Diagnosis and management of early inflammatory arthritis

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Intellectual property and publication statements

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.

The background literature review is based on a book chapter entitled Early Arthritis published in the EULAR Textbook on Rheumatic Diseases. Permission has been granted to use the publication in this thesis by the European League Against Rheumatism who have copyright of the book.

Chapters 6 and chapter 7 are based on work from two jointly authored publications, the first by Dr Nam and Dr Villeneuve and the second by Dr Nam and Dr Rakieh. For the work in chapter 6, Dr Nam and Dr Villeneuve recruited the patients and obtained the data. Dr Nam interpreted the results and wrote the manuscript. In chapter 7 the Dr Nam and Dr Rakieh recruited patients and obtained the data. Dr Nam performed the ultrasound scans of the patients. Both authors contributed to the analysis plan, interpretation of the results and writing of the manuscript.

The publications are as follows:

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Nam JL, Villeneuve E, Hensor EM, Conaghan PG, Keen HI, Buch MH, Gough AK, Green MJ, Helliwell PS, Keenan AM, Morgan AW, Quinn M, Reece R, Van Der Heijde DM, Wakefield RJ, Emery P. A randomised controlled trial of etanercept and methotrexate to induce remission in early inflammatory arthritis: the EMPIRE trial. *Ann. Rheum. Dis.* 2014;**73**(6):1027-36.

Rakieh C, Nam JL, Hunt L, Hensor EM, Das S, Bissell LA, Villeneuve E, Mcgonagle D, Hodgson R, Grainger A, Wakefield RJ, Conaghan PG, Emery P. Predicting the development of clinical arthritis in anti-CCP positive individuals with non-specific musculoskeletal symptoms: a prospective observational cohort study. *Ann. Rheum. Dis.* 2014(DOI: 10.1136/annrheumdis-2014-205227).

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List of publications/presentations arising from this thesis

Original articles

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Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, Emery P, Gaujoux-Viala C, Gossec L, Nam J, Ramiro S, Winthrop K, De Wit M, Aletaha D, Betteridge N, Bijlsma JW, Boers M, Buttgereit F, Combe B, Cutolo M, Damjanov N, Hazes JM, Kouloumas M, Kvien TK, Mariette X, Pavelka K, Van Riel PL, Rubbert-Roth A, Scholte-Voshaar M, Scott DL, Sokka-Isler T, Wong JB, Van Der Heijde, D. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann. Rheum. Dis.* 2014;**73**(3):492-509.

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Nam JL*, Villeneuve E*, Hensor EM, Conaghan PG, Keen HI, Buch MH, Gough AK, Green MJ, Helliwell PS, Keenan AM, Morgan AW, Quinn M, Reece R, Van Der Heijde DM, Wakefield RJ, Emery P. A randomised controlled trial of etanercept and methotrexate to induce remission in early inflammatory arthritis: the EMPIRE trial. *Ann. Rheum. Dis.* 2014;**73**(6):1027-36.

Rakieh C*, Nam JL*, Hunt L, Hensor EM, Das S, Bissell LA, Villeneuve E, McGonagle D, Hodgson R, Grainger A, Wakefield RJ, Conaghan PG, Emery P. Predicting the development of clinical arthritis in anti-CCP positive individuals with non-specific musculoskeletal symptoms: a prospective observational cohort study. *Ann. Rheum. Dis.* 2015;**74**(9):1659-1666.

Nam JL, Hunt L, Hensor EMA, Emery P. Enriching case selection for imminent RA – the use of anti-CCP antibodies in individuals with non-specific musculoskeletal

symptoms: a cohort study. *Ann. Rheum. Dis 2015*.(DOI: 10.1136/annrheumdis-2015-207871).

Review articles

Nam JL, Emery P. Is there a place for initial treatment with biological DMARDs in the early phase of RA? *Best practice & research. Clinical rheumatology* 2013;**27**(4):537-54.

Fechtenbaum M*, Nam JL*, Emery P. Biologics in rheumatoid arthritis: where are we going? *Br J Hosp Med (Lond)* 2014;**75**(8):448-9, 51-6.

Book chapter

Nam J, Combe B, Emery P. Early Arthritis. In: Bijlsma JW, editor. *EULAR Textbook on Rheumatic Diseases*. First ed. London: BMJ Group and European League Against Rheumatism, 2012:185-205.

Oral presentations

Nam JL, Villeneuve E, Hensor EMA, Conaghan PG, Keen HI, Gough AK, Green MJ, Helliwell P, Keenan A-M, Morgan AW, Quinn M, Reece R, Van Der Heijde DM, Wakefield RJ, Emery P. Inhibition of structural damage with two intensive treatment strategies using infliximab or high dose intravenous steroid followed by treat to target in DMARD naive rheumatoid arthritis (the IDEA study) - a preliminary report. *Ann. Rheum. Dis.* 2012;**71**(Suppl3):106. Presented at *European League Against Rheumatism Annual Meeting, Berlin, Germany*.

Nam JL. Systematic literature review: Biological DMARDs in rheumatoid arthritis. *Ann. Rheum. Dis.* 2013;**72**(Suppl3):43.Presented at *European League Against Rheumatism annual meeting, Madrid, Spain.*

Nam JL. Predicting RA development in individuals at risk. Presented at *Meeting of Study Group for Risk Factors for RA at European League Against Rheumatism Annual Meeting, Paris, France, 2014.*

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(*denotes joint first authorship)

Abstract

Rheumatoid arthritis (RA) represents a disease continuum from the pre-clinical period, through undifferentiated inflammatory arthritis (IA) to early then established RA. Improved patient outcomes in recent years reflect early diagnosis, prompt disease-modifying anti-rheumatic drug (DMARD) therapy, treat-to-target strategies and use of biological therapies (bDMARDs) particularly following failure of conventional synthetic therapies (csDMARDs). Optimal use of bDMARDs in early disease, however, has not been established. Early detection in the pre-clinical stage is potentially achievable with modern diagnostics but understanding of how to use these biomarkers is lacking.

A systematic literature review on the use of bDMARDs was performed and confirmed the efficacy of bDMARDs in patients with established RA. Few studies were found addressing their use in early disease.

Two randomised controlled trials were performed to explore early bDMARD intervention. The first, in early DMARD-naïve RA, compared methotrexate and infliximab to methotrexate and high-dose intravenous methylprednisolone as induction therapy, followed by a treat-to-target strategy; both arms demonstrated efficacy with no significant between-group differences. In the second, early DMARD naïve IA patients treated with combination etanercept and methotrexate had earlier clinical improvement than methotrexate monotherapy; however both groups achieved good 12 month outcomes.

In a longitudinal cohort study conducted in secondary care, 50% of patients with musculoskeletal (MSK) symptoms and anti-cyclic citrullinated peptide (anti-CCP) antibodies progressed to clinical IA. Use of additional biomarkers including rheumatoid factor, shared epitope and ultrasound enabled further risk stratification for progression. In a primary care cohort, the anti-CCP antibody was positive in 2.8% with new nonspecific MSK symptoms with almost half progressing to IA.

In summary, in early DMARD naïve IA, use of bDMARD may not be superior to csDMARDs with a treat-to-target approach. In patients with MSK symptoms, anti-CCP testing identifies individuals at risk of developing IA; additional biomarkers improve prediction and are feasible for clinical use.

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List of Abbreviations

a	abstract only
Ab	antibodies
ABT	abatacept
ADA	adalimumab
Anti-CarP antibodies	anti-carbamylated protein antibodies
Anti-CCP antibodies	anti-cyclic citrullinated peptide antibodies
ACPA	anti-citrullinated protein antibodies
ACR	American College of Rheumatology
ANA	Antinuclear antibodies
bDMARD	biological disease-modifying antirheumatic drug
BMI	body mass index
bsDMARD	biosimilar disease-modifying antirheumatic drug
CMC	carpometacarpal
CCP	cyclic citrullinated peptide
CDAI	clinical disease activity index
CI	confidence interval
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CTLA4	cytotoxic T-lymphocyte antigen 4
CTX-I	C-terminal crosslinking telopeptides of type I collagen
CTX-II	C-terminal crosslinking telopeptides of type II collagen
CZP	certolizumab pegol
DAS	disease activity score
DAS28	disease activity score based on a 28 joint count
DAS44	disease activity score based on the Ritchie articular index and a 44 swollen joint count

DIP	distal interphalangeal
DMARD	disease-modifying antirheumatic drug
EMA	European Medicines Agency
EMS	early morning stiffness
EQ-5D-3L	Euroqol 5-dimensional 3-level response standardised health outcome tool
ERO	erosion
ESR	erythrocyte sedimentation rate
ETN	etanercept
EULAR	European League Against Rheumatism
FDR	first degree relative
GLM	golimumab
GM-CSF	granulocyte-macrophage colony-stimulating factor
GP	general practitioner
GS	grey scale
H	high
HAQ-DI	Health Assessment Questionnaire Disability Index
HCQ	hydroxychloroquine
HLA	human leukocyte antigen
HR	hazard ratio
hsCRP	high sensitivity C-reactive protein
IA	inflammatory arthritis
ICAM	intracellular adhesion molecule
IFX	infliximab
IL	interleukin
IM	intramuscular
IQR	interquartile range
ITT	intention to treat

IV	intravenous
JAK	Janus-associated kinase
JLN	Jacqueline Leong Nam
JSN	joint space narrowing
KT	Kaoru Takase
L	low
LDA	low disease activity
LDAS	low disease activity score
LDAS28	low disease activity using a 28 joint count
LEF	leflunomide
LN	Liz Neilly
MCP	metacarpophalangeal
MLG	Mario Leon Garcia
MI	multiple imputation
MMP	matrix metalloproteinase
MP	methylprednisolone
MRI	magnetic resonance imaging
MSK	musculoskeletal
MTP	metatarsophalangeal
MTX	methotrexate
mTSS	van der Heijde modified total Sharp score
NIHR	National Institute of Health Research
NHL	non-Hodgkin’s lymphoma
NPV	negative predictive value
NSAIDS	non-steroidal anti-inflammatory drugs
NTSJ	no tender or swollen joints
OPG	osteoprotegerin
OR	odds ratio

PD	power Doppler
PAD	peptidyl arginine deiminase
PBO	placebo
PET	positron emission tomography
PIP	proximal interphalangeal
PPV	positive predictive value
PsA	psoriatic arthritis
RA	rheumatoid arthritis
RAI	Ritchie articular index
RAMRIS	rheumatoid arthritis magnetic resonance imaging score
RANK	receptor activator of nuclear factor kappa-B
RANKL	receptor activator of nuclear factor kappa-B ligand
RAQoL	rheumatoid arthritis quality of life score
RCT	randomised controlled trial
RF	rheumatoid factor
ROB	risk of bias
SC	subcutaneous
SD	standard deviation
sDMARD	synthetic disease-modifying antirheumatic drug
SE	step-up
SDAI	simplified disease activity index
SDC	Smallest detectable change
SF-36	short form 36
SF-36 MCS	short form 36 mental component score
SF-36 PCS	short form 36 physical component score
SJC	swollen joint count
SLE	systemic lupus erythematosus
SLR	systematic literature review

SR	Sofia Ramiro
SSZ	sulphasalazine
STAT	signal transducer and activator of transcription
SYK	spleen tyrosine kinase
TCZ	tocilizumab
TNF	tumour necrosis factor
TNF- α	tumour necrosis factor alpha
TNFi	tumour necrosis factor inhibitor
tsDMARD	targeted synthetic disease-modifying antirheumatic drug
U	unclear
UA	undifferentiated arthritis
UK	United Kingdom
US	United States
VAS	visual analogue scale
(R)-^{11}C-PK11195	1-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3-isoquinoline carboxamide
^{18}F-FDG	^{18}F-fluorodeoxyglucose

Chapter 1 Introduction

1.1 Background

Rheumatoid arthritis (RA) can be conceptualised as a continuum of disease - from patients at risk, progressing to undifferentiated inflammatory arthritis (IA), through to early and established RA (figure 1.1). It is the most common of all the inflammatory arthritides, affecting about 1% of the population.[3-5] Untreated, RA can have serious consequences leading to joint destruction, functional impairment and increased mortality.[6 7] However, over the past two decades, with the availability of effective therapies and the use of early intervention strategies, disease outcomes have improved considerably.[8 9] The goal of treatment has changed from one of symptom control to aiming for suppression of inflammation and remission.[10]

In addressing the management of this condition, it is important to note that the concept of early IA has evolved over time. First, classification of the phases along the IA disease continuum has undergone change with revision of the classification of RA and the introduction of the classification of patients 'at risk'. Second, the understanding of the term 'early' has also changed over time.

Until recently RA has been classified according to the 1987 American College of Rheumatology (ACR) criteria.[11] Whilst accepted classification criteria, it was felt to be inadequate for patients with early disease. The 2010 ACR/EULAR classification criteria were subsequently designed to identify patients requiring disease-modifying antirheumatic drug (DMARD) therapy at an earlier stage.[12] Patients with IA who do not fulfil criteria for RA are classified as having unclassified or undifferentiated arthritis (UA). With research into the phases of the disease prior to detection of clinical synovitis, terminologies for individuals 'at risk' have also been defined.[13] A schematic diagram of the IA disease continuum is illustrated in figure 1.1.

A wide range of definitions have been used in the literature to define early IA or early RA. Previously, studies used a cut-off of less than five years to define early disease. By the 1990s, symptom duration of less than 12 to 24 months was considered early. This duration was chosen because at the end of this period, most patients have incurred significant damage when treated conventionally. It is now recognised that this period may be limited to weeks or months. There is also increasing evidence that very early disease, within the first 12 weeks, may be an immunopathologically distinct phase compared to later disease.[14]

Many IA treatment studies now also group patients in terms of previous DMARD therapies i.e. those who have had not received previous DMARDs - DMARD-naïve, those that may have had DMARD therapy but no methotrexate (MTX) – MTX-naïve, methotrexate incomplete responders – MTX-IR and those with incomplete response to a tumour necrosis factor inhibitor (TNFi) – TNFi-IR. Where appropriate, the recently proposed nomenclature for DMARDs and abbreviations have also been used in this thesis: biological- (bDMARD), biosimilar- (bsDMARD), conventional synthetic- (csDMARD) and targeted synthetic- (tsDMARD) disease-modifying antirheumatic drugs.[15]

Although it is widely agreed that patients should be seen and treated at the earliest opportunity to achieve optimal disease control, a number of challenges remain. These include the decision regarding choice of initial therapy and in particular the use and timing of the newer biological therapies in patients with early disease. Treating patients in the earlier stages of the disease with early UA has also not been widely investigated.

The importance of early treatment has also placed increasing emphasis on the need for early diagnosis. The diagnosis of RA in the earliest phases however can prove challenging as patients often present with non-specific symptoms. Several biomarkers e.g. rheumatoid factor (RF) have been used. In recent years newer serological markers e.g. anti-cyclic citrullinated peptide antibodies (anti-CCP), and the use of newer imaging techniques such as ultrasonography have come to the fore, but their use in early diagnosis is not yet established.

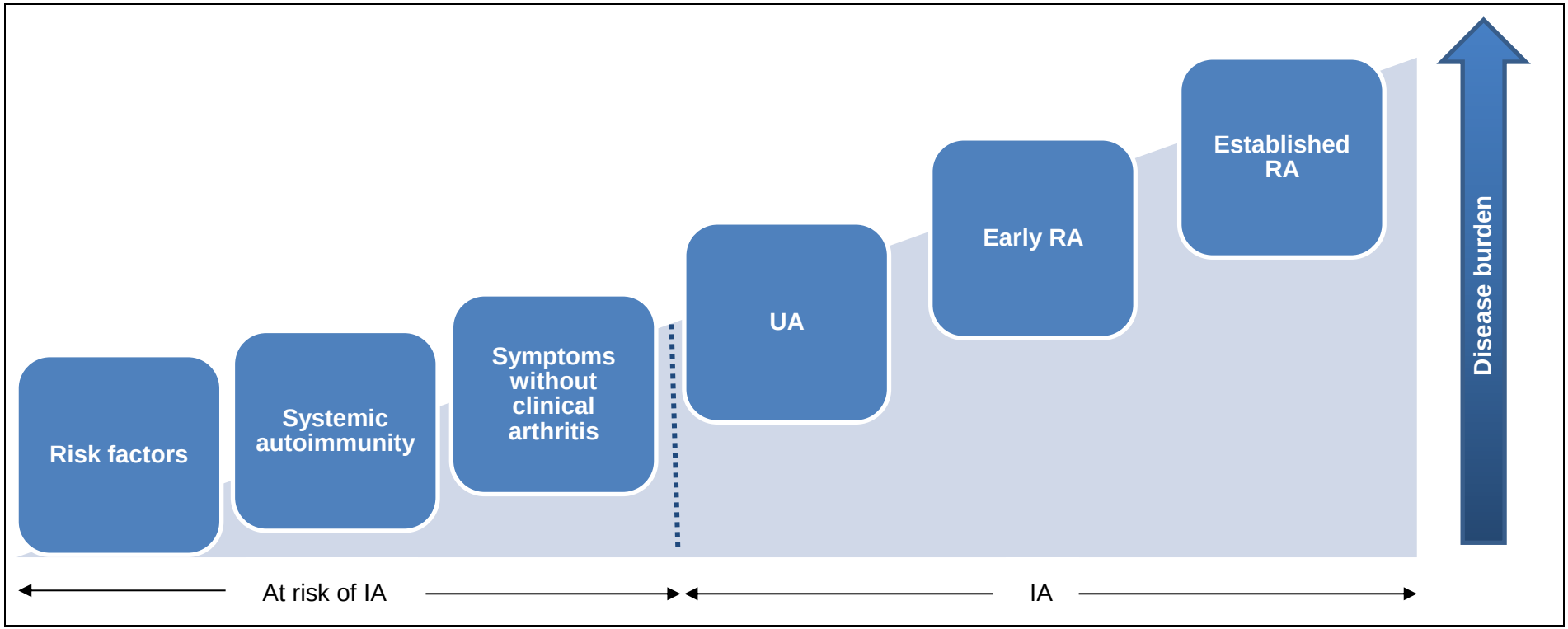


Figure 1.1 Schematic diagram of the inflammatory arthritis disease continuum

Adapted from Gerlag D. et. al 2012.[13] IA, inflammatory arthritis; RA, rheumatoid arthritis; UA, undifferentiated arthritis

1.2 Structure of the thesis

The hypotheses underlying this thesis are that applying the most effective RA therapy (bDMARDs) to early IA will improve patient outcomes, and applying modern diagnostics will improve early detection (enabling subsequent earlier intervention).

The structure of the thesis and summary of content of each chapter are outlined below. Figure 1.2 depicts the areas along the IA disease continuum that will be addressed in each of the chapters.

Chapter Two: Literature review

A review of the literature was undertaken to address the current diagnostic and treatment strategies for patients with IA. It aimed to address the current management principles, providing context to this thesis.

Chapter Three: A systematic literature review of the efficacy of bDMARDs across the IA disease continuum

A systematic review of the literature (SLR) was undertaken to evaluate the RCT evidence for the efficacy of bDMARDs and treatment strategies incorporating bDMARDs in patients with IA.

Chapter Four: A randomised controlled trial of infliximab with methotrexate vs. intravenous methylprednisolone with methotrexate as induction therapy in DMARD-naïve early RA

This chapter aimed to compare the use of two induction strategies, (1) using infliximab and methotrexate compared to (1) high dose intravenous glucocorticoid and methotrexate, together with a treat-to-target approach in patients with early DMARD-naïve RA.

Chapter Five: A randomised controlled trial of etanercept with methotrexate vs. methotrexate monotherapy in DMARD-naïve early IA

In this chapter the use of etanercept and methotrexate was compared to placebo and methotrexate in patients with early DMARD-naïve IA.

Chapter Six: The use of clinical, genetic, serological and imaging biomarkers in anti-CCP positive patients with nonspecific musculoskeletal (MSK) symptoms to identify early IA in secondary care

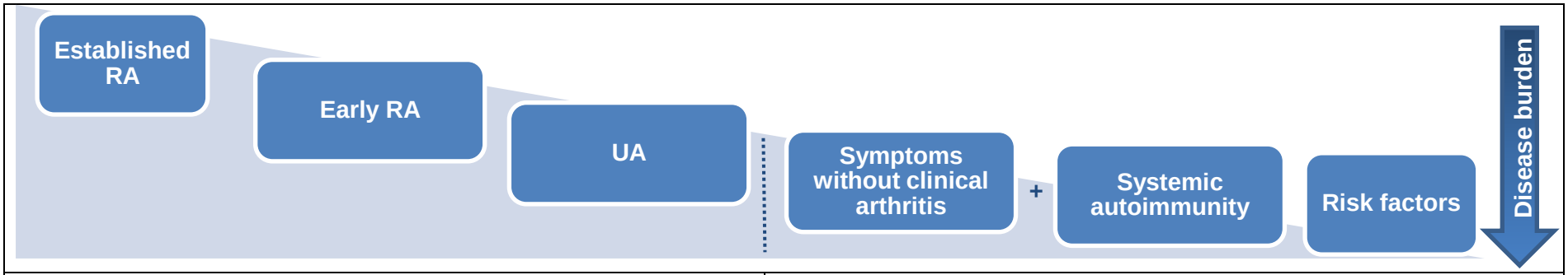
This longitudinal study sought to address the use of several biomarkers in clinical practice in secondary care to identify patients with nonspecific MSK symptoms and anti-CCP antibodies who are at risk of progression to IA.

Chapter Seven: The use of anti-CCP antibodies in patients with new nonspecific MSK symptoms to identify patients at risk of early IA in primary care

In this section the use of anti-CCP antibodies was explored as a biomarker to identify individuals at increased risk of developing IA by testing those with new, nonspecific MSK symptoms presenting in primary care.

Chapter Eight: Discussion, conclusions and future directions

This final chapter reviewed the conclusions drawn from each chapter to provide a final summary of the work from this thesis, some of which have been used to inform the European League Against Rheumatism (EULAR) guidelines for the treatment of RA. The discussion also addressed the limitations of the work that has been done, placed it in the context of recent literature, and identified further areas of research in the diagnosis and treatment of early IA.



Chapter 3					
SLR on the efficacy of bDMARDs across the IA disease continuum[16]					
	Chapter 4	Chapter 5	Chapter 6	Chapter 7	
	RCT of infliximab with methotrexate vs. IV methylprednisolone with methotrexate in DMARD-naïve early RA[17]	*RCT of etanercept with methotrexate vs. methotrexate monotherapy in DMARD-naïve early IA*[18]	*Use of clinical, genetic, serological and imaging biomarkers in anti-CCP positive patients with musculoskeletal symptoms in secondary care to detect early IA*[19]	*Use of anti-CCP antibodies in patients with new-nonspecific musculoskeletal symptoms in primary care to identify patients at risk of early IA*[20]	

Figure 1.2 Outline of thesis results chapters - addressing the inflammatory arthritis disease continuum

anti-CCP, anti-cyclic citrullinated peptide antibodies; bDMARD, biological disease-modifying antirheumatic drug; DMARD, disease-modifying antirheumatic drug; IA, inflammatory arthritis; IV, intravenous; RA, rheumatoid arthritis; RCT, randomised controlled trial; SLR, systematic literature review; UA, undifferentiated arthritis

Chapter 2 Literature Review

This chapter aimed to review the current management principles of patients with inflammatory arthritis, address diagnostic and treatment strategies across the inflammatory arthritis disease continuum, and highlight some of the challenges and unanswered questions in this area.

2.1 The inflammatory arthritis disease continuum

Inflammatory arthritis is a term used to describe a group of systemic autoimmune diseases with predominant joint involvement. The disease affects not only the individuals themselves but also has an impact on their families and places a major burden on healthcare.[21 22] Data from the Arthritis Research UK showed that in 2000, there were an estimated 1.9 million general practitioner (GP) consultations in the United Kingdom (UK) for IA with almost 46 000 hospital admissions between 1999 and 2000.[23] Of the inflammatory arthritides, RA is the most common. Untreated it can have serious consequences, causing irreversible joint damage, functional impairment and increased mortality.[6 7 24] The focus of this thesis will therefore be on the IA pathway leading to the development of RA, which may be describe as a continuum of disease - from patients at risk, developing undifferentiated arthritis (UA), progressing to early and then established RA (figure 2.1).

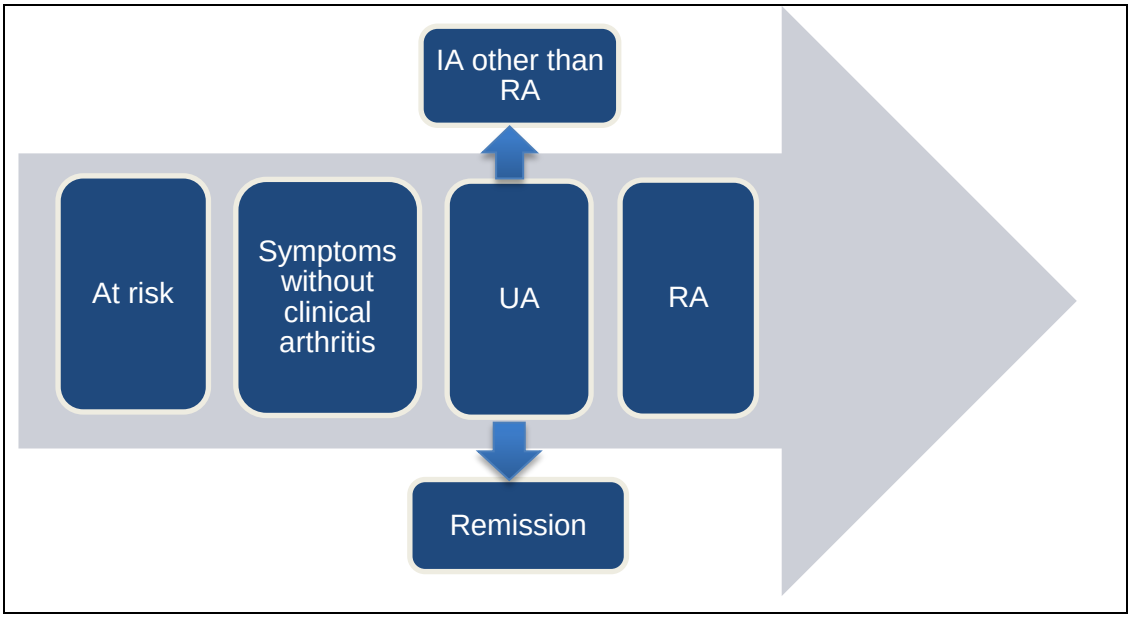


Figure 2.1 Inflammatory arthritis disease continuum

IA, inflammatory arthritis; RA, rheumatoid arthritis; UA, undifferentiated arthritis

This thesis will focus, in particular, on the early stages of the disease continuum. From clinical studies there is evidence confirming that joint damage and loss of function occur early in the disease process. Radiographic outcome studies have shown that 70% of patients with recent onset RA develop bony erosions within the first 3 years[25] and erosions have been reported in 25% of patients within 3 months of disease onset. [26] Newer and more sensitive imaging techniques such as magnetic resonance imaging (MRI) and ultrasound have confirmed evidence of damage within weeks of symptom onset.[27 28] Early radiographic erosions have also been shown to predict the future development of further lesions and those seen on ultrasound and MRI shown to correlate with later radiographic erosions.[29]

The concept of a 'window of opportunity' for the treatment of RA suggests that there is a phase early in the disease during which there may be the potential to alter or possibly even reverse the disease course with a complete return to normality.[30] Treatment during this period is thought to have a much more profound effect in terms of halting disease progression and achieving remission than treatment at a later stage (figure 2.2).

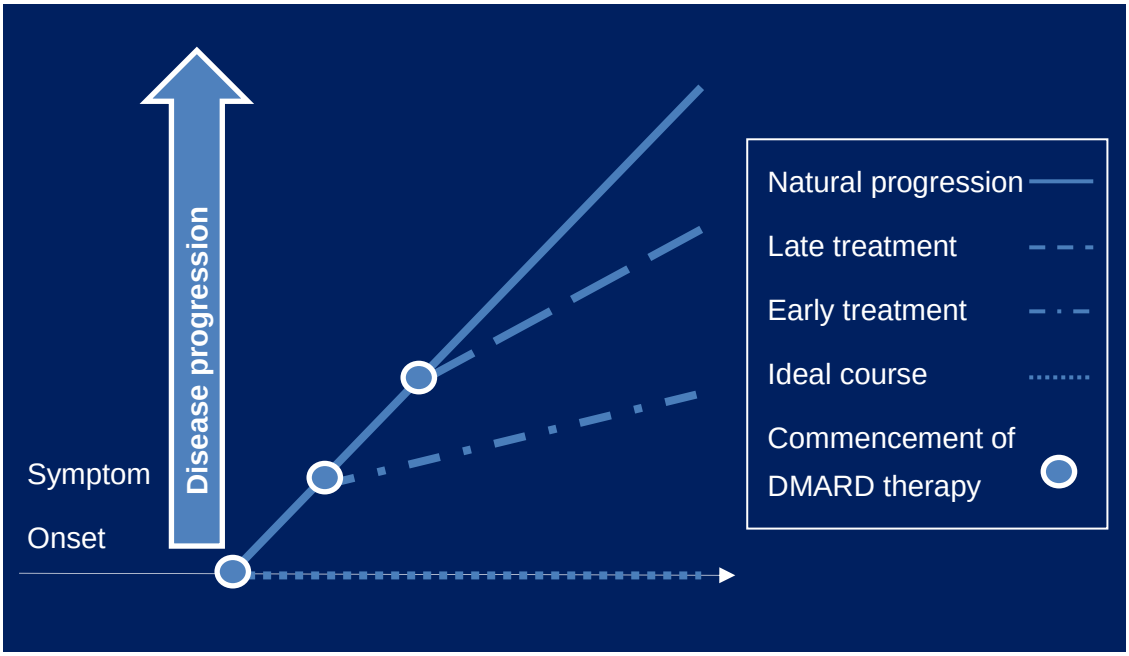


Figure 2.2 Altering the course of early inflammatory arthritis.
Adapted from Breedveld FC.[31] DMARD, disease-modifying antirheumatic drug

Results from clinical trials confirm the importance of early treatment. [8] A meta-analysis of 12 trials examined the effect of early csDMARD therapy on the long-term radiographic progression in patients with early RA (less than 2 years at

presentation). The average time interval between early and late therapy was 9 months. After a median of 3 years of observation, radiographic progression was 33% lower in those who received early treatment compared to those in which treatment was delayed. [9] Disease duration at the time of starting treatment is therefore a significant predictor of response to therapy.

It has been suggested that the window for early treatment may be much shorter, possibly within 12 weeks of symptom onset. [32] In a study by Green et al. in which a single dose of glucocorticoid was administered to patients with mild early IA, disease duration less than 12 weeks at time of therapy was noted to be the strongest predictor of remission at six months. [33] In a SLR by van Nies et al. [34], a meta-analysis of three early arthritis datasets also showed symptom duration to be independently associated with DMARD-free sustained remission (the outcome chosen as deemed the closest proxy of cure in RA) with a hazard ratio (HR)(95%CI) 0.989 (0.983 to 0.995) and a HR 0.88 using 12 weeks at treatment initiation. Radiographic progression was also lower with shorter symptom duration. In a sub-analysis of the COMET study, a RCT of 417 early RA patients, treatment with etanercept and methotrexate in patients with disease duration less than 4 months was associated with significantly higher proportions reaching remission and low disease activity than when the same treatment was used with a longer disease duration.[35]

With evidence that joint damage occurs early and that early treatment has a significant impact on outcomes, increasing emphasis has been place on the early phases of the IA disease continuum.

The first few weeks or months of symptoms, therefore, represent a potentially important therapeutic window in patients with early IA. In practice, these patients should be seen early and treated at the earliest opportunity. However, managing patients within the early stages presents several challenges:

1. Identifying and assessing patients with IA early. Seeing patients at the earliest opportunity requires early recognition and referral to rheumatology services for assessment and decisions regarding therapy. In the earliest phases of the disease, however, patients may present with nonspecific MSK symptoms.
2. Predicting which patients with early IA will develop RA and thus require DMARD therapy. As rheumatologists continue to see patients earlier in the course of disease, it has also become clear that a proportion of patients, who present with an IA, may have UA – a form of arthritis that does not fulfil criteria for a more definitive diagnosis. Whilst a proportion will progress to RA, [36] some may undergo spontaneous remission whilst others may progress to other diseases

(e.g. systemic lupus erythematosus (SLE) or a spondyloarthropathy) [37] (figure 2.1).

3. Determining how such patients should be treated.

2.2 Classification

In moving towards earlier patient identification, there have been some changes in the nomenclature within the IA continuum.

1. The classification criteria for RA have been revised with the 2010 ACR/ EULAR RA classification criteria[12] replacing the 1987 ACR RA classification criteria,[11] and
2. New terminology have been developed within the group of individuals at risk.[13]

2.2.1 Classification of rheumatoid arthritis

2.2.1.1 1987 ACR RA classification criteria

As there is no single marker for patients with RA, a combination of clinical features and laboratory tests are used for the classification of the disease. Until recently the 1987 ACR classification criteria have been used for patients with RA.[11] They were based on seven criteria (table 2.1). A patient was classified with RA if he/she has satisfied at least four of the seven criteria, with criteria 1 to 4 being present for at least six weeks. However, as these criteria were developed in populations with long-standing disease, studies have found that they did not perform as well for the diagnosis of recent-onset RA. A SLR found that sensitivity and specificity of the 1987 ACR criteria in early RA was 77% (68% to 84%) and 77% (68% to 84%) respectively using the list format.[38] With the relatively poor sensitivity, patients with early RA may not fulfil these criteria and may therefore be misclassified. The relatively low specificity means that non-RA conditions such as post-viral arthropathies, early spondyloarthropathies and other self-limiting arthritides may satisfy the classification criteria.

Table 2.1 1987 ACR RA classification criteria

Criterion	Definition
1. Early morning stiffness	Early morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
3. Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint.
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician.
6. Rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects.
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on antero-posterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal

2.2.1.2 2010 ACR-EULAR RA classification criteria

The 2010 ACR/EULAR RA classification criteria were later developed through a collaborative initiative between the ACR and EULAR aiming to define RA at an earlier stage. [12] The aim of these classification criteria was to identify patients with an IA with relatively short symptom duration who would benefit from early diagnosis and early institution of DMARD therapy (table 2.2).

For the classification criteria to be applied, patients must meet two mandatory requirements. First, there must be clinical evidence of synovitis (i.e. swelling) in at least one joint. All joints of a full joint count may be assessed for this purpose with the exception of the distal interphalangeal (DIP) joints, the first metatarsophalangeal (MTP) joints, and the first carpometacarpal (CMC) joints as these joints are typically involved in osteoarthritis. Second, the synovitis should not be better explained by another diagnosis (e.g. SLE, psoriatic arthritis, and gout). Classification as definite RA is then based on achieving a total score of 6 or more out of 10 from individual scores in four domains. These are the:

- number and site of involved joints (score range 0–5);
- serological abnormality (score range 0–3);
- elevated acute phase response (score range 0–1); and
- symptom duration (score range 0–1).

As a caveat, patients with RA type erosions on X-ray with a typical history of RA may also be classified as such and the scoring system need not be applied.

Table 2.2 2010 American College of Rheumatology/ European League Against Rheumatism classification criteria for rheumatoid arthritis

Joint involvement[1]	
1 large[2] joint	0
2–10 large joints	1
1–3 small[3] joints (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints[4] (at least one small joint)	5
Serology[5] **(at least one test result is needed for classification)**	
Negative RF AND negative ACPA	0
Low positive RF OR low positive ACPA	2
High positive RF OR high positive ACPA	3
Acute phase reactants[6] **(at least one test result is needed for classification)**	
Normal CRP AND normal ESR	0
Abnormal CRP OR abnormal ESR	1
Duration of symptoms[7]	
<6 weeks	0
≥6 weeks	1

(1) Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Categories of joint distribution are classified according to the location and number of the involved joints, with placement into the highest category possible based on the pattern of joint involvement.(2) Large joints refer to shoulders, elbows, hips, knees and ankles.(3) Small joints refer to the wrists, metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, thumb interphalangeal (IP) joints, and metatarsophalangeal (MTP) joints 2–5. (4) In this category, at least one of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (eg, temporomandibular, acromioclavicular, and sternoclavicular joints).(5) Negative refers to international unit (IU) values that are ≤ULN for the lab and assay. Low titre refers to IU values that are >ULN but ≤3X ULN for lab and assay. High titre positive is >3X ULN for lab and assay. Where RF is only available as positive or negative, a positive results should be scored as 'low positive' for RF. (6) Normal/abnormal is determined by local laboratory standards. (Other causes for elevated acute phase reactants should be excluded) (7) Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g. pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status. ACPA, anti-citrullinated protein/peptide antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; ULN, upper limit of normal. Reproduced with permission from Aletaha et al [12].

2.2.2 Classification of undifferentiated arthritis

There are currently no specific criteria for undifferentiated or unclassified arthritis. This term is generally used to define cases in which there is clinical synovitis not fulfilling RA classification criteria and not due to another disease e.g. crystal arthropathy, reactive arthritis, a spondyloarthropathy or SLE.[34] It is important to note, particularly when reviewing the literature that patients not fulfilling the 1987 ACR RA classification criteria who were previously classified as UA may now fulfil the 2010 ACR/EULAR classification criteria for RA.

2.2.3 Classification of individuals at risk

Increasingly work has also been done looking at the phases prior to the development of clinical synovitis aiming to identify patients at the very earliest stages. Research into these early stages had led to the formation of a 'Study Group for Risk Factors for Rheumatoid Arthritis'.[13] The group has published recommended terminology to define the specific phases up to the development of RA in order to phenotype/ characterise these and to standardise further research in the field (table 2.3).

Table 2.3 Recommendation for terminology to be used to define specific phases up to the development of RA [13]

Phases up to the development of RA
In prospective studies individuals would be described as having: a. Genetic risk factors for RA b. Environmental risk factors for RA c. Systemic autoimmunity associated with RA d. Symptoms without clinical arthritis e. Unclassified arthritis f. RA
The term 'arthritis' is used to denote clinically apparent soft tissue swelling or fluid (not bony overgrowth alone).
(a) to (e) can be used in a combinatorial manner for example, an individual may have (a)+(b), or (a)+(b)+(c) or (a)+(b)+(d) etc.
The prefix 'pre-RA with:' can be used before any/any combination of (a) to (e) but only to describe retrospectively a phase an individual was in once it is known that they have developed RA.

2.3 Epidemiology

2.3.1 Incidence and prevalence

Recognising the need to diagnose patients with IA early led to the development of Early Arthritis Clinics. These enabled patients with suspected IA rapid access to rheumatology services.[39] Data from these clinics together with that from the general population have provided information on the incidence of early IA, UA and RA, and the proportions and risk factors for the progression from UA to RA.[40]

Three population based studies have reported on the incidence of early IA, including RA and UA. In Finland the reported annual incidence of clinically observed early IA was 271/100 000 adult population, with that of RA of 36/100 000 and that of UA 149/100 000 adults.[41] Data from a study in South Sweden estimated an annual incidence of new IA in adults of 115/100 000 - 24/100 000 for RA and 41/100 000 for UA.[42] In a Spanish study, early arthritis (defined as > 1 painful or swollen

metacarpophalangeal (MCP) or MTP joint with early morning stiffness (EMS) > 30 minutes and the presence of symptoms > 1 month and < 1year)[43] was estimated to occur in 25/100 000 population.[44] After 6 months follow up, 8/100 000 adults were diagnosed with RA (1987 ACR criteria) and 3/100 000 were regarded to have UA. It is likely that the difference in the definitions used for early IA account in part for the differences in incidence rates between these populations. It is also know that the incidence of RA varies according to geographic location.[45]

RA, the most common IA, has a worldwide prevalence of approximately 0.5-1%. [3-5] [46] In Northern Europe and the USA, the reported prevalence according to the 1987 ACR RA classification criteria was between 500-100/100 000 population with an annual incidence of approximately 40/100 000. It was estimated that about 387 000 adults in the UK have RA [4] with approximately 12 000 new cases per year. In Southern Europe, China and South America, reported prevalence has been slightly lower (<500/100 000).[45] Age of onset is commonly over 50 years, however it may occur at any age. [4 47] From the Rochester Epidemiology Project, there was a rise with age with a peak incidence in patients between 65-74 years of age (89/100 000).[48] The female-to-male ratio is about 3:1.

With the change in the RA classification criteria, the incidence of RA in the UK was reviewed using data from the Norfolk Arthritis Register (NOAR).[49] This primary care inception cohort comprised patients ≥ 16 years with IA in two or more swollen joints, notified between 1990 - 1995 with symptom onset in 1990. The incidence of RA was 40/100 000 applying the 2010 ACR/EULAR criteria and 32/100 000 using the 1987 ACR criteria at baseline. Applying the criteria cumulatively over 5 years, incidence rates were similar for both criteria (48/100 000 for the 2010 ACR/EULAR criteria and 44/100 000 for the 1987 ACR criteria) suggesting that whilst both classified similar patients with RA over this period, the new criteria identified patients with RA who presented with an IA earlier in the course of their disease.

2.3.2 Aetiology

The exact aetiology of IA leading to RA is unknown. As with other autoimmune diseases, the hypothesis is that it occurs in a genetically susceptible individual with an environmental exposure or 'trigger'.[50]

Twin studies have shown concordance rates of 5% among dizygotic twins and 15-30% among monozygotic twins.[51] The human leucocyte antigens (HLA-DRB1) alleles is the main genetic risk factor for inflammatory polyarthritis with the HLA-DRB1*0404 conferring the greatest risk.[52] Other genetic factors have also been

identified and will be discussed in more detail later in the chapter. The heritability of RA has been estimated to be 60%, suggesting that 40% of the risk of developing RA may be determined by environmental factors.[51 53]

Several environmental risk factors have been identified.[54] Of these, cigarette smoking is the most significant and is associated with an increased risk of RA and the development of RF.[55 56] Smokers who possess the shared epitope genes in particular are at increased risk of ACPA-positive RA.[57] Smoking is estimated to be responsible for 35% of ACPA-positive RA and in homozygous patients, 55% of ACPA-positive RA was attributable to smoking.[58] Use of the oral contraceptive pill and pregnancy have been associated with a lower incidence or RA.[59]

More recently studies have suggested that the initiating site of inflammation in IA may take place in areas outside the joint, with particular focus on mucosal sites.[60] An association between periodontitis and RA has been described in several clinical studies.[61-63] *Porphymonas gingivalis*, an oral pathogen and a common cause of periodontitis, is one mucosal pathogen that has been implicated in the disease pathogenesis. [64] It is capable of expressing the enzyme peptidyl arginine deiminase, type IV (PADI4) which is needed to generate citrullinated peptides. Increases in intestinal *Prevotella copri* have also been described in patients with new-onset untreated RA.[65]

The trigger for the subsequent loss of systemic tolerance is still unclear. Local biomechanical, micro-trauma, microvascular and neurologic-related mechanisms have been suggested as possible factors. [50] The subsequent immune dysregulation, with release of pro-inflammatory cytokines and chemokines, neoangiogenesis, activation of endothelial cells and fibroblasts and leucocyte infiltration into the synovium, lead to the inflammation of synovial tissue. Perpetuation of this immune response results in cartilage and bone destruction and the systemic consequences seen in patients with RA.

2.3.3 Natural history

It has been suggested that in one third of patients with recent onset IA it may not be possible to come to a definitive diagnosis at presentation.[66] The outcome of these patients may vary and the diagnosis may change over the period of follow-up. Some patients will progress to RA, and some to other rheumatic diseases. Others will remain undifferentiated or enter into remission. Data from several inception cohorts have suggested that of the patients that present with UA, 40-50% will remit and 30% will evolve into RA (based on the 1987 ACR criteria). [37 66 67] It is almost certain that

proportions classified as UA will be lower and those with RA higher using the newer classification criteria.

In patients with RA spontaneous remission is rare. In a cohort of 458 patient with RA followed up for 1131 patient years, 14% achieved remission without treatment.[68] In another study of 183 RA patients with a follow-up of 5 years, a remission rate of 20% was described; 11% were spontaneous and 9% were drug-induced.[69] In the majority of patients therefore who progress to RA, the disease persists. In many, untreated this results in joint damage, functional decline and may lead to premature mortality.

2.4 Diagnosis

There is no single diagnostic test for patients with early IA. Evaluation requires a combination of clinical features and laboratory tests. The key issue when seeing these patients is determining their prognosis - differentiating those with self-limiting disease from those at risk of developing persistent inflammatory and erosive arthritis to allow the initiation of appropriate DMARD therapy for those that will progress and prevent unnecessary treatment for those that will resolve.

The following steps have been suggested as an approach to evaluate patients with early arthritis:[70]

- Recognise the presence of IA
- Exclude diseases other than RA or UA that present as an early IA (e.g. SLE, psoriatic arthritis or other spondyloarthropathies).
- Estimate the risk of developing persistent or erosive irreversible arthritis in patients with RA or UA using a combination of clinical features, laboratory tests and imaging techniques.

The development of the 2010 ACR/EULAR RA classification criteria are based on these principles and have helped to identify patients with RA at a early stage.

All new patients with symptoms of an IA should be referred to a rheumatologist as early as possible, ideally within 6 weeks of symptom onset.[71] As a proportion of patients will have normal/ negative results at disease onset, they should be referred regardless of blood test results or radiographic findings. If tests are done in primary care referral should not be delayed while waiting for results.

2.4.1 History

The clinical evaluation remains the cornerstone for evaluating early IA - determining whether arthritis is present or not, differentiating between inflammatory or non-inflammatory disease and deciding aetiology of the arthropathy. Articular symptoms may be the presenting manifestation of many infectious, inflammatory or malignant conditions. The clinical feature may also provide clues to identify those at risk of developing persistent erosive disease (table 2.3).

A thorough history includes the distribution of the symptomatic joints, duration of symptoms and early morning stiffness, response to non-steroidal anti-inflammatory drugs (NSAIDS), any prodromal illness and associated symptoms. Family history is important for RA, psoriasis and other autoimmune diseases. Personal and past medical histories including smoking history should also be noted.

2.4.2 Clinical features

The clinical finding of joint swelling not caused by trauma or bony swelling suggests a diagnosis of early IA, especially if it includes involvement of at least two joints and/or EMS lasting 30 minutes or more. Hand or foot involvement is common in inflammatory arthropathies. A positive MCP or MTP ‘squeeze test’ has been used to identify patients at risk of developing RA early (figure 2.4). [43]

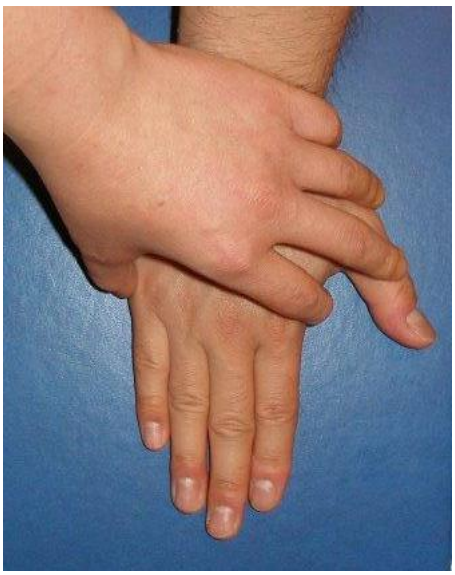


Figure 2.3 Metacarpophalangeal squeeze test

While joint symptoms predominate early in disease, extra-articular manifestations of RA (e.g. nodules, keratoconjunctivitis sicca) are seldom present early. In other forms of polyarthritis, extra-articular manifestations may be present early and may precede the onset of synovitis, providing clinical clues to the diagnosis. This is particularly true with SLE (malar rash, serositis), reactive arthritis (urethritis, conjunctivitis), psoriatic arthritis (psoriasis, nail pitting or other nail changes) and sarcoidosis (lung involvement, fever) [72] (table 4).

2.4.3 Investigations

Laboratory investigations and imaging are ancillary measures for the diagnosis and prognosis of patients presenting with early IA and should be tailored to the individual. These have their limitations - in the early phases of the disease in particular tests can be within normal limits. Imaging techniques are potentially helpful in this setting.

Most cases of suspected IA will warrant a complete blood count, inflammatory markers, basic serology including RF, ACPA and antinuclear antibodies, renal and liver function tests and a urine analysis.

More specific tests may be directed by the clinical presentation including tests for uric acid, cultures where infection may be suspected, serology for atypical infections e.g. Lyme disease, virology e.g. hepatitis B, C or B19 parvovirus (immunoglobulin M (IgM) antibodies), serum angiotensin-converting enzyme, specific autoantibodies and genetic markers. In cases of suspected crystal arthropathy or infection, an aspirate of a joint effusion will be of value in making a definitive diagnosis. Findings on X-rays may further assist in making the diagnosis of a specific arthropathy e.g. the presence of cartilage calcification in calcium pyrophosphate dihydrate deposition disease (CPPD). Large asymmetric erosions with periosteal reaction and late development of “pencil in cup” deformities may be seen in psoriatic arthritis, joint space narrowing with sclerosis and hook like osteophytes of MCP 2 and 3 in hereditary hemochromatosis, large asymmetric, erosions with sclerotic rims in gout and joint space narrowing with subchondral sclerosis and osteophyte formation sparing MCP joints in osteoarthritis.

