for at least six weeks. Due to the frequency of missing SJC44, RAI and patient VASDA data at baseline, the eligibility for inclusion was based on DAS28-CRP3v to maximise the study population. A minimum of six weeks of therapy was considered necessary to assess response. Patients receiving an alternative non-RA diagnosis within six months were excluded.

8.3.1 Outcomes

The primary outcomes assessed were remission (DAS28-CRP3v<2.6) and EULAR response (based on DAS28-CRP3v) at six months after the commencement of methotrexate. The EULAR response was calculated from the level of disease activity at either baseline or the time of commencement of methotrexate, whichever time-point demonstrated the highest DAS28-CRP3v. This was deemed appropriate to allow for an expected reduction in disease activity with use of corticosteroids

which may have been administered prior to methotrexate in the instance of a delay in the commencement of methotrexate. Outcomes based on DAS28-CRP3v were selected over those based on disease activity scores using more extensive joint counts and patient VASDA measurements in order to minimise potential bias due to the frequency of missing data for these variables.

Secondary outcomes at six months after the commencement of methotrexate were DAS28-CRP3v low disease activity (DAS28-CRP3v<3.2), Boolean remission (SJC44≤1, TJC53≤1, CRP≤10mg/dL and patient VASDA≤10mm) and change from baseline (or time of commencement of methotrexate, whichever time-point demonstrated the highest DAS28-CRP3v) in: swollen joint counts (SJC28 and SJC44), tender joint counts (TJC28 and RAI), CRP, DAS28-CRP3v, patient VASDA and HAQ score.

8.3.2 Statistics

Patients were grouped in two-ways, as follows: into UA and RA groups (according to clinical fulfilment of 2010 RA criteria) and into ACPA-negative and ACPA-positive IA groups. Differences between these groups, in baseline and treatment variables, were assessed using Chi-Squared or Fisher's exact tests for categorical variables (as appropriate for numbers of expected values) or t-tests for continuous variables following a normal distribution. For non-parametric data Mann-Whitney-U testing was carried out. The differences in outcomes between the groups were evaluated using univariable logistic regression analysis. Wilcoxon signed-ranks tests for paired data were also used to determine whether there was any significant improvement in the secondary outcome measures from baseline.

For primary outcomes, multivariable logistic regression models were also constructed. The following variables were entered into models due to their expected association with methotrexate response (Wevers-de Boer, K. V. C. et al., 2012): age, gender, symptom duration, baseline DAS28-CRP3v and either fulfilment of 2010 RA criteria or ACPA status. Due to the high weighting of serological status within the 2010 RA criteria, separate models were constructed for fulfilment of the criteria and ACPA status to avoid errors that may be introduced by the inclusion of overlapping variables.

On the basis of clinical trial data suggesting approximately one third of patients may achieve DAS28 remission with methotrexate monotherapy (Emery et al., 2008; Emery et al., 2009; Wevers-de Boer, K. V. C. et al., 2012; de Jong et al., 2013), a sample of 150 patients was expected to be required to ensure these models were robust (i.e. 50 expected events, with 5 variables per model). Two sensitivity analyses were planned. Firstly, RF status was considered within the definition of seropositivity in the model, defining seropositivity as positivity for either ACPA or RF, or both. Secondly, patients receiving concomitant hydroxychloroquine were also included, due to the frequent use of methotrexate and hydroxychloroquine combination therapy in local clinical practice.

8.3.3 Missing data

For patients in whom primary outcome data were not available at six months after the commencement of methotrexate, data collected at the closest assessment within the preceding or following three months were used. Patients who were lost to follow-up were excluded. In the instance of either an adverse event necessitating the cessation of methotrexate or an inadequate response requiring the escalation of therapy, observations were carried forward from the time of cessation/escalation of therapy.

8.4 Results

8.4.1 Patients

Of 333 DMARD-naïve patients with new-onset UA or RA identified in the observational study (Figure 3, section 6.4.1), 163 met the inclusion criteria for this analysis. Two further patients were excluded due to loss to follow-up (Figure 12). Characteristics at baseline are shown in Table 28.

Patients with UA (n=19) differed significantly ($p<0.05$) from those with RA (n=142), at baseline. Age, rates of seropositivity, clinical disease activity measures and prevalence of radiographic erosion were all lower in patients with UA. At least one feature of SpA was also more likely to be recorded in patients with UA. Significant

differences were also identified between patients with ACPA-negative IA (n=57) and ACPA-positive patients (n=104). Positivity for ACPA was associated with an increased rate of RF-positivity, fulfilment of RA classification criteria and worse physical function (greater HAQ score).

Figure 12. Disposition of patients registered in the longitudinal prospective observational study and included in the analysis of the efficacy of methotrexate.

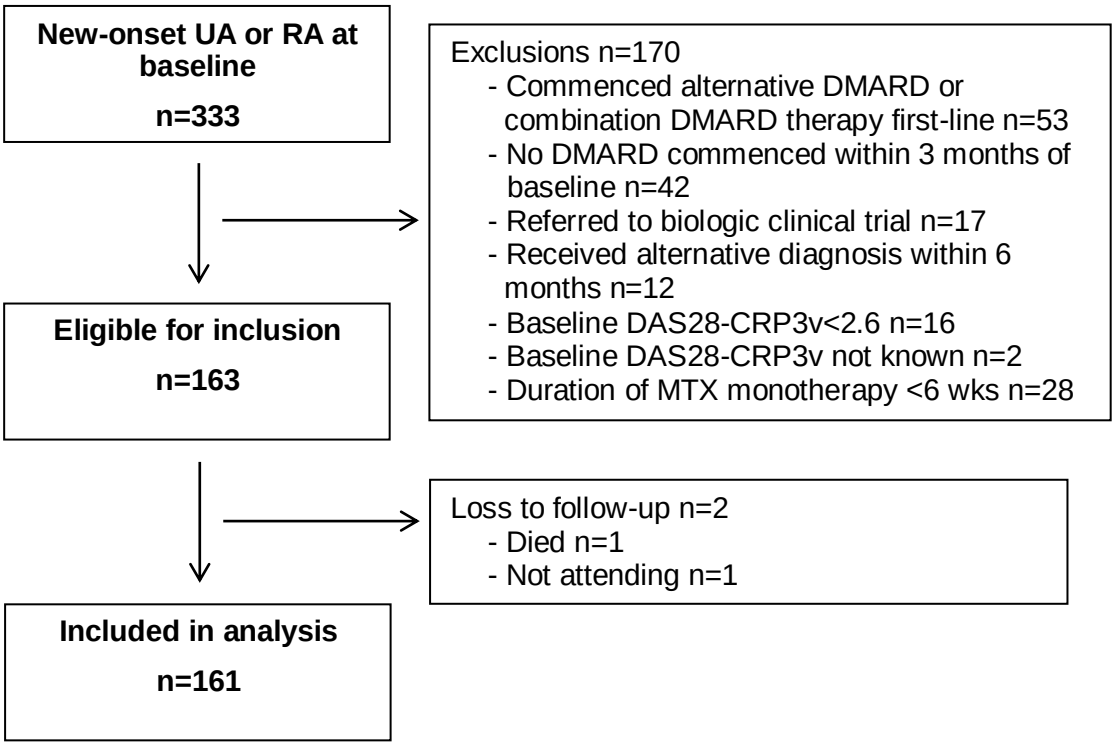


Table 28. Baseline characteristics of patients with UA and RA receiving methotrexate monotherapy first-line, with grouping according to fulfilment of 2010 ACR/EULAR RA criteria and ACPA status.

Values are median (IQR) or n (%), unless otherwise stated.	**All patients n=161**	**Grouped by fulfilment of 2010 RA criteria**			**Grouped by ACPA status**		
		UA n=19	**RA n=142**	**p**	**Negative n=57**	**Positive n=104**	**p**
Age, mean (SD)	55 (15)	**45 (14)**	**56 (15)**	**0.002**	53 (15)	56 (15)	0.3
Female	114 (71%)	11 (58%)	103 (73%)	0.2	37 (65%)	77 (74%)	0.2
Symptom duration, months	7 (4-13)	9 (4-17)	7 (4-13)	0.3	7 (4-13)	7 (4-13)	0.9
Current/previous smoker	89 (56%)[a]	12 (67%)[b]	77 (55%)[b]	0.3	29 (52%)[b]	60 (58%)[b]	0.4
Number of comorbidities: 1	49 (30%)	4 (21%)	45 (32%)	0.5	17 (30%)	32 (31%)	0.6
2	29 (18%)	2 (11%)	27 (19%)		11 (19%)	18 (17%)	
3	19 (12%)	3 (16%)	16 (11%)		6 (11%)	13 (13%)	
≥4	8 (5%)	1 (5%)	7 (5%)		2 (4%)	6 (6%)	
History/current evidence of coexistent osteoarthritis	60 (37%)	4 (21%)	56 (39%)	0.1	21 (37%)	39 (38%)	0.9
≥1 feature of SpA	12 (7%)	**4 (21%)**	**8 (6%)**	**0.04**	6 (11%)	6 (6%)	0.3
RF positive	102 (63%)	**2 (11%)**	**100 (70%)**	**<0.001**	**15 (26%)**	**87 (84%)**	**<0.001**
ACPA positive	104 (65%)	**1 (5%)**	**103 (73%)**	**<0.001**	**-**	**-**	-
Fulfilment of RA classification criteria: 1987 ACR RA	107 (66%)	**5 (26%)**	**102 (72%)**	**<0.001**	**32 (56%)**	**75 (72%)**	**0.04**
2010 ACR/EULAR RA	142 (88%)	**-**	**-**	**-**	**39 (68%)**	**103 (99%)**	**<0.001**
Early Morning Stiffness ≥60 min	126 (78%)	12 (63%)	114 (80%)	0.2	44 (77%)	82 (79%)	0.5
TJC28	8 (4-14)	**4 (3-5)**	**8 (4-15)**	**<0.001**	8 (4-15)	8 (4-14)	1.0
SJC28	5 (2-9)	**2 (1-4)**	**5 (3-10)**	**<0.001**	4 (2-8)	5 (3-9)	0.2
RAI	8 (4-11)[c]	**5 (3-7)[d]**	**8 (4-11)[e]**	**0.04**	8 (4-12)[f]	8 (4-10)[g]	0.7
SJC44	5 (3-11)[c]	**2 (2-4)[d]**	**6 (3-12)[e]**	**0.001**	5 (3-10)[f]	6 (3-12)[g]	0.5
Patient VASDA, mm	56 (30-79)	49 (28-69)	60 (31-80)	0.8	55 (26-71)	58 (33-80)	0.6
CRP, mg/L	14 (0-38)[h]	14 (0-28)[i]	14 (0-39)[j]	0.5	18 (4-36)[k]	13 (0-43)[c]	0.4
DAS28-CRP3v	4.5 (3.7-5.5)	**4.0 (3.1-4.5)**	**4.6 (3.7-5.7)**	**0.002**	4.5 (3.8-5.5)	4.5 (3.6-5.5)	0.9
DAS44-CRP3v	3.0 (2.3-3.6)[c]	**2.5 (2.2-2.8)[d]**	**3.1 (2.3-3.7)[e]**	**0.03**	3.1 (2.3-3.7)[f]	3.0 (2.2-3.6)[g]	0.8
HAQ	1.0 (0.5-1.6)[l]	0.9 (0.1-1.1)[l]	1.1 (0.5-1.6)[m]	0.07	**0.9 (0.3-1.3)[k]**	**1.1 (0.5-1.8)[n]**	**0.03**
Radiographic erosion in the hands and feet	28 (18%)[o]	**1 (<1%)[b]**	**28 (20%)[a]**	**0.04**	7 (13%)[a]	21 (20%)[b]	0.2

Missing data in [a]2, [b]1, [c]38, [d]9, [e]29, [f]14, [g]24, [h]59, [i]10, [j]49, [k]21, [l]57, [m]47, [n]36 and [o]3 cases.

8.4.2 Management

The majority of patients (134/161, 83%) commenced methotrexate at baseline (Table 29). Amongst the remaining patients (n=27) commencing methotrexate between one and three months after baseline, DAS28-CRP3v was greater at baseline than at methotrexate commencement (likely due to the use of corticosteroids) in all but two patients with ACPA-positive RA. For these two patients, variables at commencement of methotrexate, rather than baseline, were used in the determination of response.

Cessation of methotrexate or escalation to combination DMARD therapy occurred in 67 patients at a median (IQR) time of 13 (10-16) weeks. Fourteen patients stopped methotrexate due to intolerance or an adverse event. The reasons reported were: nausea and/or vomiting (n=3), subjective breathlessness (n=2), diarrhoea, mouth ulcers, hair loss, rash, lower respiratory tract infection, general malaise, headache and visual disturbance (each n=1) or were unknown (n=1).

Data were missing for DAS28-CRP3v assessment at six months in 14 patients, in whom data from the closest assessment between three and nine months were used. This gave a median (IQR) time on methotrexate monotherapy at outcome assessment for the total sample of 22 (14-26) weeks.