Table 2.4 Differentiating diseases that present as an early inflammatory arthritis [73]

Arthritis	**History**	**Typical pattern of joint involvement**	**Joints commonly affected**	**Associated features**	**Laboratory tests**
Undifferentiated Arthritis	F>M	Insidious Oligoarthritis	PIP,MCP, wrist, MTP, knee, ankle	EMS	↑CRP/ESR
Rheumatoid Arthritis	F>M 35-50 years	Insidious, progressive Symmetrical	PIP,MCP, wrist, MTP, knee, ankle	EMS	↑CRP/ESR, RF+, ACPA+
Spondyloarthropathy	Psoriasis, urethritis or cervicitis, IBD Family history of psoriasis or IBD	Persistent Asymmetric Oligoarticular	DIP, PIP, knee, feet, spine	Psoriasis, nail pitting, uveitis, Enthesitis, dactylitis	ESR/ CRP may be normal More severe course in HLA B27 +
Systemic lupus erythematosus	F > M, young	Polyarticular Symmetric Usually non-erosive	PIP, knee	Rash, serositis	Anaemia, ↑ESR/CRP, proteinuria, ANA+, dsDNA+
Rubella	Rubella epidemic and no previous	Acute Symmetric	PIP, MCP, wrist, knee	Rash, lymphadenopathy,	Rubella serology (IgM)

	vaccination Recent (2-3 weeks) rubella vaccination	Oligoarthritis or polyarthritis		fever	Virus isolation from nasopharynx or joint tissue
Alpha viruses	Mosquito-borne RNA viruses in endemic areas (Asia and Africa)	Acute Polyarthritis	PIP, wrist, MTP, ankle,	Rash, fever, tendinitis and peri-articular involvement	Serology for alpha viruses
Viral (HBV, HCV)	Hepatitis risk factors	Acute Polyarthritis	PIP, MCP, wrist, knee, ankle	Jaundice	↑ESR/CRP, ↑ LFTs, Hepatitis B and C serology
Septic Arthritis (non-gonococcal)	Peak incidence in elderly Reduced host immunity Joint prostheses	Acute Mono-articular (may be polyarticular) Often extremely painful	Knee – most common Hip, shoulder, ankle, wrist	Systemic symptoms common	Commonest cause Staphylococcus aureus Synovial fluid is gram stain positive in 50% and culture positive in 90%
Gonococcal	F > M young, sexually	Acute Oligo- or poly-arthritis	Wrist, knee	Fever, rash, skin blisters/pustules,	↑ESR/CRP, ↑WBC Synovial fluid gram

	active			tenosynovitis	stain positive in 25% and culture positive in 50% of cases
Osteoarthritis	F > M Men with knee or hip involvement ↑age	Progressive Asymmetric or symmetric, bony swelling Oligo- or poly-articular	DIP, PIP, first CMC1, knee, hip, MTP, spine		Normal laboratory tests
Gout	Men Postmenopausal women Diuretic use (especially in elderly)	Sudden onset Severe pain with attacks Oligoarticular early, polyarticular later	MTP, ankle, knee	Tophi	Synovial fluid – urate crystals ↑uric acid level – normal levels in 40% of acute attacks
Pseudogout	M=F ↑age	Chronic Oligo- or polyarticular Acute monoarticular (25%)	Knee, wrist, MCP, MTP	Associated conditions include: Hypomagnesaemia, Hypophosphataemia, Haemochromatosis,	↑CRP, ↑WBC

				Wilson's disease, Hyperparathyroidism	
Polymyalgia rheumatica	M = F Older Caucasian	Prolonged morning stiffness	Hip and shoulder girdle, PIP, wrist, knee occasionally	RS3PE	Anaemia, ↑ESR/CRP
Sarcoidosis	F>M	Acute symmetrical Chronic uncommon	Knee, ankle	Fever, Erythema nodosum, hilar lymphadenopathy with acute sarcoid	↑ESR/CRP Serum ACE
Scleroderma	F>M	Acute or occasionally insidious Symmetric or asymmetric	MCP, PIP	Tendon friction rubs (diffuse disease)	↑CRP/ESR ANA +, Scl-70+, ACA+

ACA, anticentromere antibody; ACPA, anti-citrullinated protein antibody; ANA, antinuclear antibody; CMC1, first carpometacarpal joint; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; F, female; HBV, hepatitis B virus; HCV, hepatitis C vírus; IBD, inflammatory bowel disease; LFT, liver function test; M, male; MCP, metacarpophalangeal joint; MTP, metatarsophalangeal joint; PIP, proximal interphalangeal joint; RA, rheumatoid arthritis; RF, rheumatoid factor; UA, undifferentiated arthritis; WBC, white blood cells.

2.5 Prognosis

After excluding other diseases and making a diagnosis of probable RA or UA, the next step is to determine which patients are at risk of developing persistent and/ or erosive arthritis. This prognostic assessment is important for guiding treatment strategies. Predictors of persistence and disease progression include demographic, genetic, clinical, serological and radiological factors. [74] Several of these have been incorporated into the 2010 RA classification criteria.[12]

2.5.1 Disease persistence

The potential for spontaneous remission of synovitis in patients with early IA (particularly those with symptoms of less than 3 months duration) means that a therapeutic approach which targets all patients with very early synovitis, will needlessly expose some patients to potentially toxic therapies. The ability to distinguish resolving disease from synovitis that persists and develops into RA is thus essential. Female gender, cigarette smoking, duration of symptoms, the tender and swollen joint count, hand involvement, the level of acute phase response, presence of RF and ACPA, and the fulfilment of 1987 ACR diagnostic criteria for RA are factors associated which have been associated with disease persistence (table 2.5).

On the other hand, seronegativity for rheumatoid factor (RF) and fewer active joints at baseline in early RA have been cited as markers of a favourable outcome. [69] Other studies have shown a relationship with male gender and absence of erosions with higher remission rates. [68]

Table 2.5 Candidate predictors of disease persistence in early inflammatory arthritis

Predictors of disease persistence
• Female gender • Duration of symptoms (more than 12 weeks) • High tender and swollen joint count • Hand involvement • Cigarette smoking • Elevated acute phase response • Positive rheumatoid factor • Positive anti-citrullinated protein antibodies • Erosions on X-ray • Fulfilment of 1987 ACR classification criteria for RA

ACR, American college of rheumatology

2.5.2 Disease severity

In clinical practice, treatment of early RA is often commenced and increased according to the disease activity. An alternative approach would be to initiate the most appropriate treatment based on prognostic stratification, differentiating between those with a more benign disease from those at risk of developing severe erosive disease who would benefit from more aggressive, and more expensive, treatment early on to prevent severe outcomes.

Many of the factors predicting disease persistence are also markers of disease severity. Joint damage and functional disability are the two most common outcome measures of disease severity.

Prognostic factors of radiographic damage are a high acute phase response, the presence and titre of RF and ACPA at baseline, the genetic marker HLA-DRB1*0401 allele subtype, and early erosions or a high radiographic score at disease onset. Factors that have been found to predict future disability include a high baseline health assessment questionnaire disability index (HAQ-DI) score, high Ritchie articular index, elevated erythrocyte sedimentation rate (ESR) and C-

reactive protein (CRP), and the presence of erosions on X-rays. Female gender, older age, the number of damaged joints, RF positivity and the presence of nodules (although usually a later finding in RA) at baseline are other documented factors (table 2.6).

Table 2.6 Candidate predictors of disease severity in early inflammatory arthritis

Predictors of disease severity
• Female gender [b] • High tender [b] and swollen joint [a] counts • High HAQ-DI score [b] • Elevated acute phase reactants [a, b] • Positive rheumatoid factor [a] • Positive anti-citrullinated protein antibody [a] • Shared Epitope [a] • Erosive disease [a, b] [a] Predictors of joint damage [b] Predictors of functional disability

HAQ-DI, health assessment questionnaire disability index

2.5.3 Individual factors predicting disease persistence and severity

2.5.3.1 Disease duration

Several studies have shown symptom duration at first visit to be a good predictor of disease persistence. [67 75] In a study by Green et al, 63 patients with mild untreated early IA were given a single dose of glucocorticoid at presentation. At 6 months, 49 patients (78%) had persistent inflammatory joint disease and 14 (22%) were in clinical remission. The strongest predictor of persistence was disease duration of 12 weeks.[33] With disease duration less than 12 weeks, the chance of remission was increased five-fold.

A further study examined the use of a similar protocol of intra-articular glucocorticoid injections in patients with early oligoarthritis (i.e. involvement of four or less joints) followed by an early review to assess for the presence of persistent synovitis.[76] At least 50% of patients with oligoarthritis had complete response at two weeks. The best predictor of response at 12 and 26 weeks was the presence or absence of synovitis on examination at 2 weeks follow-up. Failure to respond by two weeks indicated a high likelihood of persistent disease and the need for DMARD therapy.

Disease duration is also an important predictor of severity, with better clinical and radiographic outcomes seen in patients with shorter disease duration. [77 78]

2.5.3.2 Early morning stiffness

EMS is an early symptom of IA. It is a complex symptom and may be difficult to interpret and to discriminate from pain and functional limitation. It has been used in some models as a clinical marker of disease persistence.[79 80] Interestingly, however, during the first phase development of the 2010 ACR/EULAR RA classification criteria EMS, using the traditional cut-off of one hour, was not found to be predictive of starting methotrexate in patients with early IA and was therefore subsequently not included in the final classification criteria.[81]

2.5.3.3 Joint involvement

The number of affected joints has also been associated with disease persistence. In a cohort of 121 patients with early arthritis followed up for a median duration of 5 years, those with polyarticular disease and hand involvement were more likely to have persistent disease. [75] These findings have been confirmed by several other studies. [82 83]

Persistent joint inflammation leads to joint destruction. A high joint count is also a marker of disease severity with the number of swollen joints correlating better with radiographic progression than the number of tender joints.

2.5.3.4 Functional disability

Functional disability as measured by the Stanford HAQ-DI has also been found to be a reliable predictor of disease outcomes in early arthritis. [84] A high baseline HAQ-DI is an important risk factor for the development of future functional disability and has been predictive of both all-cause and cardiovascular mortality in patients

with early disease, as well as quality of life and work disability[85] [86] in patients with early RA. Analysis from a primary care-based inception cohort of patients with recent –onset polyarthritis has found the one year HAQ-DI score to be a better predictor of subsequent outcome than the baseline HAQ-DI score[87].

2.5.3.5 The acute phase response

A rise in the level of acute-phase reactants such as the ESR and CRP provide surrogate measures of inflammation. Both elevated ESR and CRP levels, especially if sustained, are predictive of long term radiographic progression. In a study of 130 patients with early RA (median disease duration 3 months), logistic regression analysis of baseline variables revealed that a high CRP level (≥ 20mg/L) was an independent predictor of severe progressive radiographic joint damage at 1 year (odds ratio(OR) (95% CI) 3.59 (1.53, 8.39).[88] CRP levels at presentation have also been found to be an independent predictor of functional ability assessed by the HAQ-DI.

High sensitivity CRP (hs-CRP) assays may be used to identify mild disease activity that is not detectable by routine CRP testing. [89]

2.5.3.6 Serological markers

2.5.3.6.1 Rheumatoid Factor

Rheumatoid factor (RF) is a polyclonal antibody against the Fc portion of immunoglobulin G (IgG). It is both a marker of persistence in patients with early IA [67] [90] and a predictor of radiographic progression. [91] [92] Studies have shown sensitivities ranging from 41%–66% and specificities between 87%–97% for the diagnosis of early RA. [93]

In a prospective cohort study of 9712 Danish individuals aged 20-100 years, an elevated RF level was associated with a 26-fold greater long term risk of developing RA. The absolute risk was highest at 32% in women between 50-69 years of age who smoked and had RF levels > 100 IU/mL. A doubling in RF level was associated with a 3.3 fold (95% CI 2.7 to 4.0) increased risk of RA.[94]

2.5.3.6.2 Anti-citrullinated protein antibodies

Research into autoantibodies other than RF in sera of RA patients led to the discovery of antibodies to citrulline, a non-standard amino acid is generated by the post-translational modification of arginine residues by the enzyme peptidylarginine deiminase (PAD). The assay using the second generation cyclic citrullinated

peptide (anti-CCP 2) as an artificial auto-antigen is currently the most commonly used test in clinical practice to identify ACPA. A review of data has shown that anti-CCP 2 has a similar sensitivity to RF in early RA cohorts, but a greater specificity.[93] Anti-CCP positivity has also been shown to be an independent predictor of radiographic damage and progression.[95]

A SLR evaluating the diagnostic value of anti-CCP and RF for the diagnosis of RA, in which data from 24 studies were pooled, showed that positivity for both anti-CCP and RF yielded a sensitivity (95% CI) of 57% (55% to 59%), specificity (95% CI) 96% (96% to 97%), positive likelihood ratio (LR) (95% CI) 13.84 (10.56 to 18.12), negative LR (95% CI) 0.46 (0.40 to 0.52) and odds ratio (OR) (95% CI) 33.02 (23.89 to 45.64). When either anti-CCP antibody or RF were positive, results were as follows: sensitivity (95% CI) 78% (76% to 80%), specificity (95% CI) 82% (81% to 84%), positive LR (95% CI) 4.24 (3.61 to 4.97), negative LR (95% CI) 0.27 (0.22 to 0.34), OR (95% CI) 16.95 (12.96 to 22.18).[96] The performance of RF and anti-CCP 2 in early RA cohorts are summarized in table 2.7.

Table 2.7 Performance of immunoglobulin M-rheumatoid factor and anti-citrullinated peptide antibodies (anti-CCP 2) assays in early rheumatoid arthritis cohorts.

	Anti-CCP 2	**IgM-RF**	**Anti-CCP 2 or IgM-RF**	**Anti-CCP 2 and IgM-RF**
Sensitivity range (%)	41–63	41–66	52–67	33–58
Specificity range (%)	91–100	81–97	72–82	98–100

Adapted from Aggarwal et al. [93]

Anti-CCP 2, second generation anti-cyclic citrullinated peptide antibody; IgM-RF, Immunoglobulin M rheumatoid factor

2.5.3.6.3 Other serological and immune markers

Despite the diagnostic value of ACPA and RF, a proportion of patients with IA will still be classified as seronegative RA. Research has led to the finding of several other autoantibodies including antibodies to carbamylated antigens (anti-CarP).[97] These autoantibodies recognise carbamylated but no citrullinated protein antigens. IgG anti-CarP and IgA anti-CarP antibodies have been described in 16% and 30%

of ACPA negative individuals with IA and the presence of these antibodies have been associated with greater radiographic progression.[98]

In addition to autoantibodies, levels of cytokines and chemokines, including interleukin (IL)-1α, IL-1β,IL-6, IL10 and tumour necrosis factor alpha (TNF–α), have also been shown to be elevated in pre-clinical RA with increasing numbers present in cases nearer to the time of RA diagnosis. [99]

These findings add to the armamentarium of potential biomarkers for the diagnosis of early arthritis. Further studies will determine their use in clinical practice.

2.5.3.7 Genetic markers

Genetic factors play an important role in the development of RA. Twin studies have estimated heritability to account for about two-thirds of the risk for ACPA-positive as well as ACPA-negative disease. [53]

A group of the major histocompatibility complex class II, DR beta 1 (HLA-DRB1) alleles provides the strongest genetic associated with RA. A number of these alleles in particular DRB1*0401 and *0404 share a similar amino acid sequence which is important in antigen presentation - the shared epitope. Several studies have shown a correlation between shared epitope and disease persistence. [33 100] Others, however, have found the presence of shared epitope of less value as an independent predictor of disease persistence [80 101] but rather an indicator of disease severity in patients with RA. [101 102]

Among the different HLA-DRB1 alleles, HLA-DRB1*401 and DRB1*0404 have also been associated with radiographic erosions in different ethnic groups. This association appears to be dose dependent with patients with two RA-associated alleles (DRB1*04 or DRB1*01) having had more radiographic erosions and more joint replacements than those with non-disease associated-alleles. [103] Studies have shown that individuals who were homozygous for HLA-DRB1*0404 were 4 times more likely to develop erosions than those who were shared epitope negative. [100 104]

A number of other genetic polymorphisms have been identified including *PTPN22*, a negative regulator of T-cell activation. [105 106] This is the first non-HLA (human leucocyte antigen) genetic variation associated with the susceptibility to a number of autoimmune diseases including RA. Other genetic markers include TRAF-1 C5 [107] and STAT4 [108]. The *150V IL4* single-nucleotide polymorphism and the *TNFA-308* polymorphism have also been shown to be markers for early radiographic bone erosions, suggesting that functional alterations in cytokine regulation are also involved in the disease pathogenesis and may have an effect on disease

persistence and damage. More recently, the functional leukocyte immunoglobulin-like receptor A3 (*LILRA3)* gene has been found to be associated with RA in a Northern and Southern Han Chinese cohort.[109]

2.5.3.8 Smoking

Smoking is the most recognised environmental risk factor for the development of RA.[55 56] There is also a strong association between smoking and the development of rheumatoid nodules in early seropositive RA.

Studies addressing the role of smoking in the pathogenesis of RA, have shown that smoking increases the risk of the development of ACPA. In the presence of the shared epitope alleles, this risk is further increased – up to 20 times in homozygotes as compared to shared epitope negative non-smokers. [110 111] It is possible that, smoking, in a genetically predisposed individual, induces apoptosis and protein-citrullination, followed by an anti-citrulline specific immune response. Former smokers are also at an increased risk for RA up to 20 years after smoking cessation with a gradual decreasing risk over time. [112]

Outcomes of studies assessing the effect of smoking on disease severity, however, vary. Several cross sectional studies have demonstrated significant associations between radiographic joint damage and smoking [113 114] and disease activity, response to treatment and smoking, with poorer outcomes seen in smokers compared to non-smokers [115]. Others, including a large observational study of 2004 RA patients,[116] have found no effect of overall current or past smoking, [117 118] suggesting that smoking may be more important in the initiation of RA than in the perpetuation of the erosive disease process.

2.5.3.9 Imaging

2.5.3.9.1 Conventional radiographs

Conventional radiographs remain the most widely used imaging modality in many centres given the low cost and availability. Radiographic erosions have a high specificity in discriminating between self-limiting and persistent arthritis.[79] Early radiographic changes are also predictive of disease progression. In a cohort of patients with UA, the presence of two or more erosive joints at baseline had a positive predictive value for persistent disease of 68%. [119]

Radiographic examination should include the assessment of the hands and the feet as erosions may start in the feet, and in approximately 14-18% of cases are only

detected in the feet. [120] In general antero-posterior views are done. Other views e.g. lateral or oblique views may be requested if clinically indicated.

Radiographic damage at baseline is also the best predictive factor of poor structural outcome. Irrespective of the scoring systems used (e.g. Larsen[121], Sharp[122] or modified Sharp scores[123]), the initial radiographic score consistently predicts future radiographic damage.[88]

X-rays are however not very sensitive for detecting change in early RA. Joint erosions and joint space narrowing seen on X-rays are generally late findings. Newer imaging modalities e.g. MRI and ultrasound have both been shown to be more sensitive for visualizing early inflammatory and destructive change and predicting future radiographic damage.

2.5.3.9.2 Magnetic resonance imaging

MRI can assess all structures of the inflamed joint. Synovitis and bone oedema are two features of early IA seen on MRI. Histopathology and mini-arthroscopy have confirmed that these findings represent true inflammation. [124] [125] Bone oedema, which is a specific MRI finding and probably represents a cellular infiltrate within bone,[126] occurs in various arthritides and is common in early RA. [127]

MRI is a sensitive indicator of active disease [128] and more sensitive than clinical examination for detecting synovitis. [129] Erosions are also detected earlier on MRI than conventional radiographs,[130] and may help classify patients with undifferentiated IA as having RA. In a cohort of patients with undifferentiated polyarthritis followed up over 2 years, MRI of the most symptomatic hand and whole-body scintigraphy correctly classified RA according to the 1987 classification criteria and non-RA in 39 of 41 patients.[131] The positive and negative predictive values for the development of RA of were 1.0 and 0.87 respectively. In another study assessing the diagnostic value of MRI, the presence of symmetric periarticular enhancement in the wrists, MCP or proximal interphalangeal (PIP) joints increased the sensitivity for the clinical diagnosis of RA from 77% to 96%. [132]

There is also evidence that MRI findings (synovitis, bone oedema, and bone erosions) may predict subsequent radiographic progression. Notably, however, changes resembling mild synovitis or small bone erosions are occasionally found in the joints of healthy subjects.[133]

The use of MRI has recently been addressed in patients with symptoms of an IA but no synovitis. In a cohort of 93 patients with arthralgia and inflammatory symptoms, 44% had subclinical MRI inflammation. Patients with MRI inflammation were more frequently anti-CCP antibody positive than those without MRI inflammation (p=

0.049). Ten out of 29 patients (34.5%) with MRI inflammation developed an IA within at least two months of follow-up.[134]

Higher costs, longer examination times and lower availability in some centres however are some disadvantages of MRI compared to conventional radiographs.

2.5.3.9.3 Ultrasound

The use of ultrasonography for the management of patients with early IA has increased over the years. Similar to MRI, studies have shown ultrasound to be more sensitive than clinical examination for detecting synovitis. Use of the Doppler technique can further assist in detecting inflammation. Power Doppler (PD) [135] in particular is suited for assessing tissues with low velocity blood flow, such as the synovium. When compared to findings on MRI scans, PD findings have proven reliable for detecting joint inflammation.

Ultrasound is also more sensitive than conventional radiography for detecting joint erosions in patients with RA. In one study 6.5 fold more MCP erosions were documented using ultrasound compared to X-rays. [28] The higher sensitivity relates to the multi-planar capability of ultrasound (compared to the two-dimensional image with conventional radiography) and its ability to detect smaller erosions.

Ultrasound has also been shown to be of value in determining persistence of very early IA. [136] Of a cohort 50 of patients with ≤ 12 weeks of inflammatory symptoms, in those who were RF and CCP negative, the use of this imaging modality raised the probability of IA from 30% using clinical and radiographic features to 94% with the addition of ultrasound.

Ultrasound, in particular the use of PD, has also been found to be a sensitive and reliable method for longitudinal assessment of the inflammatory activity in early RA.[137] In patients on DMARDs in clinical remission, ultrasound synovitis may still be found suggesting that it may be a more accurate measure of disease activity than currently used clinical scores.[138] [139]

The advantages of ultrasound are that it is relatively inexpensive, non-invasive and allows many joints to be assessed at any one time. The main disadvantage is that it is operator-dependant.

2.5.3.9.4 Hand bone densitometry

With newer therapies for RA, erosion progression is lower, requiring more sensitive measures to assess treatment outcomes. In RA, bone loss, particularly in the hands, takes place early in the disease process. Measuring hand bone loss may therefore be useful for diagnosis and as a marker of disease activity. Dual energy x-ray absorptiometry (DEXA) measures bone density with high precision, making it

sensitive enough to detect even small changes in bone mass. Studies in RA assessing bone mineral density (BMD) have shown good correlation between BMD loss in the spine [102] and hand [140] with disease activity. In a study comparing the role of hand DEXA and conventional radiography in 58 patients with early RA (mean disease duration 8.5 months), DEXA was found to be a more sensitive tool for measuring disease related bone damage. Fifty percent of patients demonstrated significant loss of hand BMD after 24 weeks compared to only 22% showing radiographic deterioration as measured by the modified Sharp score at 48 weeks.[141]

2.5.3.10 Histology

Studies using arthroscopy have confirmed imaging findings of subclinical synovitis examining asymptomatic joints of newly diagnosed RA. Distinct macroscopic vascular patterns have been seen in early RA and psoriatic arthritis. Comparison of histopathological features of synovial tissue in early RA and non-RA synovitis has shown subtle differences in histological features, cytokine and protease expression patterns, as well as apoptosis. An analysis of synovial biopsies of 95 patients with early arthritis showed that the higher scores for the number of CD38+ plasma cells and CD 22+ B cells in RA were the best discriminating markers comparing RA to non-RA patients. The number of CD68+ macrophages in the synovial tissue of patients with RA was also increased.[142] Features in synovial tissue biopsies in patients with early RA fulfilling the 2010 ACR/EULAR RA classification criteria were found to be similar to those fulfilling the 1987 ACR classification criteria.[143] Thus far, the clinical value of the histopathological characteristics of synovial tissue in early arthritis is yet to be proven.[144] Widespread use of synovial biopsies in the clinical setting is still limited by its invasiveness.

2.5.3.11 Biomarkers of joint destruction

Molecular markers that reflect synovial, bone and cartilage turnover have been studied as potential tools for early identification of patients with RA at high risk of rapid disease progression.[74] These include urinary glucosyl-galactosyl-pyridinoline, a marker of destruction of the synovium, and C-terminal crosslinking telopeptides of type I and type II collagen (CTX-I and CTX-II), markers of bone and cartilage destruction. High baseline levels of CTX-I and CTX-II have been shown to predict an increased risk of radiographic progression. Elevated levels have also been described in patients with no radiographic evidence of joint destruction at baseline suggesting that they may be useful for detecting patients at risk of joint damage early in the course of the disease.

Raised levels of matrix metalloproteinases (MMP), enzymes involved in the degradation of articular cartilage in RA, have been found in tissue, synovial fluid and the systemic circulation of patients with RA. Studies have shown a correlation with increased MMP levels and progression of joint damage.[145]

Osteoclasts play a key role in the mechanism of joint destruction in RA. Receptor activator of nuclear factor kappa-B ligand (RANKL) and its receptor RANK are central in the stimulation of osteoclast formation and activation. The soluble receptor-like molecule osteoprotegerin (OPG) is a natural inhibitor of RANKL. Bone resorption is regulated by the balance between RANKL and OPG. The ratio between OPG: RANKL may be another marker of joint destruction with low levels predictive of more rapid progression.[146]

An analysis of cartilage and bone biomarkers in predicting 10 year radiographic progression in RA have shown a weak association between CTX-1 and radiographic damage. Neither this nor any of the other tested biomarkers however were found to be more useful than current predictors e.g. ACPA and the presence of early radiographic damage.[147] In daily clinical practice therefore, the role of these biomarkers is yet to be demonstrated.

2.5.4 Models to predict disease persistence

In general, a combination of predictive factors has been found to be superior to single variables in predicting those who will develop a persistent erosive IA. Several models have been developed using a combination of the most reliable markers to determine which patients with UA will progress to develop RA (defined by the 1987 ACR classification criteria) [80], and to predict disease severity[148], radiographic progression[149 150] and functional outcome.[151]

Several studies have been done evaluating the performance of the 2010 ACR/EULAR criteria for the classification of RA.[152] A SLR by Radner et al. has shown a pooled sensitivity of 82% (95% CI 0.79-0.84) and specificity of 61% (95% CI 0.59-0.64) for RA (defined by different reference standards).[153] Excluding other diagnoses, the sensitivity of the 2010 ACR/EULAR RA classification criteria was 21% higher than the 1987 ACR RA classification criteria but the specificity 16% lower. Similar results were found in another SLR and meta-analysis.[154] Thus whilst the 2010 ACR/EULAR criteria have enabled the classification of a greater proportion of patients with RA, it is balanced by the risk of over-classifying patients without the disease. There are also a proportion of patients with RA not fulfilling the 2010 criteria – these are often patients who are seronegative.[155] It has been suggested that clinical judgment and other tools e.g. imaging with ultrasound[156] or

MRI and other biomarker assays may be useful to better refine these criteria for use in clinical practice.[157] Further work is also required to determine the value of the criteria prospectively in clinical practice and the effect on long-term outcomes e.g. radiographic damage and disability.[152 155] Thus far one retrospective cohort study has shown the ability of the 2010 criteria for identifying patients at increased risk of mortality by identifying a higher proportion of at-risk patients soon after their presentation to a healthcare service (HR 1.37 vs. 1.24 for the 2010 ACR/EULAR vs. the 1987 ACR RA classification criteria).[158] Data from another cohort study suggested that patients identified using the 2010 classification criteria have a milder disease with patient fulfilling these criteria demonstrating lower radiographic progression (p=0.023). There was also trend towards achieving DMARD free sustained free remission more often than those fulfilling the 1987 criteria (HR(95% CI) 1.18 (0.93 to 1.50)).[159]

Work has also been done in the earlier phases of the disease looking at the development of IA in patients with seropositive arthralgia. [160] In a prospective cohort of 374 patients seropositive for anti-CCP and/ or IgM RF, a prediction rule was developed consisting of nine variables: first degree relative (FDR) with RA, alcohol non-use, symptom duration < 12 months, upper and lower extremity arthralgia, presence of intermittent symptoms, pain visual analogue scale (VAS) ≥50, EMS ≥ 1 hour, patient reported joint swelling and antibody status. Using a composite score based on these variables, patients were categorised into three groups: low (0-4 points), intermediate (5-6 points) and high risk (7-13) groups. The hazard ratio (HR; 95% CI) for the intermediate risk group was 4.52 (2.42-8.77) and for the high risk group 14.86 (8.40-28.32) for the development of IA compared to the low risk group.

2.6 Treatment

The primary goal of treating the patient with early IA is to maximize long-term health-related quality of life through symptom control, prevention of structural damage and normalization of function. [10] To achieve this, requires early effective therapy and regular monitoring, adjusting treatment to minimize the burden of disease. Patients require care from a multi-disciplinary team using a combination of pharmacological and non-pharmacological therapy.[2 161 162]

2.6.1 Non-pharmacological treatment

General lifestyle measures are important. Smoking cessation in particular should be advised. Ensuring an appropriate body weight by following a healthy diet and

maintaining physical activity are necessary for general wellbeing and can also improve symptoms.

Several other non-pharmaceutical interventions - such as dynamic exercises, occupational therapy, physiotherapy and hydrotherapy – have shown beneficial symptom relieving effects in established RA. These are also recommended in patients with early disease.

As part of the management of any chronic disease, patients should be provided with information concerning the disease and its treatment. Education programmes may be used as adjunctive measures, aimed at coping with pain and disability and the maintenance of work ability.

Patients with an IA who do not meet criteria for a specific diagnosis and do not have poor prognostic factors are more likely to do well. Although patients may feel disappointed when a specific diagnosis is lacking, they may be reassured of a better outcome.

2.6.2 Pharmacological treatment

The first principle of pharmacological therapy is early intervention with effective, appropriate treatment. The second is one of treating to target [10] to achieve tight control of disease activity. In practice, this means that therapy is increased if disease activity is not suppressed below a predefined level (ideally remission).

A suggested algorithm for the management of patients with early IA is shown in figure 2.5. The principles of management and different treatment approaches will be discussed below. Chapter 3 will provide a systematic review of the literature addressing the efficacy of the bDMARDs across the IA disease continuum.

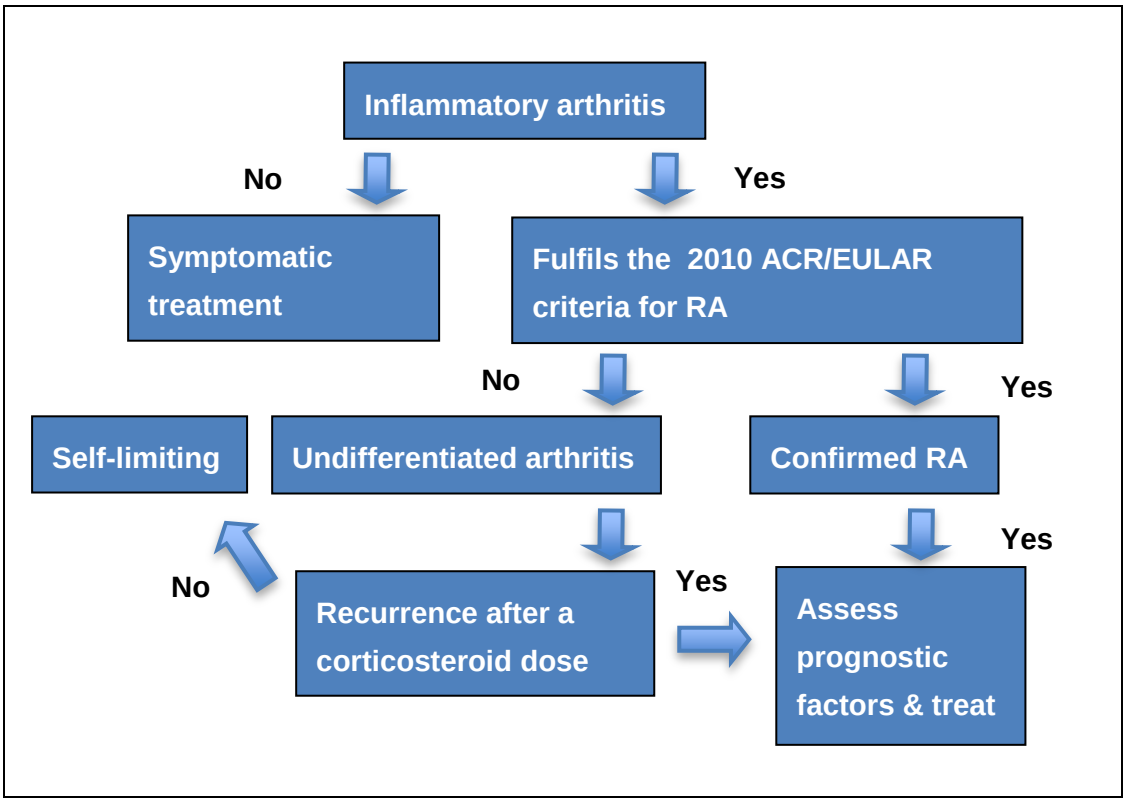


Figure 2.4 An algorithm for the management of early inflammatory arthritis

2.6.2.1 Pharmacological treatment of RA

2.6.2.1.1 Glucocorticoids

Glucocorticoids have demonstrated disease-modifying as well as anti-inflammatory properties. [163] Rapid clinical improvements have been seen with high dose oral steroid use. [164] Intravenous (IV) steroid, whilst less widely studied, has shown high remission rates in a small group of patients who were MTX-naïve but may have failed other csDMARDs.[165]

In established RA, several RCTs and SLRs [166 167] have shown that systemic low dose glucocorticoids, typically prednisone ≤ 10 to 15 mg/day, are effective in relieving short-term signs and symptoms in patients. They are therefore often used as bridging therapy at the start of DMARD therapy or when switching from one DMARD to another to improve symptom control until treatment with the new drug has become effective. Studies have also shown that glucocorticoids – either alone or in combination with other DMARD therapy – are effective in slowing radiographic progression in early and established RA. [164 168-170]. They have also been used as part of tight control treatment strategies, the concept of which will be discussed later in this chapter.

Concerns, however, are often raised about the side effects of glucocorticoids. Evidence suggests the side effect profile depends on the dose used and the disease being treated. A review of the published literature has shown that in RA, low doses of glucocorticoids may have very few side effects. [171] Those known to occur in other diseases treated with higher doses of glucocorticoids may not occur when low dose glucocorticoids are used to treat RA. These include increased cardiovascular risk, lipid abnormalities and osteoporosis.

Newer glucocorticoids and glucocorticoid analogues that will target inflammatory tissues or specific gene activations have been investigated, aiming to obtain the anti-inflammatory effect of the drug with minimal or no increased risk of adverse reactions. [172-174]

2.6.2.1.2 Conventional synthetic DMARDs

Early treatment with DMARDs is one of the key principles in the management of early IA. There is good evidence that patients with recent onset polyarthritis who receive earlier DMARD treatment have better outcomes in terms of radiographic progression, function, and ability to work than those in whom DMARD treatment is delayed by a few months .[8 9 26 34]

Conventional synthetic DMARDs have an effect on the disease process within weeks to months. Methotrexate, sulphasalazine, and leflunomide are commonly used csDMARDs which have been shown to improve clinical outcomes and delay radiographic progression. Of the csDMARDs, methotrexate is considered the anchor drug and is generally used as part of the first-line treatment strategy because of its clinical and radiographic efficacy, relatively beneficial safety profile as well as its benefit in treatment combinations with other csDMARDs and biological DMARDs (bDMARDS). [175 176] Leflunomide and sulphasalazine have similar clinical efficacy and are considered good alternatives.

Despite early treatment, substantial structural damage may still occur in some early RA patients treated with csDMARDs alone. [92 177] In a cohort of very early RA patients with symptom duration of less than 3 months, 64% developed erosive disease by 3 years.

2.6.2.1.3 Biological DMARDs

The first bDMARD for the treatment of RA, infliximab, was discovered in the 1990's.[178] Infliximab exerts its effect by blocking TNF-α, a cytokine central to the inflammatory cascade. It has modulatory effects on many aspect of cellular and humoral immunity and has an important role in persistence of early RA. Since its discovery there has been a rapid expansion of bDMARDs used in RA. Within the

tumour necrosis factor alpha inhibitor (TNFi) class of agents, these include the monoclonal TNFi, adalimumab and the soluble recombinant TNF receptor fusion protein, etanercept as well as the newer therapies, golimumab - a fully human antibody - and certolizumab-pegol - a humanised recombinant antibody conjugated with a polyethylene glycol chain. Two other cytokine inhibitors are the IL-1 receptor antagonist, anakinra and the IL-6 receptor blocking monoclonal antibody, tocilizumab. Therapies targeting alternative pathways include the anti-CD20 B-cell depleting agent, rituximab and the cytotoxic T-lymphocyte antigen-4 (CTLA-4) fusion protein, abatacept.

From systematic reviews of the literature, all of the bDMARDs, particularly when combined with methotrexate, have been shown to provide rapid control of inflammation and have proven efficacy both in terms of clinical outcomes and structural damage in RA. Results of these findings will be detailed in chapter 3. Even in cases in which clinical activity have not been optimally suppressed ('poor response'), radiographic progression appeared to be significantly retarded with bDMARD use compared to methotrexate monotherapy. [179]

Of these RCTs, the Combination of Methotrexate and Etanercept (COMET) study [180] was the first major study looking at remission as the primary endpoint in patients with early RA. Patients with symptom duration of 2 years or less were randomised to receive methotrexate or methotrexate and etanercept for a year. At week 52, remission as defined by a DAS 28<2.6 was achieved in 49.8% with methotrexate plus etanercept vs. 27.8% with methotrexate alone ($p< 0.001$) (figure 2.6). Radiographic progression at week 52 was also significantly lower in the group receiving combination therapy. No differences were seen between the two groups in terms of serious adverse events, serious infections or malignancies. No cases of tuberculosis were reported in either group.

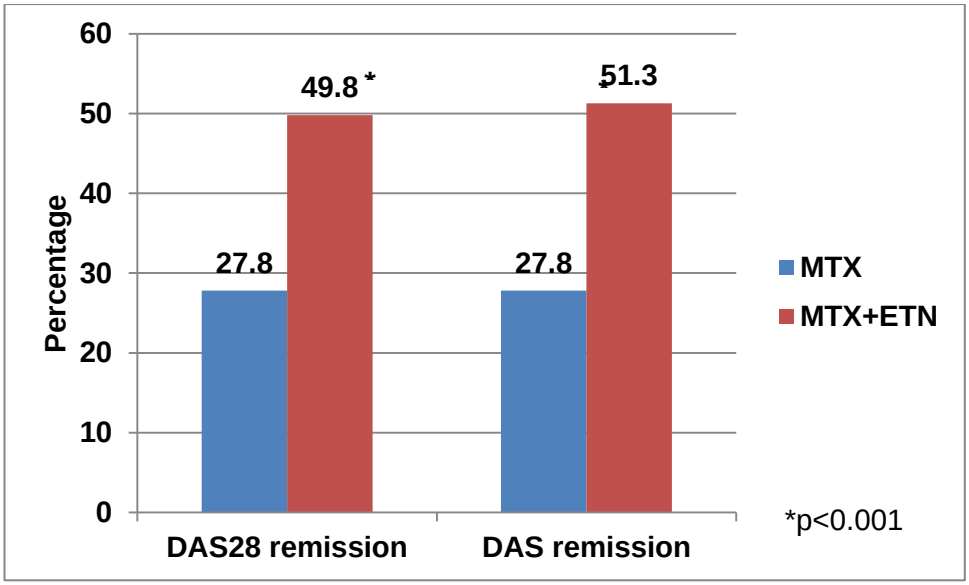


Figure 2.5 Percentage of patients achieving DAS28 remission (primary endpoint) and DAS remission at Week 52 in the groups receiving methotrexate vs. methotrexate plus etanercept in the COMET trial. [180]

2.6.2.1.4 Biological DMARD strategies

Biological DMARDs have not only been studied in patients who have failed DMARD therapies, but as treatment induction. The therapeutic approach of induction and maintenance has been used in several fields of medicine including oncology and transplant medicine.[181] There are several principles governing this treatment approach. The first is that the period of greatest immune reactivity occurs early. This is the time when the most intensive therapy is required then settling on the lowest maintenance dose required to maintain immunosuppression but minimise drug toxicity. The second is to use low doses of several drugs with toxicities that do not overlap rather than higher doses of fewer drugs. The third is to avoid immunosuppression which can have numerous side effects including the risk of infection.

The placebo controlled RCT by Quinn et al [182] was one of the first studies addressing the use of TNFi therapy in DMARD-naïve RA, introducing the concept of induction with a bDMARD and methotrexate followed by methotrexate maintenance. In this study of 20 RA patients with poor prognostic factors, treatment with infliximab and methotrexate results in less MRI detected erosions at 12 months than treatment with methotrexate alone. Function and quality of life benefits achieved with infliximab after one year was sustained at two years without further infliximab therapy. This study provides evidence for the rationale for early intensive therapy with a bDMARD and methotrexate with the potential for treatment de-escalation.

Another study that compares the use of these various therapeutic options and addresses the optimal treatment paradigms for early RA is the Behandel Strategieën (BeSt) trial. This multi-centre single blinded trial of 508 RA patients with less than 2 years of symptoms, compared four treatment strategies including a sequential monotherapy (group1), step-up combination therapy (group2), a triple step-down strategy with methotrexate, sulphasalazine, and high dose prednisone (group3), and initial combination therapy with infliximab plus methotrexate (group4).[183] Treatment was adjusted at three monthly intervals with a goal of achieving a DAS of 2.4 or less. The two groups with initial intensive treatment (groups 3 and 4) showed a more rapid clinical response and a better radiographic outcome than groups 1 and 2 at two years. Progression of joint damage remained better suppressed in groups 3 and 4 (median Sharp-van der Heijde scores of 2.0, 2.0, 1.0 and 1.0 in groups 1, 2, 3 and 4 respectively (p=0.004)). In addition, less treatment adjustments were required in groups 3 and 4 to achieve suppression of disease activity. No significant differences in toxicity were noted between the groups.

After 8 years, 68% of patients continued follow up within the study. Of these 52% were in clinical remission (DAS44 <1.6) with 29%, 22%, 45% and 66% in groups 1-4 respectively still on the initial treatment step (p<0.001). Radiographic progression was lower in the initial combination groups in first 2 years of treatment. Thereafter, between years 3-8 annual progression was comparable across the groups. By year 8, joint damage progression remained low in all groups. The proportions of patients on infliximab was not significantly different between groups (21%, 10%, 13% and 24% in groups 1-4 (p=0.06)). Drug free remission was achieved in 10%, 19%, 17% and 15% of groups 1-4 respectively (p=0.90).[184]

A further analysis from the BeSt trial comparing patients who received initial infliximab treatment (group 4) with patients receiving infliximab at a later stage (groups 1-3) showed that 56% of patients in group 4 were able to successfully stop infliximab compared to only 15% in the other groups at 2 years. This suggests that by achieving remission within the ‘therapeutic window of opportunity’, patients may require less treatment later on in the disease course. [185]

Discontinuation of infliximab after achieving low disease activity (LDA) has also been evaluated in several other studies including the RRR (remission induction by Remicade in RA) study. [186] The mean disease duration of 114 RA patients was 5.9 years, mean DAS28 5.5 and mean van der Heijde modified total Sharp score (mTSS) 63.3. Infliximab was discontinued in 102 patients after maintaining LDA for >24 weeks. At 1 year, 55% continued to have DAS28<3.2 after stopping infliximab.

Radiographic non-progression (ΔmTSS <0.5) was achieved in 67% and 44% of the RRR-achieved and RRR-failed groups, respectively.

These studies provide evidence for the rationale for early intensive treatment strategies, with the potential to de-escalate therapy when optimal disease control is achieved.

2.6.2.1.5 Biological DMARD safety

The issue of bDMARD safety has been reviewed in a SLR[187] informing the 2010 EULAR RA treatment recommendations[188] and recently updated.[189] Safety data was evaluated from observational studies and registry data which included a comparator arm (either patients on non-bDMARD therapy or the general population) rather than RCTs as their duration of follow-up are relatively short and results may be potential biased as patients with significant co-morbidities are often excluded.

Compared to patients on csDMARDs, patients on TNFi have been shown to be at higher risk of serious infections (adjusted HR 1.1-1.8)[190-192] and tuberculosis.[193 194] Some studies suggested an increased risk of herpes zoster,[195 196] although this has not been confirmed in all.[197] There has been no signal of increased risk of malignancy,[198 199] lymphoma[200 201] or non-melanoma skin cancer[201 202] in patients on TNFi therapy. There was a suggestion that the risk of melanoma may be slightly increased (adjusted HR 1.5 (1.0-2.2)).[203] The absolute risk however was relatively low, corresponding to an additional 20 cases per 100 000 person years.

Information from the majority of non-TNFi biological observational studies that have been published have not had a comparator arm. Data from these registries suggest similar safety profiles to those of the TNFi therapies.[204-206]

2.6.2.1.6 Summary of bDMARD therapy in RA

The use of bDMARDs has changed the face of RA. For many rheumatologists, bDMARD therapy has become part of routine clinical practice. They are however substantially more expensive than traditional csDMARDs. With cost remaining an important point of consideration, [207] many guidelines place them after failure of one or more csDMARD. [162 208 209]

2.6.2.2 Pharmacological treatment of UA

Recognising that there is a potential window of opportunity for the treatment of RA, studies have aimed to address treatment at the earlier phase of the disease, that of UA.

2.6.2.2.1 Glucocorticoids

An approach for patients who present with very early UA (less than 12 weeks of symptoms) may be to give a single dose of glucocorticoid to provide rapid improvement of symptoms and demonstrate the reversibility of disease.[33] Results of an open study of 100 patients with UA suggest that a single dose of intramuscular or intra-articular steroids may induce remission in these patients.[210]

Two RCTs also investigated the benefits of a limited course of intramuscular (IM) steroids in patients with early UA. The steroids in very early arthritis (STIVEA) trial[211 212] aimed to determine whether treatment of recent onset inflammatory polyarthritis with 3 weekly injections of IM glucocorticoids could suppress evolution to RA. Two hundred and sixty-five patients with 4–11 weeks of symptoms, two or more tender and swollen joints and hand involvement were enrolled and randomised to receive 3 weekly doses of methylprednisolone 80 mg IM or placebo. Patients were followed up for 12 months and assessed for the initiation of DMARD therapy. At 6 months, 76% of the placebo group and 61% of the steroid group had either started or been referred for DMARD therapy [OR (95% CI) 2.11 (1.16, 3.85), p=0.015]. At 12 months, the arthritis had resolved in 20% (22/111) of patients in the glucocorticoid arm compared with 10% (11/111) in the placebo arm.

In the SAVE study, a similar patient population, however, a single dose of intramuscular methylprednisolone 120mg was not effective in inducing remission or delaying development of RA. Of 383 patients, 17.0% (65/383) achieved persistent remission: 17.8% (33/185) of the placebo group and 16.2% (32/198) of the patients receiving methylprednisolone (OR (95% CI) 1.13 (0.66 to 1.92), p=0.6847). DMARDs were started in 162 patients: 56.7% in the placebo arm and 50.3% methylprednisolone arm (OR (95% CI) 0.78 (0.49 to 1.22), p=0.30). Significantly more patients with polyarthritis than with oligoarthritis received DMARDs (OR(95% CI) 2.84 (1.75 to 4.60), p<0.0001).

Although study outcomes differed, results suggest that the use of IM steroids in some patients with very early inflammatory polyarthritis may postpone the initiation of DMARD therapy.

2.6.2.2.2 Conventional synthetic DMARDs

Use of csDMARD therapy in patients with UA before the stage of fulfilling 1987 ACR RA classification criteria was first addressed in the PROMPT study. In this double-blind RCT, 110 patients were randomized to treatment with methotrexate or placebo for 12 months. Forty percent (22/55) of patients in the methotrexate group progressed to RA compared with 53% (29/55) in the placebo group. In the methotrexate group patients also fulfilled the 1987 ACR classification criteria for RA

at a later time point than in the placebo group (P = 0.04) and fewer patients showed radiographic progression over 18 months (P = 0.046). This study suggests that methotrexate may also delay the development of RA and retard radiographic joint damage in UA patients. Further analysis showed that these findings were mainly seen in the subgroup of patients who demonstrated the presence of ACPA.[213]

2.6.2.2.3 Biological DMARDs

Studies have also started to address the role of bDMARDs in patients with UA. A pilot RCT by Saleem et al. aimed to assess the ability of a TNFi to induce remission and prevent progression to RA in patients with poor prognosis UA. [214] Seventeen patients with UA who had relapsed after a single parenteral glucocorticoid injection were randomized to receive infliximab (n=10) or placebo (n=7) at week 0, 2, 6 and 14. Methotrexate was added if no clinical response was achieved. At week 26 only three patients were in clinical remission (2 in the infliximab and 1 in the placebo groups). By week 52 all patients in the infliximab arm and 71% (5/7) in the placebo arm developed RA (1987 ACR classification criteria). The study was stopped early due to the poor patient outcomes. More recently larger studies have been performed using bDMARDs in patients with UA. These will be discussed in Chapter 3.

2.6.2.3 Pharmacological treatment of individuals at risk

Treating patients with inflammatory arthritis in the pre-clinical stages requires early identification of subclinical disease. To date there have been no clinical trials published on the use of DMARD therapy in these patients.

2.6.2.4 Monitoring of disease activity and achieving tight control

Regular monitoring and increasing treatment aiming at specific therapeutic targets has improved outcomes and reduced the risk of organ damage in several areas of medicine (e.g. diabetes mellitus and hypertension). A similar approach has been adopted in patients with early IA.