A significantly greater number of patients with ACPA-positive IA escalated therapy in comparison to ACPA-negative patients. No other statistically significant differences in treatment were identified between patients with UA and RA, or ACPA-negative and ACPA-positive patients.

Table 29. Management over six months in patients with UA and RA commencing methotrexate monotherapy first-line.
Patients are grouped according to fulfilment of 2010 ACR/EULAR RA criteria and ACPA status. Values are median (IQR) or n (%).

	All patients n=161	**Fulfilment of 2010 RA criteria**			**ACPA status**		
		UA n=19	**RA n=142**	**p**	**Negative n=57**	**Positive n=104**	**p**
Time from baseline to MTX commencement, months: 0	134 (83%)	14 (74%)	120 (85%)		45 (79%)	89 (86%)	
1	18 (11%)	5 (26%)	13 (9%)	0.3	9 (16%)	9 (9%)	0.3
2	6 (4%)	0	6 (4%)		0	6 (6%)	
3	3 (2%)	0	3 (2%)		3 (5%)	0	
Stopping MTX due to adverse event	14 (9%)	2 (11%)	12 (8%)	0.7	6 (11%)	8 (8%)	0.6
Escalating treatment	53 (33%)	3 (16%)	50 (35%)	0.09	**12 (21%)**	**41 (39%)**	**0.02**
Time on MTX monotherapy at outcome assessment, weeks	22 (14-26)	23 (13-29)	22 (14-26)	0.4	23 (15-26)	21 (13-26)	0.3
Average weekly dose of MTX, mg	19 (15-20)	17 (15-20)	19 (15-20)	0.6	19 (15-20)	19 (15-20)	0.9
Receiving significant total steroid dose:							
≥120mg methylprednisolone	110 (68%)	12 (63%)	98 (69%)	0.6	42 (74%)	68 (65%)	0.3
≥150mg prednisolone	37 (23%)	3 (16%)	34 (24%)	0.6	10 (18%)	27 (26%)	0.2
≥80mg triamcinolone	11 (7%)	0	11 (8%)	0.4	5 (9%)	6 (6%)	0.5
Total methylprednisolone dose, mg	120 (0-240)	120 (0-240)	120 (38-240)	0.5	120 (80-240)	120 (0-240)	0.4

8.4.3 Outcomes

At a median (IQR) time of 22 (14-26) weeks on methotrexate, a total of 56 (35%) patients achieved DAS28-CRP3v remission, 66 (41%) achieved a good EULAR response and 111 (69%) achieved at least a moderate EULAR response. Remission, defined by DAS28-CRP3v<2.6, was observed in 8/19 (42%) patients with UA versus 48/142 (34%) patients with RA (p=0.5). Rates of good and moderate EULAR response were 7/19 (37%) and 11/19 (58%) in patients with UA, versus 59/142 (42%) and 100/142 (70%) in patients with RA (p=0.3 and p=0.7 comparing rates of good and moderate EULAR responses, respectively).

With grouping according to ACPA status, DAS28-CRP3v remission was achieved in 16/57 (28%) patients with ACPA-negative disease versus 40/104 (38%) patients who were ACPA-positive (p=0.2). Good and moderate EULAR responses were observed in 21/57 (37%) and 37/57 (65%) patients with ACPA-negative disease versus 45/104 (43%) and 74/104 (71%) patients who were ACPA-positive (p=0.4 comparing the rates of both good and moderate responses).

Secondary outcomes are shown in Table 30. Change in SJC28 was statistically significantly lower in patients with UA versus patients with RA (p=0.04), however SJC28 at baseline was also lower amongst these patients. No statistically significant differences were identified in outcomes between ACPA-negative and ACPA-positive patients.

Figures 13 to 16 illustrate improvement from baseline in the majority of outcome measures across the patient groups. No statistically significant improvement from baseline was observed in RAI and patient VASDA amongst patients with UA or patients with ACPA-negative disease. A significant improvement in HAQ score was also only observed in patients with RA. Of note, missing data precluded analysis of these outcomes in a subset of patients.

Table 30. Outcomes in patients receiving methotrexate monotherapy at follow-up (median 22, IQR 14-26 weeks) according to fulfilment of 2010 ACR/EULAR RA criteria and ACPA status (univariable logistic regression analyses).
Values are median (IQR) and n (%).

	All patients n=161	**Fulfilment of 2010 RA criteria**				**ACPA status**			
		UA n=19	**RA n=142**	**OR (95% CI)**	**p**	**Negative n=57**	**Positive n=104**	**OR (95% CI)**	**p**
DAS28-CRP3v Remission (DAS28-CRP3v<2.6)	56 (35%)	8 (42%)	48 (34%)	0.70 (0.26-1.86)	0.5	16 (28%)	40 (38%)	1.60 (0.80-3.22)	0.2
DAS28-CRP3v Low Disease Activity (DAS28-CRP3v<3.2)	85 (53%)	12 (63%)	73 (51%)	0.62 (0.23-1.66)	0.3	29 (51%)	56 (54%)	1.13 (0.59-2.15)	0.7
EULAR Response (based on DAS28-CRP3v): Good Moderate	66 (41%) 111 (69%)	7 (37%) 11 (58%)	59 (42%) 100 (70%)	1.22 (0.45-3.28) 1.73 (0.65-4.61)	0.7 0.3	21 (37%) 37 (65%)	45 (43%) 74 (71%)	1.31 (0.67-2.54) 1.33 (0.67-2.66)	0.4 0.4
Boolean Remission (SJC44≤1, TJC53≤1, CRP≤10mg/dL, VASDA≤10mm)	9 (8%)[a]	2 (17%)[b]	7 (7%)[c]	0.39 (0.07-2.16)	0.3	3 (8%)[d]	6 (9%)[e]	1.14 (0.27-4.85)	0.9
Change from baseline: SJC28	3 (1-6)	**1 (1-3)**	**3 (1-7)**	**1.12 (1.00-1.26)**	**0.04**	3 (1-5)	3 (1-6)	1.01 (0.95-1.09)	0.7
TJC28	3 (0-9)	2 (0-4)	4 (0-10)	1.06 (0.99-1.13)	0.1	3 (0-10)	4 (0-8)	1.00 (0.96-1.04)	0.9
SJC44	3 (1-7)[f]	2 (1-3)[g]	3 (1-8)[h]	1.10 (0.97-1.26)	0.1	3 (1-9)[i]	3 (1-6)[j]	0.99 (0.92-1.07)	0.9
RAI	2 (-1-6)[f]	2 (0-3)[g]	2 (-1-6)[h]	1.03 (0.91-1.16)	0.7	1 (-3-6)[i]	2 (0-6)[j]	1.02 (0.95-1.10)	0.6
CRP, mg/dL	8 (0-29)	7 (0-21)	8 (0-30)	1.01 (0.99-1.02)	0.5	8 (0-28)	8 (0-30)	1.00 (0.99-1.01)	0.7
Patient VASDA, mm	8 (-10-33)[k]	-2 (-16-18)[l]	8 (-6-38)[m]	1.01 (0.99-1.04)	0.3	15 (-15-26)[n]	6 (-5-41)[o]	1.00 (0.99-1.02)	0.6
HAQ score	0.1 (-0.1-0.4)[p]	0.3 (-0.6-0.7)[l]	0.1 (-0.1-0.4)[q]	1.15 (0.37-3.58)	0.8	0.3 (-0.1-0.4)[r]	0 (-0.1-0.5)[s]	1.00 (0.51-1.97)	1.0

Missing data in [a]53, [b]7, [c]46, [d]18, [e]35, [f]52, [g]9, [h]43, [i]16, [j]36, [k]82, [l]13, [m]69, [n]31, [o]51, [p]90, [q]77, [r]34 and [s]56 cases.

Figure 13. Boxplots of: A) SJC28, B) TJC28, C) SJC44, and D) RAI, at baseline and follow-up (median 22, IQR 14-26 weeks) in patients grouped according to fulfilment of 2010 ACR/EULAR RA criteria.

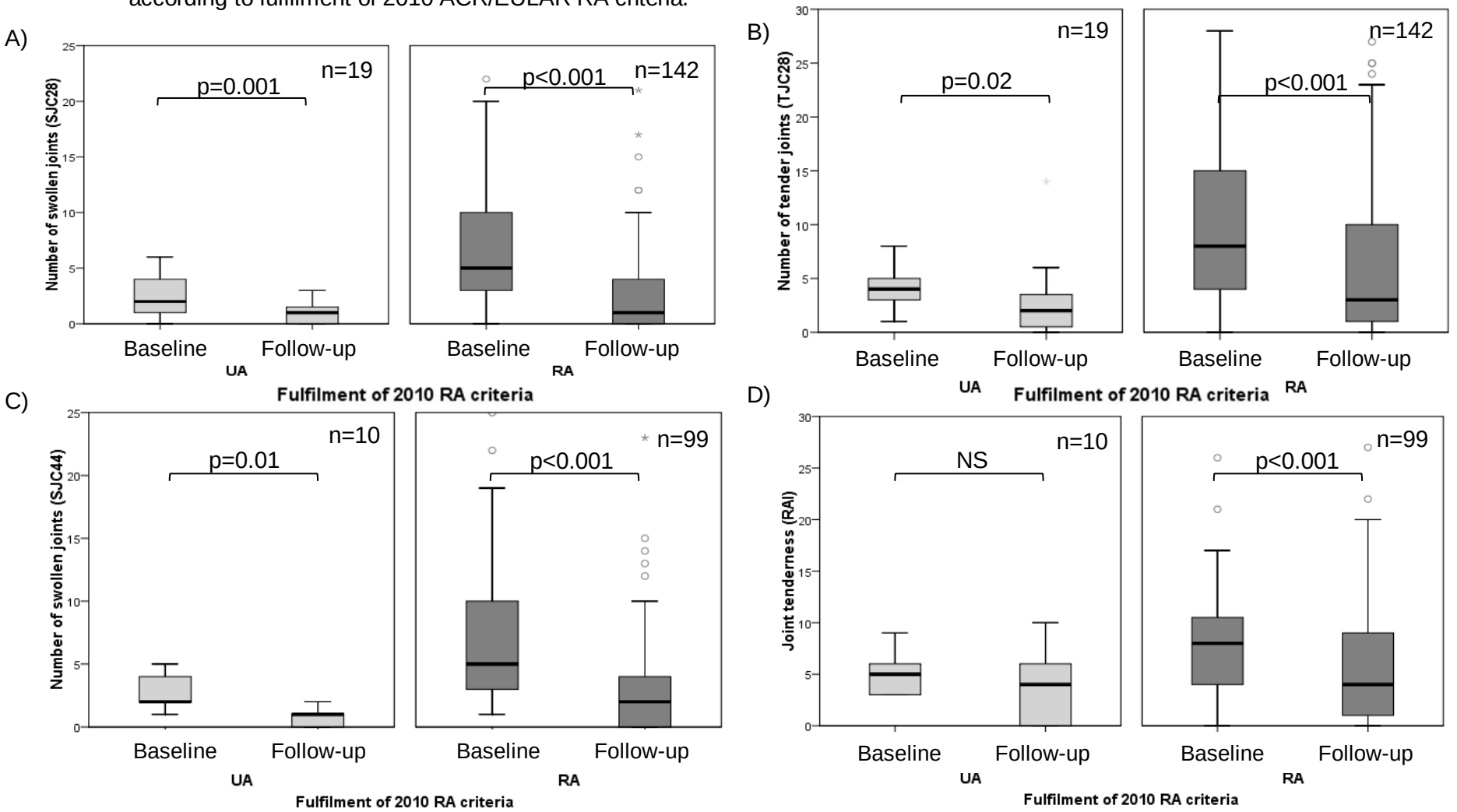


Figure 14. Boxplots of: A) CRP level, B) DAS28-CRP3v, C) patient VASDA and D) HAQ score, at baseline and follow-up (median 22, IQR 14-26 weeks) in patients grouped according to fulfilment of 2010 ACR/EULAR RA criteria.