In the Tight Control in Rheumatoid Arthritis (TICORA) study, 110 RA patients with less than 5 years disease duration were randomly assigned to receive intensive treatment or routine clinical care. [215] Patients in the intensive TICORA group were examined monthly and DMARD therapy escalated according to a predefined strategy if DAS44 >2.4. Those in the routine care group were seen three monthly without formal assessment and treatment was adjusted according to clinician judgment. The group receiving more intensive monitoring and treatment had

significantly greater EULAR and ACR responses and higher remission rates than the control group at 18 months (figure 2.7). Radiographic damage was also lower in the TICORA group. This strategy also resulted in higher treatment retention rate, a lower discontinuations due to side effects, and lower costs per patient (based on lower admission costs) than routine care. Of note, more intra-articular steroids were used in this treatment group.

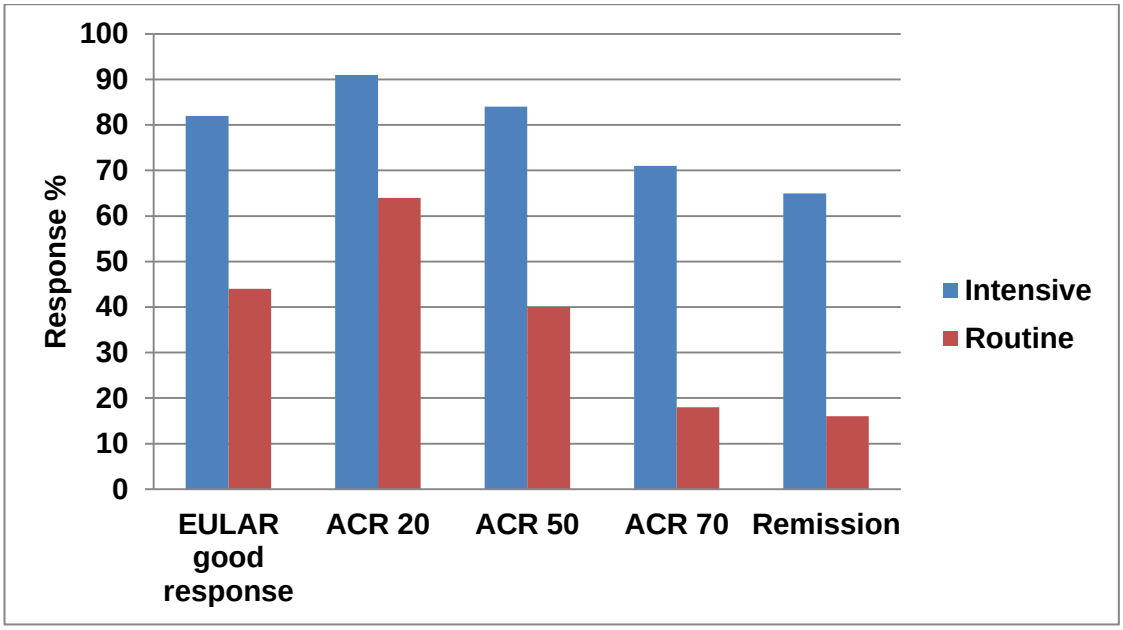


Figure 2.6 Intensive versus routine monitoring - results from the Tight Control in Rheumatoid Arthritis (TICORA) study.

Adapted from Grigor et al. [215] ACR, American College of Rheumatology; EULAR, European League Against Rheumatism

The CAMERA (computer-assisted management of early RA) trial [216] also showed intensive treatment and monitoring to be more beneficial than routine care. Two hundred and ninety nine patients with early RA were randomised to intensive treatment or routine treatment, with oral methotrexate. If necessary, therapy was changed to subcutaneous methotrexate and cyclosporine added to achieve disease control. Patients in the intensive treatment group were seen more frequently in clinic and dosages were adjusted based on predefined criteria and tailored to achieve remission using a computer assisted programme. At 2 years, results showed that more patients in the intensive-management group achieved sustained remission for at least 3 months than in the routine care group (50% vs. 37%: $p<0.03$). Median area under the curve for all clinical variables (ESR, early morning stiffness, visual analogue scale for pain, visual analogue scale for general wellbeing, number of swollen joints and number of tender joints) were significantly

better in the intensive-management group than in the routine-care group. Patients in the intensive-management group also used less NSAIDs anti-inflammatory drugs than the routine care group.

Results of the BeSt study,[183] discussed earlier in this chapter, showed good clinical outcomes in all patients irrespective of the initial treatment group and sustained clinical and functional benefit for up to 5 years, reinforcing the importance of early intervention and tight control in the treatment of RA.[217] Several other trials have also shown better outcomes where intensive care was based on regular monitoring of disease activity and treatment to target. [218-220]

Regular monitoring of disease activity and adverse events, therefore, should guide decisions on choice and changes in treatment strategies. This includes both csDMARDs and bDMARDs. Based on evidence from a SLR[221] and expert opinion on best practice, recommendations for achieving optimal therapeutic outcomes using treat-to-target approach have been developed and recently updated for the management of RA.[10 222] It is suggested that when monitoring treatment, measures of disease activity should be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (e.g. every 3–6 months) for patients in sustained low disease activity or remission. Assessments should include composite disease activity measures which include joint counts. Structural damage should be assessed with X-rays approximately every 12 months during the first few years. Functional assessment (e.g. using the HAQ-DI) may be used to complement the disease activity and structural damage monitoring. Drug therapy should be adjusted at least every 3 months until the desired treatment target is reached. The patient should be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist. The desired treatment target should be maintained throughout the remaining course of the disease (figure 2.8).

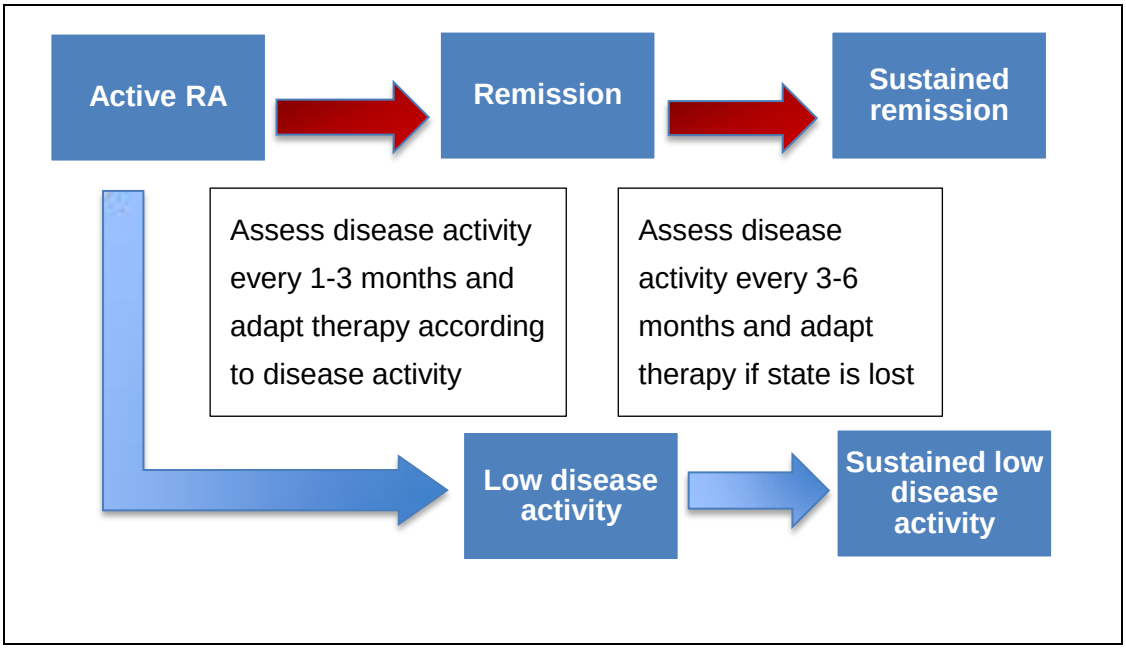


Figure 2.7 Algorithm for treating rheumatoid arthritis to target based on European League Against Rheumatism treat-to-target recommendations.

Adapted from Smolen et al.[10] The main target (remission and sustained remission), indicated by the red arrows, and the alternative target (low disease activity in patients with long-term disease) indicated by the blue arrows are shown as separate threads. Remission, defined as the absence of signs and symptoms of significant inflammatory disease activity, is the primary target for treatment of RA. In certain instances (e.g. in established long-standing disease), low disease activity may be an acceptable alternative therapeutic goal. The approach to attain the targets and sustain them are similar. (RA, rheumatoid arthritis)

2.7 Summary

A review of the literature on early IA, of which RA is the most common, confirms the importance of early diagnosis and treatment. With increasing treatment options available and improved strategies for treating RA with regular monitoring and tight disease control, remission and prevention of structural damage are achievable goals.

In terms of treatment, non-pharmacological and lifestyle measures form part of the treatment strategy. Of these, reduction or cessation of smoking is a known factor that could and prevent the development of early RA and decrease the risk of cardiovascular complications of the disease and should therefore be strongly encouraged.

Early institution of effective pharmacological therapy forms the cornerstone of treatment for patients with early IA. Disease-modifying therapy should be commenced in all patients with early IA in whom the disease is likely to develop into a persistent and/or erosive arthritis classifiable as RA. In terms of the risk –benefit

ratio and the cost effectiveness of these therapies, initial treatment with csDMARD therapy are advocated with glucocorticoids as adjunctive therapy. In most cases methotrexate is considered as part of first-line treatment. Other DMARDs e.g. sulphasalazine and leflunomide are suitable alternatives. The use of bDMARDs in clinical practice, particularly in RA patients failing csDMARDs, is supported by evidence from many clinical studies confirming their efficacy. [187 223] In patients with significant disease activity and/ or risk factors for adverse outcome e.g. (high titre) rheumatoid factor or ACPA, earlier use of a more intensive strategy including the use of bDMARDs may be necessary. Whilst the concept of bDMARD induction and maintenance with csDMARDs is an attractive treatment option, their role in early DMARD-naïve RA and UA is still unconfirmed.

With the need for early treatment, increasing emphasis is also being placed on importance of early diagnosis. In the early stages of the disease patients may present with UA. A combination of clinical, imaging and laboratory measures allows the clinician to differentiate different causes of IA, identify those who will progress to RA and determine their severity. Conventional radiography is the mainstay imaging modality although the use of ultrasound and MRI are coming to the fore. At present, non-HLA genetic markers, histology and biochemical markers remain more research based tools rather than investigations for day to day patient care. The development of the 2010 ACR/EULAR classification criteria have helped to aid earlier identification of patients with RA. At an even earlier phase patients may present with arthralgia or non-specific MSK symptoms. The role of the different biomarkers in patients at risk presenting without clinical synovitis are yet to be determined.

The following chapters will review the use of bDMARDs across the IA disease continuum, address the use of bDMARDs in early DMARD-naïve RA and UA and explore the use of ACPA together with other biomarkers in order to identify patients with early IA in the ‘pre-clinical’ phase.

2.8 Thesis Aims

This body of work initially aims to examine the literature on the efficacy of bDMARDs across the IA disease continuum. Second, the thesis aims to investigate the use of treatment strategies with bDMARDs in DMARD-naïve early RA and IA in RCTs. Last, through a longitudinal study, it will assess the use of anti-CCP together with other biomarkers available in clinical practice to enable the identification of patients with IA patients with MSK symptoms but without clinical synovitis.

Chapter 3 Systematic literature review of the efficacy of biological DMARDs across the inflammatory arthritis disease continuum

This chapter presents the results of a systematic literature review of RCTs addressing the efficacy of bDMARDs with inflammatory arthritis across the disease spectrum from early undifferentiated arthritis to rheumatoid arthritis.

3.1 Introduction

The use of bDMARDs has changed the outlook for patients with IA. Review of the literature in Chapter 2 showed that achieving remission, normal function and prevention of joint damage is now possible for patients with these therapies.

In 2010, EULAR recommendations were initially developed to guide the management of RA with cs- and bDMARDs to address the increasing number of therapeutic options available.[188] SLRs was performed to inform these recommendations. These included one on bDMARD efficacy and safety,[187] and another on treatment strategies in RA, some of which incorporated bDMARD therapy. [223] Results from these literature reviews showed good efficacy and safety profiles for bDMARDs in both in early and established disease and highlighted the benefit of treat-to-target type strategies. Data were available mainly for patients who had previously had at least one DMARD. There were fewer studies addressing their efficacy in DMARD-naïve RA.[182 183]

Since then, several additional bDMARD studies have been published. There have also been an increasing number of studies evaluating, not only the efficacy of bDMARDs vs. csDMARDs, but also addressing different treatment approaches using bDMARDs (strategy-type studies). Data are also emerging on biosimilar DMARDs (bsDMARDs) [224] and tofacitinib, a new tsDMARD inhibiting Janus kinase. In addition, trials have also addressed the use of bDMARDs earlier in the inflammatory arthritis disease continuum – in patients with UA.

3.2 Aims

This SLR aimed to review the evidence for the efficacy of bDMARDs in patients with RA to inform the updated EULAR Task Force treatment recommendations.[209] The search also aimed to investigate the use of these therapies in patients presenting earlier with UA.

3.3 Methods

3.3.1 Literature search strategy

The requirements for the literature search were discussed and performed with a librarian with expertise in the field (JL with LN). The titles and abstracts of articles retrieved from the search were then reviewed independently by two of the authors (JLN and SR). A search of ACR abstracts and EULAR abstracts were also performed (JLN and MLG). Potential articles were then obtained for detailed review and decision regarding inclusion. Discrepancies were resolved by discussion. Data from relevant articles were then extracted and checked by two of the authors (JLN and KT).

The search was performed for trials evaluating one of nine bDMARDs: infliximab, etanercept, adalimumab, certolizumab pegol, golimumab, anakinra, abatacept, rituximab and tocilizumab. Information was also sought on bsDMARDs in phase 3 development and tsDMARDs in studies comparing these to bDMARDs. The previous SLR included studies to 2009.[187] This updated literature review was therefore done for the period from January 2009 to February 2013. The databases used were Medline, Embase and Cochrane. The search terms used in Medline are provided in table 3.1. Conference abstracts from ACR 2011–2012 and EULAR 2011-2013 were also reviewed. Where full papers of these abstracts were found, the latter were used for data extraction.

Table 3.1 Medline search terms and limits

1. arthritis, rheumatoid/ or caplan's syndrome/ or felty's syndrome/ or rheumatoid nodule/	16. mabthera.mp.
2. rheumatoid arthritis.mp.	17. anakinra.mp.
3. (early adj2 arthritis).mp.	18. kineret.mp.
4. inflammatory arthritis.mp	19. tocilizumab.mp.
5. Biological Therapy/	20. actemra.mp.
6. biologic$.mp.	21. golimumab.mp.
7. infliximab.mp.	22. certolizumab.mp.
8. remicade.mp.	23. cimzia.mp.
9. etanercept.mp.	24. biosimilar.mp
10. enbrel.mp	25. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
11. adalimumab.mp.	26. 1 or 2 or 3 or 4
12. humira.mp.	27. 26 and 25
13. abatacept.mp.	28. limit 27 to English language
14. orencia.mp.	29. limit 28 to yr="2009-2013"
15. rituximab.mp.	

3.3.2 Outcome measures and data extraction

The criteria for study selection were as follows:

1.RCTs. As in the previous SLRs,[187 223] these were double-blind for RCTs evaluating a bDMARD vs. a csDMARD; for strategy-type trials, open label studies were also included.

2.patients with RA defined according to the 1987 ACR[11] or the 2010 ACR/EULAR RA classification criteria[12] or patients with UA, at risk of developing RA

3.trials evaluating one of the nine bDMARDs or a bsDMARD in phase 3 development or a tsDMARD of compared with a bDMARD

4.trials of 6 months' duration or greater

5.trials with at least 50 patients

6.publications in English

Published SLRs and meta-analyses were also reviewed and considered for inclusion where relevant.

In order to reflect current clinical practice and trial design, studies were grouped according to the following categories: (1) no previous DMARD therapy (DMARD-naive); (2) no previous methotrexate therapy (MTX-naive); (3) inadequate response to methotrexate (MTX-IR); (4) inadequate response to any csDMARD, not necessarily methotrexate (mixed DMARD-IR) and (5) inadequate response to a TNFi (TNFi-IR).

For each trial, information on the demographic features, disease duration, baseline disease activity scores and function (measured by the HAQ-DI),[225] treatment allocation and follow-up duration were recorded. The Cochrane risk of bias assessment tool for RevMan 5.1 was used to assess the quality of the trials.[226]

Data were extracted for clinical, patient reported and radiographic outcomes. For clinical signs and symptoms, measures included the ACR response criteria (20/50/70), changes in the DAS44 and DAS28 and EULAR-response criteria. Patient reported outcomes included the HAQ-DI for measure of function, the Physical Component Score and Mental Component Score of the Short Form-36[227] for quality of life and the FACIT [228 229] and fatigue visual analogue scale (FAS) scores for fatigue. For evaluation of structural damage, change in radiographic scores and the proportion of patients achieving radiographic non-progression (defined within individual studies) were collected.

Careful consideration was taken of the inherent biases when comparing studies of different patient populations, using different compounds, each powered for different endpoints and using different statistical analysis plans. The heterogeneous nature of the studies evaluating different treatment strategies introduced additional challenges when analysing and the interpreting the results. Where possible, meta-analyses of studies comparing combination bDMARD and csDMARD to csDMARD-monotherapy or combination therapy were performed. Due to the differences in the strategy-type studies, data for these are presented in tables.

The Oxford Centre for Evidence-based Medicine levels of evidence (http://www.cebm.net/index.aspx?o=1025) was used to assign levels of evidence using these data.

3.4 Results

The search yielded 10,265 articles for title and abstract screening, of which 123 were selected for detailed review. With the additional conference abstracts and full-papers obtained from a hand search, 50 full-papers and 57 abstracts fulfilled the inclusion criteria (figure 3.1).

The data are summarised addressing three main areas of bDMARD use: (1) bDMARD efficacy (in combination therapy with csDMARDs or as monotherapy, head-to-head bDMARD studies and bDMARD switching); (2) treatment strategies using bDMARDs and addressing the possibility of bDMARD stopping or dose reduction; and (3) studies including bDMARDs and new therapies (bsDMARDs and tsDMARDs).

Preliminary analyses and abstracts of the IDEA[17] and EMPIRE[18] studies were available at the time the SLR was performed and have been included. Both studies investigated the use of bDMARDs as part of an induction strategy and with the potential to de-escalate or stop therapy. In the IDEA study this was in patients with early DMARD-naïve RA and the EMPIRE study included patients with UA. Both have now been published as full manuscripts and will be discussed in detail in Chapters 4 and 5.

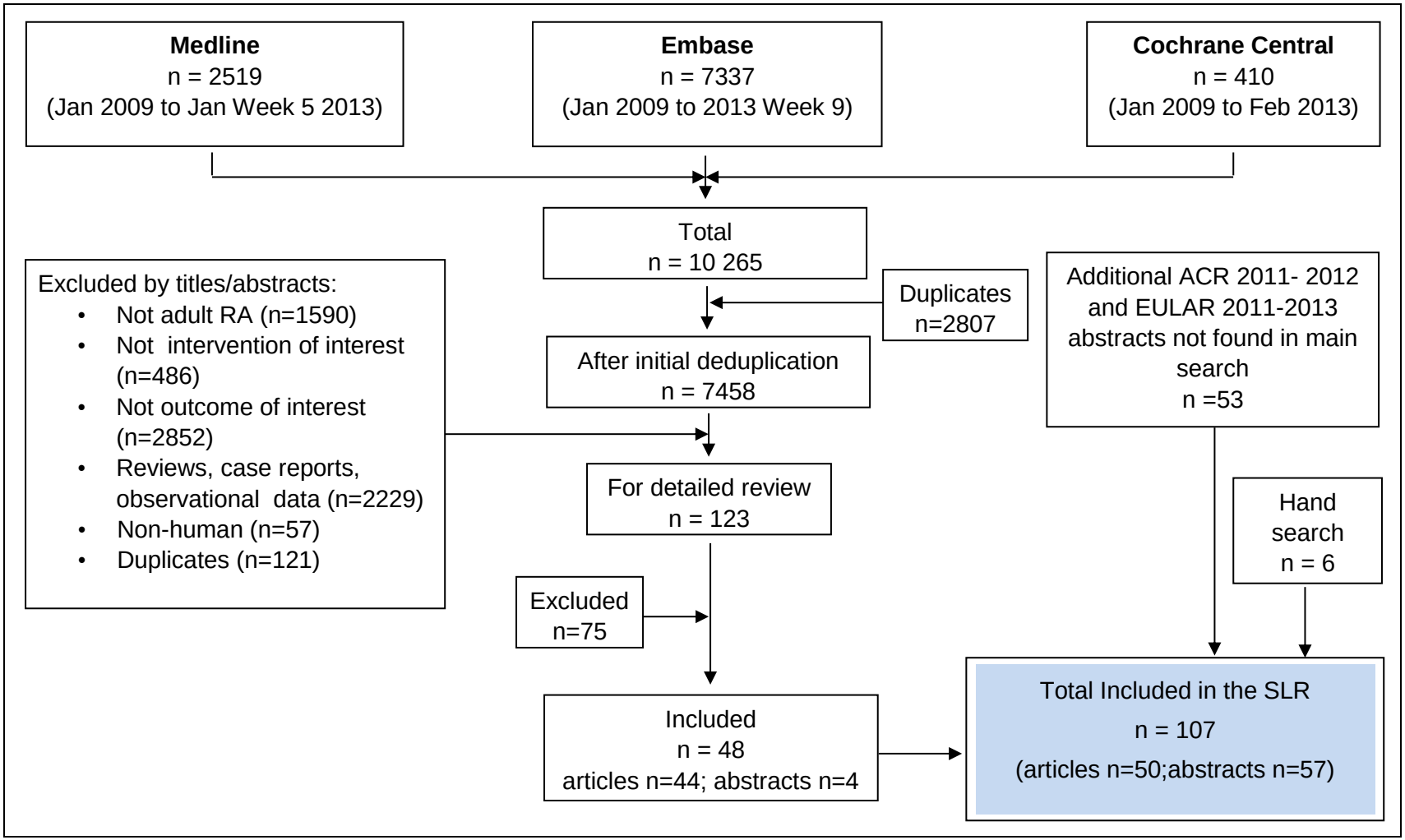


Figure 3.1 Systematic literature review flow chart

3.4.1 Risk of bias assessments

Risk of bias for the clinical trials was assessed using the Cochrane risk of bias assessment tool for RevMan 5.1.[226] This addresses seven aspects of clinical studies, namely (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of the outcome assessment, (5) incomplete outcome data, (6) other bias and (7) selective reporting, This information can be found in tables 3.2 to 3.13.

Overall the risk of bias was found to be low across the studies that were selected. There were some in which the information in the reported trials were not sufficient to assess all domains of the Cochrane risk of bias assessment tool.[230-236] Some studies were open label, leading to a high risk of bias in these domains.[237-240] A few studies reported difficulty with recruitment which may have affected the power of the studies.[240-242] In some of these the main analyses were also completer- only analyses which may have contributed to a high risk of bias in terms of incomplete outcome data.[241 242] It was however noted in these studies that similar results obtained when other sensitivity analyses were performed. The findings from the risk of bias assessments of all of the studies were taken into account when interpreting and drawing conclusion from the clinical trial data.

Table 3.2 Cochrane risk of bias assessment: Biological DMARDs in RA patients who are DMARD naïve

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Detert 2013 (HIT HARD)[230]	ADA	U	U	U	U	L	L	L

ADA, adalimumab, ROB, risk of bias

a = abstract only, H= high risk; L = low risk; U = unclear risk

Table 3.3 Cochrane risk of bias assessment 5.1: Biological DMARDs in RA patients who are MTX naïve

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Westhovens 2009[231]	ABT	U	U	L	L	L	L	L
Kavanaugh 2013 (OPTIMA)[232]	ADA	L	L	L	U	L	L	L
Emery 2009 (GO-BEFORE)[233]	GLM	L	L	L	U	L	L	L
Emery 2011 (GO-BEFORE and GO-FORWARD)[243]	GLM	o	o	o	L	o	o	o
Tak 2011 (IMAGE)[244]	RTX	L	L	L	L	L	L	L
Burmester EULAR 2013 (FUNCTION)[245]	TCZ	a	a	a	a	a	a	a

ADA, adalimumab; GLM, golimumab; ROB, risk of bias; RTX, rituximab; TCZ, tocilizumab

a = abstract only, o= refer to original manuscript; H= high risk; L = low risk; U = unclear risk

Table 3.4 Cochrane risk of bias assessment 5.1: Biological DMARDs in RA patients who are MTX inadequate responders (MTX IR)

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Bao 2011[234]	ANA	U	U	L	U	U	L	L
Yamamoto ACR 2011[246]	CZP	a	a	a	a	a	a	a
Choy 2012[247]	CZP	L	L	L	L	L	L	L
Kang EULAR 2012[248]	CZP	a	a	a	a	a	a	a
Keystone 2010 (GO-FORWARD)[249]	GLM	o	o	o	L	o	o	o
Emery 2011 (GO-BEFORE and GO-FORWARD)[243]	GLM	o	o	o	L	o	o	o
Tanaka 2012 (GO-FORTH)[250]	GLM	U	U	L	U	L	L	L
Tanaka EULAR 2012 (GO-FORTH)[235]	GLM	a	a	a	a	a	a	a
Li EULAR 2013[251]	GLM	a	a	a	a	a	a	a
Kremer 2010[252]	IV GLM	L	L	L	L	U	L	L
Weinblatt EULAR 2013[253]	IV GLM	a	a	a	a	a	a	a

Emery 2010 (SERENE)[254]	RTX	U	U	L	U	L	L	L
Kremer 2011 (LITHE)[255]	TCZ	U	U	L	L	L	L	L

ANA anakinra; CZP,certolizumab pegol; GLM, golimumab; ROB, risk of bias; RTX, rituximab; TCZ, tocilizumab; IV, intravenous

a = abstract only, o= refer to original manuscript, H= high risk; L = low risk; U = unclear risk

Table 3.5 Cochrane risk of bias assessment 5.1: Biological DMARDs in RA patients who are mixed DMARD IR

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Smolen EULAR 2011 (CERTAIN)[256]	CZP	a	a	a	a	a	a	a
Smolen EULAR 2012 (CERTAIN)[257]	CZP	a	a	a	a	a	a	a
Yamomoto ACR 2011[258]	CZP	a	a	a	a	a	a	a
Takeuchi EULAR 2011 (GO-MONO)[259]	GLM	a	a	a	a	a	a	a
Takeuchi ACR 2011 (GO-MONO)[260]	GLM	a	a	a	a	a	a	a
Takeuchi EULAR 2012 (GO-MONO)[261]	GLM	a	a	a	a	a	a	a
Jones 2010 (AMBITION)[262]	TCZ	U	U	L	L	L	L	L
Yazici 2013 (ROSE)[263]	TCZ	U	U	L	U	L	L	L

CZP,certolizumab pegol; GLM, golimumab; ROB, risk of bias; TCZ, tocilizumab

a = abstract only, H= high risk; L = low risk; U = unclear risk

Table 3.6 Cochrane risk of bias assessment 5.1: Biological DMARDs in RA patients who are TNF IR

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Smolen 2009 (GO-AFTER)[264]	GLM	L	L	L	U	L	L	L
Keystone 2009 (REFLEX)[265]	RTX	o	o	o	L	L	L	L

GLM, golimumab; ROB, risk of bias; RTX, rituximab

a = abstract only; o= refer to original manuscript; H= high risk; L = low risk; U = unclear risk

Table 3.7 Cochrane risk of bias assessment 5.1: Biologic monotherapy vs. biological DMARD + MTX in RA patients who are MTX IR

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Kameda 2010 (JESMR)[266]	ETN	U	U	H *	U	L	L	L
Kameda 2011 (JESMR)[237]	ETN	o	o	H *	L	o	L	L
Dougados ACR 2011 (ACT-RAY)[267]	TCZ	a	a	a	a	a	a	a
Dougados EULAR 2012 (ACT-RAY)[268]	TCZ	a	a	a	a	a	a	a
Dougados ACR 2012 (ACT-RAY)[269]	TCZ	a	a	a	a	a	a	a
Dougados 2013 (ACT-RAY)[270]	TCZ	U	L	L	L	L	L	L
Takeuchi EULAR 2013 (SURPRISE)[271]	TCZ	a	a	a	a	a	a	a

ETN, etanercept ; NR, not recorded ; ROB, risk of bias; TCZ, tocilizumab

a = abstract only; o= refer to original manuscript; H= high risk; L = low risk; U = unclear risk; * = not blinded

Table 3.8 Cochrane risk of bias assessment 5.1: Head to head biological DMARDs in RA patients who are MTX IR

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Weinblatt 2013 (AMPLE)[239]	ABT vs. ADA	U	U	H *	L	L	L	L
Fleischmann EULAR 2013 (AMPLE work)[272]	ABT vs. ADA	a	a	a	a	a	a	a
Fleischmann EULAR 2013 (AMPLE)[273]	ABT vs. ADA	a	a	a	a	a	a	a
Schiff EULAR 2013 (AMPLE)[274]	ABT vs. ADA	a	a	a	a	a	a	a
Gabay 2013 (ADACTA)[275]	TCZ vs. ADA	L	L	L	L	L	L	L
Kavanaugh ACR 2012 (ADACTA)[276]	TCZ vs. ADA	a	a	a	a	a	a	a

ADA, adalimumab; ABT, abatacept ; eow, every other week; ROB, risk of bias; TCZ, tocilizumab

a = abstract only, H= high risk; L = low risk; U = unclear risk, * = not blinded

Table 3.9 Cochrane risk of bias assessment 5.1: Biological DMARDs strategies RCTs without treat-to-target

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Emery 2010 (ADJUST)[236]	ABT	U	U	U	U	U	L	L
Moreland 2012 (TEAR)[277]	ETN	L	L	L	L	H**	U***	L
van der Kooij 2009 (BeSt)[278]	IFX	o	o	o	o	L	L	L
van Vollenhoven 2009 (SWEFOT)[240]	IFX	L	L	H*	H*	H**	L	L
van Vollenhoven 2012 (SWEFOT)[279]	IFX	L	L	H*	H*	H**	L	L
Kavanaugh 2013 (OPTIMA)[232]	ADA	L	L	L	U	L	L	L
Fleischmann ACR 2012 (OPTIMA)[1]	ADA	a	a	a	a	a	a	a
Kavanaugh ACR 2011 (OPTIMA)[280]	ADA	a	a	a	a	a	a	a

Emery 2010 (COMET)[281]	ETN	L	L	L	L	L	L	L
O'Dell ACR 2012 (RACAT)[282]	ETN	a	a	a	a	a	a	a
O'Dell EULAR 2013 (RACAT)[283]	ETN	a	a	a	a	a	a	a
O'Dell 2013 (RACAT)[242]	ETN	U	U	L	L	H**	U***	L
Li EULAR 2013[251] §	GLM	a	a	a	a	a	a	a

ABT, abatacept : ADA, adalimumab ; ETN, etanercept ; GLM, golimumab ; IFX, infliximab; ROB, risk of bias

a = abstract only, o= refer to original manuscript ; H= high risk; L = low risk; U = not blinded, * = open label study,** = difficulty with recruitment, trial ended early – possible effect on power of the study, *** main analysis = completer- only analysis, although noted that similar results obtained with other statistical analyses, § MTX arm: cross-over from MTX to MTX + GLM

Table 3.10 Cochrane risk of bias assessment 5.1: Biological DMARDs strategies RCTs with treat-to-target

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Heimans EULAR 2012 (IMPROVED)[284]	ADA	a	a	a	a	a	a	a
Heimans 2013 (IMPROVED)[285]	ADA	L	L	H*	U	L	L	L
Horslev-Petersen ACR 2011 (OPERA)[286]	ADA	a	a	a	a	a	a	a
Horslev-Petersen 2013 (OPERA)[287]	ADA	L	L	L	U	L	L	L
Van Eijk 2012 (STREAM)[288]	ADA	U	U	U	L	L	L	L
Villeneuve ACR 2011 (EMPIRE)[289]	ETN	a	a	a	a	a	a	a
van der Kooij 2009 (BeSt)[290]	IFX	o	o	o	L	o	L	L
van der Kooij 2009 (BeSt)[291]	IFX	o	o	o	o	o	L	L
van der Kooij 2009 (BeSt)[278]	IFX	o	o	o	o	L	L	L

Klarenbeek 2011 (BeSt)[217]	IFX	o	o	L	o	L	L	L
Rantalaiho EULAR 2012 (NEO-RACo)[292]	IFX	a	a	a	a	a	a	a
Leirisalo-Repo 2013 (NEO-RACo)[293]	IFX	L	L	L	U	L	L	L
Nam ACR 2011 (IDEA)[294]	IFX	a	a	a	a	a	a	a
Nam EULAR 2012 (IDEA)[295]	IFX	a	a	a	a	a	a	a
Nam 2013 (IDEA)[296]	IFX	L	L	L	L	L	L	L

ADA, adalimumab; ETN, etanercept; IFX, infliximab; ROB, risk of bias

a = abstract only, o= refer to original manuscript ; H= high risk; L = low risk; U = unclear risk, * = not blinded

Table 3.11 Cochrane risk of bias assessment 5.1: RCTs addressing Biological DMARD stopping or dose reduction

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Detert ACR 2011 (HIT HARD)[297]3	ADA	a	a	a	a	a	a	a
Detert 2013 (HIT HARD)[230]	ADA	U	U	U	U	o	o	o
Horslev-Petersen EULAR 2013[298]	ADA	a	a	a	a	a	a	a
van der Kooij 2009 (BeSt)[291]	IFX	o	o	o	o	o	o	o
Dirven 2011 (BeSt)[299]	IFX	a	a	a	a	a	a	a
Klarenbeek 2011 (BeSt)[300]	IFX	o	o	o	o	o	0	0
van den Broek 2011 (BeSt)[301]	IFX	o	o	H*	L	L	L	L
Nam 2013 (IDEA)[296]	IFX	L	L	L	L	L	L	L
Kavanaugh EULAR 2012 (OPTIMA)[302]	ADA	a	a	a	a	a	a	a
Smolen EULAR 2012	ADA	a	a	a	a	a	a	a

(OPTIMA)[303]								
Emery EULAR 2013 (PRIZE)[304]	ETN	a	a	a	a	a	a	a
Smolen ACR 2011 (PRESERVE)[305]	ETN	a	a	a	a	a	a	a
Smolen EULAR 2012 (PRESERVE)[306]	ETN	a	a	a	a	a	a	a
Smolen 2013 (PRESERVE)[307]	ETN	L	L	L	L	L	L	L
Huizinga EULAR 2013 (ACT-RAY)[308]	TCZ	a	a	a	a	a	a	a
Fautrel ACR 2012 (STRASS)[309]	ADA & ETN	a	a	a	a	a	a	a
Fautrel EULAR 2013 (STRASS) (1)[310]	ADA & ETN	a	a	a	a	a	a	a
Fautrel EULAR 2013 (STRASS) (2)[311]	ADA and ETN	a	a	a	a	a	a	a
Smolen ACR 2011 (CERTAIN)[312]	CZP	a	a	a	a	a	a	a
Smolen EULAR 2012 (CERTAIN)[257]	CZP	a	a	a	a	a	a	a
van Vollenhoven	ETN	a	a	a	a	a	a	a

ACR 2012 (DOSERA)[313]								
van Vollenhoven EULAR 2013[314]	ETN	a	a	a	a	a	a	a

ADA, adalimumab, CZP, certolizumab pegol, ETN, etanercept, IFX, infliximab; ROB, risk of bias; TCZ, tocilizumab

a = abstract only, o= refer to original manuscript ; H= high risk; L = low risk; U = unclear risk, * = not blinded

Table 3.12 Cochrane risk of bias assessment 5.1: RCT that included both Biological and targeted synthetic DMARDs

Study	Targeted synthetic and Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
van Vollenhoven EULAR 2012[315]	Tofa and ADA	a	a	a	a	a	a	a
van Vollenhoven ACR 2011[316]88	Tofa and ADA	a	a	a	a	a	a	a
vanVollenhoven 2012 (ORAL-STANDARD)[317]	Tofa and ADA	L	L	L	U	L	L	L

ADA, adalimumab; ROB, risk of bias; Tofa, tofacitinib

a = abstract only, H= high risk; L = low risk; U = unclear risk

Table 3.13 Cochrane risk of bias assessment 5.1: RCT that included both Biological and targeted synthetic DMARDs

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Yoo EULAR 2012 (CT-P13)[318]	CT-P13 vs. IFX	a	a	a	a	a	a	a
Yoo 2013 (PLANETRA)[319]	CT-P13 vs. IFX	U	U	U	U	L	L	L
Yoo EULAR 2013 (PLANETRA)[320]	CT-P13 vs. IFX	a	a	a	a	a	a	a

IFX, infliximab; ROB, risk of bias;

a = abstract only, H= high risk; L = low risk; U = unclear risk

3.4.2 Biological DMARD efficacy

The efficacy outcomes in this group will focus mainly on those relating to signs and symptoms with the ACR70 responses shown by way of example in the forest plots. The ACR responses remain one of the most frequently reported measure of efficacy. Of these, the ACR70 was chosen as it was felt to be the most clinically meaningful response, most closely representing low disease activity [321].

3.4.2.1 Biological DMARD and methotrexate combination vs. conventional synthetic DMARD

3.4.2.1.1 DMARD-naïve RA

In the SLR performed in 2010 there were no studies fulfilling the inclusion criteria comparing a bDMARD and methotrexate to methotrexate or another csDMARD monotherapy in patients with newly diagnosed IA who were DMARD naive.[187] One study showed benefit of methotrexate and infliximab vs. methotrexate due to the sample size (n=20) was not included in the analysis.[182] In this updated SLR one RCT was identified. In the HIT HARD study,[230] patients with early active DMARD-naïve RA were randomised to receive adalimumab 40mg subcutaneously every 2 weeks and methotrexate 15mg subcutaneously weekly or placebo and methotrexate 15mg subcutaneously for 24 weeks. Thereafter, the adalimumab and placebo were stopped and patients continued with methotrexate monotherapy to week 48. The results from the first 24 weeks confirm the efficacy of bDMARD and methotrexate combination therapy compared to methotrexate monotherapy in patients DMARD-naïve RA. Whilst the ACR 20 were not significantly different between the two groups, the ACR50 and ACR 70 responses were also higher in the methotrexate and adalimumab group (ACR 20/50/70: 79% vs. 67.6% (p=0.10), 63.8% vs. 49.7% (p=0.049) and 48.0% vs. 26.8% (p=0.006) in the methotrexate and adalimumab vs. methotrexate and placebo groups respectively). Patients who received methotrexate and adalimumab also achieved lower DAS28 scores than those with moderate dose methotrexate monotherapy (15mg weekly) at 6 months (mean (SD) 3.0 (1.2) vs 3.6 (1.4) in the methotrexate and adalimumab vs. methotrexate and placebo groups respectively; adjusted difference (95% CI) 0.53 (0.13 to 0.93), p = 0.009). DAS28 remission and improvement in function were also significantly greater in the group receiving combination therapy (DAS28 remission

47.9% vs 29.5%, p=0.021 and HAQ-DI 0.49±0.6 vs 0.72±0.6, p=0.0014 in the methotrexate and adalimumab vs. methotrexate and placebo groups).

3.4.2.1.2 MTX-naïve RA

RCTs of seven bDMARDs (abatacept,[231] adalimumab,[232 322 323] etanercept,[180] golimumab,[233] infliximab[324] , rituximab[244] and tocilizumab[245]) were included in the MTX-naïve RA group. These confirmed superior efficacy of starting methotrexate and bDMARD vs. starting methotrexate monotherapy (pooled RR (95% CI) 1.68 (1.54, 1.84) for ACR 70 responses) (figure 3.2) (level of evidence 1A).

DAS28 remission rates were also higher with methotrexate and bDMARD combination therapy in this group with a pooled RR for DAS28 remission at 12 months (95% CI) of 1.77 (1.56 to 2.00). Radiographic data showed less progression for abatacept,[231] adalimumab,[232] etanercept,[180] golimumab,[243] infliximab,[324] rituximab [244] and tocilizumab [245] in combination with methotrexate than for methotrexate monotherapy and radiographic non-progression was higher for abatacept,[231] adalimumab,[323] etanercept [180] and golimumab. [243] Improvements in HAQ-DI at 12 months were also greater for abatacept,[231] adalimumab,[322 323] etanercept,[325] infliximab,[324] rituximab [244] and tocilizumab [245] in combination with methotrexate.

3.4.2.1.3 MTX-IR and Mixed DMARD-IR RA

From the SLR performed in 2010, there were data for all nine bDMARDs in patients with MTX-IR.[234] Since then, additional studies for this group and the mixed DMARD-IR group have been published foranakinra,[234] certolizumab pegol,[247 248] and golimumab [235 251-253]. All confirm efficacy of a bDMARD and methotrexate vs. placebo and methotrexate in MTX-IR (pooled RR (95% CI) 4.07 (3.21, 5.17)) (figure 3.3) and bDMARD and a csDMARD vs. csDMARD in mixed DMARD –IR (pooled RR (95% CI) 4.74 (2.63, 8.56)) (figure 3.4) (level of evidence 1A).

3.4.2.1.4 TNFi-IR RA

In a SLR and meta-analysis of four RCTs in TNFi-IR, [326-330] which were included in a previous SLR,[187] the pooled RR for ACR 70 (95% CI) was 5.40 (2.93, 9.98) (figure 3.5) (level of evidence 1A). Whilst there were no new RCTs fulfilling inclusion criteria in this group, approximately 40% of patients in the 12-week REALISTIC RCT in which were TNFi-IR and sub-analysed accordingly, confirming clinical efficacy of certolizumab pegol.[331]

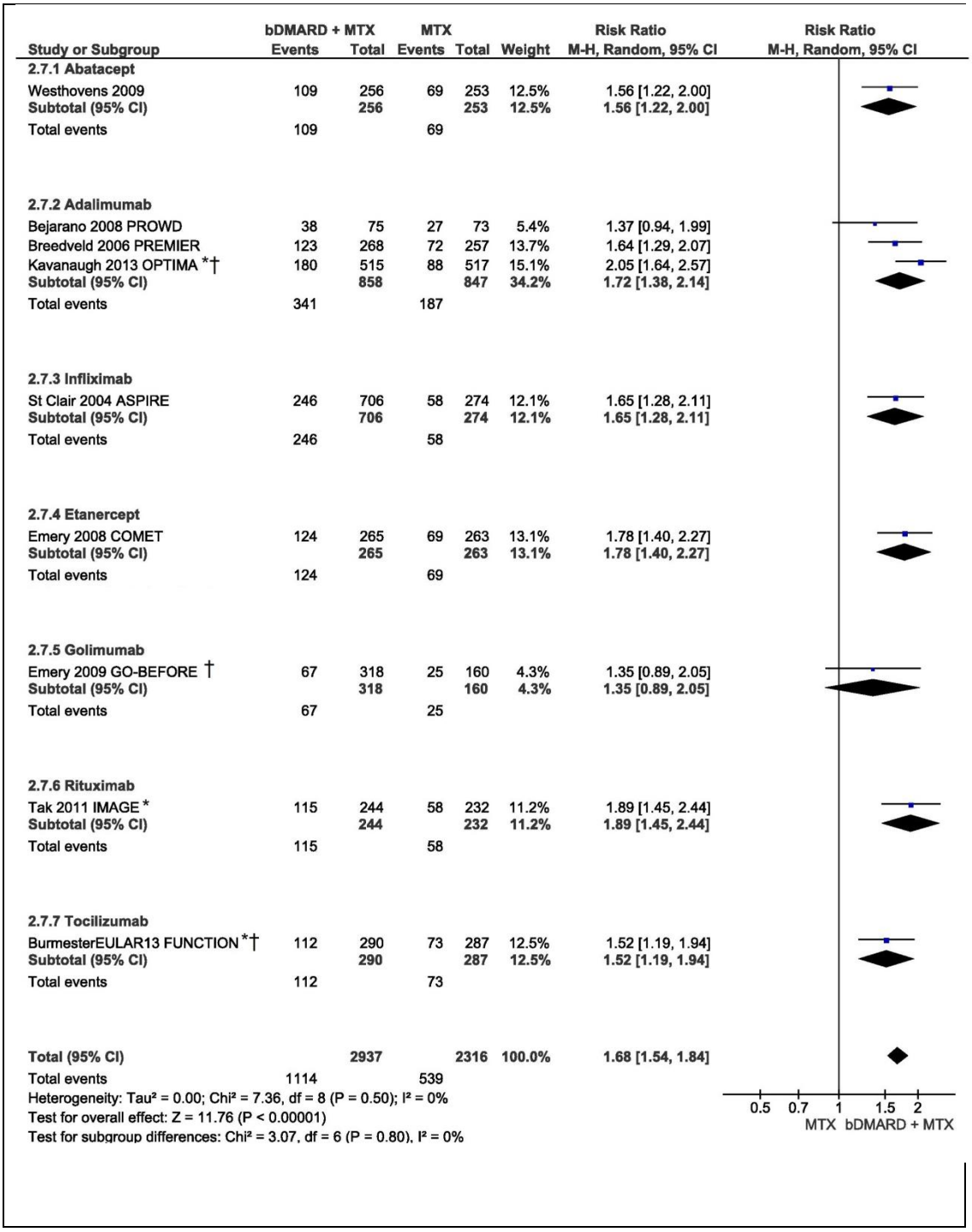


Figure 3.2 Risk ratios for the ACR 70 responses comparing a biological disease-modifying antirheumatic drug (bDMARD) plus methotrexate (MTX) versus MTX monotherapy in patients with early rheumatoid arthritis who are MTX-naïve.

ACR, American College of Rheumatology; *additional study since the 2010 systematic literature review [187]; † ACR 70 responses at 6 months for Kavanaugh 2013 OPTIMA, Emery 2009 GO-BEFORE and Burmester EULAR 2013 FUNCTION; all other ACR 70 responses are at 12 months.

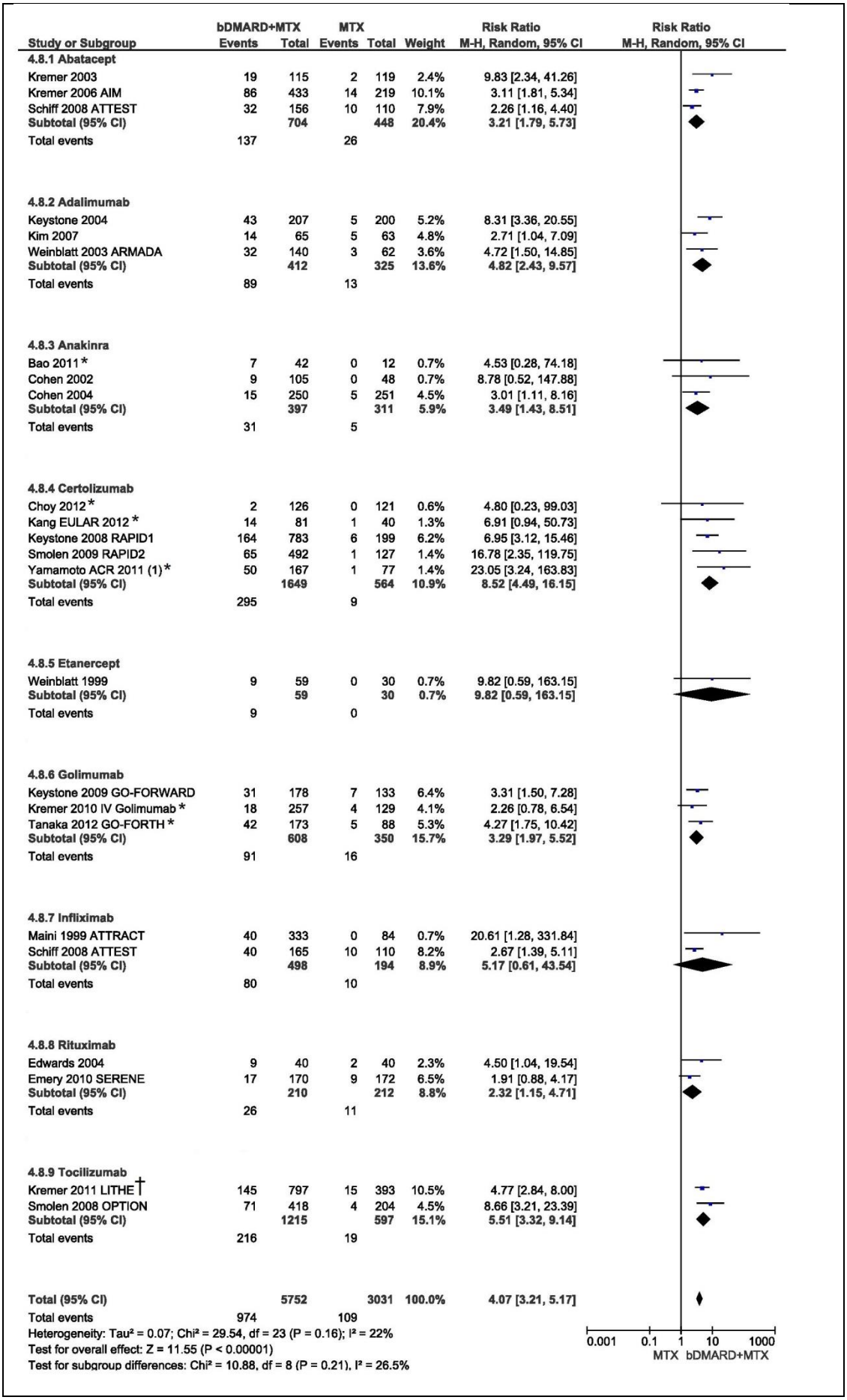

bDMARD+MTX
MTX
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
4.8.1 Abatacept
Kremer 2003 19 115 2 119 2.4% 9.83 [2.34, 41.26]
Kremer 2006 AIM 86 433 14 219 10.1% 3.11 [1.81, 5.34]
Schiff 2008 ATTEST 32 156 10 110 7.9% 2.26 [1.16, 4.40]
Subtotal (95% CI) 704 448 20.4% 3.21 [1.79, 5.73]
Total events 137 26
4.8.2 Adalimumab
Keystone 2004 43 207 5 200 5.2% 8.31 [3.36, 20.55]
Kim 2007 14 65 5 63 4.8% 2.71 [1.04, 7.09]
Weinblatt 2003 ARMADA 32 140 3 62 3.6% 4.72 [1.50, 14.85]
Subtotal (95% CI) 412 325 13.6% 4.82 [2.43, 9.57]
Total events 89 13
4.8.3 Anakinra
Bao 2011 * 7 42 0 12 0.7% 4.53 [0.28, 74.18]
Cohen 2002 9 105 0 48 0.7% 8.78 [0.52, 147.88]
Cohen 2004 15 250 5 251 4.5% 3.01 [1.11, 8.16]
Subtotal (95% CI) 397 311 5.9% 3.49 [1.43, 8.51]
Total events 31 5
4.8.4 Certolizumab
Choy 2012 * 2 126 0 121 0.6% 4.80 [0.23, 99.03]
Kang EULAR 2012 * 14 81 1 40 1.3% 6.91 [0.94, 50.73]
Keystone 2008 RAPID1 164 783 6 199 6.2% 6.95 [3.12, 15.46]
Smolen 2009 RAPID2 65 492 1 127 1.4% 16.78 [2.35, 119.75]
Yamamoto ACR 2011 (1) * 50 167 1 77 1.4% 23.05 [3.24, 163.83]
Subtotal (95% CI) 1649 564 10.9% 8.52 [4.49, 16.15]
Total events 295 9
4.8.5 Etanercept
Weinblatt 1999 9 59 0 30 0.7% 9.82 [0.59, 163.15]
Subtotal (95% CI) 59 30 0.7% 9.82 [0.59, 163.15]
Total events 9 0
4.8.6 Golimumab
Keystone 2009 GO-FORWARD 31 178 7 133 6.4% 3.31 [1.50, 7.28]
Kremer 2010 IV Golimumab * 18 257 4 129 4.1% 2.26 [0.78, 6.54]
Tanaka 2012 GO-FORTH * 42 173 5 88 5.3% 4.27 [1.75, 10.42]
Subtotal (95% CI) 608 350 15.7% 3.29 [1.97, 5.52]
Total events 91 16
4.8.7 Infliximab
Maini 1999 ATTRACT 40 333 0 84 0.7% 20.61 [1.28, 331.84]
Schiff 2008 ATTEST 40 165 10 110 8.2% 2.67 [1.39, 5.11]
Subtotal (95% CI) 498 194 8.9% 5.17 [0.61, 43.54]
Total events 80 10
4.8.8 Rituximab
Edwards 2004 9 40 2 40 2.3% 4.50 [1.04, 19.54]
Emery 2010 SERENE 17 170 9 172 6.5% 1.91 [0.88, 4.17]
Subtotal (95% CI) 210 212 8.8% 2.32 [1.15, 4.71]
Total events 26 11
4.8.9 Tocilizumab
Kremer 2011 LITHE † 145 797 15 393 10.5% 4.77 [2.84, 8.00]
Smolen 2008 OPTION 71 418 4 204 4.5% 8.66 [3.21, 23.39]
Subtotal (95% CI) 1215 597 15.1% 5.51 [3.32, 9.14]
Total events 216 19
Total (95% CI) 5752 3031 100.0% 4.07 [3.21, 5.17]
Total events 974 109
Heterogeneity: Tau² = 0.07; Chi² = 29.54, df = 23 (P = 0.16); I² = 22%
Test for overall effect: Z = 11.55 (P < 0.00001)
Test for subgroup differences: Chi² = 10.88, df = 8 (P = 0.21), I² = 26.5%
0.001
0.1
1
10
1000
MTX
bDMARD+MTX

Figure 3.3 Risk ratios for the ACR70 responses comparing the use of a biological disease-modifying antirheumatic drug (bDMARD) plus methotrexate (MTX) versus MTX monotherapy in patients with rheumatoid arthritis (RA) who are MTX incomplete responders.