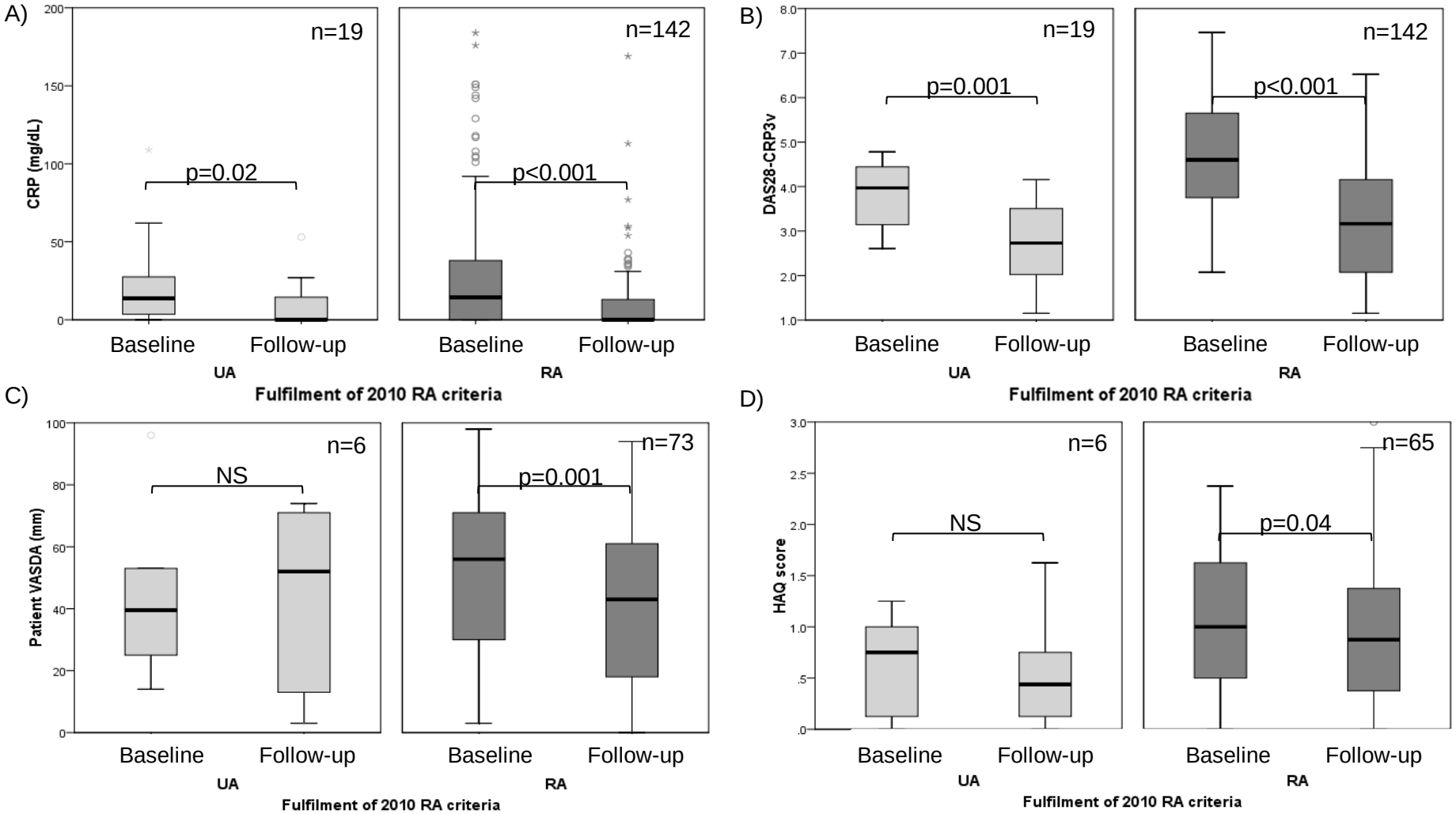


Figure 15. Boxplots of: A) SJC28, B) TJC28, C) SJC44, and D) RAI, at baseline and follow-up (median 22, IQR 14-26 weeks) in patients grouped according to according to ACPA status.

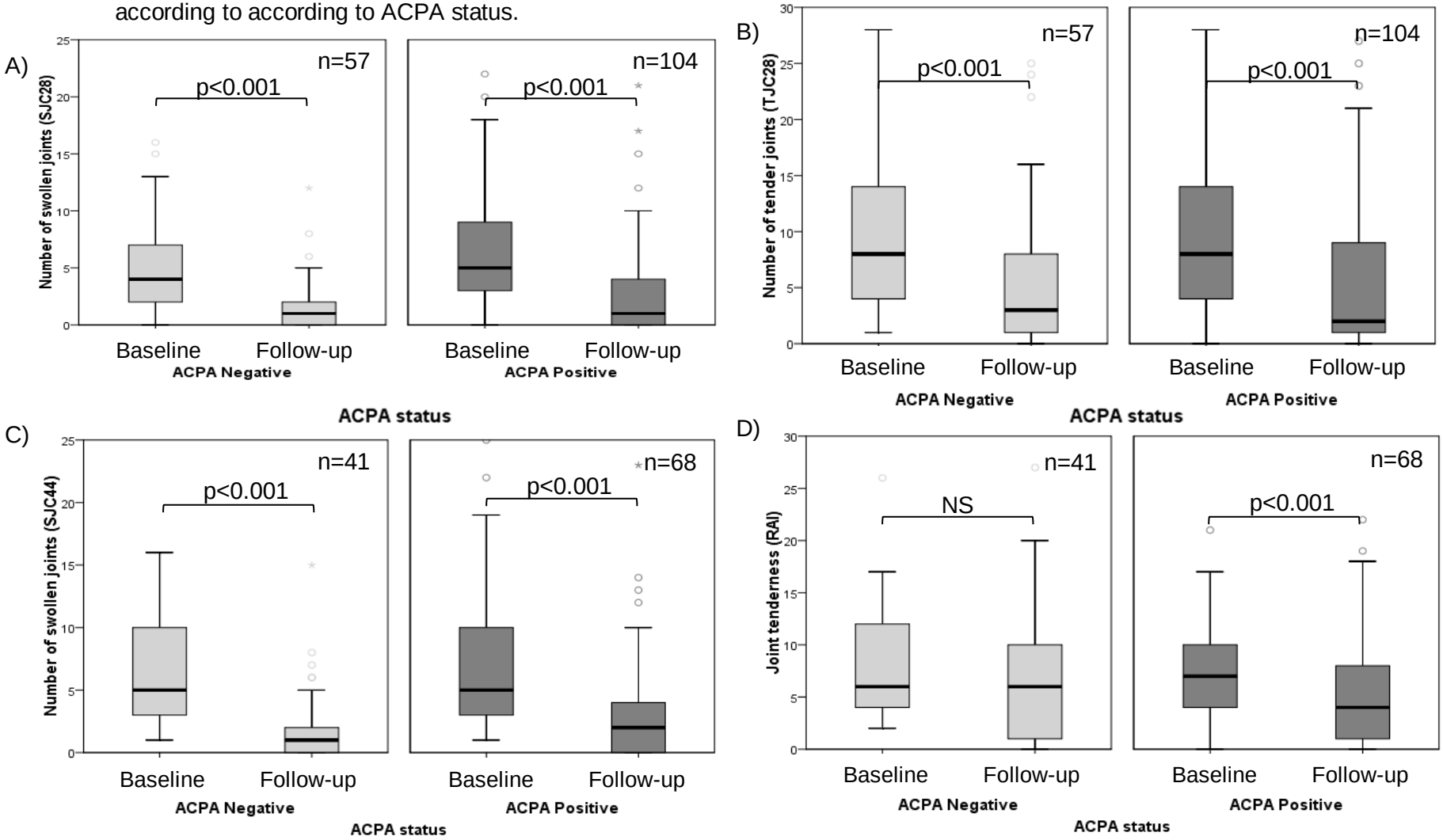
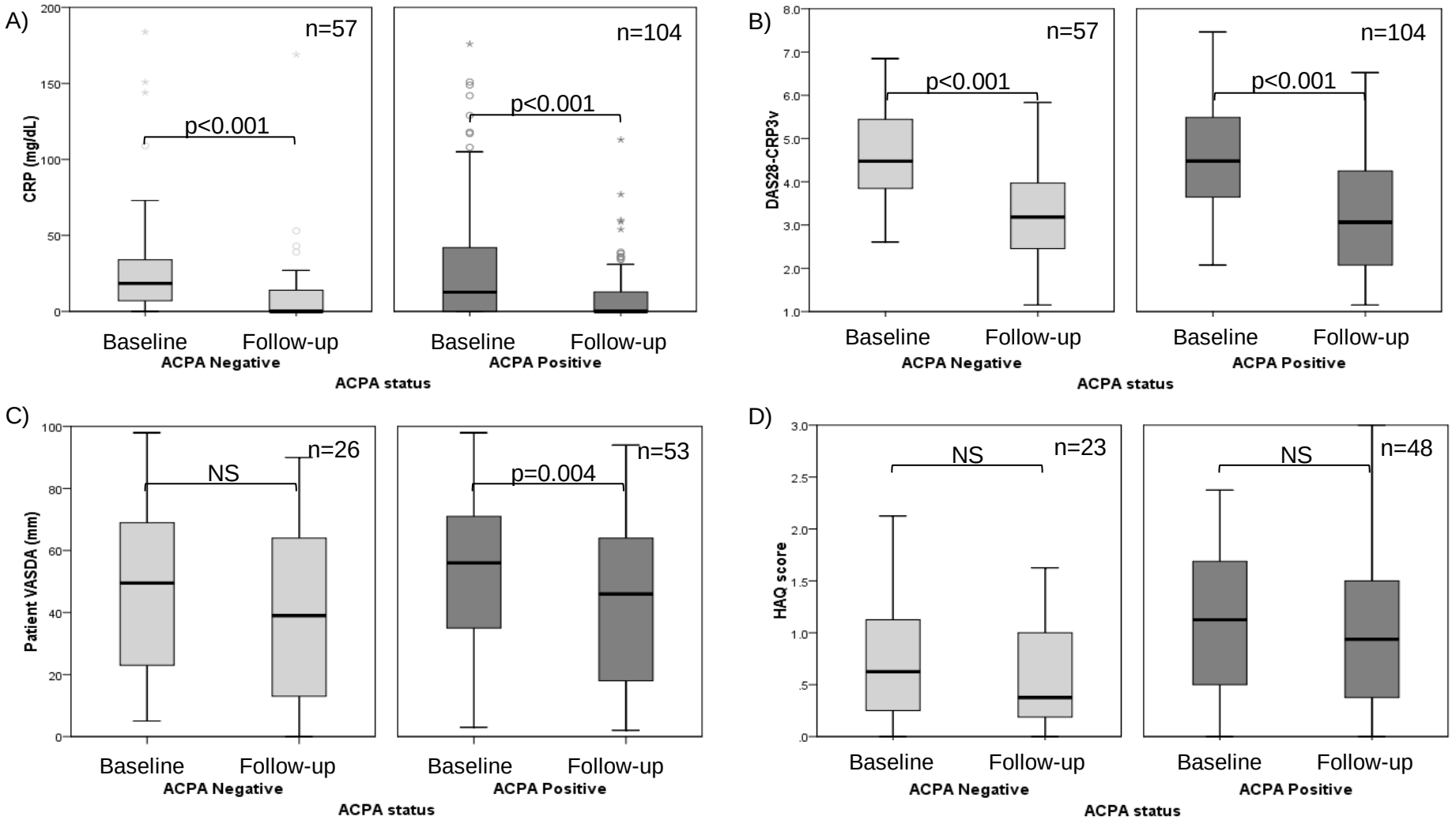


Figure 16. Boxplots of: A) CRP level, B) DAS28-CRP3v, C) patient VASDA and D) HAQ score, at baseline and follow-up (median 22, IQR 14-26 weeks) in patients grouped according to according to ACPA status.



8.4.4 Multivariable Analyses

After adjustment for age, gender, symptom duration and baseline DAS28-CRP3v, neither fulfilment of 2010 ACR/EULAR RA criteria nor ACPA-positivity were associated with the primary outcomes, DAS28-CRP3v remission or EULAR response at follow-up (Table 31).

Table 31. Odds ratios for DAS28-CRP3v remission and EULAR response, in patients receiving methotrexate monotherapy, according to fulfilment of 2010 ACR/EULAR RA criteria or ACPA status, with adjustment for age, gender, symptom duration and baseline DAS28-CRP3v (multivariable logistic regression analyses).

Response Outcome	Baseline Variable	OR (95% CI) for Response	p
DAS28-CRP3v Remission (DAS28-CRP3v<2.6)	Age	1.01 (0.98-1.04)	0.5
	Female	**0.43 (0.19-0.95)**	**0.04**
	Symptom duration, months	**0.92 (0.87-0.98)**	**0.01**
	Baseline DAS28-CRP3v	**0.44 (0.31-0.64)**	**<0.001**
	Fulfilling 2010 RA criteria	*1.02 (0.31-3.31)*	*1.0*
DAS28-CRP3v Remission (DAS28-CRP3v<2.6)	Age	1.01 (0.98-1.03)	0.6
	Female	**0.40 (0.18-0.88)**	**0.02**
	Symptom duration, months	**0.92 (0.87-0.98)**	**0.01**
	Baseline DAS28-CRP3v	**0.45 (0.31-0.65)**	**<0.001**
	ACPA-positive	*1.76 (0.79-3.91)*	*0.2*
EULAR Response (at least Moderate)	Age	1.01 (0.99-1.03)	0.4
	Female	0.89 (0.39-2.01)	0.8
	Symptom duration, months	0.98 (0.96-1.01)	0.2
	Baseline DAS28-CRP3v	**1.86 (1.32-2.63)**	**<0.001**
	Fulfilling 2010 RA criteria	*0.85 (0.28-2.59)*	*0.8*
EULAR Response (at least Moderate)	Age	1.01 (0.98-1.03)	0.5
	Female	0.84 (0.37-1.88)	0.7
	Symptom duration, months	0.98 (0.96-1.01)	0.3
	Baseline DAS28-CRP3v	**1.86 (1.32-2.62)**	**<0.001**
	ACPA-positive	*1.32 (0.63-2.80)*	*0.5*

8.4.5 Sensitivity Analyses

Substituting ACPA-positivity with seropositivity for ACPA and/or RF) did not affect the conclusion. Odds ratios (95% CI) were 0.91 (0.38-2.18) and 1.33 (0.53-3.29) for achieving DAS28-CRP3v remission and a moderate EULAR response, respectively, on multivariable analyses.

For analyses of response to methotrexate with or without hydroxychloroquine, a total of 167 patients with complete outcome data were identified. These were patients who commenced methotrexate either alone or in combination with hydroxychloroquine, and either remained on methotrexate monotherapy or escalated from first-line methotrexate monotherapy to combination treatment with hydroxychloroquine. Outcomes were assessed at six months after commencement of methotrexate (with/without hydroxychloroquine) or carried forward from the last assessment in patients either stopping methotrexate due to an adverse event/intolerance or escalating therapy to receive an alternative or additional DMARD (other than hydroxychloroquine) or biologic therapy (provided they had received at least six weeks of methotrexate). This gave a median (IQR) duration of methotrexate (with/without hydroxychloroquine) at outcome assessment of 25 (19-27) weeks. Outcomes were: DAS28-CRP3v remission in 65/167 (39%) patients and EULAR response (at least moderate) in 121/167 (72%) patients. Neither fulfilment of 2010 ACR/EULAR RA classification criteria, nor ACPA-positivity, were independently associated with either outcome; OR (95% CI) for achievement of DAS28-CRP3v remission with fulfilment of 2010 RA criteria were 1.20 (0.37-3.84) and with ACPA-positivity were 1.98 (0.93-4.24), and for achievement of at least a moderate EULAR response were 1.43 (0.48-4.23) and 1.27 (0.58-2.77), respectively.

8.5 Discussion

This study is the first to report remission rates achieved with methotrexate in patients with early UA and RA, defined according to 2010 RA criteria, in a clinical setting. In ESPOIR, clinical response to methotrexate was assessed using mean DAS28 levels at six months (Gaujoux-Viala et al., 2012). Notably, suboptimal dosing of methotrexate was identified, whereas the majority of patients in our study in Leeds were treated with methotrexate doses above 15mg weekly.

Approximately one third of all IA patients (42% of patients with UA and 34% of patients with RA) in our study achieved DAS28-CRP3v remission at follow-up. This is lower than that observed in the methotrexate arm of the double-blind randomised controlled trial, EMPIRE. In EMPIRE, DAS28-CRP remission was achieved in 44% of patients at 12 weeks and 49% of patients at 26 weeks (Nam et al., 2014b). All

patients were seropositive (presence of at least one of ACPA, RF or the shared epitope) with at least one swollen and tender joint; only 7 (6%) patients did not fulfil 2010 RA criteria at baseline, in comparison to the 19 (12%) patients in our observational study. Explanations for a lower rate of response in our observational Leeds cohort include differences in patient characteristics, differences in inclusion criteria and likely differences in management approach. Patients studied in the context of a clinical trial may be expected to be more homogeneous in terms of the nature of their disease (with more restrictive, defined criteria for inclusion/exclusion) and their treatment (with perhaps greater adherence to more protocollised treatment regimens). Other plausible explanations include the potential underestimation of the efficacy of methotrexate in our observational study. Approximately half of patients discontinued or stepped up to combination therapy at a time that may have been too early to assess full response. Bias may also have been generated through non-attendance of the least symptomatic patients.

Other clinical trials in early IA (not restricted to patients with RA) have reported rates of DAS44 remission with methotrexate monotherapy in combination with oral corticosteroids. In IMPROVED, 291/479 (61%) of patients with RA (defined by 2010 RA criteria) and 79/122 (65%) of UA patients (not fulfilling 2010 RA criteria) achieved DAS44 remission at four months (Wevers-de Boer, K. V. C. et al., 2012). In tREACH, the rate was 28/90 (31%) amongst patients assessed at three months (de Jong et al., 2013). The tREACH study included a similar proportion of patients with UA, not fulfilling 2010 criteria, to our study (12%), although response was not reported amongst this important subgroup.

Whilst no statistically significant differences in response were identified between patients with UA and RA, and patients with ACPA-negative and ACPA-positive disease in the primary outcome measures, the use of DAS28-CRP3v may not be ideal for patients with predominant disease in the feet. Unfortunately, the number of patients with complete data for analyses based on DAS44-CRP was not sufficient in order to achieve an adequate sample size to allow adjustment for the selected variables. Secondary outcomes show that significant improvement in SJC44 was observed in all groups, although changes in RAI, VASDA and HAQ were not significant in patients with UA or ACPA-negative IA. Contributory factors may be the

low baseline levels of some of these variables, particularly HAQ (median scores 0.9), and small patient numbers due to missing data.

Controlling for corticosteroids and determining the speed of response was not possible within the observational study design. The sample size did not permit adjustment for further variables such as steroid exposure, or fitting treatment duration as an interaction term, within the multivariable analyses. Importantly, no significant differences were detected in the use of steroids or duration of methotrexate between the groups.

Research to date remains inconclusive regarding possible superior or more rapid response to methotrexate in ACPA-positive patients, in comparison to ACPA-negative patients, with early IA. Multivariable analysis of the IMPROVED study identified ACPA-positivity amongst independent predictors for DAS44-ESR remission after four months with adjustment for baseline DAS44-ESR, but not with adjustment for the number of involved small and large joints (Wevers-de Boer, K. V. C. et al., 2012). At one year (after four months of methotrexate followed by a DAS44-steered treatment regimen), no significant difference was observed between the rates of DAS44-ESR remission achieved amongst ACPA-positive and ACPA-negative patients (Wevers-de Boer, K.V.C. et al., 2012). In the PROMPT study, methotrexate monotherapy significantly delayed progression to RA in comparison to placebo only amongst ACPA-positive patients. Radiographic progression was also significantly lower with methotrexate only amongst ACPA-positive patients. However this was based on a subgroup analysis in a study powered to detect a treatment difference in the whole patient group and the majority of ACPA-negative patients did not show any progression (van Dongen et al., 2007). The EMPIRE study also indicates a trend towards earlier clinical response to methotrexate in ACPA-positive patients, with significant differences in response observed at week two and 26, but not at week 12 or 52, after adjustment for confounders (Nam et al., 2014b).

These results support the ongoing first-line use of methotrexate in patients with early IA, including those with UA and ACPA-negative disease. Step-up to combination DMARD therapy may be required in up to two-thirds of patients, in the context of treatment-to-target guidelines for the management of early RA, in clinical

practice (Smolen et al., 2010). To delineate subtle differences in response according to fulfilment of the 2010 criteria or ACPA status further studies are required, ideally within the context of a trial controlling for the use of steroids.

Chapter 9 : **Evaluation of a Treat-To-Target Management Strategy in Patients with Early RA in a Clinical Practice Setting.**

Discordance between the predictors of clinical and imaging remission.

9.1 Introduction

Randomised controlled trials reveal patients with early RA may achieve superior outcomes with treatment-to-target strategies in comparison to conventional care (section 2.4.1) (Grigor et al., 2004; Verstappen et al., 2007; Knevel et al., 2010). Guidelines, first published in 2010 by EULAR, recommend this approach (Smolen et al., 2010; Smolen, Josef S et al., 2014; Smolen et al., 2017). Monitoring of disease activity, using a validated composite measure, is recommended at least every three months, with optimisation of treatment to achieve a pre-defined target, primarily remission. In 2011, ACR/EULAR remission criteria were developed for use in clinical trials (Felson et al., 2011) and are now recommended as the optimal target for treatment (Smolen, Josef S et al., 2014; Smolen et al., 2017). Two alternative definitions are proposed, based on either the simplified disease activity index (SDAI≤3.3) or that developed using a Boolean approach: swollen joint count, tender joint count, CRP (mg/dl), and patient global self-assessment (0 to 10 scale) all less than or equal to one.

There is evidence, however, that such clinical definitions of remission are imperfect in delineating patients with a true absence of any inflammatory disease activity (section 2.4.1.5). Data from randomised trials indicates approximately half of patients achieving SDAI remission and one third of patients achieving Boolean remission (using a 28-joint count), after 12 months of treatment with methotrexate, experience worsening radiographic scores and/or a decrease in physical functioning over the following 12 months (Felson et al., 2011). Observational data confirms over half of patients with early RA achieving SDAI or Boolean remission experience a deterioration in radiographic and/or HAQ scores over the following 12-24 months (Zhang et al., 2012). This highlights the need for ongoing monitoring.

Imaging studies in patients with established RA confirm that despite achievement of a clinical remission state, subclinical inflammatory disease activity may persist. In patients achieving 2011 ACR/EULAR Boolean remission, PD on ultrasound examination has been demonstrated in up to approximately half of patients within the hands and wrists (Saleem et al., 2011; Geng et al., 2014) and one third of patients within 22 joints including the hands, wrists, elbows and knees (Zufferey et al., 2014). The relevance of PD in clinical remission and low disease activity states is evident from its relationship with radiographic progression (Brown et al., 2008; Foltz et al., 2012) and future disease flare (Scirè et al., 2009; Foltz et al., 2012; Saleem et al., 2012) (section 2.3.2.1). Conversely, studies suggest the clinical remission criteria may be too stringent in a subset of patients, notably those with comorbidities (Thiele et al., 2013).

Ultrasound, by directly assessing the pathology of RA, may enable a more comprehensive approach to defining remission and could therefore guide therapeutic decisions. Indeed, imaging remission has been proposed as a future goal for therapy (van der Heijde, 2012). Recent interventional studies have failed to demonstrate superiority of targeting disease activity evident on ultrasound in comparison to clinical targets in terms of primary outcomes assessed, however deficiencies in study methods imply further investigations are needed in order to determine the value of targeting imaging remission (Dale et al., 2016; Haavardsholm et al., 2016; D'Agostino et al., 2017) (section 2.4.1.5). Further studies have been proposed (Wakefield et al., 2012).

Further data are needed to inform the use of the 2011 ACR/EULAR remission criteria and ultrasound in clinical practice. Evidence of success of treat-to-target strategies in unselected patients with early RA in clinical practice remains limited (van Hulst et al., 2010; Bosello et al., 2011; Vermeer et al., 2011; Vermeer et al., 2012; Gremese et al., 2013; Farman et al., 2015). In addition, data regarding the relationship between clinical and imaging remission in early disease, in particular with respect to the new 2011 ACR/EULAR Boolean criteria, are limited (Scirè et al., 2009; Balsa et al., 2010; Sakellariou, Garifallia et al., 2013) (section 2.4.1.5). Several studies have examined predictors of clinical remission in observational, open-label and randomised controlled studies (Möttönen et al., 2002; Gossec et al.,

2004; Bosello et al., 2011; Contreras-Yanez et al., 2012; Ma et al., 2012; Wevers-de Boer, K. V. C. et al., 2012; Gremese et al., 2013) (see Tables 5 and 6, section 2.2). However, less is understood regarding the predictors of clinical and imaging remission in daily practice which may ultimately facilitate decisions regarding choice of first-line therapy or treatment strategy for individual patients.

9.2 Aims and Objectives

To assess how the EULAR treat-to-target guidelines and the paradigm for targeting clinical remission in early RA translate into clinical practice, particularly in relation to ultrasound imaging. Specific objectives were to evaluate:

- Adherence to the EULAR treat-to-target guidelines and identify potential barriers to adherence in clinical practice.
- The rates of DAS28 remission, DAS44 remission, 2011 ACR/EULAR Boolean remission and imaging remission.
- Agreement between these clinical remission states and imaging remission.
- Predictors of achievement of these clinical and imaging remission outcomes.

9.3 Methods

A prospective, observational study was conducted in patients with new-onset, DMARD-naïve IA (Chapter 4). Patients were selected from this cohort according to the following criteria: (i) fulfilment of RA criteria (1987 ACR and/or 2010 ACR/EULAR RA classification criteria) at baseline, (ii) active disease at baseline or time of commencement of DMARD (DAS28-CRP≥2.6, or in the instance of missing patient VASDA, DAS28-CRP3v≥2.6), and (iii) commencement of DMARD therapy within three months of baseline. Patients receiving an alternative non-RA diagnosis within the following 12 months or with incomplete 12-month outcome data were excluded.

9.3.1 Assessments

Clinical disease activity and ultrasound assessments are described in sections 4.2 and 4.3.

9.3.1.1 Outcomes

- *Adherence to guidelines*

Adherence to guidelines was assessed by calculating the proportion of patients in whom DAS28-CRP was recorded at least every three months until achievement of the target (DAS28-CRP<2.6), and DMARD or corticosteroid treatment was escalated at least every three months if the target was not met. Escalation in DMARD treatment was defined as addition or switch of synthetic DMARD (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide or other) or biologic DMARD, or an increase in dose of DMARD. Corticosteroid treatment escalation was defined as either the initiation, or increase in dose of oral prednisolone, or administration of intramuscular, intra-articular or intravenous methylprednisolone, or intramuscular triamcinolone.