ACR, American College of Rheumatology; *additional study since the 2010 systematic literature review [187]; †ACR 70 response at 12 months for Kremer 2011 LITHE; all other ACR 70 responses are at 6 months.

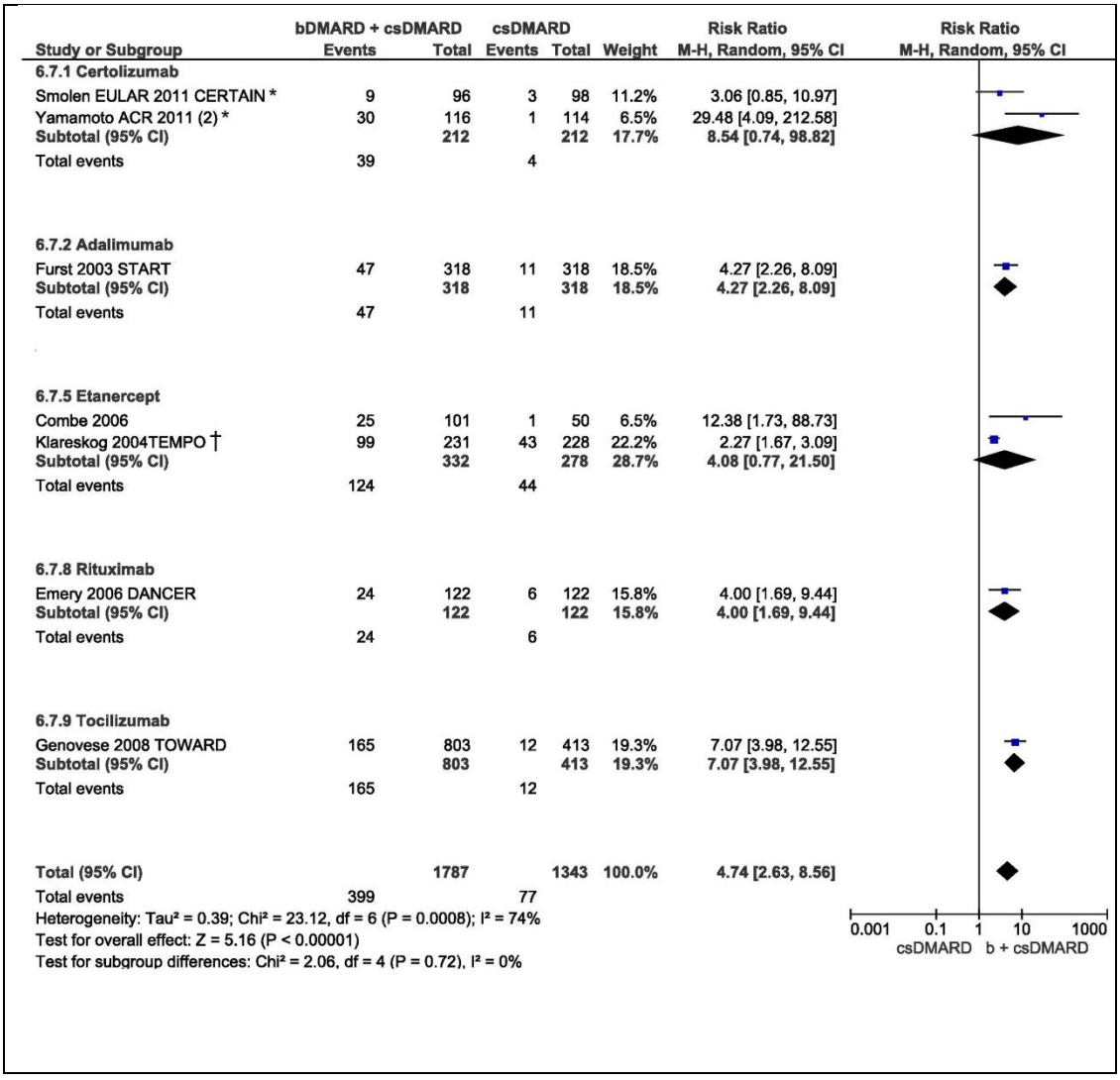


Figure 3.4 Risk ratios for the ACR70 responses comparing the use of a biological disease-modifying antirheumatic drug (bDMARD) plus synthetic disease-modifying antirheumatic drug (csDMARD) versus csDMARD monotherapy in patients with rheumatoid arthritis for whom a csDMARD (not necessarily MTX) has failed.

ACR, American College of Rheumatology; *additional study since the 2010 systematic literature review. [187]; † ACR 70 response at 12 months for Klareskog 2004 TEMPO; all other ACR 70 responses are at 6 months.

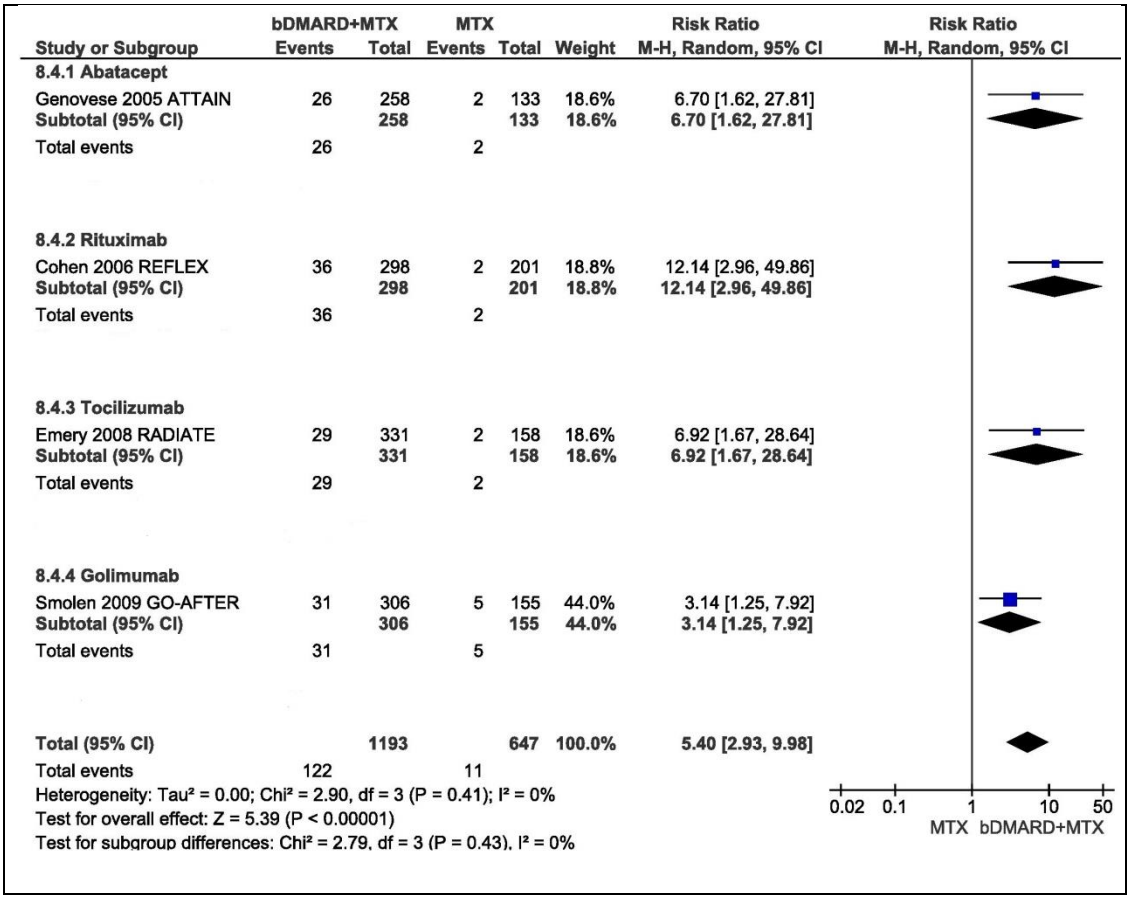


Figure 3.5 Risk ratios for the ACR 70 responses comparing a biological disease-modifying antirheumatic drug (bDMARD) plus methotrexate (MTX) versus MTX monotherapy in patients with rheumatoid arthritis who have failed a TNF-inhibitor.

ACR, American College of Rheumatology

3.4.2.2 Biological DMARD monotherapy vs. conventional synthetic DMARD

From the previous SLR, bDMARD monotherapy was not superior to csDMARD monotherapy.[187] Reviewing the literature again, results for this group have varied with no clear benefit from sub-assessments of these patients in three recent golimumab RCTs.[237 243 252 332] In the FUNCTION study, which addressed the efficacy and safety of tocilizumab with/without methotrexate vs. methotrexate in MTX- naive early RA, the primary endpoint was met (DAS28 ESR remission at 6 months: 38.7% vs. 15% in the tocilizumab 8mg/kg monotherapy vs. methotrexate monotherapy respectively, p≤0.0001). This endpoint however favours therapies that, like tocilizumab, interfere with the acute phase responses. The ACR responses and changes in physical function, however, which do not, were similar between the two groups. At 12 months, radiographic progression was lower in patients receiving

tocilizumab than those receiving methotrexate, and lowest in the tocilizumab 8mg/kg and methotrexate combination therapy group.[245]

3.4.2.3 Biological DMARD and methotrexate combination vs. biological DMARD monotherapy

Several previously published clinical trials have demonstrated better clinical and radiographic outcomes with bDMARD and methotrexate than with bDMARD monotherapy.[323 333] This has been confirmed in more recent RCTs in MTX-naïve RA (figure 3.6). [243 245 334]

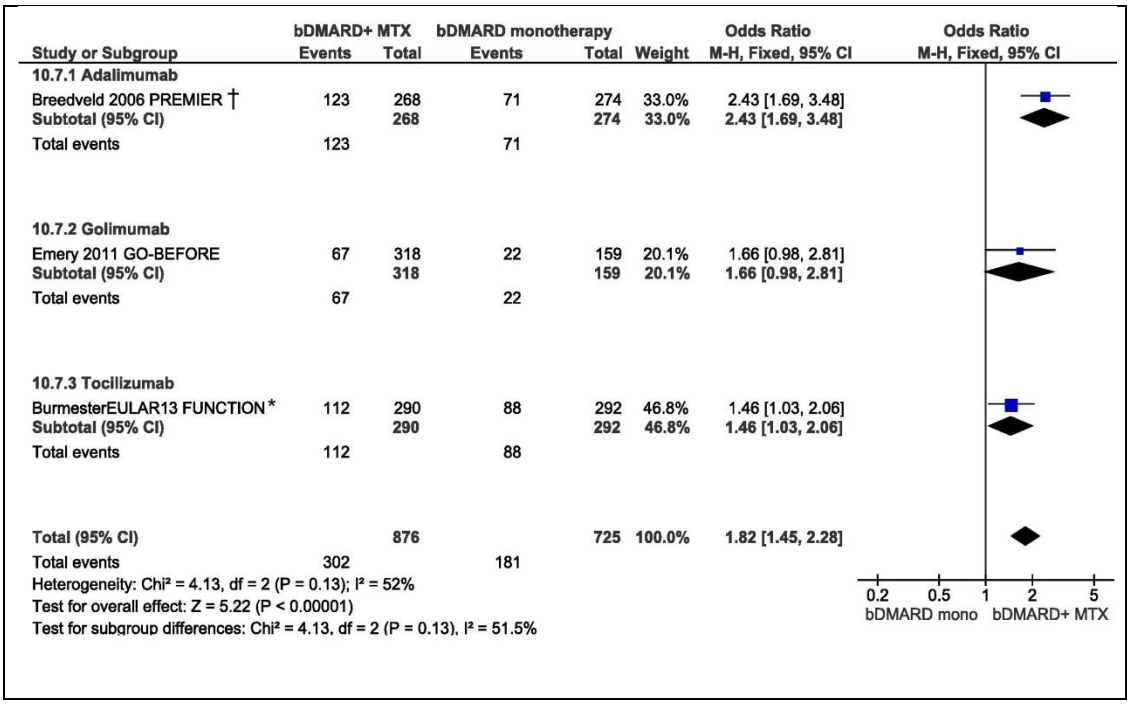


Figure 3.6 Risk ratios for the ACR70 responses comparing the use of a biological disease-modifying antirheumatic drug (bDMARD) plus methotrexate (MTX) versus bDMARD monotherapy in patients with rheumatoid arthritis who are MTX-naïve.

ACR, American College of Rheumatology; *additional study since the 2010 systematic literature review [187] ; † ACR 70 response at 12 months for Breedveld 2006 PREMIER; all other ACR 70 responses are at 6 months.

In a 16-week open label study of patients with MTX—IR RA however, similar clinical and patient reported outcomes were seen with etanercept and methotrexate compared to etanercept monotherapy.[335 336] In this SLR there were three studies, all in the MTX-IR group, comparing bDMARD and methotrexate combination therapy vs. bDMARD monotherapy. In the open label JESMR study, combination therapy

with etanercept and methotrexate was superior to etanercept monotherapy for clinical outcomes. Although there was less radiographic progression with combination therapy, the between group difference was not statistically significant.[237 266] Two studies compared adding tocilizumab to methotrexate (combination therapy) to switching from methotrexate to tocilizumab monotherapy (methotrexate-withdrawal). In the ACT-RAY study [270] and the non-inferiority SURPRISE study, [271] ACR 70 responses were similar in both groups at 6 months (figure 3.7). However, in contrast to the 6 month outcomes, 12 month results from the ACT-RAY study showed higher proportions of remission and radiographic non-progression in the tocilizumab and methotrexate combination group (DAS28 remission 37% vs. 46%, p=0.03 and radiographic non-progression 86% vs. 92%, p=0.007 in the tocilizumab monotherapy and tocilizumab and methotrexate groups respectively)[268] (figure 8).

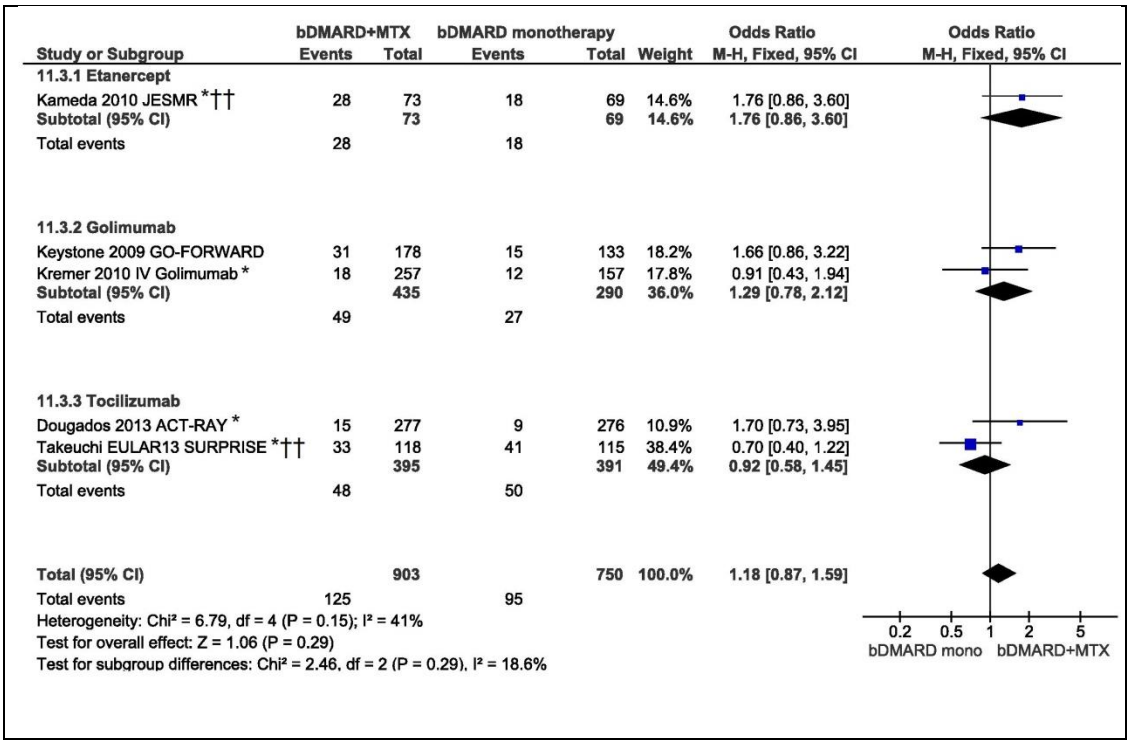


Figure 3.7 Risk ratios for the ACR70 responses comparing the use of a biological disease-modifying antirheumatic drug (bDMARD) plus methotrexate (MTX) versus bDMARD monotherapy in patients with rheumatoid arthritis who are MTX incomplete responders.

ACR, American College of Rheumatology; *additional study since the 2010 systematic literature review [187]; ACR 70 responses are at 6 months; †† open label studies

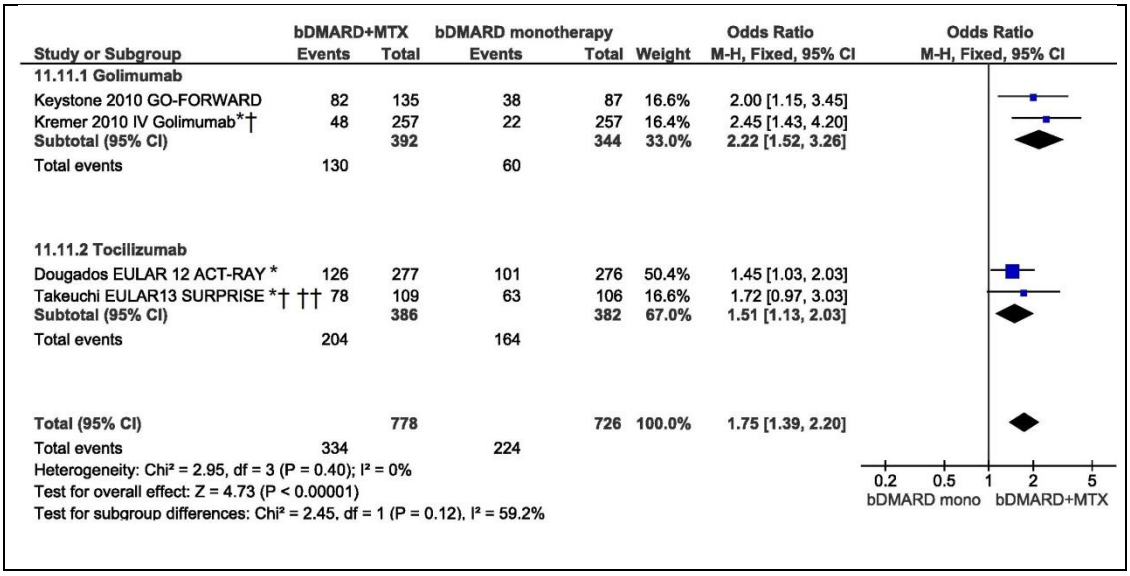


Figure 3.8 Risk ratios for the DAS28 remission comparing the use of a biological disease-modifying antirheumatic drug (bDMARD) plus methotrexate (MTX) versus bDMARD monotherapy in patients with rheumatoid arthritis who are MTX incomplete responders.

*Additional study since the 2010 systematic literature review. [187] ; † DAS28 remission at 6 months for Kremer 2010 IV Golimumab and Takeuchi EULAR 2013 SURPRISE and ACR 70 at 12 months for Keystone 2010 GO-FORWARD and DOUGADOS EULAR 2012 ACT-RAY; †† open label study

The possibility of stepping down from bDMARD and methotrexate to bDMARD monotherapy was addressed in one study. In the COMET trial, patients were randomised at baseline for a 2-year period to methotrexate for a year then continuing with methotrexate monotherapy or adding etanercept, or to methotrexate and etanercept for one year then continuing or stopping methotrexate. [281] At 2 years DAS28 remission in the group continuing methotrexate and etanercept (EM/EM) and the group stepping down to etanercept monotherapy (EM/E) was 45% and 37% respectively. In both groups radiographic non-progression was high, but higher in those on combination therapy (EM/EM vs. EM/E 90% vs. 75%, p 0.008) (table 4).

3.4.2.4 Head to head biological DMARD studies

Two studies, both in the group of patients with MTX-IR RA, have done 'head-to-head' comparisons, directly comparing two different bDMARDs. The non-inferiority study AMPLE study compared combination therapy abatacept and methotrexate to adalimumab and methotrexate in patients with early RA (less than 2 years). [239]The study met its primary end-point (ACR20 response at 12 months). The ACR50 and 70 responses between the two groups were also similar (ACR20, 50 and 70

responses: 65%, 46% and 29% vs. 63%, 46% and 26% in the abatacept and methotrexate and adalimumab and methotrexate groups, respectively). In the ADACTA study tocilizumab monotherapy was compared to adalimumab monotherapy.[275] There was a significantly greater change in DAS28 from baseline to 6 months in the tocilizumab 8mg/kg monotherapy vs. adalimumab 40mg subcutaneous (SC) monotherapy group (difference (95% CI): -1.5 (-1.8 to -1.1), $p<0.0001$) in this superiority study. The 6 month ACR responses were also higher with tocilizumab monotherapy (ACR20, 50 and 70 responses: 65%, 47% and 33% vs. 49%, 28% and 18% in the tocilizumab and adalimumab monotherapy groups respectively) as was the change in clinical disease activity index (CDAI) (which does not include an acute phase reactant) (table 3.2).

3.4.2.5 Switching between biological DMARDs

No RCTs were found fulfilling inclusion criteria for switching between bDMARDs.

Table 3.14 ACR responses of head-to head biological DMARD RCTs

Trial (reference)	**Treatment group**	**Patients evaluated (n)**	**Time-point evaluated (months)**	**ACR 20 (%)**	**p**	**ACR50 (%)**	**p**	**ACR70 (%)**	**p**
Weinblatt 2013 (AMPLE) [239]	MTX + ABT 125mg weekly	318	12	64.8	referent	46.2	referent	29.2	referent
	MTX + ADA 40mg every 2 weeks	328		63.4	NS	46.0	NS	26.2	NS
Gabay 2013 (ADACTA) [275]	ADA 40mg every 2 weeks	162	6	49.4	referent	27.8	referent	17.9	referent
	TCZ 8mg/kg every 4 weeks	163		65.0	0.0038	47.2	0.0002	32.5	0.0023

ABT, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; MTX, methotrexate; RCTs, randomised controlled trials; TCZ, tocilizumab

All RCTs are in MTX incomplete responders

3.4.3 Strategy trials with biological DMARDs

Increasingly, with the number of treatment options and evidence of the benefit of regular monitoring to optimise disease control (treat-to-target approach),[10] studies have looked, not only at direct comparisons between a bDMARD and methotrexate vs. methotrexate monotherapy but use of bDMARDs in different treatment strategies. The BeSt trial,[183] identified in one of the EULAR SLRs done in 2010[223] and discussed in the previous chapter, was one of the pioneering studies to do so. Since then several strategy studies, using different trial designs and primary outcome measures, have been published aiming to address the place of bDMARD therapy in treating patients with IA. For purposes of discussion, these can broadly be divided into two groups addressing (1) stepping up to or induction with a bDMARD compared to other treatment strategies and (2) the possibility of bDMARD withdrawal or dose reduction. Some studies have addressed both aspects and will be discussed in both groups. Within each group studies have also addressed the use of bDMARDs in both (a) RA and (b) UA. These will be discussed as subsections within each group.

3.4.3.1 Strategy trials addressing stepping up to or induction with a biological DMARD

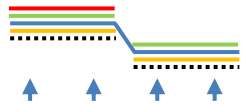
3.4.3.1.1 Strategy trials addressing stepping up to or induction with a bDMARD in RA

These have addressed (i) initial methotrexate monotherapy then stepping up to csDMARD combination therapy vs. methotrexate and bDMARD in the case of MTX-incomplete response (SWEFOT,[240] TEAR,[241] RACAT[242]), (ii) induction with csDMARD combination therapy or methotrexate and a bDMARD (TEAR[241]), (iii) methotrexate monotherapy then stepping up to methotrexate and a bDMARD vs. methotrexate and bDMARD as induction therapy (TEAR,[241] OPTIMA,[1 2 232] COMET [281]) (iv) induction with a bDMARD and methotrexate vs. csDMARD within a treat-to-target approach, in which patients were seen at regular intervals with treatment changes if the desired outcome (e.g. low disease activity or remission) was not met (Neo-RACo,[293] OPERA,[337] IDEA[17]). Table 3.3 provides a schematic diagram of the different types of study designs illustrating some of the RCTs by way of example.

A number of RCTs which compared a bDMARD and methotrexate vs. methotrexate monotherapy also incorporated a cross-over arm from methotrexate monotherapy to combination therapy with methotrexate and bDMARD. These provided further information on induction therapy with a bDMARD and methotrexate vs. initial

methotrexate monotherapy then stepping up to a bDMARD and methotrexate.[243 251 253 260]

Table 3.15 Schematic of strategy-type designs in RA

Study design	**Example RCT**	**Comparator groups**	
MTX step up to csDMARD combination vs. MTX step up to MTX + bDMARD	SWEFOT (van Vollenhoven 2009)[240 279]	MTX then MTX + SSZ+ HCQ	
		MTX then MTX + IFX	
Induction with csDMARD combination vs. Induction with MTX + bDMARD	TEAR (Moreland 2012)[241] *	MTX+ SSZ + HCQ	
		MTX + ETN	
MTX step up to MTX + bDMARD vs. Induction with MTX+ bDMARD	OPTIMA (Fleischmann ACR 2012[1] , Smolen 2014[2])**	MTX then MTX + ADA	
		MTX+ ADA	
Induction with csDMARD + T2T vs. Induction with a bDMARD + MTX +T2T	NeoRA-Co (Leirisalo-Repo 2013)[293]	MTX + SSZ+ HCQ+ Pred+ T2T	
		MTX + SSZ+ HCQ+ Pred+T2T+ IFX for 26 weeks then stop IFX	

Legend:

ADA, adalimumab (—); ETN, etanercept (—); HCQ hydroxychloroquine (—); IFX, infliximab (—); MTX, methotrexate (—);

Pred, prednisolone (·····); RA, rheumatoid arthritis; SSZ, sulphasalazine (—); T2T, treat–to-target (↑ ↑), *only two of the four treatment arms in the TEAR trial are illustrated here; the other two arms are similar in design to the two arms in the SWEFOT trial; For the OPTIMA trial, the ACR abstract by Fleichmann et al. [1] was used for the published manuscript, the data in this thesis has been updated using the data from the published manuscript by Smolen et al.[2]

3.4.3.1.2 Initial methotrexate monotherapy then stepping up to csDMARD combination therapy vs. methotrexate and bDMARD in the case of methotrexate - incomplete response

The SWEFOT[240] study was a 24 month study in which 487 patients were enrolled and received initial treatment with methotrexate monotherapy. Of a group of 258 who did not achieve LDA (DAS 28 ≤ 3.2) after three to four months, 130 were randomised to receive triple csDMARD therapy with methotrexate, sulphasalazine, and hydroxychloroquine and 128 to methotrexate and infliximab. At 12 months, a significantly greater clinical response was seen in the group receiving bDMARD therapy (EULAR good response 50/128 (39%) vs. 32/130 (25%), RR (95% CI) 1.59 (1.10 to 2.30), p=0.0160 in the methotrexate and infliximab vs. the methotrexate, sulphasalazine and hydroxychloroquine groups respectively).[240] At 24 months these were similar between the two groups (EULAR good response 49/128 (38%) vs. 40/130 (31%), p=0.204) however radiographic progression remained lower in the methotrexate and infliximab group (mean (SD) change in mTSS 4.00 (10.0) vs. 7.23 (12.72), p=0.009)[279] (table 3.4).

The TEAR study was a double blind 2x2 factorial design RCT in which four treatment strategies were compared.[241] Similar to the SWEFOT study, there were two step- up treatment groups: ST (step-up from methotrexate monotherapy to triple therapy) and SE (step-up from methotrexate monotherapy to methotrexate and etanercept) if DAS28 ESR ≥ 3.2 at week 24. The study also aimed to address induction therapy with combination csDMARD therapy with methotrexate, sulphasalazine and hydroxychloroquine (IT [immediate triple therapy]) and induction with a bDMARD (IE [immediate methotrexate and etanercept]). Eight percent of patients in this study were DMARD-naïve. The primary end-point, DAS28-ESR from week 48 to week 102, and DAS28-ESR remission at week 102 were similar between groups (IE/IT/SE/ST: 56.5 %/ 59.1 %/ 52.9%/ 56.5%, p=0.93). Remission was achieved earlier with both of the initial combination therapy groups with methotrexate and etanercept and triple csDMARDs (IE+IT vs. SE+ST p<0.0001). Greater depth of response however was seen in the etanercept therapy groups (week 102 ACR70: IE+SE vs. IT+ST 18.25 vs. 11.3%, p=0.01). Radiographic non-progression was not significantly different comparing each of the four groups however those receiving etanercept (IE+SE) had less progression than those receiving triple csDMARD therapy (IT+ST) (p=0.02)(table 3.4).

It has been suggested that confounding by low recruitment (and therefore insufficient power) and other factors need to be considered for these trials[240 241] and

that perhaps more significant between-group differences may have been seen if this was not the case.[338] Never-the-less, findings suggest that more rapid achievement of clinical outcomes are achieved with more intensive treatment strategies seen with significantly more patients achieving ACR 70 responses and less radiographic progression with bDMARD therapy.

The RACAT study was a 48-week, double blind, non-inferiority study comparing methotrexate and etanercept to triple csDMARD therapy (methotrexate, sulphasalazine and hydroxychloroquine) in MTX-IR RA. The original primary endpoint was the difference in proportion of participants with DAS28 ≤ 3.2 at week 48. Due to unexpected low recruitment, this was changed to a continuous outcome – that of change in DAS28 at week 48. In the completers-only analysis of 309 patients, the mean (SD) difference between the two groups this was 0.17 (0.15). With the 95% upper confidence interval limit (0.41) below the non-inferiority margin of 0.60, triple therapy was found to be non-inferior to methotrexate and etanercept. There was also no significant difference in radiographic progression between the two groups (table 3.6).

3.4.3.1.3 Induction with csDMARD combination therapy or methotrexate and a bDMARD

The TEAR trial [241] was the only RCT found comparing induction therapy with triple csDMARDs (methotrexate, sulphasalazine and hydroxychloroquine) to methotrexate and a bDMARD, in this case, etanercept. The results are detailed above and in table 3.4 showing similar clinical responses with the two treatment strategies but lower radiographic progression with methotrexate and etanercept.

3.4.3.1.4 Methotrexate monotherapy then stepping up to methotrexate and a bDMARD vs. methotrexate and bDMARD as induction therapy

The results of the first year of the COMET study,[180] which were included in the SLR done in 2010[187] and discussed in the previous chapter, showed that clinical and radiographic responses were superior with methotrexate and etanercept combination therapy than with methotrexate monotherapy. During the second year of the COMET study, patients in the methotrexate group were randomised to receive methotrexate (M/M) alone or methotrexate and etanercept (M/EM) and those in the methotrexate and etanercept group to continue with combination therapy (EM/EM) or to receive etanercept alone (EM/E). At year 2 clinical outcomes were superior in the groups that received etanercept compared to the group receiving methotrexate alone. DAS28 remission was achieved in 62/108 (57%) and 51/88 (58%) for the EM/EM and M/EM groups respectively – this was significantly

greater than that in the M/M group (33/94 [35%]) (p = 0.002 for the EM/EM group vs. the M/M group; p = 0.003 for M/EM group vs. the M/M group) but not significantly greater than that in the EM/E group (54/108 [50%]) (table 3.5). Radiographic progression was also lower in those who received etanercept with the lowest rate of progression seen in the groups treated with etanercept early (figure 3.9).[77]

In the OPTIMA study, induction therapy with methotrexate and adalimumab was compared to methotrexate monotherapy for 26 weeks in achieving stable low disease activity (LDA: DAS28 (CRP) ≤ 3.2 at weeks 22 and 26).[339] Patients completing period 1 were then re-randomised in period 2 according to response to therapy. Responders in the combination therapy group either continued or stopped adalimumab and those on methotrexate monotherapy continued treatment. These results will be discussed later in the chapter. Incomplete responders received open label rescue-therapy with adalimumab. The primary endpoint was a composite score of DAS28 ≤ 3.2 and radiographic non-progression between weeks 0 and 78. A significantly higher proportion of patients in the methotrexate and adalimumab group achieved this combined measure compared to those receiving methotrexate monotherapy (70% (73/105) vs. 54% (61/112), mean difference (95% CI) 15% (2-28%), p=0.0225, in the methotrexate and adalimumab and methotrexate monotherapy groups respectively) (table 4). In the methotrexate monotherapy group who did not achieve sustained low disease activity in period 1 and received additional treatment with adalimumab (adalimumab-rescue), clinical improvements between weeks 26 and 52 were similar to those of patients who received induction therapy with methotrexate and adalimumab during period 1 at week 26 (mean (SD) DAS28 3.27 (1.27) vs 3.32 (1.44) with adalimumab-rescue at week 78 vs. induction with methotrexate and adalimumab at week 26. As in the COMET study, radiographic progression with methotrexate monotherapy at week 26 (mean (SD) ΔmTSS 1.2 (4.22)) was reduced with the addition of a bDMARD (mean ΔmTSS 0.1 with methotrexate and adalimumab) (table 3.5).

Table 3.16 Biological DMARD strategy RCTs in early DMARD-naïve RA without a treat-to-target approach –study outcomes

Outcome	Result
van Vollenhoven 2009/ 2012 (SWEFOT) [240 279]	
EULAR good response at 12 months*	MTX+ SSZ +HCQ vs. MTX+ IFX : 25% vs. 39%, (RR 1.59 [95% CI 1.1-2.3]), p=0.016
EULAR good response at 24 months	MTX+ SSZ +HCQ vs. MTX+ IFX : 31% vs. 38%, p=0.204
Mean radiographic progression (SD) at 2 years	MTX+ SSZ +HCQ vs. MTX+ IFX : 7.23 (12.72) vs. 4 (10.05), p=0.009
Moreland 2012 (TEAR) [241] ****	
DAS28-ESR from week 48 to week 102*	IE (n=244) vs. IT (n=132) vs. SE(n=255) vs.ST (n=124); completers only analysis: No difference between groups (p=0.28) MTX + ETN (IE+SE) vs. TT (IT+ST), p=0.48; Immediate (IE+IT) vs. step up (SE+ST), p=0.55
DAS28 ESR at week 24	IE+IT vs. SE+ST p<0.0001
DAS28 ESR remission (%) at week 102	IE/IT/SE/ST : 56.5/ 59.1/ 52.9/ 56.5, p=0.93
ACR responses (%) at week 102	IE/IT/SE/ST : ACR20 and ACR 50, p=NS; ACR70: IE+SE vs. IT+ST: 18.25 vs. 11.3%, p=0.01
Radiographic non-progression (%) at week 102	IE/IT/SE/ST: 79.4/64.9/71.1/68.3, p=0.33; IE+SE vs. IT+ST: 76.8 vs. 66.4, p=0.02

DMARD, disease modifying antirheumatic drug ETN, etanercept; HCQ, hydroxychloroquine; IFX, infliximab; MTX, methotrexate; SD, standard deviation; SSZ, sulphasalazine; TT, triple therapy (MTX, SSZ and HCQ)

IE, immediate treatment with MTX and ETN; IT, immediate oral triple therapy (MTX, SSZ and HCQ); SE, step-up form MTX monotherapy to MTX plus ETN; ST, step up from MTX monotherapy to MTX, SSZ and HCQ; *primary endpoint; **80% of patients were DMARD naive

Table 3.17 Biological DMARD strategy RCTs in early MTX-naïve RA without a treat-to-target approach – study outcomes

Outcome	Result
Emery 2009 (COMET) [281]	
Remission (DAS28<2.6) at 2 years	EM/EM, EM/E, M/EM, M/M 62/108, 54/108, 51/88 and 33/94 (p<0.01 for EM/EM and M/EM vs. M/M)
Radiographic non-progression (mTSS ≤ 0.5) at 2 years	EM/EM (n=111), EM/E (n=111), M/EM (n=90), M/M (n=99): 89/99, 74/99, 59/79 and 56/83 (p<0.01 EM/EM vs. other groups)
Kavanaugh 2013, [232] Fleischmann ACR 2012 [1], Smolen 2014[2] (OPTIMA)	
Stable LDA at weeks 22 and 26	ADA+MTX (n=517) vs. Placebo+MTX (n=515): 44% vs. 24% (p<0.001)
Composite score: DAS28(CRP)<3.2 at week 78 mTSS ≤ 0.5 at week 78*	ADA+MTX (n=105) vs. Placebo+MTX (n=112): 70% vs. 54% (p=0.025)
Mean (SD) DAS28CRP in ADA-rescue at week 78	MTX then MTX+ADA if not in LDA at week 26: ADA+MTX from week 0 to 26: 3.27 (1.27) vs. 3.32 (1.44)
Mean ∆mTSS week 26 and weeks 26-78 in ADA-rescue	MTX then MTX+ADA if not in LDA at week 26: 1.2 (4.22) then 0.1

ADA, adalimumab; DMARD, disease-modifying antirheumatic drug; E, etanercept; EM, etanercept and methotrexate; ETN, etanercept; LDA, low disease activity; mTSS, van der Heijde modified total Sharp score; M, methotrexate; MTX, methotrexate; * primary endpoint; SD, standard deviation

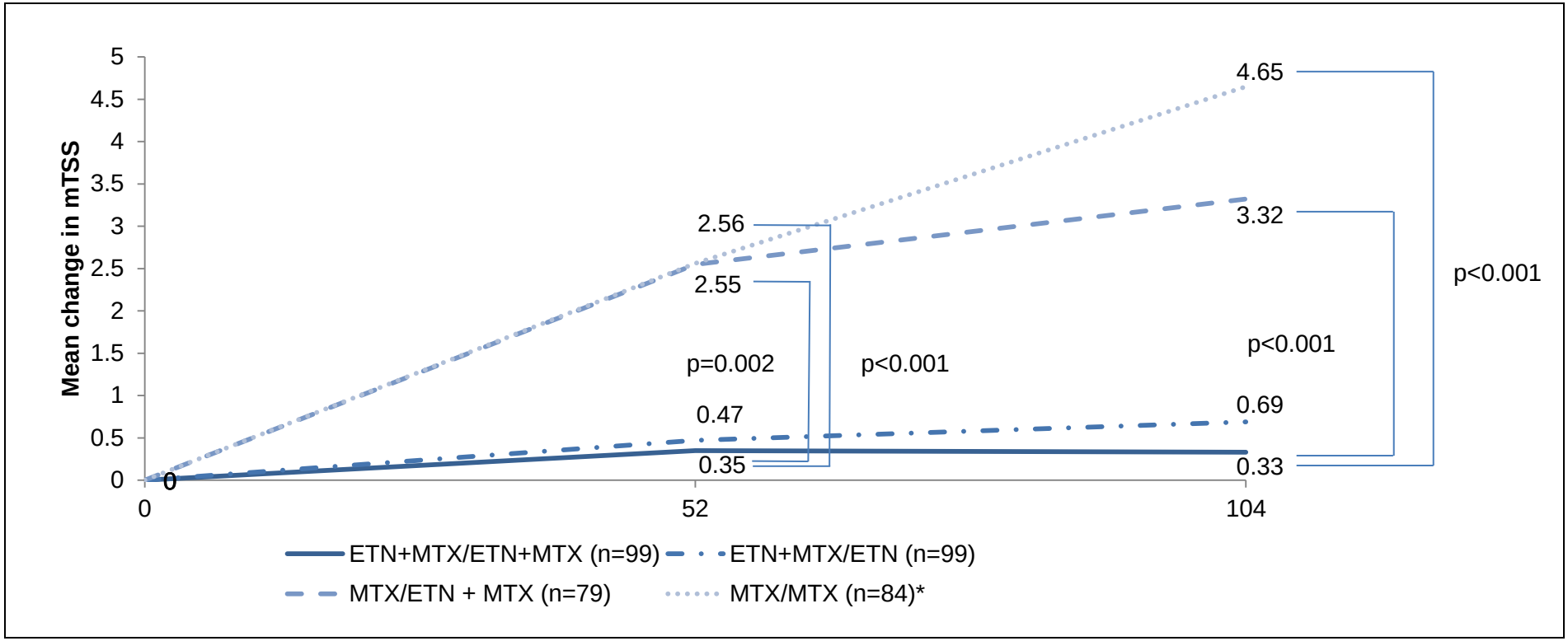


Figure 3.9 Radiographic progression over 2 years in the COMET trial

Adapted from Emery et al, Ann Rheum Dis 2010[281]

Mean changes in van der Heijde modified Sharp score (mTSS) from week 0 to week 104, based on the last observation carried forward analysis. (ETN = etanercept: MTX = methotrexate. * = 1 subject did not have a valid radiograph at week 52 but did at baseline and week 106; changes from week 52 to week 104 cannot be assessed.)

Table 3.18 Biological DMARD strategy RCT in MTX IR RA without a treat-to-target approach – study outcomes

Outcome	**Result**
O'Dell 2013 (RACAT) [242] (n=353)	
Mean (SD) ΔDAS28 at week 48*	MTX+SSZ+HCQ vs. ETN+MTX *(completers only analysis):* -2.12 (1.28) vs. -2.29 (1.30) (p=0.26)
Mean (SD) ΔDAS28 at week 24	-1.79 (1.20) vs. -2.06 (1.35) (p=0.06)
Mean (SD) ΔmTSS at week 24	0.42(1.91) vs. 0.003 (3.62) (p=0.20)
Mean (SD) ΔmTSS at week 48	0.54 (1.93) vs. 0.29(3.32) (p=0.43)

DMARD, disease-modifying antirheumatic drug; ETN, etanercept; HCQ, hydroxychloroquine; mTSS, van der Heijde modified total Sharp score; MTX, methotrexate; * primary endpoint; SD, standard deviation; SSZ, sulphasalazine

3.4.3.1.5 Induction with a bDMARD and methotrexate vs. csDMARD within a treat-to-target approach

The Neo-RACo was one of the RCTs addressing bDMARD induction within a treat-to-target setting.[293] Patients received methotrexate, sulphasalazine, hydroxychloroquine and prednisolone 7.5mg daily (the Fin-RACo regime) and placebo or the Fin-RACo regime and infliximab 3mg/kg for 26 weeks. Additional glucocorticoids were permitted during the study period. The modified ACR remission at 2 years (study primary endpoint) was 66% in the Fin-RACo and infliximab group and 53% in the Fin-RACo + placebo groups (p=0.19). DAS28 remission for both groups was 82%. Radiographic progression however was lower and the proportion achieving non-progression higher in the group receiving infliximab (24 month mean ∆mTSS: 0.2 vs. 1.4 (p=0.0058) and ∆mTSS ≤0.5: 80% vs. 53% (p=0.006) in the Fin-RACo and infliximab vs. the Fin-RACo and placebo groups respectively). The proportion of patients in remission at 5 years remained high (modified ACR remission (95% CI): FIN-RACo and infliximab vs. FIN-RACo and Placebo 59% (43 to 73) vs. 60% (45 to 74) (p=0.87), DAS28 remission (95% CI) 83% (69 to 92) vs. 88% (75 to 95))[292] (table 3.7).

The other studies addressing bDMARD use within a treat-to-target setting were OPERA[337] and IDEA[17]. Both used a monoclonal TNFi with methotrexate – adalimumab in OPERA and infliximab in IDEA. In the OPERA study, induction with methotrexate and adalimumab combination was compared to methotrexate monotherapy with intra-articular glucocorticoids as part of the treat-to-target strategy. At each visit swollen joints were injected with triamcinolone (maximum of four joints per visit). Additional DMARDs were also prescribed if LDA was not achieved. LDA at 12 months, the primary endpoint, was similar between groups (methotrexate and adalimumab 80% vs. methotrexate monotherapy 76% (p=0.65)). Proportions of patients achieving remission was higher in the methotrexate and adalimumab group (methotrexate and adalimumab 74% vs. methotrexate monotherapy 49% (p=0.0008)) (table 3.7). Further details on the IDEA[17] study will be provided in Chapter 4.

Table 3.19 Biological DMARD strategy studies* with a treat-to-target approach – study outcomes

Outcome	Result
Leirisalo-Repo 2012 (NEO-RACo) [293]	
Modified ACR remission** 2 year	MTX SSZ+HCQ+Pred + IFX vs. MTX+SSZ+HCQ+Pred + Placebo:66% vs. 53% (p=0.19)
Sustained modified ACR remission[#] 2 year	MTX+SSZ+HCQ+Pred + IFX vs. MTX+SSZ+HCQ+Pred + Placebo:26% vs. 10% (p=0.042)
DAS28 remission	Both groups: 82% (NS)
Mean ∆mTSS 2 year	MTX+SSZ+HCQ+Pred + IFX vs. MTX+SSZ+HCQ+Pred + Placebo:-0.2 vs. 1.4 (p=0.0058)
Radiographic non-progression 2 year	MTX+SSZ+HCQ+Pred + IFX vs. MTX+SSZ+HCQ+Pred + Placebo:80% vs. 53% (p=0.006)
Horslev-Petersen 2013 (OPERA) [337] (n=180)	
DAS28CRP < 3.2 at 1 year**	ADA + MTX vs. Placebo + MTX: 80% vs. 76% (p=0.65)
DAS28CRP (median (95% CI) at 1 year	ADA + MTX vs. Placebo + MTX: 2.0 (1.7 to 5.2) vs. 2.6 (1.7 to 4.7) (p=0.009)
DAS28 CRP < 2.6 at 1 year	ADA + MTX vs. Placebo + MTX: 74% vs. 49% (p=0.0008), NNT 4.0 (2.6 to 9.1)
Nam 2013 (IDEA)[17] (n=112)	
∆mTSS score (mean) at 1 year**	IFX + MTX vs. IV steroid + MTX: 1.20 vs. 2.81 (p=0.132)
mTSS <2.0 at 1 year**	IFX + MTX vs. IV steroid + MTX: 81% vs. 71% [OR (95% CI) 1.77 (0.56, 5.61); p=0.328]

DAS44 remission at 1 year	IFX + MTX vs. IV steroid + MTX: 49% vs. 36% [OR (95% CI) 2.13 (0.91, 5.00); p=0.082)
DAS44 remission at 1.5 year (week 78)	IFX + MTX vs. IV steroid + MTX : 48% vs. 50% [OR (95% CI) 1.12 (0.47, 2.68); p=0.792]

ADA, adalimumab; DAS, disease activity score; FIN-RACo = methotrexate, sulphasalazine, hydroxychloroquine and prednisolone; IFX, infliximab; MTX, methotrexate; mTSS = van der Heijde modified total Sharp score; *all DMARD-naïve RA studies; **primary endpoint; # Sustained remission = remission at each visit from 6 to 24 months

3.4.3.1.6 Strategies trials addressing stepping up to or induction with a bDMARD in UA

Studies have also begun to focus on patients at earlier stages of the IA disease continuum. These have aimed to address the use of bDMARDs in patients presenting with UA or in those fulfilling the 2010 ACR-EULAR classification criteria[12] but not all fulfilling the 1987 ACR criteria[11] for RA (ADJUST,[236] STREAM, [288] IMPROVED,[238] EMPIRE [18 289]). Table 3.8 provides a schematic of the different types of the different study designs in this group of patients and table 3.9 the results.