- *Clinical outcomes*

The clinical outcomes were DAS28-CRP remission (DAS28-CRP<2.6) and low disease activity (DAS28-CRP<3.2), DAS44-CRP remission (DAS44-CRP<1.6) and low disease activity (DAS44-CRP<2.4), and 2011 ACR/EULAR Boolean remission (SJC44≤1, TJC53≤1, CRP≤10mg/dL and patient VASDA ≤10mm).

- *Imaging outcomes*

Imaging outcomes were defined using the sum of the semi-quantitative scores for PD assessed in 26 joints (maximum total score 78). Absence of PD was defined as a total score of zero. In order to allow for low-level PD which may be observed, particularly at the wrist and first MTPs in healthy individuals (Terslev et al., 2004; Hameed et al., 2008; Millot et al., 2011; Carotti et al., 2012; Kitchen and Kane, 2015) and/or patients with osteoarthritis (Keen et al., 2008; Mathiessen et al., 2016), two alternative definitions of absent/minimal PD were also considered. These were: (i) total PD score≤1 (i.e. presence of a maximum of grade 1 PD in a maximum of any one of the 26 joints), and (ii) PD≤grade 1 at any or all of the wrists and first

MTPs and up to one other joint examined, with absence of PD (grade 0) in the remaining 21 joints (i.e. allowing for a maximum total PD score=5, comprising PD=grade1 in both wrists and first MTPs and any one of the other joints examined: elbow, MCP2-3, PIP2-3, knee, ankle or MTP2-5 joints).

9.3.2 Statistics

Prevalence and bias adjusted kappa (PABAK) statistics were calculated to examine the relationship between the clinical remission endpoints and imaging outcomes. Univariable logistic regression was conducted to investigate factors associated with the clinical remission and imaging outcomes. Multivariable logistic regression analysis was also planned, entering baseline variables demonstrating statistical significance ($p<0.05$) on univariable analysis.

9.4 Results

9.4.1 Patients

Between June 2010 and September 2012, 217 patients fulfilling RA criteria were eligible for inclusion in the analysis. Patient disposition is displayed in Figure 17 and baseline characteristics are shown in Table 32. No significant difference was observed between baseline DAS28-CRP scores, DAS44-CRP scores or ultrasound parameters in patients included in the analyses (n=105) and those who were lost to follow-up or in whom follow-up data was incomplete (n=112). However, they differed significantly ($p<0.05$) in the following manner: mean age was higher and SJC28, TJC28, SJC44 and RAI were generally lower amongst included patients.

Figure 17. Disposition of patients included in the analysis of outcomes of patients with RA receiving DMARDs according to a treatment-to-target strategy.

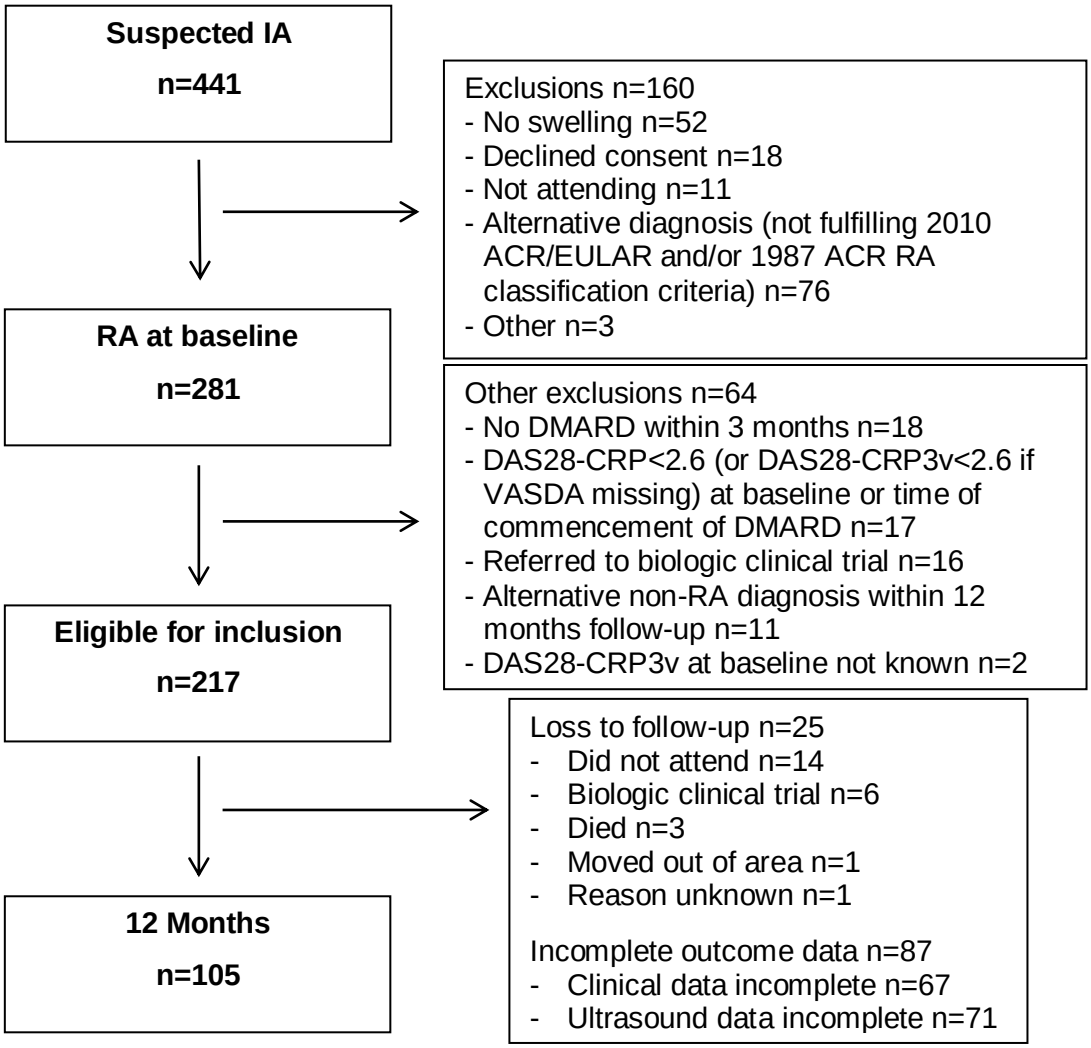


Table 32. Baseline characteristics of patients with new-onset RA receiving DMARDs according to a treatment-to-target strategy. Values are median (IQR) and n (%), unless otherwise stated.

	Included in analysis		**Excluded due to missing follow-up data**		**p**
	(n=105)	Missing Values	**(n=112)**	Missing Values	
Age, mean (SD)	**59 (13)**	-	**53 (15)**	-	**0.002**
Female	79 (75%)	-	80 (71%)	-	0.5
BMI, mean (SD)	27 (5)	13	29 (6)	12	0.1
Symptom duration, months	6 (4-13)	-	7 (4-13)	-	0.5
Current/previous smoker	65 (62%)	-	67 (60%)	1	0.8
Number of comorbidities: 1 2 3 ≥4	34 (32%) 19 (18%) 15 (14%) 7 (7%)	-	25 (22%) 31 (28%) 14 (13%) 7 (6%)	-	0.9
History/current evidence of coexistent osteoarthritis	46 (44%)	-	37 (33%)	-	0.1
RF positive	78 (74%)	-	72 (64%)	-	0.1
ACPA positive	81 (77%)	-	73 (65%)	-	0.05
Fulfilment of RA classification criteria: 1987 ACR RA	73 (70%)	-	83 (74%)	-	0.5
2010 ACR/EULAR RA	101 (96%)	-	109 (97%)	-	0.7
TJC28	**7 (3-13)**	-	**10 (5-17)**	-	**0.003**
SJC28	**4 (2-8)**	-	**6 (3-10)**	-	**0.03**
RAI	**7 (4-10)**	17	**9 (5-13)**	24	**0.01**
SJC44	**5 (3-9)**	17	**7 (4-13)**	24	**0.01**
CRP, mg/L	21 (7-45)	-	13 (0-40)	-	0.2
Patient VASDA, mm	50 (31-77)	27	61 (35-82)	44	0.3
DAS28-CRP3v	4.5(3.8-5.2)	-	4.7(3.7-5.8)	-	0.1
DAS28-CRP	4.9(4.0-5.5)	27	5.1(3.9-6.1)	44	0.5
DAS44-CRP	3.1(2.6-3.6)	34	3.4(2.6-4.0)	46	0.1
HAQ	1.3(0.8-1.9)	30	1.4(0.5-1.8)	40	0.9
Ultrasound of 26 joints:					
Total GS score	17 (10-25)	21	19 (12-26)	33	0.2
Total PD score	3 (0-8)	21	3 (0-9)	33	0.9
Absence of PD (total PD=0)	23 (27%)	21	55 (28%)	33	0.9
Absent/minimal PD (total PD≤1)	34 (40%)	21	61 (35%)	33	0.5
Radiographic erosion in the hands and feet: Any	18 (17%)	-	20 (18%)	2	0.8
1987 ACR definition	11 (10%)		16 (14%)	2	0.4
2010 ACR/EULAR definition	9 (9%)		9 (8%)	2	0.9

9.4.2 Management

The majority of patients commenced DMARDs at baseline (72%) or within four weeks of baseline (15%). Choice of first DMARD was methotrexate monotherapy in 86%, hydroxychloroquine monotherapy in 10% and sulfasalazine monotherapy in 4% of patients. Methotrexate in combination with another DMARD was commenced in the remaining 1%. A contraindication to early commencement of methotrexate was recorded in 5% of patients, comprising chronic obstructive airways disease, recent or concurrent infection and deranged liver function tests. Over 12 months, 9 (9%) and 20 (19%) patients failed treatment with methotrexate or an alternative DMARD, respectively, due to intolerance or an adverse event. Table 33 provides further details of patient management.

Table 33. Management of patients with new-onset RA receiving DMARDs according to a treatment-to-target strategy over 12 months.

Values are median (IQR) and n (%).

		RA n=105
Ongoing Treatment at 12 months:	MTX monotherapy	38 (36%)
	SSZ monotherapy	3 (3%)
	HCQ monotherapy	5 (5%)
	MTX + other DMARD	36 (34%)
	2 DMARDs (excluding MTX)	1 (1%)
	MTX + SSZ + HCQ	8 (8%)
	Biologic therapy	5 (5%)
	Referred to Biologics Clinical Trial	2 (2%)
	Other DMARD	2 (2%)
	Steroid alone	4 (4%)
	None	1 (1%)
Ongoing MTX use at 12 months:	Administered orally	75 (76%)
	Administered subcutaneously	14 (13%)
	Weekly dose, mg	25 (20-25)
Receiving significant total steroid dose over 12 months:		
	≥80mg triamcinolone	10 (10%)
	≥150mg prednisolone	30 (29%)
	≥120mg methylprednisolone	84 (80%)
Total methylprednisolone dose over 12 months, mg		240 (120-360)
Adherence to treatment-to-target guidelines:		
- Clinical assessment at least every 3 months until the target for treatment (DAS28-CRP <2.6) was met		97 (92%)
- DAS28-CRP available at least every 3 months until the target for treatment (DAS28-CRP <2.6) was met		76 (72%)
- DAS28-CRP available at least every 3 months and DMARD therapy escalated if the target was not met		53 (51%)
- DAS28-CRP available at least every 3 months and DMARD or corticosteroid therapy escalated if the target was not met		61 (58%)

9.4.3 Adherence to treat-to-target guidelines

The DAS28-CRP score was recorded at least every three months up to 12 months, or until the target was met, in 76 (72%) patients. Appropriate escalation of DMARDs (excluding corticosteroids), i.e. at least every three months if DAS28-CRP≥2.6, was observed in 53/76 (70%) of these patients. In a further eight (10%) patients, corticosteroid therapy was increased or administered without a change in DMARD. Amongst the remaining 15 patients in whom treatment was not escalated despite awareness of DAS28-CRP≥2.6, reasons throughout the 12 months were: awaiting effect of previous treatment escalation (n=6), physician impression of non-inflammatory symptoms only (n=4, simultaneous ultrasound assessments revealed total PD scores ranging between zero and three), physician judgement of acceptable disease control (n=4, simultaneous ultrasound assessments were available in n=3 cases with total PD scores ranging between one and three), contraindication to treatment escalation (n=2), patient declining (n=2), considering biologic clinical trial (n=2) and isolated flare (n=1).

As the target DAS28-CRP<2.6 allows the presence of clinical swelling (Mäkinen et al., 2005), there is still a role for clinical assessment as recommended within EULAR guidelines. In fact, out of 121 visits at which DAS28-CRP<2.6 was observed, treatment was escalated (including steroid administration) due to a clinician impression of ongoing inflammatory disease activity at 44 (36%) visits. Standardised ultrasound examination of 26 joints was conducted at 31/44 of these visits, confirming presence of PD in 22/31 (71%) cases. This compares to the availability of ultrasound at 43/77 visits at which DAS28-CRP<2.6 and treatment was not escalated, with PD confirmed in 18/43 (42%) of these cases.

9.4.4 Clinical outcomes

At 12 months, rates of DAS28-CRP remission and low disease activity were 45/105 (43%) and 63/105 (60%). Rates of DAS44-CRP remission and low disease activity were 41/105 (39%) and 77/105 (73%). The rate of 2011 ACR/EULAR Boolean remission was 15/105 (14%). The thirty patients achieving DAS28-CRP<2.6 but not meeting the Boolean definition of remission missed the latter due to patient VASDA>10mm (n=23), TJC53>1 (n=9), SJC44>1 (n=6) and/or CRP>10mg/L (n=6).

Amongst 70 patients attaining DAS28-CRP remission at least once over the 12 month period, the median (IQR) time to first achievement of DAS28-CRP<2.6 was 6 (3-9) months. In patients achieving DAS28-CRP remission prior to month 12 (n=61), first DAS28-CRP remission was sustained over the remaining follow-up in 27 (44%) patients. The majority of these patients achieved DAS28-CRP remission within the first six months; 41% achieved remission within the first three months and 70% had achieved remission by six months.

9.4.5 Imaging outcomes

Absence of PD (total PD score=0) was observed in 42 (40%) patients at 12 months. Absent/minimal PD, defined by (i) total PD score≤1, was observed in 60 (57%) patients. Absent/minimal PD, defined by (ii) PD≤grade 1 at any or all of the wrists and first MTPs and up to one other joint examined and PD=grade 0 in all other joints (i.e. accepting low-grade PD at the wrists and/or first MTP joints and one other joint), was observed in seven additional patients; a total of 67 (64%) patients.

9.4.6 Agreement between clinical and imaging outcomes

Poor agreement was demonstrated between clinical and imaging outcomes (Table 34). In patients achieving clinical remission at 12 months, absence of PD (total PD score=0) was observed in 19/45 (42%) patients achieving DAS28-CRP<2.6, 18/41 (44%) patients achieving DAS44-CRP<1.6, and 6/15 (40%) patients achieving Boolean remission. Absent/minimal PD, defined by (i) total PD score≤1, was observed in 28/45 (62%), 27/41 (66%) and 10/15 (67%) patients, respectively. The less stringent definition for absent/minimal PD, (ii), was observed in slightly more patients achieving DAS28-CRP and DAS44-CRP remission (rates were 31/45 (69%) and 29/41 (71%), respectively), whilst the rate amongst patients achieving Boolean remission was unchanged.

In patients achieving DAS28-CRP<2.6 with ongoing imaging evidence of synovitis (n=26), PD was observed at the following sites: wrists (n=16), MCPs2-3 (n=13), MTP1 (n=4), MTPs2-5 (n=4), PIP2-3 (n=4), elbows (n=2) and the knee (n=1). In patients achieving Boolean remission, PD affected the following joint regions: MCPs2-3 (n=5), wrists (n=4), MTPs2-5 (n=1), PIP2-3 (n=1), and elbows (n=1).

In patients lacking any PD, but with active disease as indicated by DAS28-CRP≥2.6 (n=23), median (IQR) values for the DAS28 component variables were TJC28 5 (2-9), SJC28 1 (0-2), patient VASDA 57 (40-57) mm and CRP 9 (0-18) mg/dL. Amongst 36 patients lacking any PD but not achieving Boolean remission, patient VASDA>10mm was the most frequent preclusion to fulfilment of the Boolean criteria (n=32), followed by TJC53>1 (n=24), CRP>10mg/dL (n=15) and SJC44>1 (n=9).

Table 34. Agreement between clinical remission outcomes and; A) absence of power Doppler activity and B) absent/minimal power Doppler activity, at 12 months in patients with new-onset RA receiving DMARDs according to a treatment-to-target strategy.

Values are n (%), unless otherwise stated.

A) Agreement between Clinical Remission and Absence of PD.

Clinical Outcomes	Absence of PD in 26 joints (total PD score=0)				
	Clinical and imaging outcome	Clinical outcome only	Imaging outcome only	Neither clinical nor imaging outcome	PABAK
DAS28-CRP remission (DAS28-CRP<2.6)	19 (18%)	26 (25%)	23 (22%)	37 (35%)	0.07
DAS44-CRP remission (DAS44-CRP<1.6)	18 (17%)	23 (22%)	24 (23%)	40 (38%)	0.10
Boolean remission	6 (6%)	9 (9%)	36 (34%)	54 (51%)	0.14

B) Agreement between Clinical Remission and Absent/Minimal PD.

Clinical Outcomes	Absent/minimal PD in 26 joints									
	(i) Total PD score≤1					(ii) PD≤grade1 at any or all of the wrists and first MTPs and up to one other joint examined, PD=grade 0 all other joints				
	Clinical and imaging outcome	Clinical outcome only	Imaging outcome only	Neither clinical nor imaging outcome	PABAK	Clinical and imaging outcome	Clinical outcome only	Imaging outcome only	Neither clinical nor imaging outcome	PABAK
DAS28-CRP remission (DAS28-CRP<2.6)	28 (27%)	17 (16%)	32 (30%)	28 (27%)	0.07	31 (30%)	14 (13%)	36 (34%)	24 (23%)	0.05
DAS44-CRP remission (DAS44-CRP<1.6)	27 (26%)	14 (13%)	33 (31%)	31 (30%)	0.10	29 (28%)	12 (11%)	38 (36%)	26 (25%)	0.05
Boolean remission	10 (10%)	5 (5%)	50 (48%)	40 (38%)	-0.05	10 (10%)	5 (5%)	57 (54%)	33 (31%)	-0.18

9.4.7 Predictors of clinical and imaging outcomes

Univariable analyses demonstrated achievement of the various clinical remission outcomes was significantly associated with being male and having a shorter duration of symptoms, fewer tender joints and lower HAQ score at baseline (Table 35). In comparison, the baseline parameters predictive of achievement of good imaging outcomes were lack of coexistent osteoarthritis, seronegativity, fewer swollen joints, lower CRP and lower total PD score. A lower DAS28-CRP score at baseline was also significantly associated with all outcomes. Using the less stringent definition for the outcome absent/minimal PD, (ii) PD≤grade 1 at any or all of the wrists and first MTPs and up to one other joint examined, did not reveal any differences in the results, in comparison to the alternative definition, (i) total PD score≤1 amongst all 26 joints. Therefore, only results for total PD score≤1 amongst all 26 joints are presented.

Results of multivariable analyses, entering baseline variables demonstrating statistical significance ($p<0.05$) on univariable analyses, are shown in Table 36. The composite score (DAS28-CRP) was assessed in univariable analyses, but not in multivariable analysis, because of overlap with its component variables.

Table 35. Baseline variables predictive of achievement of clinical and imaging outcomes at 12 months in patients with new-onset RA receiving DMARDs according to a treatment-to-target strategy (univariable logistic regression analyses).

	DAS28-CRP<2.6		**DAS44-CRP<1.6**		**Boolean Remission**		**Absence of PD (Total PD score=0)**		**Absent/minimal PD (Total PD score≤1)**	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Age	1.01(0.98-1.04)	NS	1.01(0.98-1.04)	NS	1.01(0.96-1.05)	NS	0.98(0.95-1.01)	NS	0.98(0.95-1.01)	NS
Female	0.45(0.18-1.11)	NS	**0.36(0.15-0.89)**	**0.03**	**0.31(0.10-0.95)**	**0.04**	0.58(0.24-1.42)	NS	0.63(0.25-1.59)	NS
BMI[a]	0.94(0.87-1.02)	NS	0.96(0.88-1.04)	NS	0.94(0.82-1.07)	NS	1.01(0.93-1.09)	NS	1.00(0.93-1.09)	NS
Symptom duration, months	**0.92(0.86-0.99)**	**0.03**	**0.93(0.87-1.00)**	**0.05**	1.00(0.92-1.08)	NS	0.99(0.94-1.05)	NS	1.03(0.97-1.10)	NS
Current or previous smoker	0.63(0.28-1.39)	NS	0.94(0.42-2.1)	NS	0.66(0.22-1.99)	NS	1.41(0.62-3.17)	NS	1.15(0.52-2.55)	NS
Number of comorbidities	0.86(0.63-1.16)	NS	1.02(0.76-1.37)	NS	0.67(0.40-1.13)	NS	1.01(0.75-1.36)	NS	0.89(0.67-1.20)	NS
History or current evidence of concurrent osteoarthritis	0.76(0.35-1.67)	NS	0.73(0.33-1.61)	NS	0.83(0.27-2.54)	NS	**0.41(0.18-0.93)**	**0.03**	0.70(0.32-1.52)	NS
RF positive	1.38(0.56-3.40)	NS	1.12(0.45-2.77)	NS	0.94(0.27-3.26)	NS	0.52(0.21-1.26)	NS	**0.37(0.14-0.97)**	**0.04**
ACPA positive	1.68(0.65-4.37)	NS	1.76(0.66-4.7)	NS	2.10(0.44-10.05)	NS	0.73(0.29-1.84)	NS	**0.36(0.13-1.00)**	**0.05**
SJC28	0.98(0.89-1.08)	NS	0.97(0.87-1.07)	NS	1.00(0.87-1.14)	NS	**0.85(0.75-0.96)**	**0.009**	**0.88(0.79-0.98)**	**0.02**
TJC28	**0.93(0.86-0.99)**	**0.03**	**0.90(0.83-0.97)**	**0.006**	**0.87(0.77-0.99)**	**0.04**	0.96(0.90-1.03)	NS	0.97(0.91-1.03)	NS
CRP, mg/L	0.99(0.98-1.00)	NS	0.99(0.98-1.00)	NS	0.99(0.98-1.01)	NS	0.99(0.97-1.00)	NS	**0.99(0.98-1.00)**	**0.03**
Patient VAS global disease assessment, mm[b]	**0.98(0.96-1.00)**	**0.02**	0.98(0.97-1.00)	NS	0.98(0.96-1.00)	NS	0.99(0.97-1.01)	NS	0.98(0.97-1.00)	NS
DAS28-CRP3v	**0.66(0.45-0.97)**	**0.03**	**0.57(0.38-0.86)**	**0.008**	**0.53(0.30-0.95)**	**0.03**	**0.66(0.45-0.97)**	**0.04**	**0.59(0.40-0.87)**	**0.008**
HAQ score[c]	**0.46(0.23-0.93)**	**0.03**	**0.46(0.23-0.95)**	**0.04**	**0.28(0.10-0.79)**	**0.02**	0.65(0.33-1.29)	NS	0.49(0.24-1.01)	NS
Total GS score on US[d]	1.00(0.96-1.04)	NS	0.98(0.94-1.02)	NS	1.00(0.95-1.05)	NS	0.96(0.92-1.01)	NS	0.97(0.93-1.01)	NS
Total PD score on US[d]	0.98(0.92-1.05)	NS	0.97(0.91-1.04)	NS	0.98(0.89-1.07)	NS	**0.89(0.81-0.97)**	**0.01**	**0.87(0.80-0.95)**	**0.002**
Radiographic erosions	0.82(0.29-2.32)	NS	1.31(0.47-3.65)	NS	1.97(0.55-7.09)	NS	0.37(0.11-1.21)	NS	0.41(0.14-1.16)	NS

NS: Not Significant (p≥0.05). Missing data in [a]13, [b]27, [c]30 and [d]21 cases.

Table 36. Baseline variables predictive of achievement of clinical and imaging outcomes at 12 months in patients with new-onset RA receiving DMARDs according to a treatment-to-target strategy (multivariable logistic regression analyses).

Outcome at 12 months	Baseline Variable	OR (95% CI)	p	Missing Cases
DAS28-CRP<2.6	Symptom duration, months	**0.90(0.81-0.99)**	**0.04**	37
	TJC28	0.93(0.85-1.02)	NS	
	Patient VASDA, mm	0.98(0.95-1.00)	NS	
	HAQ	0.71(0.26-1.93)	NS	
DAS44-CRP<1.6	Female	**0.22(0.06-0.77)**	**0.02**	30
	Symptom duration, months	0.93(0.85-1.02)	NS	
	TJC28	**0.88(0.79-0.98)**	**0.02**	
	HAQ	0.53(0.23-1.26)	NS	
Boolean Remission	Female	0.35(0.08-1.50)	NS	30
	TJC28	0.91(0.79-1.05)	NS	
	HAQ	**0.33(0.11-0.98)**	**0.05**	
Absence of PD (Total PD score=0)	History or current evidence of concurrent osteoarthritis	**0.35(0.13-0.93)**	**0.04**	21
	SJC28	0.89(0.77-1.03)	NS	
	Total PD score	0.92(0.83-1.02)	NS	
Absent/minimal PD (Total PD score≤1)	RF-positivity	0.59(0.15-2.29)	NS	21
	ACPA-positivity	0.54(0.14-2.07)	NS	
	SJC28	0.99(0.86-1.13)	NS	
	CRP	0.99(0.98-1.01)	NS	
	Total PD score	**0.89(0.81-0.98)**	**0.01**	

NS: Not Significant (p>0.05).

9.5 Discussion

This study reveals that almost half of patients with new-onset RA were achieving the clinical target (DAS28-CRP remission) at 12 months, in daily practice using EULAR treatment-to-target recommendations as a guide to management. The rate of 2011 ACR/EULAR Boolean remission was significantly lower. In patients achieving a state of clinical remission, regardless of the outcome measure used to define remission (either DAS28, DAS44 or even 2011 ACR/EULAR Boolean remission), any PD (total PD score>0) was observed in at least half and significant PD (total PD score>1) was apparent in approximately one third of patients.