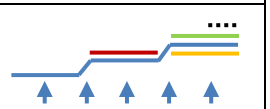
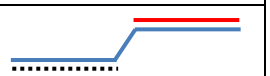
In the two year randomised double blind controlled ADJUST trial, 56 anti-CCP positive patients with undifferentiated arthritis (not fulfilling the 1987 ACR RA classification criteria) were randomised to receive IV abatacept or placebo for six months.[236] Treatment was then discontinued. At 1 year, a smaller proportion in the abatacept group developed RA (1987 criteria) (46% (1/26) vs. 67% (16/34) in the abatacept and placebo groups respectively). Radiographic progression was also lower with abatacept (total Genant-modified Sharp scores: 0 vs. 1.1 in the abatacept and placebo groups).

In the STREAM [288] study, 82 patients were randomised to conventional care or aggressive treatment with regular monitoring and treatment escalation. In the aggressive group, 19 (45%) received adalimumab. Two year remission were similar between the groups (median 66% vs. 49% (NS) in the aggressive and conventional care groups respectively) and with minimal radiographic progression (median (interquartile range(IQR)) ∆mTSS (0 (0-1.1) vs. 0.5 (0-2.5) (NS)). One of the main reasons suggested by the authors for the lack of difference in outcomes between groups was the gradual intensification of treatment in the conventional care group during the course with a higher number of glucocorticoid injections used, resulting in a lower than expected rate of radiographic damage.

In the single-blind IMPROVED study all patients were treated with methotrexate and high dose oral prednisolone for four months.[238] In those who achieved early remission (DAS44 <1.6 at 4 months), prednisolone was tapered and for those with persistent remission after 8 months methotrexate was tapered and stopped. Those not in early remission were randomized to receive methotrexate, sulphasalazine and hydroxychloroquine (arm 1) or methotrexate and adalimumab (arm 2). For those in remission after 8 months, treatment was tapered to methotrexate monotherapy. For those not in remission after 8 months, triple therapy was changed

to adalimumab (arm 1) and in those already receiving adalimumab the treatment dose was increased (arm 2). DAS remission (DAS<1.6) at 1 year was 68 % in the in early DAS remission group, 25% in arm 1 and 41% in arm 2 ($p<0.001$). Radiographic non-progression was high in all groups (ΔmTSS< 0.5: early remission group: 95%; Arm 1 96% and Arm 2 92%). Few patients who required treatment escalation however were able to achieve drug free remission (0% and 1% in arms 1 and 2 respectively). Details on the EMPIRE study will be provided in Chapter 5.

Table 3.20 Schematic of strategy-type designs in UA

Study design	**Example RCT**	**Comparator groups**	
Placebo vs. Induction with a bDMARD	ADJUST (Emery 2010) [236]	PBO	
		ABT	
Conventional care vs. Induction with MTX then protocol step up with a T2T approach	STREAM (van Eijk 2012)[288]	HCQ** then SSZ then MTX then LEF	
		MTX then MTX + ADA then MTX + SSZ + HCQ	
Induction with MTX + high dose prednisolone then step up to csDMARD combination vs. MTX + bDMARD	IMPROVED (Heimans 2014)[238]	MTX + Prednisolone then MTX + SSZ + HCQ	
		MTX + Prednisolone then MTX + ADA	
MTX vs. Induction with MTX+ETN then step down to MTX monotherapy	EMPIRE (Nam 2014)[18]	MTX	
		MTX + ETN	

Legend:

ABT, abatacept (—); ADA, adalimumab (—); ETN, etanercept (—); HCQ hydroxychloroquine (—); MTX, methotrexate (—);

PBO, placebo (—), Pred, prednisolone (·····); RA, rheumatoid arthritis; SSZ, sulphasalazine (—); T2T, treat-to-target ( ), ** from August 2005, MTX could be used as first-line therapy

Table 3.21 Biological DMARD strategy RCTs in UA – study outcomes

Outcome	**Result**
Emery 2010 (ADJUST)[236] (n=56)	
Development of RA (ACR criteria) at 1 year*	ABT vs. placebo: 1/26 (46%) vs. 16/24 (67%)
van Eijk 2012 (STREAM) [288] (n=82)	
Median (IQR) ∆mTSS at 2 years*	aggressive vs. conventional care: 0 (0-1.1) vs. 0.5 (0-2.5) NS
Median remission (DAS<1.6) at 2 years	66% vs. 49% NS
Heimans 2013 (IMPROVED) [238] (n=610)	
DAS44 remission at 1 year	MTX + high dose prednisolone[§] vs. MTX+HCZ+SSZ vs. MTX+ADA: 68 %; 25%; 41% (MTX+HCZ+SSZ vs. MTX+ADA p<0.001)
DFR remission at 1 year	MTX + high dose prednisolone[§]; MTX+HCZ+SSZ; MTX+ADA: 32%; 1%; 0%
∆mTSS< 0.5	MTX + high dose prednisolone[§]; MTX+HCZ+SSZ; MTX+ADA: 95%; 96% ; 92%
Villeneuve ACR 2011[289]/ Nam 2014[18] (EMPIRE) (n=110)	
Remission (NTSJ) at 1 year	ETN + MTX vs. Placebo + MTX : 31% vs. 29% (p=0.835)

ABT, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; DFR, drug free remission; DMARD, disease-modifying antirheumatic drug; ETN, etanercept; HCQ, hydroxychloroquine; IFX, infliximab; IQR, interquartile range; mTSS, van der Heijde modified total Sharp score; MTX, methotrexate; NTSJ, no tender or swollen joints (RAI +SJC= 0); SD, standard deviation; SSZ, sulphasalazine;* primary endpoint; [§] early DAS remission arm

3.4.3.2 Strategy trials addressing biological DMARD stopping or dose reduction

The placebo controlled RCT by Quinn et al. [182] was one of the first studies introducing the concept of induction with methotrexate plus bDMARD combination therapy and stepping down to maintenance methotrexate. In this study of 20 DMARD-naïve RA patients with poor prognostic factors, erosions on MRI were less with methotrexate and infliximab therapy than with methotrexate monotherapy at 12 months.

In this SLR, eleven studies were found evaluating bDMARD stopping or bDMARD dose reduction after achieving low disease activity or remission.[230 232 280 289 291 296 298 308 309 340-342]

In DMARD-naïve patients, long-term data from the BeSt study showed that bDMARD discontinuation was possible and more likely in those receiving methotrexate and infliximab as induction therapy compared to those receiving delayed methotrexate and infliximab combination therapy (56% vs. 29%, p=0.008 in the initial vs. delayed groups respectively.[278] In the HIT HARD study however, 6 months after methotrexate and adalimumab induction therapy, stopping adalimumab in an open label manner, clinical outcomes were similar to those in group receiving methotrexate monotherapy (mean (SD) DAS28 :3.2 (1.4) vs. 3.4 (1.6), p=0.41 at 1 year), suggesting that not all patients may be able to stop their bDMARD therapy.[230] Similarly in the OPERA study in which patients received methotrexate and adalimumab or methotrexate and placebo for the first year, then methotrexate monotherapy in the second year, there were no significant differences in clinical findings or function between the two groups[298] (table 3.10).

In the MTX-naïve group, results from the OPTIMA study showed that a high proportion of patients who achieved low disease activity using a 28 joint count (LDAS28) at 6 months were able to maintain this even after withdrawing the TNF-inhibitor. Maintenance however was somewhat higher in patients continuing adalimumab compared to those who stopped the bDMARD (18 month LDAS28: 91% vs. 81% in the ADA-continue vs. the ADA-stop groups, p=0.004 respectively).[280] The possibility of dose reduction has also been addressed. In the PRIZE study, 306 patients were treated with methotrexate and etanercept 50mg weekly for 52 weeks. Seventy percent achieved DAS28 remission. One hundred and ninety four patients were then randomised to receive placebo (drug-free group), methotrexate monotherapy (bDMARD-free group) or methotrexate and etanercept 25mg/week (dose-reduction group). After 39 weeks, approximately two-thirds of patients were able to maintain this response at 2 years with methotrexate and

etanercept 25 mg weekly (sustained DAS 28 remission [DAS28<2.6 at weeks 76 and 91 with no steroid boost]: 63.5% vs. 40% vs. 23.1% in the methotrexate and etanercept 25mg weekly vs. methotrexate monotherapy vs. placebo groups respectively) [340] (table 3.11).

Maintenance of response in patients with MTX-IR RA who reduced their etanercept dose was similarly shown in the PRESERVE study. [232] In this RCT 834 patients with moderate disease activity were included in a 36-week open label study and treated with methotrexate and etanercept 50mg/week. Of these 604 (72.4%) achieved sustained LDA and were therefore eligible for the double-blind phase. Patients were randomised to receive either methotrexate and etanercept 50mg weekly, methotrexate and etanercept 25mg weekly or methotrexate and placebo. At week 88, maintenance of LDA was greater in the dose-reduction group than in those who stopped etanercept (82.6% vs. 79.1% vs. 42.6% in methotrexate and etanercept 50mg weekly, methotrexate and etanercept 25 mg weekly and methotrexate and placebo groups respectively). DAS28 remission at week 88 was 66.7% vs. 60.2% vs. 29.4% in methotrexate and etanercept 50mg weekly, methotrexate and etanercept 25 mg weekly and methotrexate and placebo groups.

The ACT-RAY[308] and CERTAIN[256 341] studies also looked at bDMARD discontinuation in patients with MTX-IR RA. In ACT-RAY patients were randomised to either adding tocilizumab 8mg/kg IV to methotrexate or switching to tocilizumab 8mg/kg IV and placebo with additional DMARDs as part of a treat-to-target strategy during the first year. In those who achieved sustained remission in year 2, treatment was de-escalated by first stopping the tocilizumab then withdrawing other DMARDs. A high proportion of patients experienced a flare on stopping tocilizumab (86% before the end of year 2). Only a small proportion of patients achieved drug free remission. In the CERTAIN study, patients with low to moderate disease activity who achieved sustained remission after 24 weeks of certolizumab pegol stopped bDMARD therapy and continued with their csDMARDs. Few patients remained in remission at week 52 (CDAI remission in 3/17 and 2/6 in the prior certolizumab pegol and prior placebo groups respectively) (table 3.12).

Studies have also addressed the possibility of tapering bDMARDs in patients with established RA. In the STRASS study, patients in stable DAS28 remission (DAS28 ≤ 2.6 for ≥ 6 months) on etanercept or adalimumab for ≥ 1 year with no structural damage progression on X-rays since their last X-ray assessments were randomised to one of 2 arms: S (spacing adalimumab and etanercept injections) vs. M (maintain adalimumab and etanercept as full regimen).[309 343] After 18 months, 73.4% of patients in the S-arm tapered bDMARD of whom 37.5% stopped. Mean DAS28

and HAQ-DI were not significantly different between the two groups but relapses were more frequent in the S than in the M group (81 % vs. 56%, p=0.0009). Radiographic progression was not significantly different between the groups. In the DOSERA study, patients on methotrexate and etanercept 50mg weekly and in LDA or DAS28 remission for ≥ 11 months were randomised to continuing methotrexate and etanercept 50mg weekly (n=23), methotrexate and etanercept 25mg weekly (n=27) or methotrexate and placebo (n=23). The primary endpoint was the proportion of non-failures at week 48, with failure defined by DAS28 ≥ 3.2 and an increase in DAS28 ≥ 0.6. The proportion of non-failures was significantly higher in those continuing full dose etanercept (52%) and those receiving half-dose etanercept (44%) than in patients on methotrexate monotherapy (13%) (p=0.007 and p=0.044, for etanercept 50 mg weekly and etanercept 25mg weekly respectively vs. placebo)[344] (table 3.13).

Table 3.22 Biological DMARD strategy studies in DMARD-naïve RA addressing biological DMARD dose reduction or stopping – study outcomes

Outcome	Result
van der Kooij 2009 [291] / van der Kooij 2009 [278]/ Klarenbeek 2011 [217]/ Dirven 2011 [184]/ van den Broek 2011 (BeSt) [301] (n=508)	
DFR (%) at year 4; year 8 [184]	Groups 1 to 4‡: 14/12/8/18 (p=0.14); 18/19/17/15 (p=0.9)
Joint damage progression > SDC (%) at 4 years	Groups 1 to 4‡: 51/54/38/31 (p<0.05 for groups 4 vs. 1 and 3, and 3 vs. 2)
Discontinuation of IFX due to sustained DAS44 ≤2.4 2 years after IFX initiation (%)[278]	Initial vs. delayed IFX: 56 vs. 29 (OR(95% CI) 2.56 (1.27 to 5.16) p=0.008))
Discontinuation of IFX due to sustained DAS ≤ 2.4 (for 6 months) (n) [301]	Initial vs. delayed IFX: 77/120 vs. 27/109
Sustained DAS remission after IFX cessation (n (%))[301]	Initial vs. delayed IFX: 43/77 (56) vs.11/27 (41)
DFR (n (%))[301]	Initial vs. delayed IFX: 15 (27) vs. 0 after at least 1 year of follow up
Predictor of restarting IFX (for DAS > 2.4) [301]	Initial vs. delayed IFX: HR (95% CI) 1.8 (0.9 to 3.7)
Detert 2013 (HIT HARD) [230] (n=172)	
Mean (SD) DAS28 at week 48*	ADA+MTX/ MTX vs. Placebo + MTX/MTX[§]: 3.2 (1.4) vs. 3.4 (1.6) (p=0.49)
ACR responses (%) at week 48	ADA+MTX/ MTX vs. Placebo + MTX/MTX[§]: ACR 50: 52.6 vs. 51.4

	(p=0.88), ACR 70: 40.5 vs. 34.0 (p=0.40)
DAS28 remission (%) at week 48	ADA+MTX/ MTX vs. Placebo + MTX/MTX[§]: 42.4 vs. 36.8 (p=0.47)
Horslev-Petersen EULAR 2013 (OPERA) [337] (n=180)	
Median (95% CI) DAS28CRP at year 2	ADA + MTX/ MTX vs. Placebo + MTX/MTX[†] : 2.0 (1.7-4.4) vs. 2.0 (1.7 - 4.5)(p=0.97)
Remission (DAS28CRP<2.6) at year 2	ADA + MTX/ MTX vs. Placebo + MTX/MTX[†]: 66% vs. 69% (p=0.79)
Median (95% CI) HAQ-DI at year 2	ADA + MTX/ MTX vs. Placebo + MTX/MTX[†]: 0.13 (0-1.63) vs 0.13 (0-1.5) (p=0.37)
Nam 2013 (IDEA)[296] (n=112)	
Week 78: Stopped IFX due to sustained remission (n (%)) *	14/55 (25) of the IFX group

ACR , American College of Rheumatology; ADA, adalimumab, DFR, drug free remission; CI, confidence interval; IFX, infliximab, MTX, methotrexate; SD, standard deviation; SDC, smallest detectable change

§HIT HARD comparator groups: ADA+ MTX vs. Placebo + MTX for 24 weeks. After 24 weeks both groups treatment with MTX only

† OPERA comparator groups: ADA+ MTX vs. Placebo + MTX for 1 year. After 1 year both groups treatment with MTX only

‡BeSt comparator groups: Group 1 Sequential monotherapy; Group 2 Step-up combination therapy; Group 3 Initial combination with prednisone; Group 4 Initial combination with IFX

*Sustained remission = DAS< 1.6 for 6 months

Table 3.23 Biological DMARD strategy studies in MTX-naïve RA addressing biological DMARD dose reduction or stopping – study outcomes

Outcome	**Result**
Smolen EULAR 2012 (OPTIMA) [303]/ Emery EULAR 2011 (OPTIMA) [345] (n=1032)	
Maintenance of DAS28<3.2 (%) from week 52 to 78 [303]	ADA _continue vs. ADA withdrawal§ : 87 vs. 65 (p=0.002)
ACR20/50/70 (%) at week 78[345]	ADA_ continue vs. ADA_withdrawal§: 95/89/77 vs. 94/80/65 (p = 0.72/ 0.11/ 0.05)
DAS28 <3.2(%) at week 78 [345]	ADA_ continue vs. ADA_withdrawal§: 81 vs. 91 (p=0.04)
DA28<2.6(%) at week 78 [345]	ADA_ continue vs. ADA_withdrawal§: 66 vs. 86 (p=0.001)
∆mTSS ≤ 0.5(%)at week 78[345]	ADA_ continue vs. ADA_withdrawal§: 89 vs. 81 (0.06)
Emery EULAR 2013 (PRIZE) [340] (n=306)	
Sustained DAS remission at week 39 after achieving remission	ETN25+MTX vs. MTX vs. placebo: 63.5 vs. 38.5 vs. 23.1 (ETN25+MTX vs. MTX p= 0.0051; ETN25+MTX vs. placebo p<0.0001, MTX vs. placebo 0.0595)
∆mTSS ≤ 0.5(%) at week 39 after achieving remission	ETN25+MTX vs. MTX vs. placebo: 87.9 vs. 96.4 vs. 89.8 (ETN25+MTX vs. MTX 0.1124; ETN25+MTX vs. placebo 0.7609; MTX vs. placebo 0.1929)

ADA, adalimumab, ETN, etanercept; ETN25, etanercept 25mg weekly, MTX, methotrexate

§OPTIMA comparator groups: ADA_ continue vs. ADA_withdrawal: in patients who achieved LDA at with ADA + MTX at weeks 22 and 26

Table 3.24 Biological DMARD strategy studies in csDMARD IR RA addressing biological DMARD dose reduction or stopping – study outcomes

Outcome	Result
Smolen 2013 (PRESERVE) [341] (n=834) §	
Week 88 LDAS28 (%) in patients who achieved sustained LDA with ETN 50 mg weekly + MTX for 36 weeks	ETN50+ MTX vs.ETN25+MTX vs. PBO+MTX: 82.6 vs. 79.1 vs. 42.6 ETN50+ MTX vs. PBO+MTX (mean difference (95% CI) 40.8 (32.5-49.1, p<0.0001) ETN25+MTX vs. PBO+MTX (mean difference (95% CI) 35.9 (27.0 to 44.8), p<0.0001)
Huizinga EULAR 2013 (ACT-RAY) [308] (n=556) §	
TCZ discontinuation after achieving the protocol-defined sustained remission (%) at Week 104	TCZ add-on vs. switch: 57 vs. 47 (p=0.13)
Flare (%) at Week 104	TCZ add-on vs. switch: 85 vs. 87 (p=0.075)
Study DFR (%) at Week 104	TCZ add-on vs. switch: 5.1 vs. 1.8 (0.037)
Smolen EULAR 2011 / EULAR 2012 (CERTAIN) [256 341] (n=194) †	
CDAI remission at Week 52 in patients who achieved CDAI remission at both weeks 20 and 24	Remission retained in 3/17 prior CZP vs. 2/6 placebo patients

§ MTX IR; † mixed csDMARD IR; CI, confidence interval; CZP, certolizumab pegol; DFR, drug free remission; csDMARD, conventional synthetic disease-modifying antirheumatic drug; ETN, etanercept; IR, incomplete responder; LDA, low disease activity, LDAS28, low disease activity score using the 28 joint count; MTX, methotrexate; PBO, placebo; SDC, smallest detectable change; TCZ, tocilizumab

Table 3.25 Biological DMARD strategy studies in established RA addressing biological DMARD dose reduction or stopping – study outcomes

Outcome	Result
Fautrel ACR 2012 / EULAR 2013 (STRASS) [309 311 343] (n=137)	
Taper and stopping TNFi (n (%)) at 18 months	S: 47 (73.4) tapered TNFi, of whom 24 (37.5) stopped
Relapse occurred at least once (%) at 18 months	S vs. M: 81 vs. 56, p=0.0009
Structural damage progression (n (%)) at 18 months	S vs. M: in 4 (6.7) and 3 (4.5) patients (p=0.3)
van Vollenhoven ACR 2012/ EULAR 2013 (DOSERA) [342 344] (n=91)	
Non-failure[#] (%) at week 48*	ETN50 vs.ETN25 vs. placebo: 52 vs. 44 vs. 13 (ETN50 vs. placebo*: OR 7.2 (1.7-29.8 (p=0.007), ETN25 vs. placebo: OR 4.2 (1.0 – 17.0 (p=0.44), ETN50 vs. ETN25 NS)

ADA, adalimumab; ETN, etanercept; ETN25, etanercept 25mg weekly; ETN50, etanercept 50mg weekly; IFX, infliximab, LDA, low disease activity, MTX, methotrexate; TNFi, tumor necrosis factor inhibitor

S =spacing ADA and ETN injections; M =maintain full dose ADA and ETN; [#] Failure = DAS28 ≥ 3.2 and an increase of SDAS28 ≥ 0.6 or disease progression as determined by the investigator or patient; * primary endpoint

3.4.4 Biosimilar DMARDs

The PLANETRA study was the first phase 3 RCT to compare the bsDMARD CTP-13 to infliximab. In this multicentre study 606 patients with MTX-IR RA were randomised to receive CTP-13 (n=302) or infliximab (n=304). The study met its primary endpoint - the ACR 20 response at week 30 (61% vs. 59% (95% CI -6% to 10%) for methotrexate and CT-P13 vs. methotrexate and infliximab respectively).[346] ACR50 and ACR70 responses were also similar in the two groups with no significant between-group differences at one year[320] (table 3.14).

3.4.5 Targeted synthetic DMARDs in the context of existing biological DMARDs

Tofacitinib is an oral targeted synthetic DMARD, selectively inhibiting Janus kinase (JAK) 1 and JAK 3, and to a lesser extent JAK 2. In the ORAL-STANDARD study, tofacitinib and adalimumab were compared to placebo in patients with MTX-IR RA[317] . The three primary endpoints were the ACR 20 responses at 6 months, the change from baseline to 3 months in HAQ-DI and the proportion of patients in DAS28-ESR remission at 6 months. ACR 20 responses for tofacitinib 5mg and 10 mg, and adalimumab were both significantly higher than placebo (51.5% vs. 52.6% vs. 47.2% vs 28.3% in the tofacitanib 5mg, tofacitanib 10mg, adalimumab and placebo groups respectively)(table 3.14). HAQ-DI and DAS28-ESR remission was significantly higher in the groups receiving tofacitinib and adalimumab compared to placebo.

Table 3.26 RCTs comparing a bDMARD to a biosimilar or a targeted synthetic DMARD –ACR responses

Treatment group	Patients evaluated (n)	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
Yoo ARD 2013 (PLANETRA)[346]								
MTX + CT-P13 3mg/kg	302*/248**	7	60.9*/73.3**	referent	42.3**	referent	20.2**	referent
MTX + IFX 3mg/kg	304*/251**		58.6*/69.7**	NS	40.6**	NS	17.9**	NS
van Vollenhoven 2012 (ORAL STANDARD) [317] (n=717)								
Placebo	106	6	28.3	referent		referent		referent
Tofacitinib 5mg twice daily	196		51.5	<0.001		≤0.05		≤0.05
Tofacitinib 10mg twice daily	196		52.6	<0.001		≤0.05		≤0.05
ADA 40mg every 2 weeks	199		47.2	<0.001		≤0.05		≤0.05

ACR, American College of Rheumatology; ADA, adalimumab; bDMARD, biological disease-modifying antirheumatic drug; DMARD disease-modifying antirheumatic drug; IFX infliximab; MTX, methotrexate; RCTs, Randomised controlled trials;*intention-to-treat population;** per protocol population

3.5 Discussion

With the increasing use of bDMARDs as well as the introduction of newer therapies including the tsDMARD tofacitinib and emerging bsDMARDs, a systematic review of the literature was warranted.

This SLR confirmed the efficacy of all the classes of bDMARDs in patients with MTX naïve, MTX-IR and TNF-IR RA. There is also data for TNFi for patients with DMARD-naïve RA and emerging data for the TNFi and abatacept in patients with UA. . With studies showing superior long-term clinical and radiographic outcomes using a bDMARD with methotrexate, this remains the optimal treatment approach and preferred option to bDMARD monotherapy. In situations where patients may not tolerate methotrexate or another csDMARD, however, bDMARD monotherapy may be considered. [245 275 281]

There have been an increasing number of RCTs addressing the efficacy of bDMARDs in different study populations across the IA disease continuum – looking at RA according to the 1987 ACR and the 2010 ACR/EULAR classification criteria, as well as patients in the earlier phases of the disease spectrum that did not fulfil these criteria. Different study designs have also been used aiming to address the optimal treatment approach and timing of bDMARD use. In essence studies have shown earlier improvement in signs and symptoms with the more intensive strategies compared to step-up approaches. Outcomes however were similar once bDMARDs were added in patients with insufficient response to methotrexate [1 240 241 279 281 339]. In RCTs addressing different step-up therapies in patients with MTX-IR RA, combination csDMARD therapy with methotrexate, sulphasalazine and hydroxychloroquine reported similar clinical efficacy to step up bDMARD therapy.[241 242 279] Low recruitment (and therefore possibly insufficient power) however were noted in some of these studies. Nevertheless, greater depth of response (higher proportions achieving ACR 70 responses (equivalent to low disease activity) [321] or remission) was seen with the use of bDMARD therapy. [293 337 347] Radiographic progression was also lower and proportions achieving radiographic non-progression were higher with combination therapies which included a bDMARD. [1 278 281 339] These were mainly due to the early effects of treatment. [184 281] High clinical response rates and low radiographic progression were also seen in the clinical trials which incorporated treat-to-target type strategies - many of these also included glucocorticoids. [293 296 337]

Studies have also looked at the possibility of bDMARD dose reduction or stopping once achieving control of disease activity. While clinical responses were higher

when continuing the bDMARD than when stopping treatment, there was evidence responses could be maintained with bDMARD dose reduction. Biological DMARD- and drug-free remission was achievable in some, particularly with earlier bDMARD use.

This literature search confirmed an absence of RCT evidence to guide decisions on switching from one bDMARD to another after failure of a TNFi.

Newer therapies have also emerged with trials showing efficacy of CT-P13, the infliximab bsDMARD and tofacitinib, the tsDMARD. Drug developments continue with several other new agents on the horizon.[348 349]

3.6 Limitations

The literature review has its limitations. One relates to the heterogeneous nature of the studies. The different inclusion criteria, trial designs and primary endpoints in particular, pose inherent challenges to ensuring accurate interpretation of the data. Whilst the main clinical outcomes on bDMARD efficacy were addressed, other outcomes e.g. the impact of bDMARDs on work ability was beyond the scope of this SLR. Standard definitions of disease activity (e.g. DAS28 < 2.6 for remission) were used, however recent insights suggest that these patients may still have ongoing disease activity despite achieving this target, highlighting the deficiencies of such measures. This review also focused on evidence from RCTs. Whilst these trials are regarded as the highest level of evidence, they reflect a select patient population, so results may potentially be less applicable to a real-life population. Non-randomised studies and evidence from clinical practice (e.g. from national registries) would provide valuable information to complements these data. Another aspect of bDMARD therapy that needs consideration is that of safety. Given its importance, this area was reviewed in a separate SLR.[189]

3.7 Conclusions

In conclusion, this SLR confirmed the efficacy of bDMARDs across the IA disease continuum in patients with UA and RA. It evaluated different treatment strategies addressing the issue regarding when to start bDMARD therapy and the potential for treatment reduction, particularly when early disease control has been achieved. It also highlighted new emerging therapies in this field.

Finally, this review identified some areas for further research. These included the need for more studies investigating the benefit of initial induction therapy with a bDMARD compared to stepping up to a bDMARD following a csDMARD,

particularly in very early disease. Related research areas include the identification of predictors of response to targeted therapies, the search for prognostic risk factors (e.g. the presence of erosions on X-ray at baseline) [339] identifying those patients who may benefit most from a more intensive, initial bDMARD treatment strategy, as well as the search for factors predicting successful treatment withdrawal.[230 303 340 345] Data from registries will also be an invaluable source of information, providing 'real-life' data on patients who may be excluded from RCTs.

Chapter 4 Infliximab vs. intravenous methylprednisolone with methotrexate as induction therapy in DMARD-naïve early RA

In this chapter, a RCT aimed to compare the use of induction therapy using methotrexate and infliximab to methotrexate and an intravenous glucocorticoid together with a treat-to-target approach in DMARD-naïve early RA.

4.1 Introduction

From the results of the systematic literature review detailed in chapter 4, it is clear that biological therapies are efficacious in treating patients with RA.[16] The benefit of bDMARDs is well established in patients who have had incomplete response to one or more csDMARD [180 187 323 324] or bDMARD.[326-329] Some studies have also confirmed efficacy in DMARD-naïve RA.[182 183 230] In clinical practice, however, particularly with cost considerations, bDMARDs are usually prescribed after failure of one or more csDMARD.[162]

There is evidence that achieving low levels of disease activity early, particularly within the first three months of therapy, predicts remission at one year[350] and is also associated with better long-term radiographic outcomes.[351] Optimising disease control in the early phases of the disease is therefore important. The optimal strategy however still remains to be determined.[223]

Treatment options for patients with RA include the use of csDMARDs, bDMARDs and glucocorticoids or combinations of these therapies. Of the csDMARDs, methotrexate is generally recommended as part of first-line therapy given its efficacy and safety profile. [209] As noted in chapter 4, bDMARDs have been used in clinical trials for treatment induction.[182 183 230 293] Glucocorticoids have also demonstrated anti-inflammatory as well as disease-modifying properties.[163] Rapid clinical improvements have been documented with high dose oral steroids.[164] Whilst less widely studied, IV glucocorticoids, have shown high remission rates in a small group of patients with MTX-naïve RA.[165] In addition to the therapeutic considerations, there is also evidence for the benefit of regular monitoring of disease activity and escalating therapy until a treatment goal is achieved – so called 'treating to target'. [10 215 216 221]

The Infliximab as induction therapy in early rheumatoid arthritis (IDEA) study was a RCT in patients with DMARD-naïve early RA. It aimed to compare the efficacy of

methotrexate and a TNFi to methotrexate with an IV steroid for remission induction, followed by a treat-to-target approach in both groups. Infliximab was chosen as the bDMARD given the short- and long-term clinical and radiographic efficacy data available at the time of study design.[183 324] Intravenous methylprednisolone was chosen as the comparator – the use of IV steroid for its rapid onset of action and potential impact on endothelial adhesion molecules as seen with TNFi,[352] as well as ease of blinding versus infliximab. As varying degrees of subclinical disease and subsequent structural progression have been documented with clinical remission, [138] and the trial was open after 26 weeks, an objective primary outcome looking at structural progression was chosen.

4.2 Patients and methods

4.2.1 Patients

Patients included in this study were aged 18 to 80 and who fulfilled the 1987 ACR classification criteria for RA with symptom duration between 3 and 12 months, active disease defined by DAS44 > 2.4 and were DMARD-naïve. The following were exclusion criteria: treatment with a prior DMARD, glucocorticoid use within one month prior to baseline, pregnancy or planned pregnancy within 24 months of screening, an opportunistic infection within six months or a serious infection within three months of screening, HIV infection, positive hepatitis B or C serology, relevant co-morbidities or important concurrent medical conditions, a history of lymphoproliferative disease, or any other malignancy within the previous 5 years (with the exception of basal cell or squamous carcinoma of the skin that had been treated with no evidence of recurrence). Screening for tuberculosis was carried out in accordance with local recommendations.

4.2.2 Treatment allocation and intervention

The IDEA study was an 18-month multicentre, double-blind, randomised (1:1), phase 4, superiority study. It was designed by consensus of the regional rheumatologists in West Yorkshire, UK and conducted across four sites. These were Leeds, Huddersfield, Harrogate and Bradford.

Patients were randomised to receive either methotrexate and infliximab or methotrexate and IV steroid. Patient consent was obtained, after which the research nurse telephoned central pharmacy for allocation consignment. The personnel at central pharmacy were independent of the recruitment process. They assigned

subject numbers according to a block randomisation programme which was generated using random number tables, stratified by site.

Both groups of patients received methotrexate 10mg weekly. This was increased to 20mg or the maximum tolerated dose by week 6. Folic acid 5 mg daily except the day of methotrexate was also prescribed. Patients, clinical staff and assessors were blinded to the treatment allocation during the first 26 weeks. All patients received infusions over a 2-hour period from visually identical 250ml bags during this double blind phase. Those in the infliximab group received: infliximab 3mg/kg (maximum dose 1000mg) at weeks 0, 2, 6, 14 and 22. Those in the IV steroid group received IV methylprednisolone 250mg at week 0 followed by placebo infusions at weeks 2, 6, 14 and 22. Disease activity was measured at the following time points: weeks 0, 6, 14, 22, 26, 38, 50, 68 and 78. During the open label observation period, from week 26, patients continued treatment according to a predetermined study escalation protocol. If low disease activity was not achieved (DAS44>2.4) at those visits, infliximab dose adjustments or DMARD changes were made in the infliximab group and DMARD escalated in the IV steroid group as shown in figure 4.1.

A treat-to-target approach was used throughout the study. If low disease activity was not attained at weeks 6, 14, 22, 38, 50 and 62, IM methylprednisolone 120mg was administered for both groups. Intra-articular steroid could be given up to an equivalent dose of methylprednisolone 120mg if a joint required aspiration and injection. if a smaller amount was used, the remainder was given as an IM injection. In patients with a DAS28 ≥ 5.2 who had failed 2 DMARDs, bDMARDs could be considered according to NICE guidelines.[353]

Infliximab infusions were stopped in all patients in the infliximab arm at week 78 (study endpoint) or if they withdrew from the study. In patients on infliximab who achieved sustained remission (DAS44 <1.6 at all consecutive visits for 6 months), infliximab could be stopped early. Patients who withdrew but who were still willing to attend for clinical assessments continued follow up according to the study visit schedule. Prophylaxis for osteoporosis was administered at the discretion of the treating physician, guided by local guidelines.

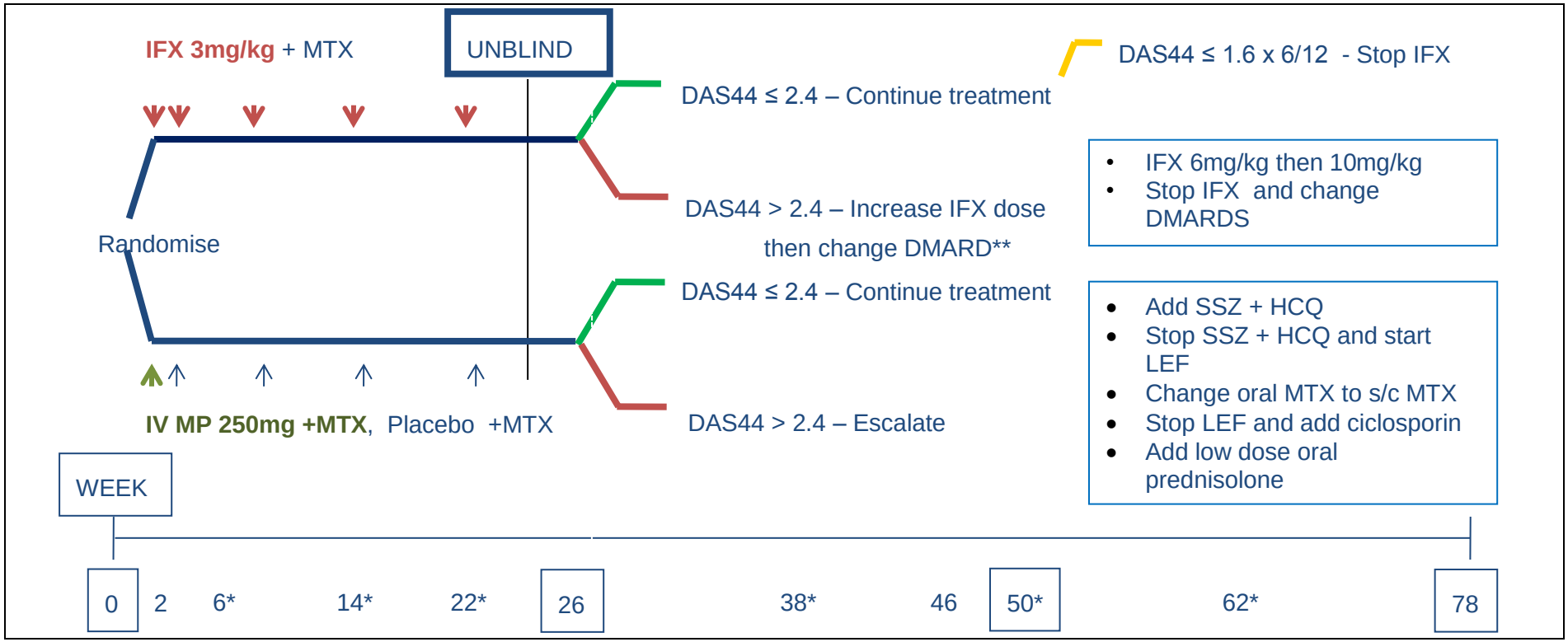


Figure 4.1 IDEA study design

DMARD, disease-modifying antirheumatic drug, IFX, infliximab , * IM methylprednisolone if DAS44 > 2.4

**DMARD escalation protocol: sulphasalazine (SSZ) 500mg daily increasing to 1g bd over a 4 week period and hydroxychloroquine (HCQ) 200mg - 400mg daily to a maximum of 6.5mg/kg, then stop SSZ and HCQ and add leflunomide (LEF)10mg daily for 1 month, then increase to 20mg daily, then one of the following: subcutaneous (s/c) methotrexate (MTX) and LEF or MTX and ciclosporin 2.5mg/kg/day or MTX, LEF and prednisolone 5-7.5mg daily. If DAS 28 ≥5.2, assess for other biological DMARD therapy according to NICE criteria or other trials and potential to exit trial.

4.2.3 Efficacy and safety outcomes

Radiographic progression, defined by the change in total mTSS at week 50, was the study primary outcome. [354] Secondary radiographic outcomes included the changes in joint space narrowing (JSN) and erosion (ERO) scores and the proportions of patients achieving radiographic non-progression (change < 0.5 units[355] and change < the smallest detectable change (SDC) for this study). X-rays were read in time order and scored independently by two experienced radiographers who were blinded to treatment allocation.

Secondary clinical outcomes included the proportion of patients achieving clinical remission (DAS44<1.6), and the proportion in sustained remission (DAS44<1.6 for 6 months) and were therefore eligible to stop infliximab. Patient reported outcomes included the HAQ-DI[225] and the RA Quality of Life score (RAQoL) which were measured at baseline and weeks 26 and 78. The proportion of patients remaining in paid employment was also calculated.

The subgroup of patients recruited in Leeds had ultrasound assessments for synovitis. These were performed using a Philips HDI 5000 machine, employing a 15-8 MHz transducer at baseline, weeks 50 and 78 by four rheumatologists trained in MSK ultrasound, with good intra- and inter-reader reliability (data not shown). The findings in 22 joints (wrists, MCP joints 2 and 3, PIP joints 2 and 3, and MTP joints 1 to 5 bilaterally) were compared between the two groups. OMERACT definitions were used to define synovitis.[356] The EULAR-OMERACT scoring system, a 0-3 semi-quantitative scale, was used to score grey scale change and power Doppler signal.[357] The clinical assessors were unaware of the ultrasound findings.

Post hoc analyses included the ACR 20/50/70 responses[358] and proportions of patients achieving low disease activity (DAS44 <2.4 and DAS28 <3.2), 3-variable DAS28 remission (<2.6) and remission based on the 2010 ACR/EULAR criteria (tender joint count ≤ 1, swollen joint count ≤ 1, patient global assessment (PGA)cm ≤ 1 and CRP mg/dL≤1) or SDAI remission (≤3.3)).[359] The proportion of patients in clinical remission (DAS44<1.6) at week 78 no longer on infliximab/placebo infusions and duration of biologic-free remission, in patients who were able to stop biological therapy early, were calculated. (Loss of this state was defined by an increase in DAS44 of 1.2, a DAS44 >1.6 or any change in disease activity score requiring an increase in therapy).[360] Differences in steroid requirements in each group were also assessed. In a subset of patients, post hoc regression analyses were also conducted to determine the association between baseline factors and outcome at 78 weeks (clinical remission (defined by DAS44<1.6), annualised radiographic progression).

Patients were asked to report new adverse events at each visit. Clinical and laboratory adverse events were documented using standard medical terms.

4.2.4 Sample size

The sample size for the study was calculated to detect a significant difference in damage progression, measured by the mTSS, between the two treatment groups. Estimated radiographic progression in each group was based on that observed in the BeSt study[183] in which 508 patients with early DMARD-naïve RA were allocated to one of four treatment groups. The change in mTSS in the step-up (mean (SD) 4.3 (6.5)) and the methotrexate and infliximab (mean (SD) 1.3 (4.0)) combination therapy groups were thought to best reflect the magnitude of expected response, and were used to power this study. With an 80 percent power to detect a difference, at a 5% two-sided significance level, 56 patients were required per group, assuming that the use of non-parametric statistics may be required if the primary outcome were skewed.

4.2.5 Statistical methods

4.2.5.1 Numbers analysed

All patients (n=112) were included in the multiple imputation analyses. For the complete case analyses, the number of patients with available data for each outcome varied. The number of patients included has been provided for each of the comparisons. There were safety data for all 112 patients.

4.2.5.2 Statistical analyses

Efficacy and safety analyses were performed on subjects who received at least one dose of the study drug. Patient data were analysed according to the groups to which they were originally assigned i.e. on an intention to treat (ITT) basis.

The SDC in mTSS was calculated according to the Bland-Altman 95% limits of agreement method. Intra-class correlation coefficients were used to quantify agreement between the change in scores of the two readers. For disease activity, values presented are for the 3-variable DAS44-CRP (lower limit for CRP = 5 mg/L). For patients where ESR measurements were more complete than the CRP measurements, values for ESR were converted to CRP using a published nomogram[361] prior to calculation of the DAS score. Where possible, provided the data were found to fit the Rasch model (lack of local dependency and differential

item functioning, demonstrating unidimensionality and achieving sufficient person separation), questionnaire scores were transformed to quasi interval scaling prior to analysis using RUMM2030.

Categorical outcomes were analysed using logistic regression and continuous outcomes (Rasch-transformed HAQ-DI, RAQoL) were analysed using linear regression. Baseline values and study site were controlled for in each analysis. Non-parametric quantile regression models were also constructed for severely skewed variables. Amongst the secondary outcomes, the threshold for statistical significance was adjusted for multiple comparisons using the Holm method. There were no adjustments made for the exploratory analyses.

Multiple imputation[362] by chained equations was performed to account for missing data. These results were combined according to Rubin's rules. This was based on the assumption that data was missing at random (MAR). For continuous variables, missing baseline data were imputed using the mean and missing indicator method. For categorical variables, a separate category was created for missing values. Data that were missing at later visits were imputed in each treatment group separately. This was done using logistic regression for categorical variables and predictive mean matching for continuous variables. Derived variables (mTSS, radiographic progression>SDC, remission) were computed passively after imputation of the component variables prior to analysis.

A sensitivity analysis which only included patients with available data (complete case, CC) was also performed. This assuming data were missing completely at random (MCAR). Further sensitivity analyses were conducted to challenge the MAR assumption in the primary analysis. This was done by increasing or decreasing the imputed values in each treatment group in order to mimic various missing not at random (MNAR) patterns. For the complete case analysis of radiographic data, only patients with baseline and follow-up radiographs were included. Annualised progression scores were analysed using linear regression of the change scores, controlling for natural log-transformed baseline values and for study site, which was entered as a fixed factor. Robust standard errors were used to account for heteroskedasticity. Because the primary outcome was right-skewed, the primary analysis was supplemented with non-parametric quantile regression, minimising differences from the median, rather than the mean. In addition to this, a per-protocol analysis was performed. Analyses were conducted in Stata 12.1.

Descriptive results are presented for harms. In cases of recurring events, only the most severe occurrence was counted in each patient. Absolute and relative

frequencies are presented together with the number of occurrences per 100 patient-years of follow-up.

4.3 Results

In total 112 patients were recruited from the 4 sites in West Yorkshire, U.K. between September 2006 to July 2009. The majority (81%) were from Leeds which was the main centre. The remaining patients were from Harrogate, Huddersfield and Bradford. Patients attended for screening (within 4 weeks prior to baseline), at the time of randomisation (baseline) and for subsequent visits for 78 weeks according to the study protocol (figure 4.2).

The demographic and baseline characteristics are presented in table 4.1. The clinical features were similar between the two groups. The methotrexate and IV steroid group had a slightly higher proportion of RF and anti-CCP positivity compared to the methotrexate and infliximab group (60.7% vs. 49% and 75% vs. 64% in the methotrexate and IV steroid an methotrexate and infliximab groups respectively). The mean radiographic scores were also somewhat higher in the methotrexate and IV steroid group at baseline (mTSS 9.23 (18.31) vs. 6.05 (10.83)).

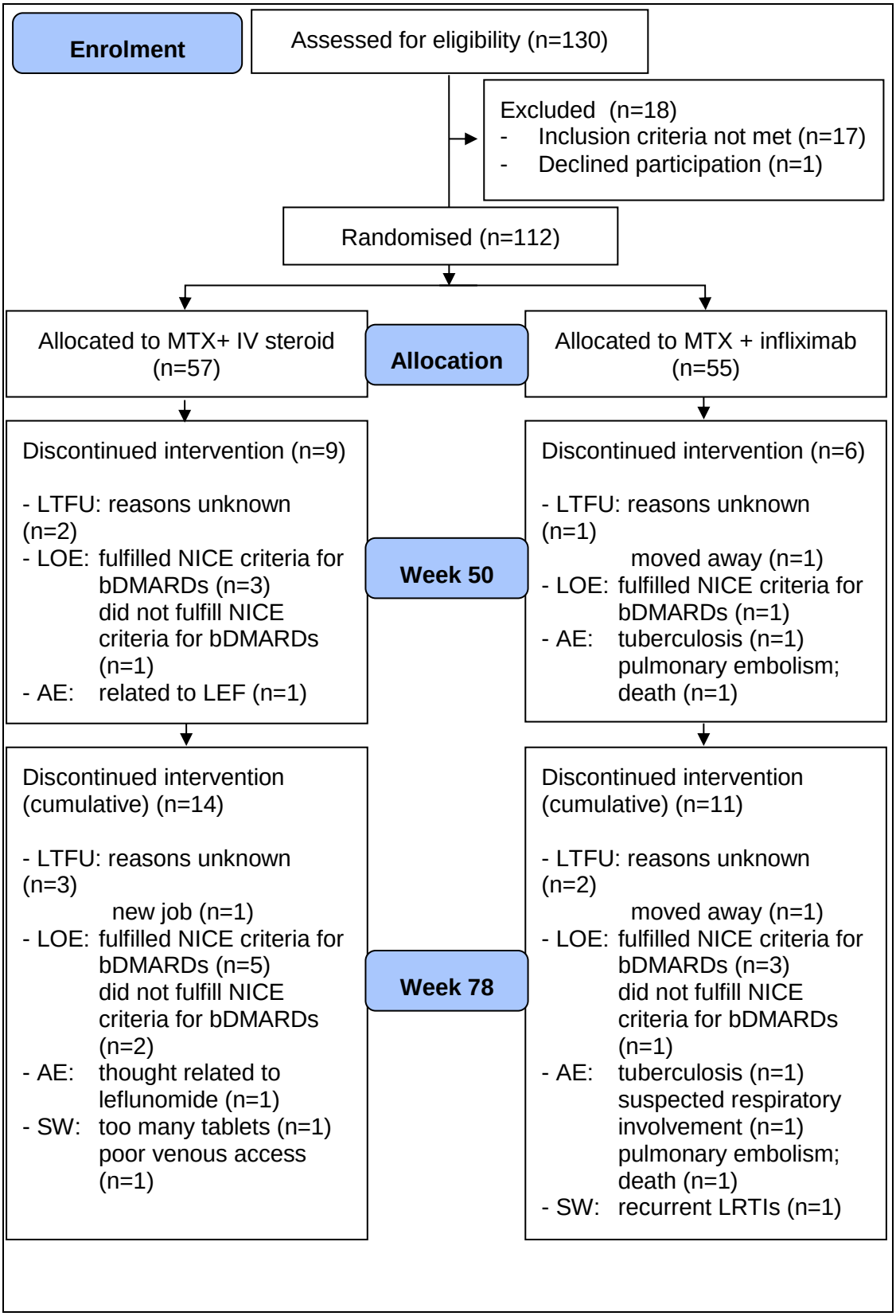


Figure 4.2 IDEA study patient disposition

AE, adverse event; bDMARD, biological disease-modifying antirheumatic drug; LEF, leflunomide; LOE, loss of efficacy; LTFU, lost to follow up; SW, subject withdrawal

Table 4.1 Baseline characteristics of patients in each treatment group

		MTX + IV steroid (n=57)	**MTX + IFX (n=55)**
Site:	**Leeds** **Huddersfield** **Harrogate** **Bradford**	n=45 n=3 n=6 n=3	n=44 n=3 n=5 n=3
Age (years):	**mean(SD)** **range**	52.9 (12.8) 19 to 77	53.7 (13.0) 28 to 78
Female:	**n (%)**	41 (71.9%)	36 (65.5%)
Disease duration (months):	**median (IQR)**	1.2 (0.7, 2.1)	1.2 (0.7, 1.7)
Symptom duration (months):	**median (IQR)**	6.9 (4.8, 9.8)	7.2 (5.1, 10.7)
ESR:	**median (IQR)**	47 (21, 80) (n=56)	35 (19, 52) (n=54)
CRP (mg/L):	**median (IQR)**	18 (10, 51)	16 (7, 61)
DAS44:	**mean (SD)**	3.56 (0.98)	4.05 (1.04)
RF positive:	**n (%)**	34/56 (60.7%)	27 (49.1%)
Anti-CCP positive:	**n (%)**	39/52 (75.0%)	32/50 (64.0%)
HAQ-DI:	**mean (SD)**	1.3 (0.54) (n=56)	1.4 (0.53) (n=55)
RAQoL:	**mean (SD)**	15.9 (4.7) (n=56)	17.9 (5.3) (n=53)
ERO:	**mean (SD)** **median (IQR)**	3.51 (8.73) (n=50) 0.50 (0.00, 3.50)	1.36 (2.91) (n=43) 0.00 (0.00, 1.50)
JSN:	**mean (SD)** **median (IQR)**	5.72 (9.93) (n=50) 2.00 (0.50, 7.00)	4.69 (8.38) (n=43) 2.00 (0.00, 7.50)
mTSS:	**mean (SD)** **median (IQR)**	9.23 (18.31) (n=50) 2.50 (1.00, 10.00)	6.05 (10.83) (n=43) 3.00 (0.50, 9.50)

Anti-CCP, anti-cyclic citrullinated peptide antibody; CRP, C-reactive protein; DAS44CRP, 3-variable disease activity score based on CRP, RAI and SJC44; ERO, erosion; ESR, erythrocyte sedimentation rate; HAQ-DI, Rasch-transformed health assessment questionnaire disability index score; IFX, infliximab; IV, intravenous; JSN, joint space narrowing; mTSS, MTX, methotrexate; van der Heijde modified total Sharp score; RAQoL, Rasch-transformed rheumatoid arthritis quality of life score; RF, rheumatoid factor

4.3.1 Radiographic outcomes

There was excellent agreement between the two readers' changes scores (ICC=0.8). The calculated SDC for this study was 2 units.