These rates of clinical remission are consistent with other observational treat-to-target RA cohorts. In an Italian EAC, the rate of DAS44 remission was reported as 46% (Bosello et al., 2011). In the multicentre Dutch Rheumatoid Arthritis Monitoring (DREAM) cohort, DAS28 remission and 2011 ACR/EULAR Boolean remission were observed in 58% (Vermeer et al., 2011) and 21% of patients (Vermeer et al., 2013), respectively. Methods of assessment in the DREAM study included 28 joint examination and patient assessment of general health, and it is not clear whether more extensive joint examination or patients' global disease assessments were available in determining 2011 ACR/EULAR Boolean remission. In DREAM, intensification of treatment in appropriate patients was not adhered to at 35% of visits, with the most frequent reasons being a physician impression of clinical remission, followed by side-effects (Vermeer et al., 2012); comparable to our findings.

This is the first study to demonstrate the discordance between DAS28 remission, or the more stringent 2011 ACR/EULAR Boolean definition of remission, and imaging remission in an early RA 'treat-to-target' cohort. Previous reports of ultrasound findings in DAS28 and Boolean remission states in patients with early RA are limited to an Italian inception cohort study (Sakellariou, Garifallia et al., 2013). Rates of sustained absence of PD were 43/56 (77%) and 21/22 (95%) amongst patients achieving DAS28 and Boolean remission at one year, respectively. However, this analysis was restricted to a subgroup of patients fulfilling 1987 ACR RA criteria, responding to methotrexate (DAS44<2.4 over one year), with complete

data (167 of 267 patients with early IA commencing DMARDs). The ultrasound assessment was also limited to 12 joints (MCPs and wrists).

The findings of persistent PD in patients achieving DAS44 remission are similar to two smaller studies of patients with early RA (Scirè et al., 2009; Peluso et al., 2011). In these studies patients were treated according to a DAS44-steered treatment protocol (including methotrexate and TNF-inhibitors). Persistence of any PD was identified in 42% of 48 patients amongst 10 joints (wrists, MCPs2-3 and PIPs2-3) (Peluso et al., 2011), and 41% of 43 patients using a 44-joint ultrasound assessment (Scirè et al., 2009). Other groups have reported ongoing PD in patients with established RA across various definitions of clinical remission (see section 2.4.1.5).

A significant proportion of patients with absent or absent/minimal PD demonstrated evidence of clinical disease activity as measured by DAS28-CRP, DAS44-CRP and non-fulfilment of 2011 ACR/EULAR Boolean remission criteria. It is likely, at least for a subset of these patients, that the standardised 26-joint ultrasound assessment missed active joint inflammation in other joints (e.g. hips, shoulders, MCPs3-5, PIPs3-5). However, reduced ultrasound joint assessments including the elbows, wrists, second and third MCPs, knees, ankles and second to fifth MTPs have previously been shown to correlate well with ultrasound assessment of 44 joints in both patients in clinical remission (Naredo et al., 2013b) and those with active disease (Naredo et al., 2008b). Moreover, the likelihood that the presence of tender joints and a high patient global assessment, which may be influenced by a complex interaction of factors other than active synovitis (such as chronic pain, side-effects of treatment and the presence of comorbidity), is also relevant. This is supported by data, given the characteristics which were evident in these patients.

Baseline predictors of clinical remission outcomes were male gender, shorter symptom duration, fewer tender joints, and lower patient VASDA and HAQ scores. In contrast, lack of osteoarthritis and objective signs of less severe disease (RF- and ACPA-negativity, fewer clinically swollen joints, and lower CRP and baseline PD) were associated with favourable imaging outcomes. The latter parameters are arguably more reflective of the primary pathology, active synovitis. Therefore, logically, they should warrant aggressive treatment or treatment

escalation if present or if increased above normal levels. These findings, therefore, support current and future research into the use of imaging within the management of early RA.

The significantly higher SJC28, TJC28 and RAI of patients with missing follow-up data in comparison to patients included in the analyses may be related to the proportion of patients who were subsequently referred to biological DMARD clinical trials or received biologic DMARDs with follow-up in biologic-monitoring clinic in which standardised ultrasound does not form part of routine assessments. Loss to follow-up of patients with more severe disease may have falsely elevated the remission rates observed.

This study provides insights into the translation of treat-to-target within clinical practice. It again highlights the challenges in data collection and adherence to treat-to-target guidelines in a clinical setting and identifies room for improving the outcomes of patients with early RA. A clinically significant proportion of patients achieving DAS28, DAS44 or 2011 ACR/EULAR Boolean remission (now recommended for use as a target for treatment by EULAR) demonstrate PD on ultrasound. More accurate measurement of inflammatory activity by ultrasound should perhaps be a key determinant in guiding treatment escalation and assessing true absence of disease activity. The differences observed between the disease characteristics at baseline which predicted clinical and imaging remission provide further support for the ongoing investigation into the use of imaging within a treat-to-target strategy; patients with unfavourable subjective factors were less likely to achieve the clinical remission outcomes, whereas factors more directly indicative of inflammatory disease activity predicted persistent active disease on imaging. Failure to achieve absent or minimal PD was associated with higher PD at baseline. As persistence of PD in clinical remission is associated with poor outcomes (Brown et al., 2008; Foltz et al., 2012; Saleem et al., 2012) the baseline PD is a warning. Ultrasound may therefore prove to be a useful tool in discerning an individual's prognosis at diagnosis as well as assessing inflammation on treatment.

Chapter 10 : **Discussion**

Aspects of the clinical phenotype of IA may be used to stratify patients according to their risk of severe, progressive disease. These include features of disease which are now contained within the new 2010 ACR/EULAR RA classification criteria, such as the pattern of joint involvement and ACPA status. However, knowledge of how these criteria perform in a modern-day clinic setting, and how the imaging phenotype of IA may be best interpreted, alongside the criteria, remains incomplete. Hence, a greater understanding of the clinical and imaging phenotypes of patients with UA and RA (defined by today's standard of the 2010 RA criteria), and the prognostic implications of such, may aid in the risk stratification of patients and directing early therapy in order to optimise patient outcomes. Other strategies for improving the management of patients with early IA which have previously been adopted include the implementation of EACs and the treatment-to-target management of RA. The impact of targeting ultrasound-detectable disease activity on disease outcomes, particularly in the long-term, is yet to be fully established.

For the purposes of better understanding the clinical and imaging phenotype of patients with early IA, identifying deficiencies in their management and potential ways to resolve these in contemporary clinical practice, a clinical audit and observational prospective cohort study were conducted in the Leeds EAC. Areas for improvement identified included the necessity to expedite the initial assessment and treatment of patients, as well as the need to optimise their management within treat-to-target regimens. The results of the observational study support the predictive utility of ultrasound which may help in addressing these needs in the future.

The audit of the Leeds EAC identified that one of the main factors limiting early initiation of DMARDs was the time lag between symptom onset and referral to a specialist. Unfortunately, from retrospective data, it was not possible to distinguish whether delay was mainly due to the patient or the GP. Nevertheless, room for improvement post-referral was also highlighted. Approaches to enable the prioritisation of IA referrals and prompt treatment initiation were recommended.

The observational cohort study of patients with suspected new-onset IA enabled the determination of the clinical and imaging phenotypes of patients with UA or RA, defined by the 2010 ACR/EULAR RA criteria. The prevalence of both subclinical synovitis and ultrasound erosions in the absence of radiographic erosions was confirmed. These findings are a development from existing evidence owing to the contemporary definitions of IA employed. Patients were classified as UA or RA with use of the recently published consensus definition of radiographic change for use in conjunction with the 2010 ACR/EULAR RA criteria (van der Heijde et al., 2013). A more extensive ultrasound examination for erosions was also carried out in comparison to previous studies in patients with early IA (Funck-Brentano et al., 2009; Sheane et al., 2009). Other novel aspects of this research include the reporting of the incidence and distribution of 'active' ultrasound erosions in patients with early IA.

Longitudinal, prospective data collection in this cohort allowed investigation of the significance of these and other aspects of disease phenotype in respect to their outcomes and responses to treatments. Greater synovitis detected by ultrasound, at baseline, was associated with a higher rate of methotrexate use and persistence of IA. In addition, GS synovitis predicted progression to RA in the subgroup of patients with UA at baseline. This appeared to be independent of clinical synovitis measures. At the joint level, PD synovitis also predicted the development of new ultrasound erosion, with adjustment for patient factors and clinical swelling. These findings are developments from existing studies, the limitations of which have been discussed (section 2.3.2.1) (Freeston et al., 2010; Salaffi et al., 2010; Filer et al., 2011; Dougados et al., 2013; Funck-Brentano et al., 2013; Kawashiri et al., 2013; Nakagomi et al., 2013; Pratt et al., 2013).

A further aim of this research was to determine the efficacy of methotrexate in patients with seronegative versus seropositive IA, due to evidence for a divergence in disease mechanisms, and possibly response to treatment, between these groups. Efficacy of methotrexate was also compared between patients with UA and RA (defined according to 2010 RA criteria) in view of the relative shortage of intervention studies in the former disease group. No significant differences in response to methotrexate were observed between patients according to serological

status or fulfilment of 2010 RA criteria, although the number of patients limited the number of potential confounding factors which could be accounted for in the analyses.

Analysis of adherence to treatment-to-target guidelines and outcomes in the subgroup of patients with early RA highlighted room for improvement in achieving the optimal treatment goal, remission. The rate of clinical remission was, however, consistent with other observational studies (Bosello et al., 2011; Vermeer et al., 2011; Vermeer et al., 2013). Power Doppler was demonstrated in a significant proportion of patients achieving clinical remission, similar to previous studies conducted in patients with established RA (Brown et al., 2006; Balsa et al., 2010; Peluso et al., 2011; Saleem et al., 2011; Foltz et al., 2012; Naredo et al., 2013b; Geng et al., 2014; Zufferey et al., 2014). This is of potential clinical relevance given the prognostic validity of PD synovitis identified in this and other studies (section 2.3.2.1) (Taylor et al., 2004; Naredo et al., 2007; Naredo et al., 2008a; Pascual-Ramos et al., 2009; Fukae et al., 2010; Dougados et al., 2013; Funck-Brentano et al., 2013). The argument for inclusion of the absence of significant PD synovitis within a definition of remission, to be utilised as a treatment target, is also strengthened by the association of favourable objective baseline measures of disease severity with achievement of imaging remission, in comparison to subjective parameters which were predictive of clinical remission.

10.1 Strengths

The observational, longitudinal study was conducted in a well-defined cohort of patients with early IA, defined according to the 2010 ACR/EULAR RA criteria. It is a considerable size for a single-centre study. All assessors were trained, supervised and working within one clinic with consensus treatment algorithms, limiting undue variation in prescribing behaviour. Management and data collection conducted in an out-patient clinic setting and the absence of strict inclusion criteria afford a degree of generalisability to daily practice. Of note, the prevalence of comorbidities was significant. In the subgroup of patients receiving treat to target management, greater than one in ten patients had a contraindication to commencement of methotrexate or intolerance to it necessitating cessation. In addition, one in five patients failed an alternative DMARD to methotrexate due to side-effects.

Whilst clinical features predictive of the course of disease have been extensively reported in the literature, novel aspects of this research are the inclusion of patients managed in the knowledge of the 2010 ACR/EULAR RA classification criteria. In addition, the innovative outcome measures (progression to RA according to 2010 criteria, new ultrasound erosion and imaging remission) are relevant to patients treated early and aggressively according to modern-day standards. The use of a standardised ultrasound examination of 26 joints also permitted the exploration of the predictive validity of ultrasound over and above prevailing clinical features of disease, including clinical examination and fulfilment of the 2010 RA criteria.

10.2 Limitations

The audit sample was a small sample of the target population, patients presenting with possible IA to the Leeds EAC. Consecutive sampling was employed as this was felt to be the most practical method for data collection in view of the logistical difficulties that may arise in obtaining clinical notes for a large number of patients. It is feasible that patients presenting within the audit period may not be representative of patients presenting throughout the course of a year. However, the shortcomings identified in the clinical pathway of patients with new IA here are important findings relevant to improving patient management that should be acknowledged. The prospective observational cohort study provided a larger sample of patients with suspected IA, presenting over the course of a two-year period.

Observational study design was selected as the objective was that the findings reflect real-life clinical practice. However, patients judged to have more severe disease are more likely to have received aggressive treatment; a key source of bias, integral to observational study design. Attempts to minimise this were made through adjustment for major prognostic factors. Due to sample size, it was not possible to include an unlimited number of variables within multivariable analyses and unidentified confounders may also have affected results. Where possible, conditional logistic regression (a statistical method of analysis for paired data) was employed to explore the predictive validity of ultrasound findings at the joint level, controlling for patient-related confounding factors.