Baseline JSN, ERO and total mTSS scores in the methotrexate and IV steroid and the methotrexate and infliximab groups are presented in table 4.1. At week 50, the mean (SD) changes in total mTSS (ΔmTSS) (primary endpoint) were 2.81 (6.88) and 1.20 (2.27) in the methotrexate and IV steroid and the methotrexate and infliximab groups respectively, with no significant between group difference (adjusted difference (95% CI) -1.45 (-3.35, 0.45), p=0.132) (table 4.2). Figure 4.3 shows a cumulative probability plot of radiographic progression at week 50. The findings were similar for JSN and ERO scores at week 50 and for JSN, ERO and total scores at weeks 26 or 78. Non-parametric analysis did not change the overall conclusions.

At week 78 radiographic non-progression, defined by ΔmTSS <0.5, was 46.7% in the methotrexate and IV steroid group and 61.9% in the methotrexate and infliximab group (p=0.116)]. Using ΔmTSS <2.0 (change <SDC) to define radiographic non-progression, this was achieved in 71.0% and 80.6% of the methotrexate and IV steroid and methotrexate and infliximab groups respectively (p=0.328).

Table 4.2 Multiple imputation analysis of radiographic changes at weeks 26, 50 and 78; results were adjusted for baseline values and study site.

Radiographic outcome	MTX + IV Steroid (n=57)	MTX + IFX (n=55)	Unadjusted difference (95% CI)	Adjusted difference (95% CI)	p
Change at week 26					
ERO mean (SD)	0.74 (1.94)	0.35 (0.89)	-0.39 (-1.03, 0.26)	-0.26 (-0.82, 0.30)	0.357
median (IQR)	0.00 (0.00, 0.65)	0.00 (0.00, 0.38)	0.00 (-0.13, 0.13)	0.00 (-0.12, 0.12)	1.000
JSN mean (SD)	0.78 (2.63)	0.48 (1.02)	-0.31 (-1.09, 0.48)	-0.29 (-0.99, 0.42)	0.420
median (IQR)	0.00 (0.00, 0.57)	0.00 (0.00, 0.64)	0.00 (-0.17, 0.17)	0.00 (-0.12, 0.12)	1.000
mTSS mean (SD)	1.52 (4.25)	0.83 (1.69)	-0.69 (-1.99, 0.60)	-0.59 (-1.70, 0.52)	0.291
median (IQR)	0.04 (0.00, 1.18)	0.00 (0.00, 1.02)	-0.04 (-0.34, 0.42)	-0.20 (-0.29, 0.25)	0.880
Change < SDC	82.5%	85.1%	OR 1.23 (0.35, 4.31)	OR 1.18 (0.31, 4.51)*	0.806
Change ≤ 0.5	63.5%	68.5%	OR 1.25 (0.52, 3.04)	OR 1.35 (0.46, 3.95)	0.579
Change at week 50					
ERO mean (SD)	1.28 (3.26)	0.49 (1.21)	-0.79 (-1.83, 0.26)	-0.58 (-1.53, 0.37)	0.224
median (IQR)	0.14 (0.00, 0.87)	0.00 (0.00, 0.64)	-0.14 (-0.68, 0.40)	0.00 (-0.21, 0.21)	1.000
JSN mean (SD)	1.53 (3.95)	0.71 (1.31)	-0.82 (-1.99, 0.34)	-0.80 (-1.87, 0.27)	0.141
median (IQR)	0.07 (0.00, 1.51)	0.00 (0.00, 0.97)	-0.07 (-0.55, 0.40)	-0.03 (-0.38, 0.32)	0.878

mTSS mean (SD) **median (IQR)**	2.81 (6.88) 0.65 (0.00, 2.37)	1.20 (2.27) 0.11 (0.00, 1.55)	-1.61 (-3.69, 0.47) -0.53 (-1.36, 0.29)	-1.45 (-3.35, 0.45) -0.16 (-0.85, 0.54)	0.132 0.651
Change < SDC	71.0%	80.6%	OR 1.68 (0.57, 4.95)	OR 1.77 (0.56, 5.61)*	0.328
Change ≤ 0.5	46.7%	61.9%	OR 1.96 (0.77, 4.47)	OR 2.13 (0.83, 5.46)*	0.116
Change at week 78					
ERO mean (SD) **median (IQR)**	1.32 (3.46) 0.07 (0.00, 0.80)	0.75 (2.03) 0.01 (0.00, 1.07)	-0.57 (-1.83, 0.70) -0.06 (-0.49, 0.38)	-0.33 (-1.46, 0.81) 0.00 (-0.28, 0.28)	0.564 1.000
JSN mean (SD) **median (IQR)**	1.87 (4.58) 0.31 (0.00, 1.90)	0.94 (1.69) 0.03 (0.00, 1.26)	-0.93 (-2.35, 0.48) -0.28 (-0.93, 0.36)	-0.90 (-2.22, 0.42) -0.04 (-0.48, 0.40)	0.178 0.856
mTSS mean (SD) **median (IQR)**	3.19 (7.75) 0.66 (0.00, 2.59)	1.69 (3.28) 0.43 (0.00, 2.17)	-1.50 (-4.01, 1.01) -0.23 (-1.16, 0.71)	-1.31 (-3.59, 0.96) -0.11 (-0.85, 0.63)	0.253 0.769
Change < SDC	66.4%	74.4%	OR 1.50 (0.50, 4.55)	OR 1.53 (0.45, 5.14)*	0.492
Change ≤ 0.5	51.1%	54.5%	OR 1.15 (0.46, 2.89)	OR 1.22 (0.45, 3.32)*	0.699

ERO, erosion; IFX, infliximab ; IV, intravenous; JSN, joint space narrowing; mTSS, van der Heijde modified total Sharp score; MTX, methotrexate; SDC, smallest detectable change in mTSS (2 units)

*Not adjusted for site because for at least 1 site the outcome was the same for all patients therefore odds ratio could not be calculated

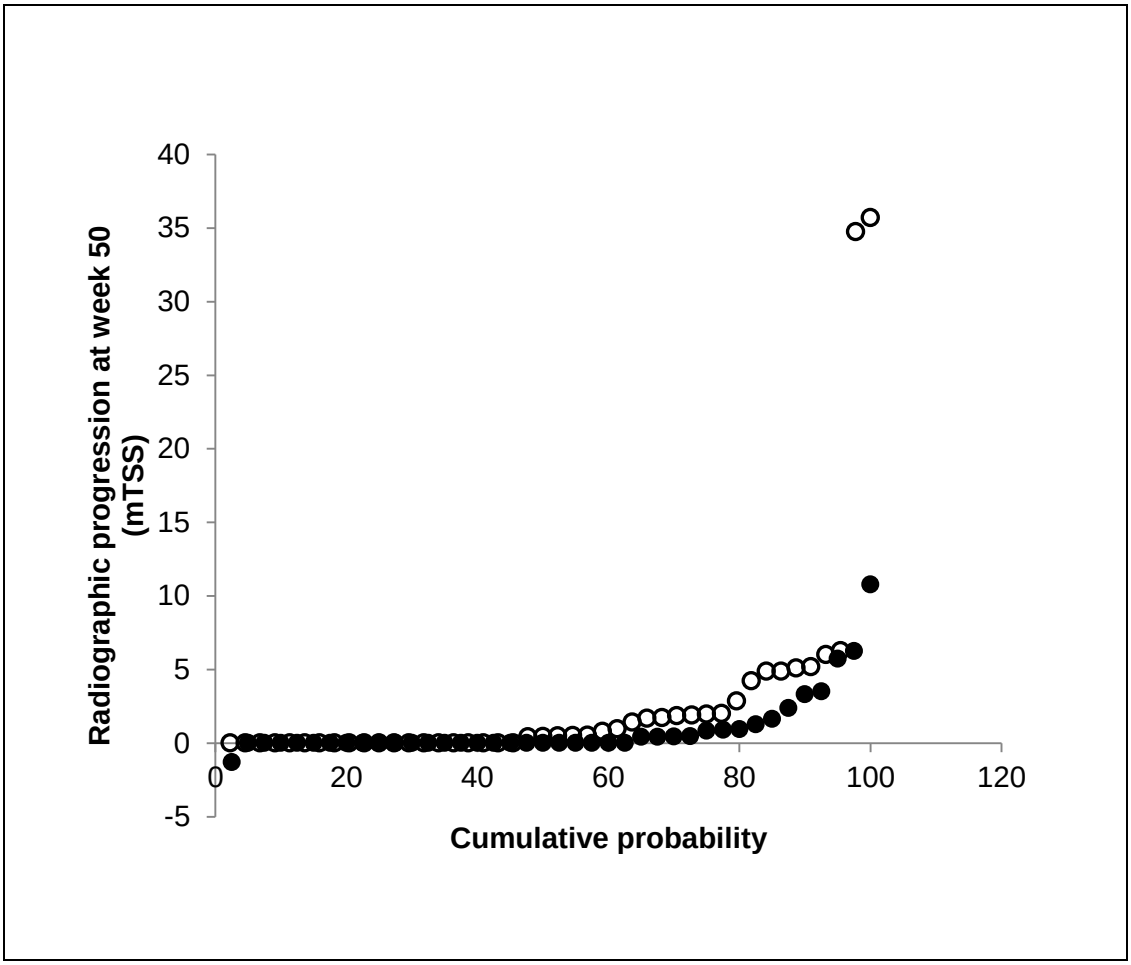


Figure 4.3 Cumulative probability plot showing radiographic progression at week 50

Patients treated with methotrexate and IV methylprednisolone (open symbols, n=44) and methotrexate and infliximab (closed symbols, n=40)

4.3.2 Clinical outcomes

4.3.2.1 Remission and low disease activity

There was no significant difference between the two treatment groups in the proportions of patients achieving DAS44 remission at weeks 26, 50 or 78 (table 4.3).

From the exploratory outcomes, a greater proportion of patients who received methotrexate and infliximab achieved early clinical responses compared to those who received methotrexate and IV steroid. At week 6, LDAS44 was 30.4% vs. 46.0% in the methotrexate and IV steroid and methotrexate and infliximab groups respectively (adjusted OR=3.75 (1.46, 9.62), p=0.006). Remission at week 6 was also higher with methotrexate and infliximab (DAS44 remission: 7.1% vs. 18.3%, adjusted OR=5.02 (1.30, 19.33), p=0.019, and DAS28 remission: 7.5% vs. 22.3% adjusted OR=6.16 (1.61, 23.54), p=0.008, in the methotrexate and IV steroid and the methotrexate and infliximab groups respectively). However by week 14 the differences between the two treatment groups were no longer apparent. There were few substantive differences between the groups at the later study time points in the proportions of patients achieving ACR 20/50/70 responses, LDAS28, LDAS44, DAS28 remission, 2010 ACR/EULAR remission (Boolean definition) or SDAI remission (table 4.3).

Sustained remission, defined by DAS44 < 1.6 maintained for ≥ 6 months, was achieved in 30.8% and 37.9% of the methotrexate and IV steroid and methotrexate and infliximab groups respectively. Assuming non-response for patients who withdrew early, the results were similar for the observed data (27.3% (15/55) vs. 34.6% (19/52)). There was no significant difference between the groups in terms of time to achieving sustained remission (unadjusted mean 60.98 vs. 59.27 weeks, site- and baseline DAS44-adjusted HR 1.48 (-0.76, 2.87), p=0.251). Sustained remission was maintained if patients remained at DAS44<1.6 at subsequent time-points, had no evidence of increase in DAS44>1.2, and no changes in treatment. Of those who achieved sustained remission in the observed data, flare occurred in three patients in the methotrexate and IV steroid group (one each at weeks 50, 62 and 78) and in four patients in the methotrexate and infliximab group (at weeks 50 & 62, two at week 78).

In the methotrexate and infliximab group, 24.5% (14/55) of patients stopped infliximab due to sustained remission (> 6 months) and of these 78.6% (11/14) maintained remission during the remainder of the study period. There was one patient who achieved sustained remission after week 26 but did not discontinue infliximab before week 78. This was due to an error in DAS44 calculation at week

38. The patient was not included in this total. In the majority of patients who achieved sustained remission and stopped infliximab did so within the first year of treatment (11/14). The earliest was at week 30 (7.5 months from baseline).

4.3.2.2 ACR 20%, 50% and 70% responses

The proportions of patients achieving ACR 20, 50 and 70 responses at weeks 26 and 78 were similar in the two treatment groups (table 4.3). Approximately half of the patients achieved an ACR70 response by week 78 (50.1% vs. 46.2% in the methotrexate and IV steroid and methotrexate and infliximab groups respectively).

4.3.3 Patient-reported outcomes

4.3.3.1 Patient-reported function and quality of life

There were substantive improvement in both groups at week 26 with continued improvement to week 78. At week 78, the mean change in HAQ-DI was -0.79 and -0.85 in the methotrexate and IV steroid and methotrexate and infliximab groups respectively (adjusted difference (95% CI) -0.03 (-0.26, 0.21), p=0.826). (table 4.3)

4.3.3.2 Maintenance of paid employment

At baseline 57.1% (32/56) of patients in the methotrexate and IV steroid group and 57.4% (31/54) in the methotrexate and infliximab group were in full-time or part-time paid employment. At week 78 there were data available for 26 patients in the methotrexate and IV steroid group who were in paid employment at baseline, 4 of whom had retired and 29 patients in the methotrexate and infliximab group, 5 of whom had retired. Of the remaining patients, 81.8% (18/22) in the methotrexate and IV steroid group compared to 91.7% (22/24) of those in the methotrexate and infliximab group remained in paid employment at week 78 (OR (95% CI)=2.44 (0.40, 14.91), p=0.333). In eight patients, employment status was unknown at week 78. Of these, four patients (3 methotrexate and IV steroid and 1 methotrexate and infliximab) remained in paid employment at week 62 and one in the methotrexate and IV steroid group was unemployed at week 62. In those who were in paid employment at week 78, no difference was seen in the proportion of patients who reported taking sick leave because of their arthritis within the previous 3 months (11.1% (2/18) vs. 18.2% (4/22), OR 1.78 (0.29, 11.04), p=0.537).

Table 4.3 Multiple imputation analysis of secondary and exploratory clinical and patient-reported outcomes at weeks 2, 14, 26, 50 and 78; results were adjusted for baseline values and study site.

Week	Clinical outcome	MTX + IV Steroid (n=57)	MTX + IFX (n=55)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p
6	**DAS44 remission**	7.1%	18.3%	OR 2.93 (0.86, 10.00)	OR 5.02 (1.30, 19.33)*	0.019
	DAS44 LDAS	30.4%	46.0%	OR 1.95 (0.89, 4.25)	OR 3.75 (1.46, 9.62)	0.006
	DAS28 remission	7.5%	22.3%	OR 3.56 (1.07, 11.80)	OR 6.16 (1.61, 23.54)*	0.008
	DAS28 LDAS	23.9%	33.5%	OR 1.60 (0.69, 3.69)	OR 2.63 (1.00, 6.93)*	0.051
	SDAI remission	3.6%	4.4%	OR 1.19 (0.16, 8.66)	OR 1.54 (0.21, 11.48)*	0.674
14	**DAS44 remission**	31.0%	34.8%	OR 1.19 (0.53, 2.65)	OR 1.89 (0.78, 4.62)*	0.161
	DAS44 LDAS	61.4%	66.8%	OR 1.27 (0.58, 2.77)	OR 3.44 (1.21, 9.76)	0.020
	DAS28 remission	40.0%	42.3%	OR 1.10 (0.52, 2.35)	OR 1.68 (0.70, 4.05)*	0.250
	DAS28 LDAS	54.1%	55.4%	OR 1.061 (0.50, 2.24)	OR 1.61 (0.670, 3.83)*	0.285
	SDAI remission	16.7%	24.5%	OR 1.61 (0.58, 4.44)	OR 2.04 (0.70, 5.92)*	0.191
26	**DAS44 remission**	40.0%	31.6%	OR 0.69 (0.31, 1.54)	OR 0.82 (0.36, 1.88)	0.644
	DAS44 LDAS	68.4%	65.9%	OR 0.89 (0.40, 2.00)	OR 1.48 (0.57, 3.84)	0.422

	DAS28 remission	50.8%	40.6%	OR 0.66 (0.31, 1.42)	OR 0.76 (0.34, 1.70)	0.510
	DAS28 LDAS	66.6%	64.6%	OR 0.92 (0.41, 2.04)	OR 1.32 (0.54, 3.27)*	0.545
	SDAI remission	24.1%	29.6%	OR 1.32 (0.56, 3.14)	OR 1.55 (0.63, 3.79)	0.340
	ACR EULAR remission	19.3%	14.5%	OR 0.71 (0.26, 1.93)	OR 0.75 (0.27, 2.08)	0.587
	ACR20	75.2%	71.0%	OR 0.81 (0.35, 1.89)	OR 0.81 (0.35, 1.89)*	0.626
	ACR50	55.1%	54.0%	OR 0.96 (0.45, 2.03)	OR 0.95 (0.45, 2.03)	0.898
	ACR70	31.8%	32.7%	OR 1.04 (0.47, 2.32)	OR 1.04 (0.46, 2.33)	0.927
	Change in HAQ-DI mean (SD)	-0.61 (0.47)	-0.70 (0.56)	-0.09 (-0.29, 0.11)	-0.05 (-0.23, 0.13)	0.568
	Change in RAQoL mean (SD)	-6.29 (5.83)	-7.87 (6.58)	-1.57 (-3.96, 0.81)	-0.88 (-3.19, 1.44)	0.454
50	**DAS44 remission**	36.1%	48.5%	OR 1.67 (0.75, 3.72)	OR 2.13 (0.91, 5.00)*	0.082
	DAS44 LDAS	70.6%	70.4%	OR 0.99 (0.42, 2.32)	OR 1.26 (0.51, 3.12)	0.617
	DAS28 remission	49.6%	55.7%	OR 1.28 (0.59, 2.76)	OR 1.71 (0.73, 3.99)	0.218
	DAS28 LDAS	63.4%	68.7%	OR 1.27 (0.55, 2.91)	OR 1.68 (0.68, 4.19)	0.264
	SDAI remission	27.2%	45.3%	OR 2.23 (0.96, 5.18)	OR 2.98 (1.18, 7.56)	0.021
	ACR EULAR remission	19.4%	16.5%	OR 0.82 (0.31, 2.17)	OR 0.84 (0.31, 2.25)*	0.729
78	**DAS44 remission**	50.0%	47.7%	OR 0.91 (0.40, 2.09)	OR 1.12 (0.47, 2.68)*	0.792

	DAS44 LDAS	80.4%	72.7%	OR 0.65 (0.23, 1.87)	OR 0.92 (0.29, 2.93)*	0.888
	DAS28 remission	65.3%	54.3%	OR 0.63 (0.27, 1.46)	OR 0.74 (0.31, 1.76)*	0.488
	DAS28 LDAS	76.4%	63.6%	OR 0.54 (0.22, 1.35)	OR 0.60 (0.23, 1.53)*	0.282
	SDAI remission	49.4%	37.6%	OR 0.62 (0.27, 1.40)	OR 0.73 (0.30, 1.76)	0.480
	ACR EULAR remission	15.9%	15.7%	OR 0.99 (0.34, 2.87)	OR 1.04 (0.35, 3.08)*	0.950
	ACR20	71.1%	70.7%	OR 0.98 (0.39, 2.46)	OR 0.98 (0.39, 2.46)*	0.973
	ACR50	63.4%	64.3%	OR 1.04 (0.44, 2.45)	OR 1.03 (0.43, 2.48)	0.953
	ACR70	50.1%	46.2%	OR 0.85 (0.39, 1.89)	OR 0.84 (0.37, 1.88)	0.669
	Change in HAQ-DI mean (SD)	-0.79 (0.54)	-0.85 (0.60)	-0.06 (-0.31, 0.19)	-0.03 (-0.26, 0.21)	0.826
	Change in RAQoL mean (SD)	-7.96 (6.32)	-9.71 (7.80)	-1.75 (-4.77, 1.28)	-0.62 (-3.34, 2.09)	0.650

DAS28, disease activity score based on a 28-joint count; DAS44, disease activity score based on RAI and SJC44; HAQ-DI=Rasch-transformed health assessment questionnaire disability index score; IFX, infliximab; IV, intravenous; LDAS, low disease activity score; MI, multiple imputation, MTX, methotrexate; RAQoL=Rasch-transformed rheumatoid arthritis quality of life score; SDAI, simplified disease activity index,

* Not adjusted for site because for at least 1 site the outcome was the same for all patients therefore OR could not be calculated

4.3.4 Use of glucocorticoids, methotrexate and other DMARDs

The unadjusted mean additional glucocorticoid requirement over the study period (total cumulative dose divided by months of follow-up) was 21.1mg methylprednisolone/month in the methotrexate and IV steroid group (n=57) and 16.0mg/month in the methotrexate and infliximab group (n=55) (adjusted mean difference (95% CI) -4.96 (-10.31, 0.38), p=0.069). Assessment of glucocorticoid use at different points in time was measured by dividing the study into six 12-week intervals (table 4.4). Overall, glucocorticoid use was greater during the earlier parts of the study. There was some evidence of greater additional IA/IM glucocorticoid use in the methotrexate and IV steroid group between weeks 13 and 26, but subsequently the amounts used in each group was comparable.

In terms of DMARD therapy, 55 patients in the methotrexate and IV steroid group achieved a maximum methotrexate dose of 20mg, and two achieved a dose of 25mg. In the methotrexate and infliximab group 53 patients achieved a maximum methotrexate dose of 20mg, one withdrew at week 2 prior to dose escalation, and another was maintained on 15mg due to abnormal liver function tests during dose escalation.

The proportions of patients requiring additional DMARD therapy treatment are presented in table 4.5. In total 38 (66.7%) patients in the methotrexate and IV steroid group and 32 (58.2%) in the methotrexate and infliximab group required a change in medication during follow-up.

Table 4.4 : Intramuscular and intra-articular steroid doses with mean and median doses of methylprednisolone (mg) per study period

Study period	Summary	MTX + IV steroid n=57	MTX + IFX n=55
Weeks 1-12	**Mean (SD)**	85 (9)	77 (59)
	Median (IQR)	0 (0, 120)	0 (0, 120)
	N patients injected	38	35
	N injections	40	35
Weeks 13-26	**Mean (SD)**	120 (99)	84 (92)
	Median (IQR)	0 (0, 240)	0 (0, 120)
	N patients injected	39	28
	N injections	57	40
Weeks 27-39	**Mean (SD)**	46 (66)	41 (72)
	Median (IQR)	0 (0, 120)	0 (0, 120)
	N patients injected	21	15
	N injections	22	19
Weeks 40-52	**Mean (SD)**	42 (69)	20 (47)
	Median (IQR)	0 (0, 120)	0 (0, 0)
	N patients injected	18	10
	N injections	21	13
Weeks 53-65	**Mean (SD)**	15 (40)	24 (58)
	Median (IQR)	0 (0, 0)	0 (0, 0)
	N patients injected	8	9
	N injections	9	11
Weeks 66-78	**Mean (SD)**	-	5 (3)
	Median (IQR)	-	0 (0, 0)
	N patients injected	0	4
	N injections	0	4

IQR, interquartile range; N, number; SD, standard deviation

Table 4.5 Escalation of DMARDs

DMARD	**MTX + IV Steroid n=57**	**MTX + IFX n=55**
IFX initiated	4 (7.0%)	55 (100.0%)
IFX 3 > 6mg/kg	0 (0.0%)	29 (52.7%)
IFX 6 > 10mg/kg	0 (0.0%)	15 (27.3%)
Sulphasalazine initiated	35 (61.4%)	7 (12.7%)
Hydroxychloroquine initiated	34 (59.6%)	5 (9.1%)
Leflunomide initiated	21 (36.8%)	1 (1.8%)
Cyclosporine initiated	2 (3.5%)	0 (0.0%)
Oral steroids prescribed	7 (12.3%)	6 (10.9%)
Etanercept initiated	2 (3.5%)	2 (3.6%)
Rituximab initiated	0 (0.0%)	1 (1.8%)
Total N patients requiring change in arthritis medication	38 (66.7%)	32 (58.2%)

DMARD, disease-modifying antirheumatic drug; IFX, Infliximab; IV, intravenous; MTX, methotrexate

4.3.5 Ultrasound

Eighty-nine patients (45 methotrexate and IV steroid and 44 methotrexate and infliximab) had ultrasound assessments. At baseline all 39 patients in the methotrexate and IV steroid group (100%) and 36/41 (87.8%) in the infliximab group who had ultrasound scans at baseline had grey scale (GS)>1 and PD>0 in at least one joint. From multiple imputation analysis, at week 50, 78.7% of patients in the methotrexate and IV steroid group compared to 40.5% of patients in the methotrexate and infliximab group has ultrasound disease activity (adjusted OR (95% CI) 0.18 (0.07, 0.50), p=0.001). At week 78 this was seen in 43.6% and 32.2% respectively (adjusted OR 0.62 (0.24, 1.58), p=0.314).

4.3.6 Factors associated with response to therapy

In the seropositive patients, rates of non-progression (ΔmTSS <SDC) at week 78 were 59% vs. 74% in the methotrexate and IV steroid and methotrexate and infliximab groups. In the seronegative patients the trend was reversed; with 96% and 76% and in the methotrexate and IV steroid and methotrexate and infliximab groups respectively achieving non-progression.

4.3.7 Sensitivity analyses

The analyses of the radiographic and clinical outcomes were repeated using only the available data (tables 4.6 and 4.7). Clinical outcomes were also analysed assuming non-response in patients who withdrew (table 4.8). The between group differences of each of these analyses were of comparable magnitude to those of the multiple imputation datasets. In particular, the adjusted mean change in the ΔmTSS according to the multiple imputation analysis was 1.45 compared to 1.21 in analysis of the observed data.

To test the robustness of the study conclusions to conditions under which data were missing not at random (MNAR), the imputed values were altered to investigate a range of alternatives. To achieve a mean difference in ΔmTSS of 3 units, the interval used to power the study, was only possible if it was assumed that patients in the methotrexate and IV steroid group with missing radiographic at week 50 week progressed by ≥ 16 units than the values that were imputed by the model, whilst patients with missing data in the methotrexate and infliximab group retained the scores that were originally imputed (range 0 to 11). Of note, change ≥16 units in the observed data occurred in only two patients. The majority (70%) progressing by <1 unit.

Table 4.6 Complete case analysis of radiographic changes at weeks 26, 50 and 78; results were adjusted for baseline values and study site.

Radiographic outcome	**MTX +IV Steroid**	**MTX +IFX**	**Unadjusted difference (95% CI)**	**Adjusted difference (95% CI)**	**p**
Change at week 26	**n=48**	**n=41**			
ERO mean (SD)	0.72 (1.97)	0.24 (0.79)	-0.48 (-1.13, 1.17)	-0.27 (-0.75, 0.21)	0.270
median (IQR)	0.00 (0.00, 0.68)	0.00 (0.00, 0.00)	0.00 (-0.16, 0.16)	0.00 (-0.09, 0.09)	1.000
JSN mean (SD)	0.82 (2.83)	0.31 (0.85)	-0.51 (-1.42, 0.40)	-0.45 (-1.26, 0.35)	0.267
median (IQR)	0.00 (0.00, 0.48)	0.00 (0.00, 0.00)	0.00 (-0.11, 0.11)	0.00 (-0.10, 0.10)	1.000
mTSS mean (SD)	1.54 (4.51)	0.55 (1.50)	-0.99 (-2.45, 0.48)	-0.79 (-1.98, 0.41)	0.194
median (IQR)	0.00 (0.00, 1.18)	0.00 (0.00, 0.42)	0.00 (-0.27, 0.27)	-0.02 (-0.24, 0.19)	0.832
Change < SDC	83.3%	90.2%	OR 1.85 (0.51, 6.66)	OR 1.67 (0.45, 6.11)*	0.441
Change ≤ 0.5	66.7%	78.1%	OR 1.78 (0.69, 4.61)	OR 1.48 (0.52, 4.23)	0.463
Change at week 50	**n=44**	**n=40**			
ERO mean (SD)	1.24 (3.38)	0.42 (1.10)	-0.83 (-1.74, 0.29)	-0.40 (-1.19, 0.39)	0.318
median (IQR)	0.00 (0.00, 0.82)	0.00 (0.00, 0.43)	0.00 (-0.20, 0.20)	0.00 (-0.16, 0.16)	1.000
JSN mean (SD)	1.63 (4.32)	0.53 (1.24)	-1.10 (-2.51, 0.31)	-0.77 (-1.90, 0.36)	0.178
median (IQR)	0.00 (0.00, 1.45)	0.00 (0.00, 0.42)	0.00 (-0.30, 0.30)	0.00 (-0.33, 0.33)	1.000

mTSS mean (SD)	2.88 (7.38)	0.95 (2.21)	-1.93 (-4.34, 0.49)	-1.21 (-3.03, 0.62)	0.192
median (IQR)	0.49 (0.00, 2.01)	0.00 (0.00, 0.91)	-0.49 (-1.01, 0.02)	0.00 (-0.41, 0.41)	1.000
Change < SDC	75.0%	85.0%	OR 1.89 (0.63, 5.70)	OR 1.72 (0.56, 5.27)*	0.341
Change ≤ 0.5	52.3%	72.5%	OR 2.41 (0.97, 5.99)	OR 2.12 (0.83, 5.42)*	0.115
Change at week 78	**n=42**	**n=35**			
ERO mean (SD)	1.25 (3.63)	0.57 (1.82)	-0.68 (-2.03, 0.67)	-0.22 (-1.25, 0.81)	0.674
median (IQR)	0.00 (0.00, 0.49)	0.00 (0.00, 0.70)	0.00 (-0.18, 0.18)	0.00 (-0.25, 0.25)*	1.000
JSN mean (SD)	1.90 (5.09)	0.61 (1.53)	-1.29 (-3.07, 0.48)	-1.08 (-2.48, 0.32)	0.130
median (IQR)	0.00 (0.00, 1.49)	0.00 (0.00, 0.45)	0.00 (-0.19, 0.19)	0.00 (-0.30, 0.30)	1.000
mTSS mean (SD)	3.15 (8.49)	1.18 (3.09)	-1.97 (-4.99, 1.04)	-1.35 (-3.62, 0.92)	0.239
median (IQR)	0.47 (0.00, 2.30)	0.00 (0.00, 0.94)	-0.47 (-1.09, 0.14)	0.00 (-0.58, 0.58)	1.000
Change < SDC	71.4%	85.7%	OR 2.40 (0.75, 7.65)	OR 2.21 (0.63, 7.76)	0.216
Change ≤ 0.5	59.5%	68.6%	OR 1.48 (0.58, 3.81)	OR 1.57 (0.57, 4.35)	0.383

ERO, erosion; IFX, infliximab; IV, intravenous; JSN, joint space narrowing; mTSS, van der Heijde modified total Sharp score; MTX, methotrexate; SDC, smallest detectable change in mTSS (2 units)

*Not adjusted for site due to problems of model separation and/or collinearity

Table 4.7 Complete case analysis of secondary and exploratory clinical and patient-reported outcomes at weeks 26, 50 and 78 (observed values only); results were adjusted for baseline values and study site. Values presented are % (n/N) unless otherwise stated.

Week	Clinical outcome	MTX + IV Steroid (n=57)	MTX + IFX (n=55)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p
6	DAS44 remission	7.1% (4/56)	18.5% (10/54)	2.95 (0.87, 10.08)	4.97 (1.29, 19.18)*	0.020
	DAS44 LDAS	30.4% (17/56)	46.3% (25/54)	1.98 (0.91, 4.32)	3.73 (1.45, 9.61)	0.006
	DAS28 remission	7.1% (4/56)	22.2% (12/54)	3.71 (1.12, 12.36)	6.22 (1.61, 24.01)*	0.008
	DAS28 LDAS	23.2% (13/56)	33.3% (18/54)	1.65 (0.71, 3.83)	2.61 (0.98, 6.94)*	0.055
	SDAI remission	3.6% (2/55)	4.0% (2/50)	1.10 (0.15, 8.15)	1.36 (0.18, 10.42)*	0.765
	ACR EULAR remission	1.8% (1/57)	1.9% (1/53)	1.08 (0.07, 17.66)	1.44 (0.08, 25.23)*	0.805
14	DAS44 remission	30.4% (17/56)	34.6% (18/52)	1.21 (0.54, 2.72)	1.85 (0.75, 4.57)*	0.181
	DAS44 LDAS	60.7% (34/56)	67.3% (35/52)	1.33 (0.60, 2.93)	3.51 (1.22, 10.15)	0.020
	DAS28 remission	39.3% (22/56)	42.3% (22/52)	1.13 (0.53, 2.44)	1.62 (0.67, 3.93)*	0.288
	DAS28 LDAS	53.6% (30/56)	55.8% (29/52)	1.09 (0.51, 2.33)	1.54 (0.65, 3.70)*	0.323
	SDAI remission	15.4% (8/52)	17.8% (8/45)	1.19 (0.41, 3.48)	1.46 (0.48, 4.45)*	0.505
	ACR EULAR remission	8.9% (5/56)	3.8% (2/53)	0.40 (0.07, 2.16)	0.46 (0.08, 2.53)*	0.371
26	DAS44 remission	40.0% (22/55)	31.4% (16/51)	0.69 (0.31, 1.53)	0.85 (0.37, 1.97)	0.703

	DAS44 LDAS	69.1% (38/55)	66.7% (34/51)	0.89 (0.40, 2.02)	1.60 (0.60, 4.22)	0.346
	DAS28 remission	50.9% (28/55)	41.2% (21/51)	0.68 (0.31, 1.46)	0.80 (0.36, 1.78)	0.579
	DAS28 LDAS	66.3% (37/55)	64.7% (33/51)	0.89 (0.40, 1.99)	1.29 (0.52, 3.20)*	0.582
	SDAI remission	24.1% (13/54)	29.4% (15/51)	1.31 (0.55, 3.13)	1.54 (0.62, 3.78)	0.350
	ACR EULAR remission	18.2% (10/55)	15.1% (8/53)	0.80 (0.29, 2.21)	0.89 (0.32, 2.53)*	0.834
	ACR20	76.4% (42/55)	73.1% (38/52)	0.84 (0.35, 2.01)	0.84 (0.35, 2.01)*	0.541
	ACR50	54.6% (30/55)	55.8% (29/52)	1.05 (0.49, 2.25)	1.05 (0.49, 2.26)	0.900
	ACR70	32.7% (18/55)	33.3% (17/51)	1.03 (0.46, 2.31)	1.03 (0.46, 2.31)	0.945
	Change in HAQ-DI mean (SD)	-0.61 (0.47), n=54	-0.68 (0.53), n=53	-0.08 (-0.27, 0.12)	-0.06 (-0.24, 0.12)	0.502
	Change in RAQoL mean (SD)	-6.42 (5.82), n=54	-7.99 (6.51), n=52	-1.57 (-3.95, 0.81)	-0.94 (-3.24, 1.36)	0.421
50	**DAS44 remission**	38.0% (19/50)	48.9% (22/45)	1.56 (0.69, 3.53)	1.97 (0.82, 4.70)*	0.128
	DAS44 LDAS	74.0% (37/50)	71.1% (32/45)	0.86 (0.35, 2.13)	1.08 (0.42, 2.80)	0.874
	DAS28 remission	50.0% (25/50)	57.8% (26/45)	1.37 (0.61, 3.08)	2.04 (0.82, 5.07)	0.123
	DAS28 LDAS	64.0% (32/50)	68.9% (31/45)	1.25 (0.53, 2.93)	1.74 (0.68, 4.47)	0.250
	SDAI remission	27.1% (13/48)	46.7% (21/45)	2.36 (0.99, 5.60)	3.44 (1.31, 9.01)	0.012

	ACR EULAR remission	20.8% (11/53)	18.0% (9/50)	0.84 (0.31, 2.23)	0.85 (0.31, 2.31)*	0.750
78	**DAS44 remission**	54.4% (25/46)	47.7% (21/44)	0.77 (0.33, 1.76)	0.96 (0.40, 2.29)*	0.922
	DAS44 LDAS	87.0% (40/46)	75.0% (33/44)	0.45 (0.15, 1.35)	0.68 (0.21, 2.23)*	0.526
	DAS28 remission	69.6% (32/46)	59.1% (26/44)	0.63 (0.26, 1.51)	0.75 (0.30, 1.87)*	0.540
	DAS28 LDAS	80.4% (37/46)	68.2% (30/44)	0.52 (0.20, 1.37)	0.58 (0.22, 1.55)*	0.275
	SDAI remission	52.2% (24/46)	39.5% (17/43)	0.60 (0.26, 1.39)	0.74 (0.30, 1.79)*	0.503
	ACR EULAR remission	17.4% (8/46)	17.8% (8/45)	1.03 (0.35, 3.02)	1.06 (0.35, 3.18)*	0.920
	ACR20 **ACR50** **ACR70**	77.1% (37/48) 72.9% (35/48) 58.3% (28/48)	76.1% (35/46) 73.9% (34/46) 58.7% (27/46)	0.95 (0.36, 2.46) 1.05 (0.42, 2.63) 1.02 (0.45, 2.31)	0.95 (0.36, 2.46)* 1.05 (0.42, 2.63)* 1.02 (0.45, 2.31)*	0.909 0.913 0.972
	Change in HAQ-DI mean (SD)	-0.77 (0.52), n=47	-0.81 (0.55), n=46	-0.04 (-0.26, 0.18)	-0.04 (-0.25, 0.17)	0.703
	Change in RAQoL mean (SD)	-7.33 (5.71), n=38	-9.72 (7.69), n=42	-2.39 (-5.43, 0.65)	-1.61 (-4.31, 1.10)	0.240

ACR, American College of Rheumatology; DAS28, disease activity score based on a 28-joint count; DAS44_3-variable, disease activity score based on RAI and SJC44; EULAR, European League Against Rheumatism; HAQ-DI=Rasch-transformed health assessment questionnaire disability index score; IFX, infliximab; IV, intravenous; LDAS, low disease activity score; MTX, methotrexate; RAQoL=Rasch-transformed rheumatoid arthritis quality of life score; SDAI, simplified disease activity index

*Not adjusted for site because for at least 1 site the outcome was the same for all patients therefore OR could not be calculated

Table 4.8 Complete case analysis of secondary and exploratory clinical outcomes at weeks 26, 50 and 78 where non-response was assumed for those who withdrew early; results were adjusted for baseline values and study site. Values presented are % (n/N) unless other

Week	Clinical outcome	MTX + IV Steroid (n=57)	MTX + IFX (n=55)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p
6	**DAS44 remission**	7.1% (4/56)	18.2% (10/55)	2.89 (0.85, 9.85)	4.97 (1.29, 19.23)*	0.020
	DAS44 LDAS	28.6% (16/56)	45.5% (25/55)	2.08 (0.95, 4.57)	4.18 (1.58, 11.07)*	0.004
	DAS28 remission	7.1% (4/56)	21.2% (12/55)	3.63 (1.09, 12.06)	6.22 (1.61, 24.08)*	0.008
	DAS28 LDAS	23.2% (13/56)	32.7% (18/55)	1.61 (0.70, 3.72)	2.60 (0.98, 6.94)*	0.056
	SDAI remission	3.6% (2/55)	3.9% (2/51)	1.08 (0.15, 7.98)	1.36 (0.18, 10.42)*	0.765
	ACR EULAR remission	1.8% (1/57)	1.9% (1/54)	1.06 (0.06, 17.33)	1.43 (0.08, 25.23)*	0.805
14	**DAS44 remission**	29.8% (17/57)	34.0% (18/53)	1.21 (0.54, 2.70)	1.92 (0.78, 4.73)*	0.158
	DAS44 LDAS	59.7% (34/57)	66.0% (35/53)	1.32 (0.60, 2.86)	3.69 (1.28, 10.67)	0.016
	DAS28 remission	38.6% (22/57)	41.5% (22/53)	1.13 (0.53, 2.42)	1.69 (0.70, 4.08)*	0.248
	DAS28 LDAS	52.6% (30/57)	54.7% (29/53)	1.09 (0.51, 2.30)	1.62 (0.68, 3.84)*	0.276
	SDAI remission	15.1% (8/53)	17.4% (8/46)	1.18 (0.41, 3.46)	1.49 (0.49, 4.55)*	0.480
	ACR EULAR remission	8.8% (5/57)	3.7% (2/54)	0.40 (0.07, 2.16)	0.47 (0.08, 2.58)*	0.382

26	**DAS44 remission**	39.3% (22/56)	30.2% (16/53)	0.67 (0.30, 1.48)	0.82 (0.36, 1.89)	0.645
	DAS44 LDAS	67.9% (38/56)	64.2% (34/53)	0.85 (0.38, 1.87)	1.50 (0.58, 3.87)	0.406
	DAS28 remission	50.0% (28/56)	39.6% (21/53)	0.66 (0.31, 1.40)	0.76 (0.35, 1.68)	0.501
	DAS28 LDAS	66.1% (37/56)	62.3% (33/53)	0.85 (0.39, 1.86)	1.20 (0.50, 2.87)*	0.688
	SDAI remission	23.6% (13/55)	28.3% (15/53)	1.28 (0.54, 3.02)	1.50 (0.61, 3.68)	0.377
	ACR EULAR remission	17.9% (10/56)	14.6% (8/55)	0.78 (0.28, 2.16)	0.88 (0.31, 2.47)*	0.804
	ACR20	75.0% (42/56)	70.4% (38/54)	0.79 (0.34, 1.84)	0.79 (0.34, 1.84)*	0.457
	ACR50	53.6% (30/56)	53.7% (29/54)	1.01 (0.48, 2.13)	1.01 (0.48, 2.13)	0.986
	ACR70	32.1% (18/56)	32.1% (17/53)	1.00 (0.45, 2.23)	1.00 (0.45, 2.24)	0.999
50	**DAS44 remission**	35.2% (19/54)	46.0% (23/50)	1.57 (0.71, 3.45)	2.05 (0.88, 4.79)*	0.096
	DAS44 LDAS	64.8% (35/54)	64.0% (32/50)	0.97 (0.43, 2.16)	1.34 (0.56, 3.22)	0.512
	DAS28 remission	46.3% (25/54)	54.0% (27/50)	1.36 (0.63, 2.95)	1.98 (0.83, 4.70)	0.122
	DAS28 LDAS	55.6% (30/54)	62.0% (31/50)	1.31 (0.60, 2.86)	1.89 (0.78, 4.44)	0.159
	SDAI remission	25.0% (13/52)	44.0% (22/50)	2.36 (1.02, 5.46)	3.40 (1.33, 8.68)	0.010
	ACR EULAR remission	19.6% (11/56)	18.2% (10/55)	0.91 (0.35, 2.35)	0.91 (0.35, 2.40)*	0.855
78	**DAS44 remission**	43.6% (24/55)	39.6% (21/53)	0.85 (0.39, 1.82)	1.12 (0.49, 2.53)*	0.789

	DAS44 LDAS	69.1% (38/55)	69.1% (33/53)	0.74 (0.33, 1.64)	1.16 (0.47, 2.82)*	0.749
	DAS28 remission	54.6% (30/55)	54.6% (26/53)	0.80 (0.38, 1.71)	1.03 (0.46, 2.30)*	0.952
	DAS28 LDAS	63.6% (35/55)	63.6% (30/53)	0.75 (0.34, 1.61)	0.89 (0.40, 2.00)*	0.782
	SDAI remission	41.8% (23/55)	41.8% (17/52)	0.68 (0.31, 1.49)	0.88 (0.38, 2.04)*	0.766
	ACR EULAR remission	14.6% (8/55)	14.6% (9/54)	1.18 (0.42, 3.31)	1.22 (0.43, 3.52)*	0.708
	ACR20	59.7% (34/57)	63.6% (35/55)	1.18 (0.55, 2.54)	1.18 (0.55, 2.54)*	0.665
	ACR50	57.9% (33/57)	61.8% (34/55)	1.18 (0.55, 2.51)	1.18 (0.55, 2.51)*	0.672
	ACR70	45.6% (26/57)	49.1% (27/55)	1.15 (0.55, 2.42)	1.15 (0.55, 2.42)*	0.713

ACR, American College of Rheumatology; DAS28, disease activity score based on a 28-joint count; DAS44_3-variable, disease activity score based on RAI and SJC44; EULAR, European League Against Rheumatism; HAQ-DI=Rasch-transformed health assessment questionnaire disability index score; IFX, infliximab; IV, intravenous; LDAS, low disease activity score; MTX, methotrexate; RAQoL=Rasch-transformed rheumatoid arthritis quality of life score; SDAI, simplified disease activity index

*Not adjusted for site because for at least 1 site the outcome was the same for all patients therefore OR could not be calculated

4.3.8 Adverse events

In total 94.7% (54/57) in the methotrexate and IV steroid group compared to 98.2% (54/55) in the methotrexate and infliximab group reported adverse events (AEs). Of the AEs, the most common were non-infectious gastrointestinal events (18.3% (68/372) in the methotrexate and IV steroid group and 15.7% (58/369) in the methotrexate and infliximab group). Upper respiratory tract/ pulmonary infections were reported in 13.8% (51/372) of the methotrexate and IV steroid and 11.3% (42/369) of the methotrexate and infliximab groups. There were 11.0 AEs per 100 patient years in the methotrexate and IV steroid group and 25.3 in the methotrexate and infliximab group. There were 9 serious adverse events (SAEs) recorded for 9 patients in the methotrexate and IV steroid group (15.8%) and 20 events recorded for 13 patients in the methotrexate and infliximab group (23.6%). A higher proportion of SAEs in the methotrexate and infliximab group (9.1% (5/55)) were due to admissions for surgical procedures unrelated to the RA or study medication. During the study period, one patient in the methotrexate and infliximab arm died due to a suspected pulmonary embolus. Serious infections were documented in two patients (3.5%) in the methotrexate and IV steroid group and two (3.6%) in the methotrexate and infliximab group. One person in the methotrexate and infliximab group had pulmonary tuberculosis which presented as a pleural effusion and another patient had an empyema. In the methotrexate and IV steroid group, one patient had a lung abscess and another had herpes zoster. There were no malignancies reported during the study period (table 4.9).