The intention was for the cohort study to be generalisable to patients with early IA, being inclusive of all patients newly-presenting with either UA or RA, i.e. prior to provision of any treatment. The proposed inclusion criteria were broad: clinical swelling of at least one joint and provision of informed consent. As the study was reflective of best clinical practice, only 18 of 441 patients recorded on the study screening log declined to participate. It is possible that a small number of eligible patients were never recorded on the study screening log, for example if they refused consent when initially approached or were otherwise not considered suitable (e.g. frailty affecting ability to attend out-patient appointments, planning to move out of area).

It may be argued that exclusion of patients lacking any joint swelling (as determined by a rheumatologist) may have excluded patients presenting with early palindromic disease or those with a very insidious onset of IA. However, such patients who developed joint swelling subsequently were later included, with their baseline assessments taken at the time of the first documented joint swelling. Furthermore, including patients lacking objective signs of synovitis may have introduced difficulty in the interpretation of results (for example, potentially preventing the inclusion of patients receiving a later diagnosis of fibromyalgia after the exclusion of IA).

No restriction was made to the duration of symptoms in order to achieve a study sample reflective of patients presenting in clinical practice. As observed in the clinical audit, a number of patients may present late in practice. This should be borne in mind when considering treatment outcomes, including comparisons with other early IA cohort studies that have restricted patients to those with short symptom durations.

Unfortunately, baseline data (particularly ultrasound data) were missing in a significant number of patients who were excluded from the analyses. A contributing factor appeared to be the requirement to provide patients with 24 hours to consider study information before giving their consent; eligible patients were provided with this at their first consultation and returned for consent at the next opportunity, at which time baseline assessments were recorded in an electronic case report form.

A proportion of patients received corticosteroids either before or at the first consultation, i.e. prior to consent. This included patients receiving treatment in primary care as well as those for whom it was deemed clinically unethical to delay such treatment in the out-patient clinic. In this instance, the baseline data recorded was that which was obtained on the basis of its clinical relevance, prior to treatment, i.e. retrospectively from clinical notes. In many cases this included full clinical and ultrasound assessments, perhaps attributable to use of a clinical pro forma in the EAC. In some cases this data was incomplete. Comparisons of baseline characteristics between included and excluded patients for the relevant analyses were conducted in order to establish any major differences between these groups. Where relevant, implications for the interpretation of results have been discussed within individual chapters (sections 6.5, 7.5, 8.5 and 9.5).

The volume of missing follow-up data highlights the challenges of obtaining research data in clinical practice. Missing clinical outcome data has been dealt with using a deterministic method, with observations from last assessments carried forward. Therefore, final estimates are likely to be less precise than if data was more complete. Results are perhaps more likely to be an overestimation of disease persistence/severity rather than an underestimate, as patients with more severe symptoms are conceivably more likely to attend for follow-up than those who are less severely affected. Other methods of imputation of missing data were not deemed appropriate due to the volume of data that was missing.

With respect to imaging outcomes, patients who were missing ultrasound follow-up were excluded. In these analyses, baseline characteristics of excluded patients indicated they might have had more severe disease. Plausible explanations include referral to specialist biologic clinics which did not include standardised ultrasound follow-up, necessity to attend a different location from clinical visits (although the ultrasound department was in reasonably close proximity to the clinic), and occasionally the need to re-attend on a different date (although attempt was made to minimise this, see section 4.3.2).

Certain outcomes in the study were susceptible to bias, such as initiation of methotrexate (relevance to the validity of results is discussed in section 7.5). Other outcomes were more objective, such as imaging remission. Ultrasonographers

were blinded to clinical assessments and treatment, although it was not possible to fully blind examiners to the time of assessment (i.e. whether the examination was at baseline or follow-up, due to the real-time nature of ultrasound). Ultrasound was performed by one of several assessors. Whilst this provides a realistic and pragmatic aspect to the study, as any proposed use for ultrasound in clinical practice would need to be considered in this context, the lack of formal evaluation of inter-reader reliability is a potential limitation of this study (Wakefield et al., 2003; D'Agostino et al., 2005; Joshua et al., 2005; Koski et al., 2006b; Strunk et al., 2006; Torp-Pedersen and Terslev, 2008; Ellegaard et al., 2009; Lee et al., 2009). All assessors were trained by an experienced EULAR teacher and consultant rheumatologist.

With respect to the duration of follow-up, six month outcomes with methotrexate treatment and one year remission outcomes in patients with RA treated according to treatment-to-target principles are very relevant to patients. Considerations in selecting these time-points were the relatively slow onset of action of the majority of DMARD therapies, as well as the significance of the early achievement of remission in determining a good outcome in the long-term (Table 5, section 2.2).

Modern-day treatment practices entail a tendency towards the early treatment of patients who are perceived to be at risk of persistent or aggressive IA (Combe et al., 2017). This implies that the outcome disease persistence at one year (defined here as the use of DMARDs/concurrent steroids and/or persistence of joint swelling) may be an imperfect outcome measure. A proportion of these patients may have experienced resolution of disease over time or with initial steroid therapy alone. The long-term outcomes for these patients, for example assessment of disease persistence at five years will give further insight in the future.

10.3 Future Directions

Progression of three key aspects of this work is desirable in order to further develop and distil the optimal management strategy for patients with early IA, and the role of ultrasound within it. Firstly, working to improve the identification of patients ‘at risk’ of aggressive/severe disease, with the aim of preventing progression to, or ‘curing’,

disease classifiable as RA with early treatment. Secondly, aiming to determine the optimal therapeutic regimen in patients with early IA; for example, in patients with early UA, not fulfilling 2010 RA criteria, further randomised trials are desirable to establish the optimal strategy for treatment. Inclusion of an initial placebo-controlled phase in such studies, as well as a long follow-up period, may help to determine whether early therapy can alter the disease course in such patients. Furthermore, it may prove possible to determine in whom first-line methotrexate is appropriate and in whom biologic therapy would be preferable. This is in the context of maximising the cost-effectiveness of biologic therapies and the evolving ambition to achieve drug-free remission in patients with IA. Thirdly, tools to assess the achievement of remission within a treatment-to-target regimen, such as ultrasound, require further investigation to establish whether altering treatment accordingly affects the rate of early and sustained remission, in addition to longer-term outcomes such as prevention of joint damage and drug-free remission. This is the focus of ongoing studies (Wakefield et al., 2012; Bruyn et al., 2015). In particular, the location and number of joints to be examined, and the ideal definition for imaging remission form an important part of the research agenda. For example, what is the added value of achieving a complete absence of PD in the context of a treatment-to-target management strategy employing DMARDs and the biologic therapies which are currently available?

Poor prognostic clinical factors are currently recognised and are of use in clinical practice (Tables 2 to 6, section 2.2). The additional predictive value of ultrasound is now emerging and is supported by this work (Chapter 7). Nevertheless, ongoing research to ascertain more sensitive and specific biomarkers is needed in order to predict, with greater reliability, individuals ‘at risk’ of severe disease in whom early aggressive treatment, perhaps with biologic therapy, may be justified. With advances in methods of genetic analysis, several polymorphisms have been identified as being potentially useful in the prediction of response to certain therapies, such as methotrexate (Kurzawski et al., 2007; Wessels et al., 2007; James et al., 2008), TNF-inhibitors (Plant et al., 2011; Mirkov et al., 2013) or tocilizumab (Wang et al., 2013). However, results have not been consistently replicated across cohorts (Stamp and Roberts, 2011; Márquez et al., 2014) and the value of genetic biomarkers alongside other clinical and imaging prognostic factors is yet to be established. The translation of immunological biomarkers in the predication of response is another emerging field of interest (Ponchel et al., 2014).

There is increasing data suggesting the presence of a window of opportunity when significantly greater benefits can be attained with early biologic intervention in particular (Quinn, M. A. et al., 2005; Emery, P. et al., 2010; Saleem et al., 2010). Hence, applying biologic therapy relatively early, especially in poor prognosis patients, is encouraged (Smolen et al., 2017). The ability of TNF-inhibitors to induce sustained remission, with biologic-free and even drug-free remission achievable in a proportion of patients, portrays an emerging treatment goal. However, the optimal application of such expensive therapies in publically-funded healthcare systems remains an area of continued research.

Even earlier in the disease spectrum, there is increasing research in the area of preclinical IA (Gerlag et al., 2012). It is now known that immunological abnormalities may pre-date the onset of clinical synovitis for several years, including development of ACPAs (Sokolove et al., 2012) and T cell abnormalities (Cuthbert et al., 2010). In ACPA-positive individuals with symptoms of arthralgia, but without joint swelling, subclinical synovitis may invariably be present (Krabben et al., 2013b; Nam et al., 2016). Synovial studies indicate histological change may precede clinical synovitis, with changes demonstrated in asymptomatic joints of patients with early RA (Kraan et al., 1998), however histological abnormalities have not been observed in synovial studies prior to the development of synovitis (with the caveat that these studies were conducted in knee joints rather than small joint which are more commonly affected in early disease) (van de Sande et al., 2011). The premise that intervention in these patients may lead to a ‘cure’ for RA is an intriguing basis for future research.

Further research in the use of ultrasound is underway, including further evaluation of the EULAR-OMERACT global synovitis score (D’Agostino et al., 2017). Such a score, if validated, may be of use as an objective outcome measure of response in future clinical studies. Advanced ultrasound techniques, as yet confined to research, may also prove to be of clinical value in the future, including the use of contrast (Klauser et al., 2002; Terslev et al., 2005; Klauser et al., 2010; Rednic et al., 2011) and 3-dimensional imaging systems (Strunk and Lange, 2004; Szkudlarek et al., 2016).

10.4 Significance for Clinical Practice

This work demonstrates that most patients who fulfil the 2010 ACR/EULAR RA classification criteria in current clinical practice receive DMARD therapy, with the majority receiving methotrexate first-line. Furthermore, a significant proportion of patients with UA (not yet fulfilling the criteria) may progress to RA, and over half may be judged to require DMARDs.

This research improves our understanding of the clinical and imaging phenotype of patients with new-onset UA and RA defined by the 2010 RA criteria. Aspects of the phenotype of disease were identified as being predictive of outcome and response to treatment. In particular, the prognostic value of ultrasound in the evaluation of synovitis was confirmed, supporting its use in clinical practice as a guide for the commencement of treatment. In regards to therapeutic options, this research provides evidence of the efficacy of methotrexate in clinical practice, including efficacy in seronegative patients and patients with UA (not fulfilling 2010 RA criteria) in whom there has been limited data to date. Data in patients with early RA suggests ultrasound may also be of use in monitoring patients on treatment. The significant rate of subclinical synovitis in clinical remission and the disparity between the predictors of clinical and imaging remission which were identified suggests ultrasound may be of value in guiding the escalation of therapy within a treatment-to-target strategy in these patients.

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List of Abbreviations

ACPA	Anti-cyclic Citrullinated Peptide Antibody
ACR	American College of Rheumatology
ANA	Anti-Nuclear Antibody
AUC	Area Under the receiver operating characteristic Curve
BMI	Body Mass Index
CDAI	Clinical Disease Activity Index
CI	Confidence Interval
CMC	Carpometacarpal joint
CRP	C-Reactive Protein
CT	Computed Tomography
DAS28-CRP	Disease Activity Score using 4 variables (SJC28, TJC28, CRP and patient VASDA)
DAS28-CRP3v	Disease activity score using 3 variables (SJC28, TJC28 and CRP)
DAS44-CRP	Disease activity score using 4 variables (SJC44, RAI, CRP and patient VASDA)
DAS44-CRP3v	Disease activity score using 3 variables (SJC44, RAI and CRP)
DIP	Distal Inter-Phalangeal joint
DMARD	Disease-Modifying Anti-Rheumatic Drug
EAC	Early Arthritis Clinic
EMS	Early Morning Stiffness
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
GS	Grey Scale synovitis
GP	General Practitioner
HAQ	Health Assessment Questionnaire
HCQ	Hydroxychloroquine

HR	Hazard Ratio
IA	Inflammatory Arthritis/Intra-Articular
IM	Intra-Muscular
IQR	Interquartile Range
MCP	Metacarpophalangeal joint
MRI	Magnetic Resonance Imaging
MTP	Metatarsophalangeal joint
MTX	Methotrexate
NA	Not Applicable
NICE	The National Institute for Health and Care Excellence
NS	Not Significant
NSAID	Non-Steroidal Anti-Inflammatory Drug
OR	Odds Ratio
PABAK	Prevalence And Bias Adjusted Kappa
PD	Power Doppler activity
PIP	Proximal Inter-Phalangeal joint
RA	Rheumatoid Arthritis
RAI	Ritchie Articular Index
RCT	Randomised Controlled Trial
RF	Rheumatoid Factor
ROC	Receiver Operating Characteristic curve
ROM	Range Of Movement
SD	Standard Deviation
SDAI	Simplified Disease Activity Index
SEM	Standard Error of the Mean
SHS	Sharp/van der Heijde Score (total score unless otherwise specified)
SJC	Swollen Joint Count

SpA	Spondyloarthropathy
SSZ	Sulfasalazine
TJC	Tender Joint Count
TNF	Tumour Necrosis Factor
UA	Undifferentiated Arthritis
US	Ultrasound
VAS	Visual Analogue Scale
VASDA	Visual Analogue Scale of global Disease Activity