Table 4.9 Summary of adverse events

	MTX + IV Steroid	**MTX + IFX**
Number of patients who experienced an AE	54/57 (94.7%)	54/55 (98.2%)
Maximum severity of AE experienced		
- Mild	5/57 (8.8%)	10/55 (18.2%)
- Moderate	40/57 (70.2%)	31/55 (56.4%)
-Severe (including SAEs)	9/57 (15.8%)	13/55 (23.6%)
Total number of AEs	372	369
Total patient-years of follow-up	81.9	79.1
Number of AEs per 100 patient-years	454.0	466.3
Patient expectation of event		
-Expected (listed in PIS)	294/372 (79.0%)	270/369 (73.2%)
Severity		
-Mild	230/372 (61.8%)	226/369 (61.2%)
-Moderate	133/372 (35.8%)	122/369 (33.1%)
-Severe (including SAEs)	9/372 (2.4%)	21/369 (5.7%)
Relation to study drug		
-Not related	120/372 (32.3%)	96/369 (26.0%)
-Probably not related	160/372 (43.0%)	197/369 (53.4%)
-Possibly related	77/372 (20.7%)	61/369 (16.5%)
-Probably related	15/372 (4.0%)	15/369 (4.1%)
Number of patients who experienced an SAE	9/57 (15.8%)	13/55 (23.6%)

Total number of SAEs	9	20
Number of SAEs per 100 patient-years	11.0	25.3
Relation to study drug		
-Not related	1/9 (11.1%)	8/20 (40.0%
-Probably not related	6/9 (66.7%)	7/20 (35.0%)
-Possibly related	2/9 (22.2%)	4/20 (20.0%)
-Probably related	0	1/20 (5.0%)
SAEs by category:		
-Blood/bone marrow	0	1 in 1/55 patients (1.8%)
-Cardiac arrhythmia	0	1 in 1/55 patients (1.8%)
-Cardiac general	2 in 2/57 patients (3.5%)	2 in 1/55 patients (1.8%)
-Gastrointestinal	1 in 1/57 patients (1.8%)	0
-Hepatobiliary/pancreas	1 in 1/57 patients (1.8%)	1 in 1/55 patients (1.8%)
-Infection - gastrointestinal	1 in 1/57 patients (1.8%)	0
-Infection - pulmonary/ upper respiratory	1 in 1/57 patients (1.8%)	2 in 2/55 patients (3.6%)
-Injury, poisoning or procedural complications	2 in 2/57 patients (3.5%)	1 in 1/55 patients (1.8%)
-Pain - musculoskeletal	0	2 in 2/55 patients (3.6%)
-Pain - neurology	1 in 1/57 patients (1.8%)	0
-Pain - pulmonary/ upper respiratory	0	1 in 1/55 patients (1.8%)
-Pulmonary/upper respiratory	0	4 in 4/55 patients (7.3%)
-Surgical and medical procedures	0	5 in 5/55 patients (9.1%)

AE, adverse event; IFX, infliximab; IV, intravenous; PIS, patient information sheet; SAE, serious adverse event

4.4 Discussion

The IDEA study was the first double-blind RCT comparing two rapid remission induction strategies, using either methotrexate and IV steroid or methotrexate and infliximab in early DMARD-naïve RA, and incorporating a treat-to-target approach in both groups.

No significant difference in radiographic progression (the primary outcome) was seen between the groups. Proportions of patients achieving radiographic non-progression in both groups were high, and at study end approximately 50% in both groups were in remission. The treatment benefits were seen across all aspects of care including function.

Several factors may explain the high proportion of radiographic non-progression in the methotrexate and IV steroid group which was similar to that observed in the methotrexate and infliximab group. Glucocorticoids, like the TNFi, are known to inhibit osteoclastic activity. The initial IV steroid administration may have minimised bone damage in the early stages of the disease. In these patients the subsequent potential for damage is likely to have been reduced by the additional treat-to-target approach, suppressing inflammation which drives joint damage. In a smaller study of MTX-naïve RA which also compared IV methylprednisolone to infliximab, but without a treat-to-target approach, clinical benefits were also seen in both treatment groups. Progression of MRI-detected erosions however was significantly higher in the group receiving IV steroid compared to the those in the infliximab group.[165] (In this study, ultrasound demonstrated greater sensitivity than clinical measures of disease activity with significant benefit seen on synovitis in the methotrexate and infliximab group.)

Whilst the efficacy of methotrexate monotherapy is well documented in patients with RA (20-40%), [183 240] a proportion still have ongoing disease with radiographic progression[138 177] and require additional therapy.[183 240] This study confirms the benefit of methotrexate and a bDMARD as induction therapy in early DMARD-naïve RA[182 183] with the potential for treatment de-escalation. In addition, the study demonstrates the benefit of combination therapy with methotrexate and a glucocorticoid,[164 165 168 220] given here as an initial single IV dose. The results of this study also supports the call to treat-to-target.[10] The target aiming to achieve low disease activity was applied throughout the study. This treatment target was similar to that in several other studies including BeSt[183], OPTIMA[232] and SWEFOT,[240] but perhaps a more stringent target e.g. aiming for remission as was the target in the NeoRACo study,[293] would have led to even better clinical outcomes.In addition to

the DMARD escalation protocol, the additional IA/IM glucocorticoid would have also been an important part of the treat-to-target approach, minimising the differences between the groups. The additional glucocorticoid was marginally higher in the methotrexate and IV steroid group compared to the methotrexate and infliximab group, suggesting that combination therapy with methotrexate and IV steroid may be somewhat more dependent on regular monitoring and treating to target than combination therapy with methotrexate and infliximab. In the OPERA study[337] which compared methotrexate and adalimumab to methotrexate and placebo, IA glucocorticoids were used as part of a treat-to-target strategy. There was no difference in the primary endpoint (LDAS) or in the ACR20. Greater improvements however were seen at the higher clinical endpoints (remission, ACR50 and ACR70) as well as in DAS28-CRP, quality of life and function in the group receiving bDMARD therapy. Similar to the IDEA study, although there was a trend toward greater glucocorticoid use in the placebo group, the cumulative dose was not significantly different between the two treatment groups.

The use of glucocorticoids often raise the concerns of side effects, particularly with high dose glucocorticoid therapy. In this study, whilst the boluses of steroid used may have appeared large (methylprednisolone 120mg if not in LDAS at the given time points), this dose is used in clinical practice as part of standard care. In the tREACH study this has been shown to be an efficient way of administering glucocorticoids.[363] In both groups in the IDEA study, the greatest glucocorticoid use occurred at the beginning of the study when patients had the highest disease activity. The total dose used however was equivalent to low dose oral prednisolone: 0.89 mg/day in the methotrexate and IV steroid groups and 0.67 mg/day in the methotrexate and infliximab group over the course of the study period.

Exploratory analysis suggests that earlier remission is achievable with infliximab (week 6 DAS44 remission in 7.1% vs 18.3% in the methotrexate and IV steroid and methotrexate and infliximab groups respectively). This is worth noting as previous clinical trials have shown that earlier control of disease activity, particularly during the first three months of therapy, predicted achievement of remission at a later time-point.[350] In the OPTIMA study, the only measures of disease activity after 12 weeks predicted clinical outcomes at week 26, [232] supporting the rationale for the use of early intensive treatment strategies.[350]

Adverse events, in particular serious infections, are of concern with both bDMARD and glucocorticoid use. In this study both treatment strategies were generally well tolerated, with no unexpected adverse events. The number of serious infections was low, with two cases (3.6%) reported in each group. The infections were similar to

those described in clinical practice and in registries. [197 364 365] There was one case of tuberculosis in the methotrexate and infliximab group, three pulmonary infections (one in the methotrexate and IV steroid and two in the methotrexate and infliximab groups) and one gastrointestinal infection in the methotrexate and IV steroid group. A case of herpes zoster manifesting as a Ramsay Hunt syndrome was recorded in the methotrexate and IV steroid group. Serious adverse events (excluding admissions for procedures unrelated to the RA or to study treatment) were similar between the groups.

Cost considerations are also important when considering the treatment of RA. Identifying prognostic factors would help determine which patients would benefit most from more intensive strategies with early bDMARD therapy. A post hoc analysis of this study showed less radiographic progression in seropositive patients receiving methotrexate and infliximab compared to methotrexate and IV steroid.

4.5 Limitations

Our study has its limitations. Missing data was one which needed careful consideration, particularly in terms of the potential effect on the lack of difference in radiographic progression seen between the two groups. Sensitivity analyses using multiple imputation were done to account for this. The adjusted means for radiographic progression at week 50 were consistent in the multiple imputation and complete case datasets (1.45 and 1.21 respectively). Results from both analyses were lower than the value used to power the study (3 units), and both were within the measurement error of 2 units. In both groups radiographic progression was less than expected and, as is often the case, a minority of patients accounted for this. The median (IQR) change in the methotrexate and IV steroid group this was 0.65 (0.00, 2.37) which is comparable to the change recorded in patients treated with infliximab in the BeSt study [0.50 (0.00, 2.30)].[183] In the methotrexate and infliximab group this was 0.11 (0.00, 1.55). Based on the unadjusted results of this study (a difference in change in the observed mTSS at week 50 of 1.93), calculations showed that even if the study was twice the size it would not show a significant difference in the primary outcome. The changes seen would still fall within the calculated smallest detectable difference of 2 units and therefore would not represent a clinically meaningful difference. Data for the secondary and exploratory outcomes were complete in more than 90% of patients, assuming non-response in those who withdrew. There were no substantive differences between the groups in these analyses.

No increase in adverse events was seen in the methotrexate and IV steroid group however, bone density was not one of the specific outcomes measured in the study. Per protocol, osteoporosis prophylaxis was prescribed at the treating physician's discretion guided by local guidelines.

Induction using other routes of glucocorticoid administration was also not investigated in this study. Oral, intramuscular and intra-articular steroids are widely used in clinical practice and have demonstrated efficacy in recently published clinical trials.[337 363] Tapering and stopping is potentially less difficult when given intravenously rather than orally.

4.6 Conclusions

In summary, the IDEA study has shown that first-line therapy with methotrexate and high dose IV steroid in DMARD-naïve RA, together with a treat-to-target approach, resulted in little structural damage. Although methotrexate and infliximab was not superior in inhibiting radiographic progression, there was a trend towards earlier clinical responses, significantly earlier achievement of DAS28 remission and greater reduction in synovitis on ultrasound.

Chapter 5 Etanercept with methotrexate vs. methotrexate monotherapy in DMARD-naïve early IA

In this chapter, a RCT aimed to compare the use of methotrexate and etanercept to methotrexate monotherapy in DMARD-naïve early IA.

5.1 Introduction

Remission is a primary goal for patients with IA.[180] Whilst this may be possible at any time during the course of the disease, the evidence suggests that this is best achieved with early DMARD therapy.[1 366]

Identifying patients with IA early is therefore paramount. RF and anti-CCP - both antibodies of which are included in the 2010 ACR/EULAR RA classification criteria[12 90-92 95 367] – as well as genetic markers, in particular shared epitope,[33 100 102] have been found to be markers of persistent inflammation and progression to RA.

In early IA the optimal induction therapy is still unknown. As discussed in previous chapters, methotrexate is generally used as part of first-line therapy in RA .[209] In patients with ACPA-positive UA, methotrexate has also been shown to delay the progression to RA. [213] In a study of early DMARD-naïve RA, the use of methotrexate and etanercept has proven effective for remission induction. [180] Efficacy was superior to methotrexate monotherapy, particularly in patients with early disease (RA disease duration ≤ 4 months). [1] The role of this combination however has not been examined in patients with early IA.

The aim of the EMPIRE (Etanercept and Methotrexate in Patients to Induce Remission in Early Arthritis) study was to compare the clinical, radiographic and functional outcomes of methotrexate and etanercept to methotrexate monotherapy in patients with DMARD-naïve early IA, with at least one joint with clinical synovitis.

5.2 Patients and methods

5.2.1 Patients

Patients between 18 - 80 years, with at least one tender and swollen joint - within three months of diagnosis of an IA - RF, anti-CCP or shared epitope positive, and DMARD-naïve were eligible to take part in the study. Exclusion criteria included current crystal or infective arthritis, important concurrent medical diseases or

relevant co- morbidities, glucorticoids within 28 days of screen and previous treatment with any cs- or bDMARD.

5.2.2 Treatment allocation and intervention

This was an 18-month, randomised, double-blind, placebo-controlled phase 3 superiority trial. The multicentre study was conducted across 4 sites in West Yorkshire, UK (Harrogate, Huddersfield, Leeds and York).

Randomisation (1:1) took place according to a computer generated list in blocks of four. There was no stratification. Treatment was assigned by central pharmacy. Patients, nurses, clinicians, local pharmacists and assessors were blinded to the treatment allocation throughout the study. The protocol and amendments received independent ethics committee and regulatory review and approval. Patient informed consent was obtained prior to study enrolment.

Patients either received methotrexate plus placebo or methotrexate plus etanercept. The etanercept 50mg SC injections or visually identical placebo (sterile lyophilized powder similar in appearance to the etanercept) SC injections were administered once weekly. The study injections were continued to week 52. In patients with no tender and no swollen joints (NTSJ) (Ritchie articular index (RAI) = 0 and 44-swollen joint count (SJC44) = 0) for 26 weeks, injections could be stopped earlier. In both treatment groups, methotrexate was started at a dose of 10mg weekly. This was increased by 5 mg every 4 weeks to 20mg. In patients who did not achieve NTSJ, the methotrexate dose could be increased further to 25 mg/week at or after week 12. In patients who achieved NTSJ by week 4, the methotrexate dose was maintained at 15mg weekly. Study subjects also received folic acid 5mg orally at least twice a week. In patients achieving sustained NTSJ for 12 weeks after stopping etanercept or placebo injections, methotrexate was weaned (figure 5.1). Where possible, data collection continued and included patients who withdrew from the trial but were still able to attend for follow up.

NSAIDS were permitted during the study. Patients were also allowed an intramuscular or intra-articular glucocorticoid injection to a maximum dose of 120mg of methylprednisolone once within the first nine months of the trial and as clinically indicated thereafter. Oral steroids were not permitted. Additional DMARD therapy was allowed after week 52 at the discretion of the investigator if there were features of ongoing disease activity.

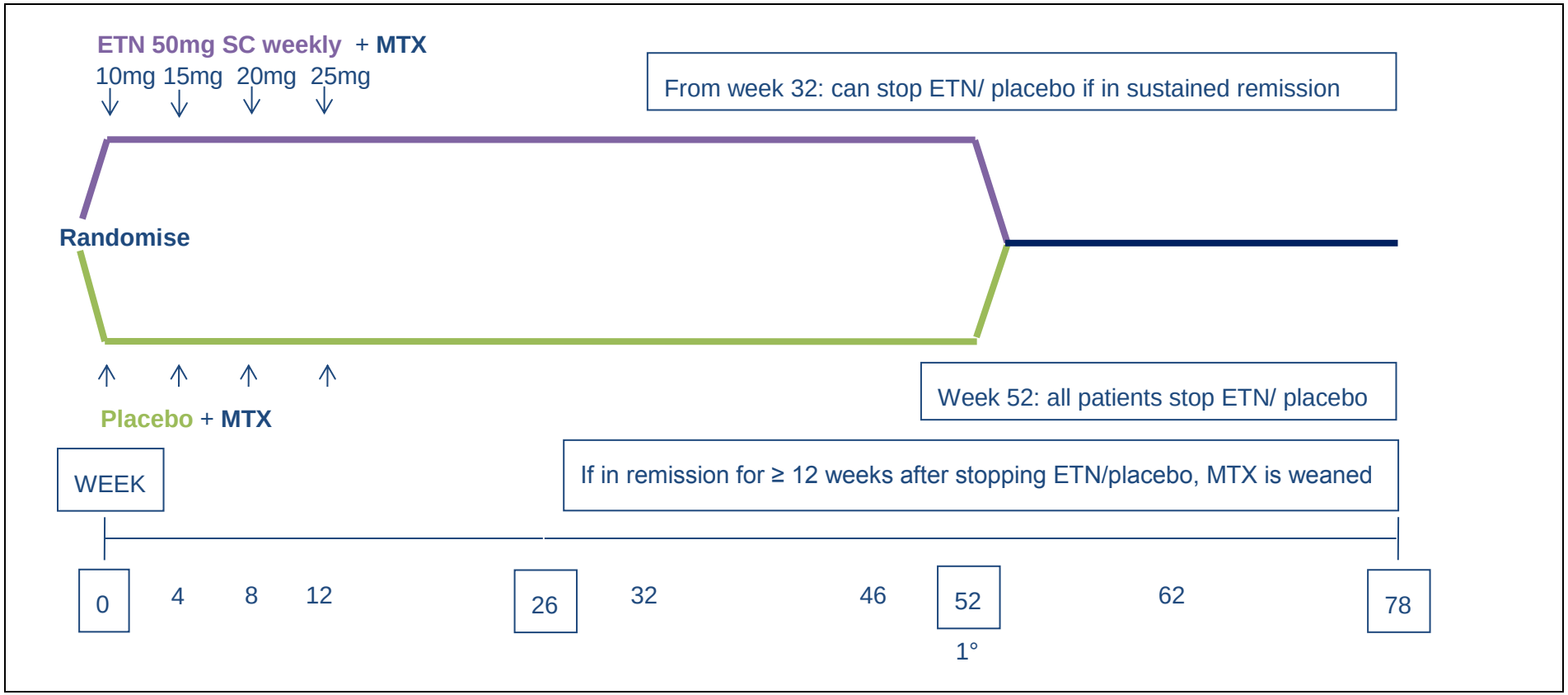


Figure 5.1 EMPIRE study design

ETN, etanercept; MTX, methotrexate; SC, subcutaneous; 1°= primary outcome at week 52

5.2.3 Efficacy and safety outcomes

The primary outcome of the study was NTSJ at week 52. Secondary outcomes included NTSJ at week 78, DAS44-CRP, remission according to the 2010 ACR/EULAR criteria, physician global assessment of disease activity, patient pain and fatigue VAS, HAQ-DI, SF36 and EQ5D at weeks 52 and 78. Other secondary outcomes were the proportions of patients in etanercept-free NTSJ (for those in the methotrexate and etanercept arm) and in drug-free NTSJ.

Secondary radiographic outcomes were the change in JSN , ERO and total mTSS,[354] and the proportions of patients achieving radiographic non-progression (change ≤0.5 units[355] or change less than the calculated SDC for this study) at weeks 52 and 78. The radiographs were scored in time order, independently by two experienced readers, who were blinded to treatment allocation.

The following were exploratory outcomes of the study: NTSJ at weeks 2, 12 and 26; other clinical responses (DAS44-CRP <1.6, DAS28-CRP <2.6, DAS44-CRP ≤2.4, DAS28-CRP ≤3.2) at weeks 2, 12, 26, 52 and 78; functional outcomes including the proportions of patients achieving a minimal clinical important difference (MCID) in HAQ-DI (decrease of ≥ 0.22 units from baseline) [368] and normal HAQ-DI status (≤0.5 [369]); additional DMARD therapy and additional glucocorticoids required during the study. In patients who were able to stop injections with/ without methotrexate early, duration of bDMARD free- and drug free- NTSJ was determined (loss of this state was defined by any change in disease activity requiring an increase in therapy, RAI>0 or SJC44> 0).[360] In addition we aimed to identify baseline variables which were predictive of clinical and radiographic outcome, whilst also testing for potential moderators of the treatment effect.

Ultrasound assessments were performed at baseline, weeks 52 and 78 in the subgroup of patients recruited in Leeds. These were done (Philips HDI 5000, employing a 15-8 MHz transducer) by three experienced rheumatologists trained in MSK ultrasound who were blinded to treatment allocation. Intra- and inter-reader reliability tests between the sonographers had been done prior to this study and shown to be good. Findings in 20 joints (bilateral wrists, MCPs 2 and 3, PIPs 2 and 3, and MTPs 1 to 5) were compared between the two groups. The OMERACT definitions were used to define synovitis.[356] The EULAR-OMERACT scoring system (a 0-3 semi-quantitative scale) was used to measure grey scale and power Doppler signal.[357] The number of ultrasound detected erosions in each joint was also determined.

At every visit, patients were asked to report any new adverse events. Clinical and laboratory adverse events were recording using standard medical terms.

5.2.4 Sample size

The study primary outcome was the proportion of patients with no symptoms and signs of IA, defined by no NTSJ at 12 months. The study null hypothesis was that there was no difference between the proportions of patients in each of the treatment groups with NTSJ. Based on previous data, [35] it was anticipated that 30% of patients receiving methotrexate monotherapy would achieve NTSJ at 12 months, compared to 60% of patients receiving methotrexate and etanercept. The sample size required to show a significant difference between these two groups, with 80% power and at the 5% significance level, was 50 per group. To allow for a 10 percent drop-out, the number of patients required was 55 per group (110 patients in total).

5.2.5 Statistical methods

Efficacy and safety analyses were performed on subjects who received at least one dose of study drug. The primary analysis was done according to the groups to which patients were originally randomised (intention-to-treat).

Multiple imputation by chained equations (Stata command: mi imputed chained) was used to account for missing data. Twenty complete datasets were generated. The size of the dataset precluded full imputation of all variables simultaneously. Separate imputation models were created for joint counts, DAS44, DAS28, SDAI and ACR remission, radiographic outcomes, patient reported outcomes (HAQ-DI, short form 36 (SF-36), EQ5D), VAS, EMS and ultrasound. Imputation models included auxiliary variables if they were substantively associated with the variable imputed or with the likelihood that the data were missing. Anti-CCP was found to be associated with the likelihood that data were missing at weeks 52 (OR 3.0) and 78 (OR 3.8) and was included in all the imputation models. Data on the 1987 ACR and 2010 ACR/EULAR RA classification criteria were included in DAS and DAS28 imputation models as these were to be used in exploratory analyses of response to treatment. Age was associated with the radiographic outcomes, particularly progression of erosion score ($r>0.3$ at both time-points). Males were slightly more likely to be missing radiographic outcome data ($OR\approx1.5$ at both time-points). RAI and HAQ-DI were associated with EMS, global pain VAS, abnormal fatigue VAS and physician VAS at both time-points (all $r>0.3$) and were more complete so were included in the VAS imputation model. Binary variables were imputed using binary

logistic regression. Predictive mean matching was used to impute all other variables. For continuous variables with missing values at baseline, the mean of the observed values was imputed and an indicator variable coded 1 for missing was also included in the imputation model and subsequent analysis models. For categorical variables with missing values at baseline, missing values were given a unique code prior to imputation and analysis. DAS28 remission, LDAS28, SDAI remission and TSS were all computed passively following imputation of DAS28, SDAI, and JSN/ erosion scores respectively.

During the analysis of the imputed datasets the Monte Carlo errors were examined to ensure these met the conditions defined by White *et al.* (2010):[370]

(1) The Monte Carlo error of $\hat{\beta}$ is approximately 10 per cent of its standard error.

(2) The Monte Carlo error of the test statistic $\hat{\beta}/se(\hat{\beta})$ is approximately 0.1.

(3) The Monte Carlo error of the p-value is approximately 0.01 when the true p-value is 0.05, and 0.02 when the true p-value is 0.1.

Additional sensitivity analyses of the primary outcome at week 52 were also done imputing non-response for patients who withdrew or were lost to follow-up. A complete case analysis was also done and included observed data only. This included patients who may have been followed up after withdrawal from study treatment.

In addition to this, a per-protocol analysis was also performed, excluding patients who withdrew or were lost to follow up, or deviated from the study protocol in any other way that could have affected the outcome. Analyses were conducted using Stata 12.1.

The SDC in mTSS was calculated based on the change scores of both readers according to the Bland-Altman 95% limits of agreement method.[371]

Linear regression was used to analyse continuous interval outcomes. Non-parametric quantile regression models with heteroscedasticity-robust standard errors were used if non-normality or heterogeneity of residuals were identified in the linear models. Binary logistic regression was used for analysis of categorical outcomes. In each analysis, baseline values and study site were controlled for.

Proportions estimated from the combined multiple imputation datasets could not be summarised in terms of the number of patients exhibiting each characteristic as these vary between the imputed sets. Numerators and denominators for proportions are therefore only presented for the observed data. The threshold for statistical significance was adjusted for multiple comparisons in the secondary outcomes

using the Holm method. There were no adjustments made for the exploratory analyses.

Descriptive results are presented for harms. Where events recurred over time, only the most severe was counted for each patient. Absolute and relative frequencies are presented with the number of occurrences per 100 patient-years of follow-up.

5.3 Results

In total, 110 patients were recruited from four sites in West Yorkshire, UK from October 2006 to May 2009 (figure 5.2). Demographics and baseline disease characteristics are summarised in table 5.1. Seventy six percent of patients were female with a mean (SD) age of 48.6 (13.3) years and median symptom duration of seven months. Fifty three percent were RF positive, 77% anti-CCP positive and 82% shared epitope positive. Forty one percent (45/110) fulfilled the 1987 ACR RA classification criteria and 94% (103/110) fulfilled the 2010 ACR EULAR criteria. Mean (SD) baseline DAS44-CRP was 2.94 (0.91). [12]

During the study the median (IQR) maximum methotrexate dose in each group was 25 (20, 25) mg/week in both groups. Five patients in the methotrexate and placebo group (9.1%) and three patients in the methotrexate and etanercept group (5.5%) were not prescribed at least 20 mg/week. Of these, two patients (one in the methotrexate and placebo and one in the methotrexate and etanercept groups) experienced adverse events which limited their tolerated dose, three patients (two in the methotrexate and placebo and one in the methotrexate and etanercept group) withdrew from the study during the treatment escalation phase, and three patients (two in the methotrexate and placebo and one methotrexate and etanercept groups) achieved NTSJ before reaching 20 mg/week.

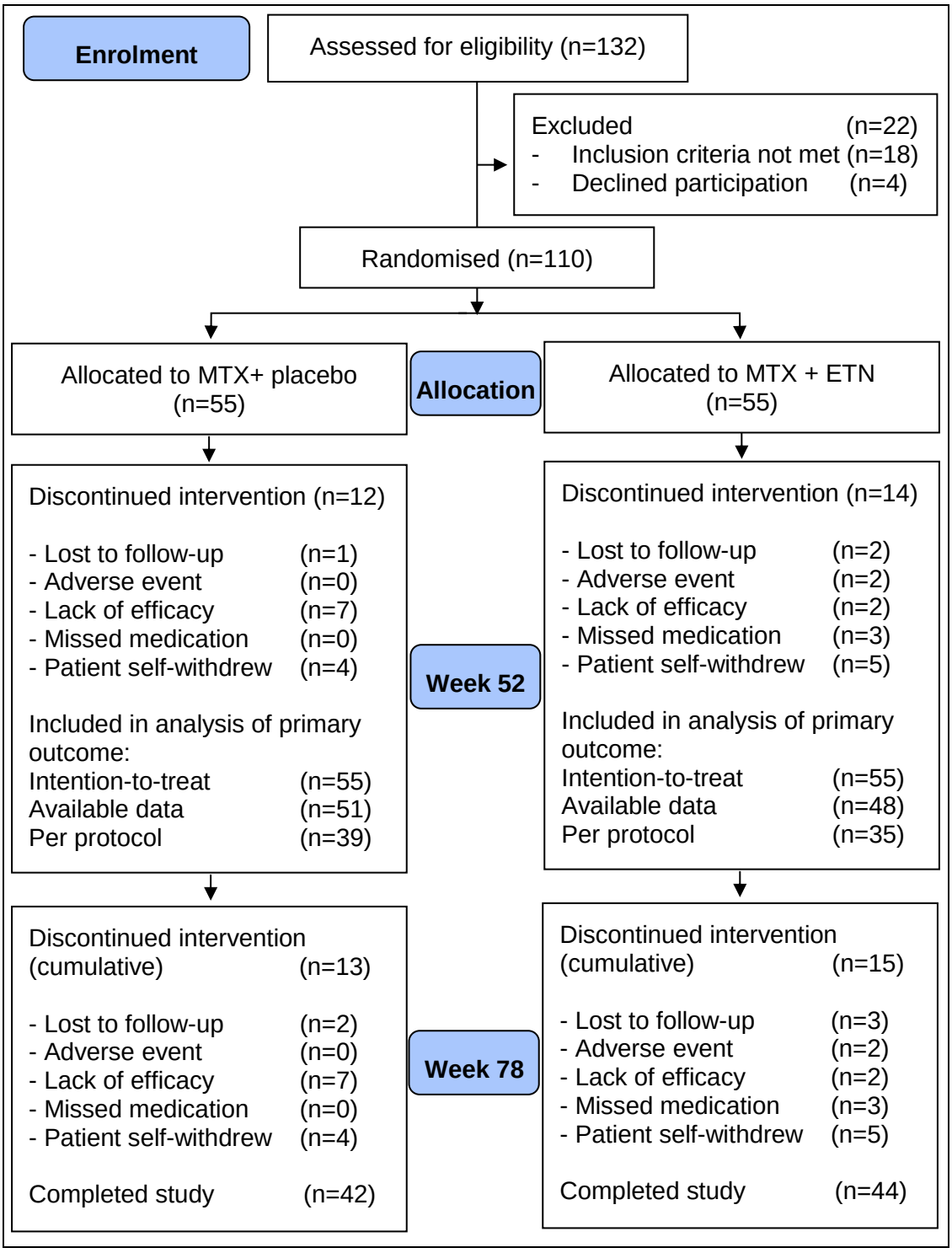


Figure 5.2 EMPIRE study patient disposition

ETN, etanercept; MTX, methotrexate

Table 5.1 Baseline characteristics of patients randomised to receive methotrexate and placebo or methotrexate and etanercept

		MTX+PBO (n=55)	**MTX+ETN (n=55)**
Site:	**Leeds** **Huddersfield** **Harrogate** **York**	n=46 n=4 n=2 n=3	n=48 n=3 n=4 n=0
Age (years):	**mean (SD),range**	48.38 (13.34), 26-79	47.91 (13.58), 18-80
Female:	**% (n)**	72.7% (40/55)	80.0% (44/55)
Symptom duration (months):	**median (IQR), range**	8 (6, 11), 3-18	6 (4, 9). 1-21
DAS44-CRP:	**mean (SD)**	2.95 (0.91)	2.94 (0.92)
DAS28-CRP:	**mean (SD)**	4.17 (1.10)	4.10 (1.14)
RF-positive:	**% (n)**	55.6% (30/54)	56.4% (31/55)
Anti-CCP-positive:	**% (n)**	80.8% (42/52)	72.2% (39/54)
SE positive (1 copy): **SE positive (2 copies):**	**% (n)** **% (n)**	63.5% (33/52) 21.2% (11/52)	43.4% (23/53) 35.8% (19/53)
HAQ-DI:	**mean (SD)**	1.00 (0.43), n=53	1.01 (0.47), n=53
SF-36 MCS:	**mean (SD)**	42.45 (12.23), n=49	46.82 (10.19), n=51
SF-36 PCS:	**mean (SD)**	35.51 (7.90), n=49	36.00 (8.04), n=51
EQ-5D-3L:	**mean (SD)** **median (IQR)**	0.569 (0.252), n=53 0.587 (0.516, 0.760)	0.578 (0.245), n=52 0.620 (0.516, 0.760)
ERO:	**mean (SD)**	1.36 (2.95), n=49	1.10 (1.84), n=40

	median (IQR)	0.0 (0.0, 1.5)	0.0 (0.0, 1.5)
JSN:	**mean (SD)**	6.65 (6.03), n=49	5.59 (4.28), n=40
	median (IQR)	4.5 (2.3, 9.5)	5.3 (1.8, 9.3)
mTSS:	**mean (SD)**	8.01 (8.06), n=49	6.69 (5.04), n=40
	median (IQR)	5.5 (2.8, 11.3)	5.5 (2.8, 10.0)

Anti-CCP, anti-cyclic citrullinated peptide antibody; DAS44CRP, disease activity score based on RAI and SJC44; EQ-5D-3L, Euroqol 5-dimensional 3-level response standardised health outcome tool; ERO, rosion; ESR, erythrocyte sedimentation rate; ETN, etanercept; HAQ-DI, Rasch-transformed health assessment questionnaire disability index score; JSN, joint space narrowing; mTSS, van der Heijde modified total Sharp score; MTX, methotrexate; RAI, Ritchie Articular Index; RAQoL, Rasch-transformed rheumatoid arthritis quality of life score; RF, rheumatoid factor; SE, shared epitope

5.3.1 Clinical outcomes

5.3.1.1 Primary clinical outcome: NTSJ

The proportions of patients achieving NTSJ at week 52 were similar between the two groups (28.1% vs. 32.5% adjusted OR (95% CI) 1.32 (0.56, 3.09), p=0.522 in the methotrexate and placebo and methotrexate and etanercept groups respectively (table 5.2)). Findings were similar with the different sensitivity analyses - imputing non-response for patients who discontinued the intervention, using complete case data and the per protocol data - with no significant differences between the groups (tables 5.3 to 5.6).

5.3.1.2 Secondary clinical outcomes

5.3.1.2.1 Remission according to the 2011 ACR/EULAR remission criteria[359]

At week 52, remission using the 2011 ACR/EULAR Boolean-based definition was 22.5% in the methotrexate and placebo and 26.7% in the methotrexate and etanercept groups. In both, remission was achieved in a higher proportion of patients when defined by SDAI≤3.3 (37.0% vs. 47.5%). No statistically significant between-group differences were seen for both outcomes at week 52 and 78 (table 5.2).

5.3.1.2.2 Drug free remission

Of those in the methotrexate and placebo group, 9.1% (5/55) stopped placebo injections after achieving sustained NTSJ. In the methotrexate and etanercept group, 7.3% (4/55) achieved sustained NTSJ (>26 weeks) by week 52; two of whom stopped etanercept early. There were also two patients in the methotrexate and etanercept group who stopped injections prematurely - each had one tender joint one swollen joint. In each group, 3.6% (2/55) had NTSJ and were drug free at week 78.

5.3.1.2.3 Exploratory clinical outcomes: DAS28-CRP

Earlier clinical responses were seen in patients receiving methotrexate and etanercept. By week 2, the proportion of patients achieving DAS28 remission and low disease activity was significantly higher in the group receiving combination therapy (DAS28-CRP <2.6: 9.2% vs. 38.5% (adjusted OR (95% CI) 8.87 (2.53, 31.17), p=0.001 and DAS28-CRP≤3.2: 22.2% vs. 55.5% (adjusted OR (95% CI) 6.03 (2.22, 16.36), p<0.001 in the methotrexate and placebo and methotrexate and

etanercept groups respectively) (figure 5.3 table 5.5). For DAS28-CRP<2.6, this difference was maintained at week 12 (43.8% vs. 65.1% (adjusted OR (95% CI) 2.49 (1.12, 5.54), p=0.026) for the methotrexate and placebo and methotrexate and etanercept groups respectively). There was no significant difference in proportions achieving DAS28-CRP≤3.2 at this time-point. By week 52, the proportions of patients achieving DAS28-CRP<2.6 and DAS28-CRP≤3.2 in both groups were high (62.5% vs. 68.8% (adjusted OR (95% CI) 1.32 (0.58, 3.04), p=0.508) and 75.1% vs. 84.5% (adjusted OR (95% CI) 1.84 (0.65, 5.24), p=0.250) in the methotrexate and placebo and methotrexate and etanercept groups respectively) (figure 5.3).

Of the patients in the methotrexate and etanercept group, 57.7% maintained DAS28-CRP≤3.2 between week 52 to week 78 and 41.9% maintained DAS28-CRP<2.6. For comparison, in the methotrexate and placebo group these figures were 64.9% and 42.9% respectively.

5.3.2 Patient-reported outcomes

5.3.2.1 Secondary outcomes: HAQ-DI and SF-36

Improvements in patient function were seen in both groups at week 52 (ΔHAQ-DI -0.31 vs. -0.4, p=0.381 in the methotrexate and placebo and methotrexate and etanercept groups respectively). These were maintained at week 78. Improvements in physical function in both groups were greater than that in mental function with no significant between group differences (Week 52 ΔSF36 PCS 6.69 vs. 8.10 and ΔSF36 MCS. 2.99 vs. 0.97 in the methotrexate and placebo and methotrexate and etanercept groups) (table 5.2).

5.3.2.2 Exploratory outcomes: MCID HAQ-DI and normal HAQ-DI

No between group differences were seen in the proportion of patients with a reduction in HAQ-DI ≥ MCID (ΔHAQ-DI ≥ 0.22 units at week 52: 58.3% vs. 59.5%, unadjusted OR (95% CI) 1.05 (0.47, 2.37); adjusted OR (95% CI)1.08 (0.47, 2.49), p=0.854 and at week 78: 62.5% vs. 58.1%, unadjusted OR (95% CI) 0.83 (0.38, 1.84); adjusted OR (95% CI) 0.85 (0.38, 1.88), p=0.682 in the methotrexate and placebo and methotrexate and etanercept groups respectively). The proportions achieving normal function were also similar between the two groups (HAQ-DI ≤0.5 at week 52: 44.5% vs. 51.5%; unadjusted OR (95% CI) 1.32 (0.60, 2.91); adjusted OR (95% CI) 1.37 (0.58, 3.26), p=0.474 and at week 78: 48.6% vs. 46.1% unadjusted OR (95% CI) 0.91 (0.42, 1.97); adjusted OR (95% CI) 0.86 (0.37, 2.02), p=0.735 in the methotrexate and placebo and methotrexate and etanercept groups). The site adjustment for these comparisons pooled sites 2-4.

5.3.3 Imaging outcomes

5.3.3.1 Secondary outcome: Radiographic findings

The SDC in mTSS for this study was calculated to be 3 units. In both groups radiographic non-progression was high. At week 52, progression ≤SDC was 95.5% and 93.1% in the methotrexate and placebo and methotrexate and etanercept groups respectively (table 5.2). At week 78 this was 80.0% and 87.1% in each group (p=0.598).

5.3.3.2 Secondary outcome: Ultrasound findings

In the subset of patients with ultrasound data at baseline (methotrexate and placebo n=46; methotrexate and etanercept n=48), 66.7% (30/45) in the methotrexate and placebo group and (62.2%) in the methotrexate and etanercept group had ultrasound synovitis (GS>1 and PD>0) in at least one joint. Baseline total ultrasound scores did not differ substantively between the groups (median (IQR) GS: methotrexate and placebo =12 (7, 17) vs. methotrexate and etanercept =14 (9, 22); PD: methotrexate and placebo =3 (1, 5) vs. methotrexate and etanercept =3 (0, 9); erosion score methotrexate and placebo =1.0 (0.0, 2.0) vs. methotrexate and etanercept =1.0 (0.0, 2.5) (n=44)).

Of these, 35.7% vs. 27.5% of patients in the methotrexate and placebo and methotrexate and etanercept groups respectively had ultrasound synovitis in at least one joint at week 52 and 38.0% vs. 41.6% at week 78. Neither the total GS score nor the total PD scores differed between the two groups at weeks 52 or 78. In both groups the number of ultrasound detected bone erosions was low with no significant between group differences seen at weeks 52 or 78 (table 5.2).

Table 5.2 Combined results from analyses of multiply imputed datasets of primary and secondary efficacy outcomes at weeks 52 and 78.

Outcome	MTX+PBO n=55	MTX+ETN n=55	Unadjusted (95% CI)	Adjusted (95% CI)	p
Week 52					
NTSJ	28.1%	32.5%	OR 1.23 (0.54, 2.84)	OR 1.32 (0.56, 3.09)*	0.522
ACR 2010 remission (Boolean)	22.5%	26.7%	OR 1.26 (0.50, 3.13)	OR 1.24 (0.49, 3.12)*	0.653
ACR 2010 remission (SDAI≤3.3)	37.0%	47.5%	OR 1.54 (0.69, 3.41)	OR 1.57 (0.68, 3.61)	0.287
DAS44CRP	-1.32	-1.45	-0.13 (-0.56, 0.30)	-0.11 (-0.47, 0.26)	0.554
Pain VAS#	-12.0 (-36.8, -0.6)	-30.4 (-54.3, -1.8)	-18.4 (-35.2, -1.6)†	-7.9 (-20.7, 4.9)†	0.222
Fatigue VAS#	-16.2 (-35.1, 9.9)	-21.4 (-41.8, -0.4)	-5.2 (-21.6, 11.2)†	-8.5 (-27.0, 10.0)†	0.363
Physician VAS#	-23.2 (-32.2, -13.4)	-27.6 (-36.8, -16.8)	-4.4 (-11.8, 3.0)†	-2.4 (-6.2, 1.4)†	0.203
EMS#	-50.0 (-79.8, -14.8)	-48.0 (-116.6, -15.7)	2.0 (-27.5, 31.5)†	-6.7 (-15.3, 1.90)†	0.126
HAQ-DI	-0.31	-0.40	-0.10 (-0.30, 0.11)	-0.09 (-0.29, 0.11)	0.381
SF36 MCS	2.99	0.97	-2.02 (-7.09, 3.05)	0.29 (-4.05, 4.64)	0.893
SF36 PCS	6.93	8.10	1.16 (-3.36, 5.68)	2.17 (-4.17, 4.60)	0.922
EQ-5D#	0.113 (0.000, 0.245)	0.128 (-0.024, 0.250)	0.016 (-0.11, 0.14)†	0.052 (-0.063, 0.166)†*	0.373

ERO	0.37	0.23	-0.14 (-0.47, 0.19)	-0.13 (-0.44, 0.18)	0.408
JSN	0.54	0.68	0.14 (-0.36, 0.64)	0.25 (-0.24, 0.74)	0.308
mTSS	0.91	0.90	0.00 (-0.64, 0.63)	0.12 (-0.47, 0.72)	0.676
ERO#	0.00 (0.00, 0.52)	0.00 (0.00, 0.47)	-0.00 (-0.15, 0.15)†	0.00 (-0.15, 0.15)†*	1.000
JSN#	0.13 (0.00, 1.13)	0.41 (0.00, 0.96)	0.29 (-0.23, 0.80)†	0.22 (-0.22, 0.66)†	0.327
mTSS#	0.50 (0.00, 1.66)	0.52 (0.00, 1.16)	0.02 (-0.46, 0.51)†	0.08 (-0.52, 0.68)†	0.791
Progression ≤0.5	54.4%	48.0%	OR 0.77 (0.32, 1.87)	OR 0.71 (0.29, 1.76)*	0.462
Progression ≤SDC	95.5%	93.1%	OR 0.67 (0.09, 4.84)	OR 0.40 (0.04, 3.75)*	0.423
S GS>1PD>0	35.7%, n=46	27.5%, n=48	OR 0.68 (0.28, 1.68)	OR 0.63 (0.23, 1.72)	0.372
US total GS score#	-1.0 (-6.4, 5.0)	-3.7 (-12.8, 2.3)	-2.7 (-8.1, 2.7)	-1.6 (-5.6, 2.4)	0.426
US total PD score#	-2.0 (-4.8, 0.0)	-3.0 (-8.0, 0.0)	-1.0 (-3.5, 1.6)	0.0 (-0.4, 0.4)	1.000
US total number of erosions#	0.0 (-0.1, 1.0), n=46	1.0 (0.0, 2.1), n=48	1.0 (-0.5, -2.5)	0.96 (-0.40, 2.32)	0.164
Week 78					
NTSJ	28.1%	24.6%	0.84 (0.34, 2.05)	0.94 (0.37, 2.41)	0.904
Achieved 26 weeks of remission	18.3%	14.5%	OR 0.76 (0.28, 2.10)	OR 0.85 (0.30, 2.41)*	0.756

ACR 2010 remission (Boolean)	20.5%	20.9%	OR 1.03 (0.40, 2.63)	OR 1.04 (0.37, 2.89)	0.947
ACR 2010 remission (SDAI≤3.3)	38.5%	39.5%	OR 1.05 (0.45, 2.41)	OR 1.08 (0.45, 2.59)	0.867
DAS44CRP	-1.33	-1.29	0.04 (-0.46, 0.54)	0.05 (-0.34, 0.44)	0.794
Pain VAS#	-19.6 (-40.7, -4.6)	-21.9 (-45.6, -1.6)	-2.3 (-19.6, 15.0)	9.1 (-4.8, 23.1)†	0.195
Fatigue VAS#	-17.7 (-37.1, 8.4)	-19.0 (-46.3, 1.2)	-1.4 (-17.9, 15.2)	-3.6 (-23.9, 16.8)†	0.725
Physician VAS#	-23.9 (-31.4, -10.5)	-23.1 (-37.4, -11.3)	0.8 (-8.2, 9.7)	0.5 (-5.3, 6.3)†	0.871
EMS#	-42.8 (-85.4, -0.3)	-29.9 (-86.2, -1.2)	12.9 (-13.2, 39.0)†	1.8 (-14.8, 18.4)†	0.826
HAQ-DI	-0.37	-0.34	0.02 (-0.20, 0.24)	0.04 (-0.17, 0.26)	0.688
SF36 MCS	2.94	2.48	-0.46 (-5.48, 4.57)	1.42 (-3.10, 5.95)	0.533
SF36 PCS	7.06	6.50	-0.56 (-4.35, 3.24)	-0.98 (-4.77, 2.80)	0.607
EQ-5D#	0.151 (-0.004, 0.276)	0.102 (-0.002, 0.236)	-0.049 (-0.156, 0.057)†	-0.029 (-0.130, 0.073)†*	0.576
ERO	0.60	0.50	-0.11 (-0.55, 0.34)	-0.10 (-0.54, 0.34)	0.653
JSN	0.99	0.87	-0.11 (-0.61, 0.39)	-0.03 (-0.52, 0.46)	0.901
mTSS	1.59	1.37	-0.22 (-0.90, 0.46)	-0.10 (-0.74, 0.54)	0.761
ERO#	0.11 (0.00, 0.71)	0.02 (0.00, 0.81)	-0.09 (-0.55, 0.36)†	0.00 (-0.22, 0.22)†*	1.000
JSN#	0.52 (0.04, 1.44)	0.62 (0.04, 1.21)	0.11 (-0.46, 0.68)†	-0.12 (-0.62, 0.38)†	0.644

mTSS#	0.97 (0.45, 2.27)	1.09 (0.36, 1.97)	0.13 (-0.55, 0.81)†	0.15 (-0.48, 0.77)†	0.642
Progression ≤0.5	35.9%	35.8%	OR 0.99 (0.36, 2.74)	OR 0.99 (0.27, 3.00)*	0.982
Progression ≤SDC	80.0%	87.1%	OR 1.69 (0.53, 5.37)	OR 1.39 (0.41, 4.76)*	0.598
US GS>1PD>0	38.0%, n=46	41.6%, n=48	OR 1.16 (0.49, 2.75)	**	0.740
US total GS score#	1.9 (-6.0, 7.8)	-0.1 (-5.6, 3.6)	-2.0 (-7.2, 3.2)	-1.6 (-6.2, 2.9)	0.472
US total PD score#	-2.0 (-3.9, 0.0)	-1.5 (-7.7, 0.1)	0.5 (-1.9, 3.0)	0.6 (-1.0, 2.2)	0.434
US total number of erosions#	0.1 (0.0, 2.1), n=46	1.1 (0.0, 3.0), n=48	1.1 (-0.4, 2.5)	0.53 (-0.72, 1.78)	0.399

Mean (SD) or median (IQR) changes from baseline and between-group differences (95% CI) are presented for continuous variables; proportions and odds ratios (95% CI) are presented for nominal variables; results were adjusted for baseline values and study site unless otherwise indicated.

ACR, American College of Rheumatology; DAS44CRP, disease activity score based on RAI and SJC44; EQ-5D-3L, Euroqol 5-dimensional 3-level response standardised health outcome tool; EMS, early morning stiffness; ERO, erosion score; ESR, erythrocyte sedimentation rate; ETN, etanercept; GS, grey scale; HAQ-DI, Rasch-transformed health assessment questionnaire disability index score; JSN, joint space narrowing score; mTSS, van der Heijde modified total Sharp score; MTX, methotrexate; NTSJ, no tender or swollen joints; PBO, placebo; PD, power Doppler; RAI, Ritchie Articular Index; RAQoL, Rasch-transformed rheumatoid arthritis quality of life score; RF, rheumatoid factor; SE, shared epitope; US, ultrasound; VAS, visual analogue scale

#Results of quantile regression; median (1st quartile, 3rd quartile) are presented for each group.

*Site adjustment pooled sites 2-4 to avoid model separation due to sparse data; **Unadjusted results presented as ultrasound data only available at a single site, and adjusting for baseline values caused analysis model to fail.

†Difference between medians

Table 5.3 Sensitivity analyses of primary efficacy outcome at week 52.

Outcome	Analysis	MTX+PBO	MTX+ETN	Unadjusted (95% CI)	Adjusted (95% CI)	p
Week 52						
NTSJ remission	**NRI***	27.3% (15/55)	27.3% (15/55)	1.00 (0.43, 2.31)	1.06 (0.45, 2.49)	0.898
	NRI, no additional meds**	34.5% (10/29)	41.2% (14/34)	1.33 (0.48, 3.71)	1.33 (0.45, 3.86)	0.598
	Complete case	29.4% (15/51)	35.4% (17/48)	1.32 (0.57, 3.06)	0.90 (0.35, 2.31)	0.822
	Per protocol	35.9% (14/39)	28.6% (10/35)	0.62 (0.23, 1.69)	0.70 (0.24, 1.98)	0.497

Results were adjusted for baseline values and study site unless otherwise stated.

ETN, etanercept; meds, medications; MTX, methotrexate; NTSJ, no tender or swollen joints; PBO, placebo

*Non-response imputed for patients who withdrew from study treatment or were lost to follow-up before week 52

**Patients were excluded if they had received oral Prednisolone, IA or IM steroid, or DMARDs other than MTX and/or ETN

Table 5.4 Analyses of secondary efficacy outcomes at weeks 52 and 78 (observed data only).

Outcome	MTX+PBO	MTX+ETN	Unadjusted (95% CI)	Adjusted (95% CI)	p
Week 52					
ACR 2010 remission (Boolean)	23.5% (12/51)	28.3% (13/46)	OR 1.28 (0.51, 3.18)	OR 1.32 (0.53, 3.33)*	0.551
ACR 2010 remission (SDAI≤3.3)	38.0% (19/50)	48.9% (22/45)	OR 1.56 (0.69, 3.53)	OR 1.88 (0.78, 4.50)	0.158
DAS44CRP	-1.34 (1.19), n=50	-1.40 (1.03), n=46	-0.07 (-0.52, 0.39)†	-0.12 (-0.50, 0.26)	0.533
Pain VAS#	-12.0 (-37.0, -2.0), n=51	-31.0 (-58.0, -5.0), n=45	-19.0 (-37.0, -1.0)†	-8.9 (-20.5, 2.8)†	0.133
Fatigue VAS#	-16.0 (-36.0, 11.0), n=51	-25.0 (-41.0, -4.0), n=45	-9.0 (-25.5, 7.5)†	-10.3 (-27.9, 7.4)†	0.251
Physician VAS#	-23.0 (-32.0, -13.0), n=50	-28.0 (-35.0, -17.0), n=45	-5.0 (-12.9, 2.9)	-3.2 (-7.0, 0.7)†	0.103
EMS#	-50 (-70, -25), n=49	-55 (-120, -20), n=47	5.0 (-16.0, 26.0)†	-6.7 (-14.5, -1.2)†	0.095
HAQ-DI	-0.29 (0.57), n=49	-0.44 (0.47), n=46	-0.14 (-0.36, 0.07)	-0.14 (-0.35, 0.08)	0.202
SF36 MCS	4.24 (14.51), n=45	1.65 (8.20), n=41	-2.59 (-7.72, 2.53)	0.83 (-3.59, 5.25)	0.709
SF36 PCS	6.92 (9.74), n=45	9.85 (10.66), n=41	2.94 (-1.44, 7.31)	2.15 (-2.12, 6.41)	0.319
EQ-5D#	0.123 (0.000, 0.244), n=49	0.159 (0.000, 0.240), n=42	0.036 (-0.09, 0.16)†	0.069 (-0.047, 0.185)†*	0.239
ERO	0.41 (0.88), n=40	0.22 (0.64), n=30	-0.18 (-0.56, 0.19)	-0.19 (-0.58, 0.20)	0.335

JSN	0.56 (1.08), n=40	0.62 (1.28), n=30	0.06 (-0.50, 0.62)	0.19 (-0.34, 0.72)	0.472
mTSS	0.97 (1.38), n=40	0.84 (1.47), n=30	-0.12 (-0.81, 0.56)	0.01 (-0.63, 0.65)	0.975
ERO#	0.00 (0.00, 0.50), n=40	0.00 (0.00, 0.48), n=30	0.00 (-0.21, 0.21)†	0.00 (-0.23, 0.23)†	1.000
JSN#	0.32 (0.00, 1.03), n=40	0.40 (0.00, 0.93), n=30	0.08 (-0.33, 0.50)†	0.11 (-0.34, 0.56)†	0.628
mTSS#	0.49 (0.00, 1.79), n=40	0.50 (0.00, 1.02), n=30	0.01 (-0.50, 0.52)†	0.00 (-0.58, 0.57)†	0.996
Progression ≤0.5	55.0% (22/40)	46.7% (14/30)	OR 0.72 (0.28, 1.85)	OR 0.70 (0.26, 1.82)*	0.459
Progression ≤SDC	95.0% (38/40)	93.3% (28/30)	OR 0.74 (0.10, 5.55)	OR 0.53 (0.06, 4.86)*	0.572
US GS>1PD>0	34.9% (15/43)	28.6% (12/42)	OR 0.75 (0.30, 1.87)	OR 0.70 (0.25, 1.94)	0.495
US total GS score#	-1.0 (-7.0, 5), n=43	-4.0 (-13.0, 3.0), n=42	-3.0 (-9.2, 3.2)	-1.6 (-5.6, 2.5)	0.444
US total PD score#	-2.0 (-4.0, 0.0), n=43	-2.9 (-7.0, 0.0), n=42	-1.0 (-3.5, 1.7)	0.0 (-0.44, 0.44)	1.000
US total erosions#	0.0 (0.0, 1.0), n=43	1.0 (0.0, 2.0), n=39	1.0 (-0.7, 2.7)	1.0 (-0.7, 2.7)	0.234
Week 78					
NTSJ remission	30.0% (15/50)	25.0% (12/48)	OR 0.78 (0.32, 1.89)	OR 0.90 (0.35, 2.32)	0.822
Achieved 26 weeks of remission	19.6% (10/51)	16.0% (8/50)	OR 0.78 (0.28, 2.18)	OR 0.86 (0.30, 2.47)*	0.777
ACR 2010 remission (Boolean)	22.0% (11/50)	22.9% (11/48)	OR 1.05 (0.41, 2.72)	OR 1.12 (0.42, 2.97)	0.826
ACR 2010 remission (SDAI≤3.3)	39.1% (18/46)	41.9% (18/43)	OR 1.12 (0.48, 2.61)	OR 1.21 (0.50, 2.92)	0.667
DAS44CRP	-1.33 (1.09), n=48	-1.33 (1.31), n=45	0.00 (-0.49, 0.49)	0.08 (-0.30, 0.46)	0.676
Pain VAS#	-22 (-41.0, -6.0), n=49	-23.0 (-50.0, -	-1.0 (-9.4, 17.4)†	11.8 (-0.9, 24.4)†	0.068

		3.0),n=47			
Fatigue VAS#	-18.0 (-37.0, 4.0), n=50	-21.0 (-47.0, -3.0),n=47	-3.0 (-19.3, 13.3)†	-7.7 (-22.5, 7.2)†	0.308
Physician VAS#	-24.0 (-32.0, -13.0), n=47	-25.0 (-38.0, -16.0), n=44	-1.0 (-9.2, 7.2)†	0.8 (-4.1, 5.7)†	0.754
EMS#	-45 (-80, -13), n=48	-30 (-110, -5), n=47	15.0 (-11.1, 41.1)†	-0.2 (-12.7, 12.3)†	0.972
HAQ-DI	-0.39 (0.65), n=48	-0.37 (0.45), n=47	0.02 (-0.21, 0.25)	0.04 (-0.19, 0.27)	0.712
SF36 MCS	4.01 (13.88), n=45	3.04 (9.65), n=44	-0.97 (-6.02, 4.08)	1.45 (-3.05, 5.94)	0.524
SF36 PCS	6.80 (9.40), n=45	8.04 (7.76), n=44	1.24 (-2.39, 4.88)	0.71 (-2.87, 4.30)	0.694
EQ-5D#	0.157 (0.000, 0.280), n=47	0.102 (0.000, 0.240), n=47	-0.055 (-0.169, 0.059)†	-0.026 (-0.108, 0.057)†*	0.543
ERO	0.64 (1.22), n=39	0.47 (0.95), n=32	-0.17 (-0.70, 0.36)	-0.29 (-0.81, 0.22)	0.254
JSN	0.94 (1.12), n=39	0.92 (1.42), n=32	-0.02 (-0.62, 0.59)	-0.04 (-0.62, 0.54)	0.890
mTSS	1.58 (1.86), n=39	1.39 (1.58), n=32	-0.19 (-1.02, 0.64)	-0.32 (-1.06, 0.42)	0.387
ERO#	0.00 (0.00, 0.50), n=39	0.00 (0.00, 0.49), n=32	0.00 (-0.24, 0.24)†	0.00 (-0.26, 0.26)†	1.000
JSN#	0.49 (0.00, 1.42), n=39	0.50 (0.00, 1.02), n=32	0.00 (-0.49, 0.50)†	-0.16 (-0.66, 0.34)†	0.535
mTSS#	0.95 (0.42, 2.03), n=39	1.02 (0.47, 1.80), n=32	0.07 (-0.71, 0.85)†	0.08 (-0.51, 0.67)†	0.792
Progression ≤0.5	38.5% (15/39)	34.4% (11/32)	OR 0.84 (0.32, 2.22)	OR 0.90 (0.31, 2.60)*	0.842
Progression ≤SDC	79.5% (31/39)	87.5% (28/32)	OR 1.81 (0.49, 6.66)	OR 1.74 (0.45, 6.77)*	0.423
US GS>1PD>0	38.1% (16/42)	41.5% (17/41)	OR 1.15 (0.48, 2.77)	OR 1.03 (0.42, 2.56)	0.944

US total GS score#	2.0 (-6.0, 8.0)	0.0 (-5.0, 4.0)	-2.0 (-7.5, 3.5)	-1.4 (-5.8, 3.0)	0.540
US total PD score#	-2.0 (-3.0, 0.0)	-1.0 (-8.0, 0.0)	1.0 (-1.3, 3.3)	1.0 (-1.1, 3.1)	0.338
US total erosions#	0.0 (0.0, 2.0), n=42	1.0 (0.0, 3.0), n=38	1.0 (-0.2, 2.2)	0.3 (-0.9, 1.4)	0.678

Mean (SD) or median (IQR) changes from baseline and between-group differences (95% CI) are presented for continuous variables; proportions (n) and odds ratios (95% CI) are presented for nominal variables; results were adjusted for baseline values and study site unless otherwise stated.

ACR, American College of Rheumatology; DAS44CRP, disease activity score based on RAI and SJC44; ERO, Euroqol 5-dimensional 3-level response standardised health outcome tool; EMS, early morning stiffness; ERO, erosion; ESR, erythrocyte sedimentation rate; ETN, etanercept; GS, grey scale; HAQ-DI, Rasch-transformed health assessment questionnaire disability index score; JSN, joint space narrowing; mTSS, van der Heijde modified total Sharp score; MTX, methotrexate; NTSJ, no tender or swollen joints; PBO, placebo; PD, power Doppler; RAI, Ritchie Articular Index; RAQoL, Rasch-transformed rheumatoid arthritis quality of life score; RF, rheumatoid factor; SE, shared epitope; SF36 MCS, short-form 36 mental component score, SF36 MCS, short-form 36 physical component score US, ultrasound; VAS, visual analogue scale.

#Results of quantile regression; median (1^{st} quartile, 3^{rd} quartile) are presented for each group; * Site adjustment pooled sites 2-4 to avoid model separation due to sparse data; †Difference between medians.

Table 5.5 Combined results from analyses of multiply imputed datasets of exploratory efficacy variables at weeks 2, 12, 26, 52 and 78.

Outcome	MTX+PBO n=55	MTX+ETN n=55	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p
Week 2					
DAS44CRP<1.6	5.5%	27.7%	6.55 (1.77, 24.26)	8.79 (2.02, 38.29)*	0.004
DAS44CRP≤2.4	32.1%	55.8%	2.67 (1.22, 5.86)	3.20 (1.30, 7.88)	0.012
DAS28CRP<2.6	9.2%	38.5%	6.21 (2.13, 18.12)	8.87 (2.53, 31.17)*	0.001
DAS28CRP≤3.2	22.2%	55.5%	4.37 (1.90, 10.07)	6.03 (2.22, 16.36)*	<0.001
Week 12					
DAS44CRP<1.6	38.5%	43.0%	1.21 (0.56, 2.63)	1.30 (0.57, 3.00)	0.534
DAS44CRP≤2.4	65.2%	77.9%	1.88 (0.81, 4.41)	1.84 (0.77, 4.40)	0.173
DAS28CRP<2.6	43.8%	65.1%	2.39 (1.10, 5.21)	2.49 (1.12, 5.54)	0.026
DAS28CRP≤3.2	65.1%	78.0%	1.90 (0.82, 4.44)	1.89 (0.76, 4.70)	0.172
Week 26					
DAS44CRP<1.6	36.8%	56.5%	2.23 (1.01, 4.90)	2.297 (1.03, 5.13)	0.043
DAS44CRP≤2.4	67.8%	84.2%	2.53 (0.99, 6.49)	2.78 (1.02, 7.56)*	0.046

DAS28CRP<2.6	49.3%	67.5%	2.14 (0.98, 4.71)	2.12 (0.94, 4.75)	0.069
DAS28CRP≤3.2	62.7%	81.5%	2.62 (1.06, 6.47)	2.51 (0.98, 6.43)	0.055
Week 52					
DAS44CRP<1.6	53.0%	57.1%	1.18(0.54, 2.58)	1.13 (0.49, 2.62)	0.770
DAS44CRP≤2.4	77.8%	83.7%	1.47 (0.55, 3.94)	1.50 (0.53, 4.25)*	0.448
DAS28CRP<2.6	62.5%	68.8%	1.39 (0.60, 3.24)	1.32 (0.58, 3.04)	0.508
DAS28CRP≤3.2	75.1%	84.5%	1.82 (0.67, 4.91)	1.84 (0.65, 5.24)*	0.250
Week 78					
DAS44CRP<1.6	60.5%	51.6%	0.70 (0.30, 1.62)	0.65 (0.27, 1.54)	0.329
DAS44CRP≤2.4	80.1%	82.5%	1.18 (0.41, 3.37)	1.18 (0.41, 3.43)*	0.755
DAS28CRP<2.6	61.4%	58.3%	0.88 (0.39, 1.98)	0.88 (0.39, 2.00)*	0.761
DAS28CRP≤3.2	81.3%	76.0%	0.73 (0.26, 2.03)	0.71 (0.25, 2.01)*	0.522

ETN, etanercept; MTX, methotrexate; PBO, placebo.

Results were adjusted for baseline values and study site unless otherwise stated.

*Site adjustment pooled sites 2-4 to avoid model separation due to sparse data

Table 5.6 Analyses of exploratory efficacy variables at weeks 2, 12, 26, 52 and 78 (observed data only).

Outcome	MTX+PBO	MTX+ETN	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p
Week 2					
DAS44CRP<1.6	5.5% (3/54)	27.8% (15/54)	6.54 (1.77, 24.18)	8.83 (2.03, 38.34)*	0.004
DAS44CRP≤2.4	31.5% (17/54)	55.6% (30/54)	2.72 (1.24, 5.97)	3.29 (1.33, 8.14)	0.010
DAS28CRP<2.6	9.3% (5/54)	38.9% (21/54)	6.24 (2.14, 18.19)	9.21 (2.61, 32.47)*	0.001
DAS28CRP≤3.2	22.2% (12/54)	55.6% (30/54)	4.38 (1.90, 10.10)	6.24 (2.29, 17.02)*	<0.001
Week 12					
DAS44CRP<1.6	36.5% (19/52)	42.6% (23/54)	1.29 (0.59, 2.81)	1.40 (0.60, 3.23)	0.433
DAS44CRP≤2.4	63.5% (33/52)	77.8% (42/54)	2.02 (0.86, 4.74)	1.96 (0.81, 4.72)	0.133
DAS28CRP<2.6	42.3% (22/52)	64.8% (35/54)	2.51 (1.15, 5.50)	2.63 (1.18, 5.91)	0.018
DAS28CRP≤3.2	63.5% (33/52)	77.8% (42/54)	2.02 (0.86, 4.74)	2.02 (0.80, 5.07)	0.135
Week 26					
DAS44CRP<1.6	36.5% (19/52)	56.9% (29/51)	2.29 (1.04, 5.05)	2.36 (1.05, 5.31)	0.038
DAS44CRP≤2.4	67.3% (35/52)	84.3% (43/51)	2.61 (1.01, 6.76)	2.90 (1.05, 7.97)*	0.040
DAS28CRP<2.6	48.1% (25/52)	68.6% (35/51)	2.36 (1.06, 5.28)	2.31 (1.02, 5.25)	0.046

DAS28CRP≤3.2	61.5% (32/52)	82.4% (42/51)	2.92 (1.17, 7.26)	2.81 (1.09, 7.21)	0.032
Week 52					
DAS44CRP<1.6	54.0% (27/50)	58.7% (27/46)	1.21 (0.54, 2.72)	1.14 (0.48, 2.69)	0.766
DAS44CRP≤2.4	78.0% (39/50)	84.8% (39/46)	1.57 (0.55, 4.47)	1.56 (0.52, 4.71)*	0.428
DAS28CRP<2.6	64.0% (32/50)	71.7% (33/46)	1.43 (0.60, 3.39)	1.36 (0.55, 3.38)	0.502
DAS28CRP≤3.2	76.0% (38/50)	87.0% (40/46)	2.11 (0.72, 6.17)	2.17 (0.70, 6.79)*	0.180
Week 78					
DAS44CRP<1.6	62.5% (30/48)	51.1% (23/45)	0.63 (0.27, 1.43)	0.60 (0.26, 1.41)	0.242
DAS44CRP≤2.4	81.3% (39/48)	82.2% (37/45)	1.07 (0.37, 3.06)	1.12 (0.38, 3.26)*	0.841
DAS28CRP<2.6	62.5% (30/48)	57.8% (26/45)	0.82 (0.36, 1.89)	0.85 (0.36, 1.97)*	0.699
DAS28CRP≤3.2	81.3% (39/48)	75.6% (34/45)	0.71 (0.26, 1.93)	0.72 (0.26, 1.99)*	0.532

ETN, etanercept; MTX, methotrexate; PBO, placebo.

Results were adjusted for baseline values and study site unless otherwise stated.

* Site adjustment pooled sites 2-4 to avoid model separation due to sparse data

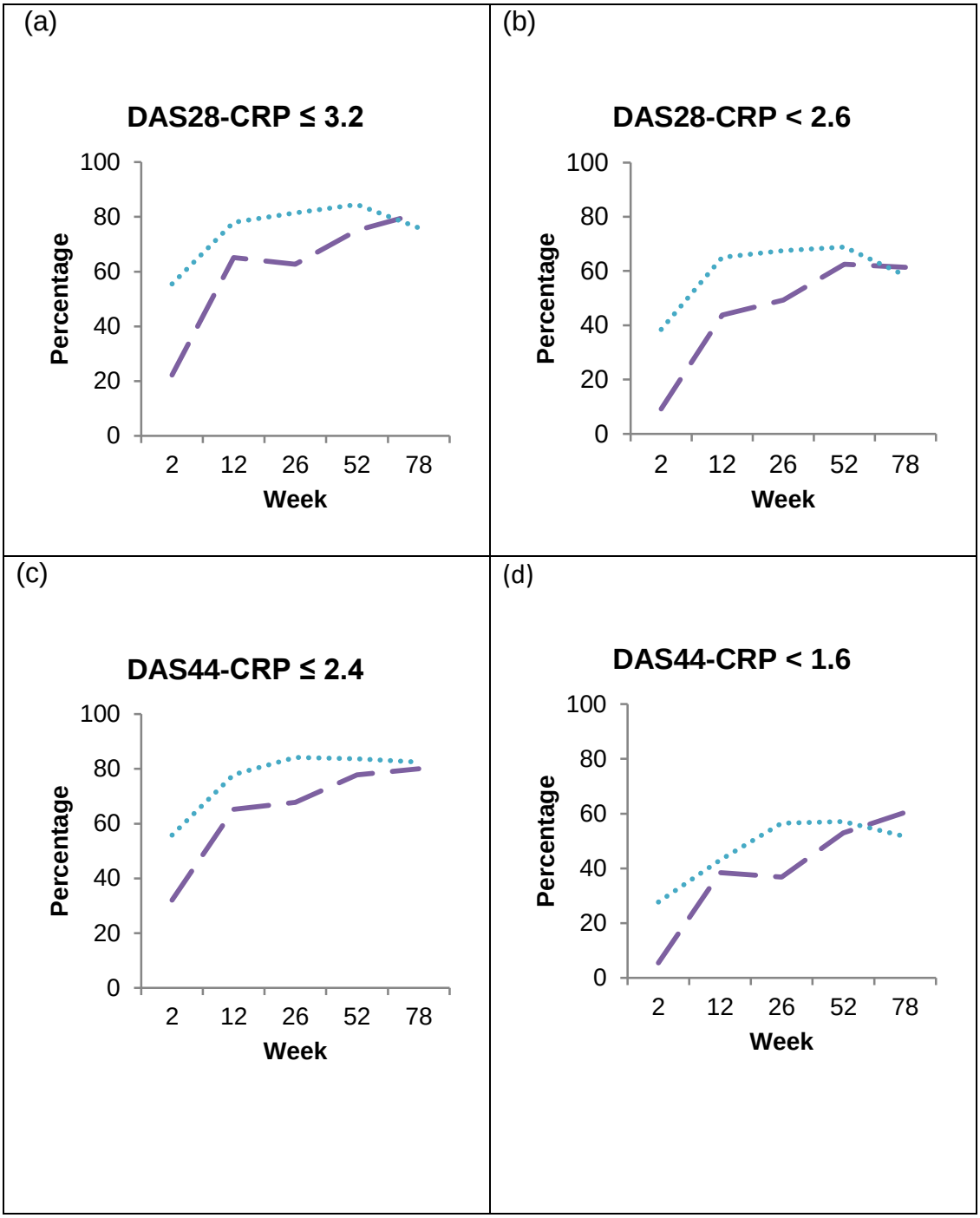


Figure 5.3 Proportions of patients in (a) LDAS28-CRP and (b) DAS28-CRP remission and (c) LDAS44-CRP and (d) DAS44-CRP remission

Legend:

Methotrexate + Placebo (n=55)

Methotrexate+ Etanercept (n=55)

5.3.4 Changes in medication

Changes in DMARD therapy and additional glucocorticoid requirements were also analysed. In total 32.7% (18/55) and 30.9% (17/55) of patients in the methotrexate and placebo and methotrexate and etanercept groups respectively required a change in DMARD during the study period. Between baseline and week 52, changes were made in 18% (10/55) and 5% (3/55) of patients in the methotrexate and placebo and methotrexate and etanercept groups; and between weeks 52 and 78 in 16% (9/55) and 25% (14/55) of patients. The number of additional csDMARDs used was similar between the groups. Biological DMARDs were added in three patients in the methotrexate and placebo group. (tables 5.7 to 5.9)

In each group approximately 50% of patients received at least one steroid injection during the trial period. The cumulative doses were similar in both groups (figure 5.4).

Table 5.7 Total additional synthetic or biological DMARD therapy from baseline to week 78

DMARD (% (n))	**MTX + PBO (n=55)**	**MTX + ETN (n=55)**
Methotrexate (subcutaneous)	9.1% (5)	10.9% (6)
Sulphasalazine	20.0% (11)	21.8% (12)
Hydroxychloroquine	10.9% (6)	10.9% (6)
Leflunomide	1.8% (1)	0
Etanercept	3.6% (2)	0
Adalimumab	1.8% (1)	0
Total number of patients requiring change in DMARDs	32.7% (18)	30.9% (17)

DMARD, disease-modifying antirheumatic drug; ETN, etanercept; MTX, methotrexate; PBO, placebo.

Table 5.8 Additional synthetic or biological DMARD therapy from baseline to week 52

DMARD (% (n))	**MTX + PBO (n=55)**	**MTX + ETN (n=55)**
Methotrexate (subcutaneous)	9.1% (5)	1.8% (1)
Sulphasalazine initiated	3.6% (2)	1.8% (1)
Sulphasalazine + hydroxychloroquine	7.3% (4)	1.8% (1)
Adalimumab initiated	1.8% (1)	0
Total number of patients requiring change in DMARDs	18% (10)	5% (3)

DMARD, disease-modifying antirheumatic drug; ETN, etanercept; MTX, methotrexate; PBO, placebo.

In one patient in the MTX and ETN arm, injections were stopped prematurely. The patient had a subsequently flare of inflammatory arthritis which was treated with sulphasalazine and the patient was withdrawn from the study.

Table 5.9 Additional synthetic or biological DMARD therapy from week 52 to week 78

DMARD (% (n))	MTX + PBO (n=55)	MTX + ETN (n=55)
Methotrexate (subcutaneous)	0	9.1% (5)
Sulphasalazine initiated	9.1% (5)	10.9% (6)
Hydroxychloroquine initiated	3.6% (2)	1.8% (1)
Sulphasalazine + hydroxychloroquine	0	7.3% (4)
Leflunomide initiated	1.8% (1)	0
Etanercept initiated	3.6% (2)	0
Total number of patients requiring change in DMARDs	16% (9)	25% (14)

DMARD, disease-modifying antirheumatic drug; ETN, etanercept; MTX, methotrexate; PBO, placebo

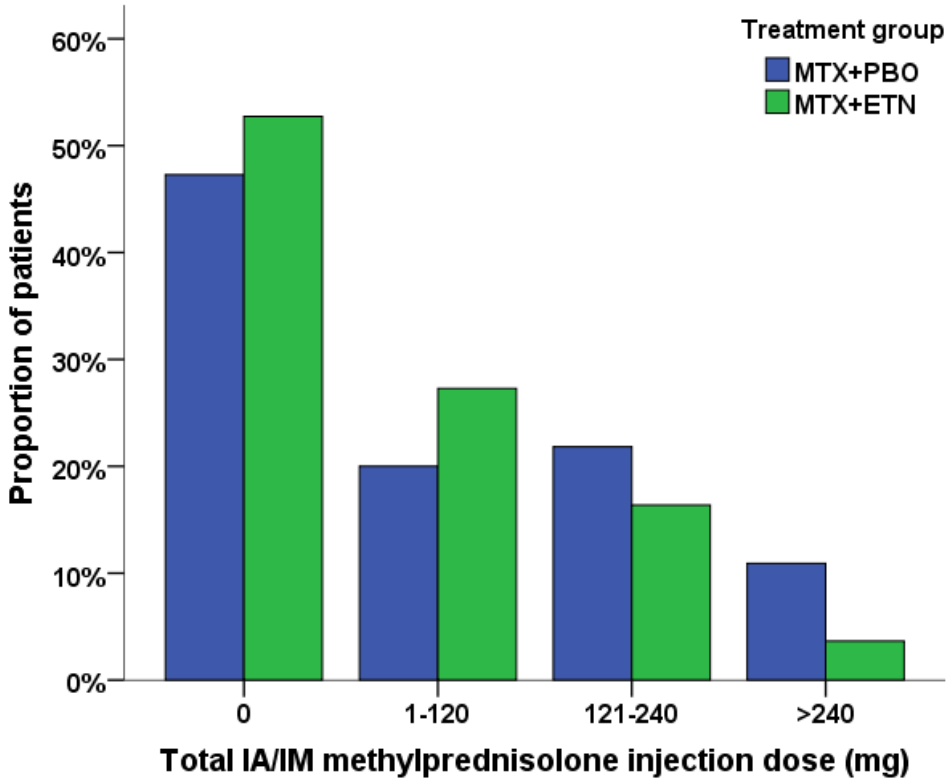


Figure 5.4 Steroid use during the study period

ETN, etanercept; IA, intra-articular; IM, intramuscular; MTX, methotrexate; PBO, placebo

Nine patients in the methotrexate and PBO group received a steroid injection (intra-articular or IM) between the week 38 and week 52 visits compared to 7 in the methotrexate and ETN group. Six in the methotrexate and PBO group required IA injection during this period compared to 5 in the methotrexate and ETN group.

5.3.5 Predictors of outcome

In a post hoc analysis of baseline predictors of outcome, earlier reduction in DAS28-CRP was seen in the anti-CCP positive compared to anti-CCP negative patients. Improvement in disease activity scores were higher in anti-CCP positive patients at week 2, controlling for treatment, study site and baseline DAS28-CRP (adjusted difference (95% CI) at week 2: -0.86 (-1.23, -0.49), p<0.001 and week 26: -0.92 (-1.46, -0.38), p=0.001). This difference was no longer seen at week 12 (-0.36 (-0.89, 0.17), p=0.179) or week 52 (-0.40 (-0.97, 0.17), p=0.163). These trends did not differ significantly between the two treatment groups (interactions all p>0.2).
The trend was reversed to an extent in the methotrexate and placebo group at week 78 (adjusted difference 0.48) compared to the methotrexate and etanercept group (adjusted difference -0.97: interaction -1.45 (-2.53, -0.37), p=0.009). It should be noted however that in each of the groups there were few anti-CCP negative patients; only those whose anti-CCP status was known at baseline were included in these comparisons (methotrexate and placebo: anti-CCP negative n=10, anti-CCP positive n=42; methotrexate and etanercept: anti-CCP negative n=15, anti-CCP positive n=39). The numbers in each group were too small to determine a difference in NTSJ.

In patients fulfilling the 1987 ACR RA classification criteria, 66% vs. 68% of the methotrexate and placebo and methotrexate and etanercept groups respectively had a DAS28-CRP<2.6 at week 52. The proportions of those not fulfilling the criteria who achieved DAS28-CRP <2.6 was similar in both groups (69% and 60%).

The 2010 ACR/EULAR RA classification criteria were fulfilled in the majority of patients. In both, all patients who did not fulfil the ACR/EULAR 2010 criteria (methotrexate and placebo: 4/4 and methotrexate and etanercept: 3/3) achieved a DAS28-CRP<2.6 at week 52. Of those who fulfilled the 2010 ACR/EULAR classification criteria, proportions achieving remission was similar in both groups (67% and 60%).

The association between DAS28-CRP<2.6 at 12 weeks and outcome at 78 weeks was also analysed. Controlling for study site and treatment, patients with DAS28-CRP<2.6 at week 12 were more likely to have a DAS28-CRP<2.6 at week 78 (OR (95% CI) 3.53 (1.46, 8.53), p=0.005). There was no substantive difference in radiographic progression (adjusted difference in median ΔmTSS (95% CI) -0.06 (-0.58, 0.47), p=0.825) according to DAS28-CRP<2.6. Those with DAS28-CRP<2.6 at 12 weeks had significantly lower HAQ-DI values (mean difference -0.53 (-0.72, -0.34), p<0.001).

5.3.6 Adverse events

The number of adverse events was comparable between the groups (events per 100 patient years methotrexate and placebo=417.3; methotrexate and etanercept=451.6). Although there was a greater number of SAEs in the methotrexate and etanercept group (16.4 per 100 patient years compared to 3.7 in the methotrexate and placebo group), the majority were related to medical or surgical procedures. Only two were considered to be possibly related to study medication and of these only one was thought to be possibly related to etanercept. This was in a patient who had persistently elevated inflammatory markers and ongoing weight loss despite good control of her inflammatory arthritis. Following further investigations she was diagnosed with metastatic breast cancer four months after baseline and study medication was discontinued. There was also one malignancy described in the methotrexate and placebo group – a case of non-Hodgkin's lymphoma (NHL). This patient completed the trial and no specific treatment was required for the NHL during the study period. (table 5.10)

In total 195 infectious episodes were recorded: 105 in 37 patients in the methotrexate and placebo group and 90 in 43 patients in the methotrexate and etanercept group. Most were due to upper respiratory tract or pulmonary infections (71.4% (75/105) vs. 77.8% (70/90) in the methotrexate and placebo and methotrexate and etanercept groups respectively). Two infections were reported as severe. Both of these were pulmonary infections and both in the methotrexate and etanercept group. All other infections were reported as mild or moderate in severity (table 5.11).

Table 5.10 Adverse events experienced by participants during follow-up

	MTX+PBO n=55	**MTX+ETN n=55**
Number of patients who experienced an AE	55 (100.0%)	53 (96.4%)
Maximum severity of AE experienced		
Mild	231/338 (68.3%)	236/358 (65.9%)
Moderate	104/338 (30.8%)	107/358 (29.9%)
Severe (including SAEs)	3/338 (0.9%)	15/358 (4.2%)
Total number of AEs	338	358
Total patient-years of follow-up	80.99	79.27
Number of AEs per 100 patient-years	417.3	451.6
Patient expectation of event		
Expected (listed in PIS)	256/338 (75.7%)	263/358 (73.5%)
Severity*		
Mild	231/338 (68.3%)	236/358 (65.9%)
Moderate	104/338 (30.8%)	107/358 (29.9%)
Severe (including SAEs)	3/338 (0.9%)	15/358 (4.2%)
Number of patients who experienced an SAE	3/55 (5.5%)	9/55 (16.4%)
Total number of SAEs	3	13
SAEs by category - relation to study drug:		
Dermatology/skin		1 - probably not
Gastrointestinal		1 - probably not
Infection - pulmonary/upper respiratory		2 - 1 probably not, 1 possibly
Malignancy - haematological	1 - probably not	
Malignancy - metastatic		1 - possibly
Musculoskeletal/soft tissue		1 – not related
Neurology	1 – probably not	
Pain - cardiovascular		1 – probably not
Pain - musculoskeletal		1 – not related
Surgical and medical procedures	1 – not related	5 – not related

AE, adverse event; PIS, patient information sheet; SAE, serious adverse event

Table 5.11 Adverse events - infections

Placebo	**Mild**	**Moderate**	**Severe**	**Total**
Auditory/ Ear	5	2	0	7
Dermatology/ Skin	0	2	0	2
Gastrointestinal	6	4	0	10
General	1	0	0	1
Lymphatic	0	2	0	2
Ocular	1	0	0	1
Pulmonary/ Upper respiratory	57	18	0	75
Renal / Genitourinary	5	2	0	7
Total	**75**	**30**	**0**	**105**
Etanercept	**Mild**	**Moderate**	**Severe**	**Total**
Auditory/ Ear	1	1	0	2
Dermatology/ Skin	3	0	0	3
Gastrointestinal	1	2	0	3
General	0	3	0	3
Lymphatic	1	0	0	1
Ocular	1	0	0	1
Pulmonary/ Upper respiratory	48	20	2	70
Renal / Genitourinary	5	2	0	7
Total	**60**	**28**	**2**	**90**
Combined treatment groups	**Mild**	**Moderate**	**Severe**	**Total**
Auditory/ Ear	6	3	0	9
Dermatology/ Skin	3	2	0	5
Gastrointestinal	7	6	0	13
General	1	0	0	1
Lymphatic	0	5	0	5
Ocular	1	0	0	1
Pulmonary/ Upper respiratory	2	0	0	2
Renal / Genitourinary	105	38	2	145
Auditory/ Ear	10	4	0	14
Total	**135**	**58**	**2**	**195**

5.4 Discussion

The EMPIRE study was the first double-blind, placebo-controlled RCT that compared methotrexate monotherapy with methotrexate and etanercept combination in early IA. Whilst the study was designed prior to the development of the 2010 ACR/EULAR RA classification criteria, [12] the principles of the trial embodied those of the 2010 classification criteria – aiming to identify and treat patients with RA in the earliest phases of the disease continuum. Of all the trial participants only 41% fulfilled the 1987 criteria whilst the majority of patients (94%) fulfilled the 2010 ACR EULAR classification criteria.

The primary outcome, NTSJ at week 52, was similar between the two groups (approximately 30%). Whilst the DAS responses were as expected, the proportion of patients achieving NTSJ was lower than initially predicted in the etanercept group (60%). The primary endpoint was chosen as it was thought that complete normalisation of disease could be achieved in this early population. It is possible that NTSJ may have been too strict an outcome and that no swollen joints alone may have been a more realistic target. On ultrasound, synovitis at week 52 (GS>1 and PD>0) was only seen in about 30% of patients.

The use of methotrexate and etanercept as combination therapy has been used in several studies of patients with RA according to the 1987 ACR criteria.[180 333 372] In the COMET study, [180] the proportion of patients achieving remission (study primary endpoint) was significantly higher using the combination therapy compared to methotrexate monotherapy (one year DAS28-ESR remission: 50% vs. 28% (effect difference (95% CI) 22,05% (13.96-30.15%, p<0.0001). Remission was higher with shorter disease duration (≤ 4 months), with between-group differences remaining significant (69.8% vs. 34.7% (p<0.05)).[35] In the PRIZE study of early DMARD naïve RA (mean disease duration six months),[339] methotrexate and etanercept was used as induction therapy - DAS28-ESR remission was achieved in 70.5% of patients. In the EMPIRE study, proportions with DAS28-CRP<2.6 and DAS28-CRP ≤3.2 were high in both groups. At one year, DAS28-CRP<2.6 was 68.8% and 62.5% with methotrexate and etanercept and methotrexate monotherapy respectively. It is likely that the high responses seen were partly due to the fact that the results were based on DAS28-CRP rather than DAS28-ESR, which is known to yield slightly lower values.[373 374] Other possible explanations for the relatively high clinical responses in this study, particularly in those receiving methotrexate monotherapy, may be that these patients had relatively early disease with a low disease burden (although the majority fulfilled the 2010 ACR/ EULAR RA classification criteria, most did not fulfil the 1987 ACR criteria). Results from the PROMPT study showed that in

anti-CCP positive patients, methotrexate delayed progression to RA.[213] It is possible that these were methotrexate responsive patients given that a high proportion were anti-CCP positive. In this study there was also a 'treat-to-target' component, in that methotrexate was increase at regular intervals to a maximum dose of 25mg/week if NTSJ was not achieved. At week 52, although the combination therapy group stopped etanercept, additional DMARDs were allowed in both groups if required. Another possible which may have played a role in the clinical outcomes of these patients, which has not been addressed in this study, is their immunological profile. Higher proportions of baseline naïve T cells have been found to correlate with remission induction in patients receiving methotrexate monotherapy. [375]

In both groups functional and radiographic outcomes were also high with almost 50% achieving normal function and 80-90% achieving radiographic non-progression by week 78. Notably, direct between-study comparisons cannot be made given the heterogeneity in study designs, patient populations and clinical outcomes. [374]

Clinical responses remained high between weeks 52 and 78, suggesting that remission induction with a bDMARD and maintenance with methotrexate monotherapy, as described by Quinn et al.[182] and in other studies including BeSt[291] and OPTIMA,[2] may be a possible treatment strategy in some patients. There was, however, a slight reduction in proportions in remission in the methotrexate and etanercept group on withdrawal of the TNFi, suggesting that not all patients may be able to achieve this. In the HIT HARD study, [230] the initial improvement in DAS at week 24 with methotrexate and adalimumab was also lost when adalimumab was withdrawn. It is likely that a proportion of patients will need to continue with bDMARD therapy. Biological DMARD dose reduction, as described in the PRIZE [340] and PRESERVE[232] studies, may be an option. In this study, the improvement in clinical responses in the methotrexate monotherapy group is likely due to the additional DMARD therapy which was allowed after week 52.

The speed of response with combination therapy was remarkable with almost 30% achieving a DAS44-CRP<1.6 and 40% a DAS28-CRP<2.6 at week 2 after a single injection. This degree of early response was likely due to the relatively mild disease and short symptom duration. There is evidence to suggest that early disease control is associated with significantly better long-term clinical [350] and radiographic outcomes.[35] From the exploratory analyses of this study, those with a DAS28-CRP<2.6 at week 12 were more likely to have a DAS28-CRP<2.6 and better function at week 78. The longer-term outcomes of these two treatments groups are still to be determined.

In this study methotrexate was started at 10mg weekly and increased at regular intervals to a maximum dose of 25mg weekly if tolerated. The impact of starting methotrexate at a higher dose on the speed of response would be of interest.

Overall both treatments were well tolerated. There were no new safety signals. The findings support the benefit of early methotrexate therapy with dose escalation. Clinical responses were achieved earlier with methotrexate and etanercept and clinical and imaging responses were maintained in the majority of patients on stopping etanercept. The value of this combination therapy, however particularly with cost consideration, still need to be determined. Presently in patients with RA, early diagnosis and treatment with csDMARDs and glucocorticoids, escalating therapy using a treat-to-target type approach remains the mainstay of treatment.[209] Ideally, understanding which patients would receive the greatest benefit in the short- and longer-term with initial intensive induction therapy with a bDMARD and the possibility of bDMARD and drug-free remission would be of importance.

5.5 Limitations

This study has its limitations. In terms of other options for induction therapy, it has not addressed the role of other combination csDMARDs and glucocorticoids which have demonstrated efficacy in these patients. [363]

Another limitation relates to that of missing data. The calculation of sample size was based on the primary outcome allowing for a 10% drop-out. There was clinical data for 51/55 (93%) of patients in the methotrexate and placebo group but for 48/55 (87%) in the methotrexate and etanercept group. This fell just below the 10% margin. Data analysis using multiple imputation to account for missing data however was no different to that for the observed-case only analysis.

5.6 Conclusions

In summary, in this group of patients with DMARD-naïve early IA, after one year of treatment, almost a third had no tender, swollen joints. A high proportion achieved DAS28-CRP<2.6 and low ultrasound synovitis. In conclusion, whilst clinical responses with methotrexate and etanercept were more rapid, the combination therapy was not superior to methotrexate monotherapy in achieving the primary outcome.

Chapter 6 Use of clinical, genetic, serological and imaging biomarkers in anti-CCP positive patients with nonspecific musculoskeletal symptoms to identify early IA in the secondary care

This longitudinal study sought to address the use of anti-CCP antibodies, together with other biomarkers, to predict progression to early IA in secondary care.

6.1 Introduction

The body of evidence from the literature and results from the clinical trials detailed in the previous chapters support the call for early DMARD therapy to achieve optimal disease control, prevent joint destruction and preserve function. Early diagnosis is therefore essential.

In patients presenting with clinically apparent IA, the 2010 ACR/EULAR RA classification criteria[12] were developed to identify patients requiring DMARD therapy early. There has also been increasing interest in the earlier phase of the disease - in patients at risk but without clinical synovitis.[13] In the so called 'pre-clinical' phase of RA, several studies have found increased levels of circulating autoantibodies including ACPA and RF.[376-381]

In clinical practice, ACPA is often measured as antibodies to synthetic cyclic citrullinated peptide. Anti-CCP are more specific than RF for RA and have been documented in the sera of RA patients up to 14 years prior to disease onset when they were asymptomatic blood donors.[376 377] Other markers that have been associated with the development of RA include smoking, prolonged EMS, the presence of shared epitope and raised inflammatory cytokines.[99 160 378 382-384] MSK imaging with ultrasound has also been shown to detect low level joint inflammation in cases of clinical examination.[385]

The year or two leading up to the development of clinical RA has sometimes been described as phase of imminent RA.[386] ACPA levels and an expansion in ACPAs to a number of citrullinated proteins (epitope spreading) has been documented during this period.[387 388]

The hypothesis of this study was that anti-CCP positive patients with new non-specific MSK symptoms would represent a population enriched for the development of IA. Identifying patients during this early phase would allow early diagnosis and allow for early treatment thus optimising treatment outcomes.

The first study aim was to determine the proportion of anti-CCP positive individuals presenting with new onset non-specific MSK symptoms progressing to IA and the time to progression. The second aim was to develop a scoring system to predict progression to IA using clinical, serological and imaging parameters in this these patients.

6.2 Patients and methods

Patients were recruited from primary care services and from rheumatology clinics in Yorkshire, UK. The primary care recruitment was adopted by the UK National Institute of Health Research Clinical Research Network (NIHR CRN) and the study was approved by the local ethics committee. Patients over 18 years with new onset MSK symptoms presenting to their GPs or other health professionals (e.g. podiatry or physiotherapy) were invited to participate. All participants signed informed consent before taking part. For those referred from primary care, the anti-CCP test was performed centrally at the Leeds Rheumatology Department using a standard commercially available anti-CCP2 test (Immunocap 250, Phadia and later Bioplex, Bio-rad). Those with a positive test were invited to a attend a dedicated research clinic at Chapel Allerton Hospital, Leeds. Patients from the Leeds rheumatology early arthritis clinic and those referred from other rheumatologists in Yorkshire were eligible to take part in the study if they had no clinical evidence of inflammatory joint swelling (deemed IA) and were anti-CCP antibody positive. The following were exclusion criteria: a history of IA diagnosed by a rheumatologist; presence of clinically detected IA at baseline confirmed by a rheumatologist; use of DMARD therapy.

6.2.1 Assessments

Patient assessments were done at baseline, then three monthly for the first year, and then as clinically indicated until they developed IA (defined by the presence of ≥ 1 tender and swollen joint confirmed by a rheumatologist). Patients could also be seen between these time-points if they developed new joint symptoms. Assessments were carried out by rheumatologists who completed the eligibility criteria and performed the clinical examinations.

6.2.1.1 Clinical and demographic assessments

The following demographic and clinical parameters were documented at baseline: age, gender, joint symptoms in the upper and lower extremities, the presence of

intermittent symptoms, duration of EMS in minutes, history of first degree relative(s) with RA, smoking history, alcohol intake, body mass index (BMI), tenderness of the small joints of the hands and feet (wrists, MCP, PIP, mid-tarsal and/or MTP joints), the RAI (scores 0-78), 44 swollen joint count and pain VAS.

6.2.1.2 Biomarkers

A number of biomarkers were also measured at baseline. Shared epitope status was considered positive if one or two copies of the following human leukocyte antigen (HLA)-DRB1 alleles were present: HLA- DRB1*01, DRB1*04, and DRB1*10.[58 389] For RF and anti-CCP antibody tests, the laboratory machines and therefore the reference ranges changed partway through recruitment. The cut-off for immunoglobulin M (IgM) RF positivity was initially 40 IU/ml and later <20 IU/ml. For anti-CCP, the cut-off was initially 7 IU/ml initially (anti-CCP2; Immunocap 250, Phadia) and later 2.99 IU/ml (anti-CCP2, Bioplex, Bio-rad). High-level RF or anti-CCP levels were defined according to the 2010 ACR / EULAR criteria by a cut-off of > 3 times the upper limit of normal.[12] High sensitivity C reactive protein (hs-CRP) was also performed and a level of ≥ 2 mg/dl, which has been associated with RA disease activity, was considered positive.[89] Ultrasound assessments were performed (Philips HDI 5000 machine 15-8 MHz transducer) by a rheumatologist experienced in MSK ultrasound. Findings in the wrists, MCPs, and PIPs were reported using standard OMERACT definitions to define synovitis.[356] The EULAR-OMERACT system (a 0-3 semi-quantitative scale) was used for scoring. PD signal was reported positive with the presence of intra-articular Doppler signal (PD ≥ 1).[357] Intra-reader reliability for the ultrasound assessor has been reported to be excellent, with 100% agreement between two repeated assessments of the presence of PD signal in 33 joints.[390]

For sample size, the potential predictive value of the variables collected in the first 100 patients were assessed, based on an estimated progression to IA of 40-50%. This would enable an estimation of the unadjusted hazard ratios (HR) for the potential predictors and to develop a simplified clinically-relevant four-variable model. For cox regression analyses, published rules of thumb recommend 10 events per variable.[391]

6.2.2 Statistical analysis

Univariable cox regression analyses were used to obtain unadjusted HR to assess the association between baseline variables with time to progression to IA. Continuous variables were dichotomised using clinically relevant cut-offs. In

addition to those listed above, the following cut-offs were used: ≥12 months for symptom duration, ≥30 minutes for EMS, ≥25 for BMI and ≥50mm for pain VAS. In each case variables were coded so that the HR was positive. When selecting variables for the multivariable model, HR ≥1.5 was considered substantive. Cases were treated as censored after their last follow-up if they had not progressed to IA.

For development of a risk stratification score, variables were considered for inclusion in the multivariable model of time to progression to IA if a) they were potentially available in clinical practice and b) they were related to the outcome to a substantive degree (HR ≥1.5). Once the model was fitted, individual variables were given scores derived from their regression coefficients, rounded to the nearest 0.5 interval and multiplied by 2. Patients' total scores depended on which risk factors were present at baseline. Risk categories were then defined according to the proportions of patients that progressed at each score level.

6.3 Results

The baseline demographic and clinical characteristics are presented in table 6.1. In total 100 patients were included - 29 from primary care referrals and 71 from rheumatology clinic referrals. Figure 6.1 presents a flow chart of participants. Patients who met inclusion criteria at the point of referral but subsequently were found to have IA at the baseline were excluded (n=21). The median follow-up period for the 100 patients included in the analysis was 19.8 months (1st quartile=7.6, 3rd quartile=34.4; range 0.1-69.0). Fifteen patients were lost to follow-up from the research clinic. For all of these patients, confirmation was obtained from their GPs or clinical records that they had not developed IA. Using the point of last patient or GP contact to determine the duration of follow-up, all but one of the patients had been followed for at least 12 months.

Table 6.1 Baseline demographic, clinical, and imaging characteristics of 100 anti-CCP positive patients with non-specific MSK symptoms. Values presented are n/N (%) unless otherwise indicated.

Characteristic		**No inflammatory arthritis at baseline (n=100)**
Age	**years***	51.2 (11.9), 24 to 77
Gender	**female**	72/100 (72.0%)
Shared epitope	**one copy** **two copies**	46/86 (53%) 17/86 (20%)
FDR with RA	**yes**	25/94 (27%)
Smoker	**ever**	70/99 (71%)
Alcohol consumer	**no**	17/75 (23%)
BMI	**score*** **≥25**	29.0 (6.5), 18.3 to 44.7 54/76 (71%)
Anti-CCP	**level** **low positive** **high positive**	246 (61, 825), 9 to 13400 17/100 (17%) 83/100 (83%)
RF	**level**** **low positive** **high positive**	21 (0, 103), 0 to 1000 15/100 (15%) 31/100 (31%)
Autoantibody status	**low positive RF and anti-CCP** **high positive RF or anti-CCP**	14/100 (14%) 86/100 (86%)
hsCRP	**level**** **≥2 mg/dl**	2.9 (0.9, 10.5), 0.1 to 30 43/74 (58%)
Symptom duration	**months**** **≥12 months**	22.7 (8.2, 42.4), 1.4 to 327.7 66/97 (68%)
Intermittent symptoms	**present**	20/97 (21%)

Tenderness of small joints	**count (0-34)**, range** **present**	0.5 (0.0, 3.0), 0-18 50/100 (50%)
Symptoms in upper and lower extremities	**present**	37/100 (37%)
EMS	**minutes**** **≥30 minutes**	10 (0, 38), 0 to 270 39/100 (39%)
Pain VAS	**mm**** **≥50mm**	24 (9 to 51), 0 to 100 25/91 (27%)

*mean (SD), range **median (1st quartile, 3rd quartile), range. FDR, first degree relative; BMI, body mass index; Anti-CCP, anti-cyclic citrullinated peptide antibodies; RF, rheumatoid factor; hsCRP, high sensitivity C reactive protein; EMS, early morning stiffness; VAS, visual analogue scale.

6.3.1 Progression to inflammatory arthritis

After a median of 7.9 months (IQR 3.2, 14.5; range 0.1-52.4), 50 patients progressed to clinically detected IA. Thirty four progressed within the first 12 months of follow-up and 44 within the first 24 months (figure 6.1). Of those who progressed to IA, 43 fulfilled the 2010 ACR/EULAR RA classification criteria. The remaining patients had undifferentiated IA. The median follow-up of those who did not progress was 30.3 months (IQR 22.5, 45.1; range 7.7-69.0).

6.3.1.1 Univariable Cox regression analysis

There were two clinical parameters which were substantively associated with an increased risk of progression to IA: EMS lasting ≥30 minutes and tenderness of small joints (table 6.2). For cut-off points for EMS, 30 and 60 minutes were both considered and showed similar predictive values. The 30 minutes cut-off was chosen as it was thought to be more sensitive.[43] There was no evidence that the risk of developing IA was substantively associated with symptom duration, BMI, pain VAS or high sensitivity CRP (hsCRP).

The following biomarkers were associated with an increased risk of progression to IA: positive RF, high positive anti-CCP or RF, presence of shared epitope, and positive ultrasound PD signal.

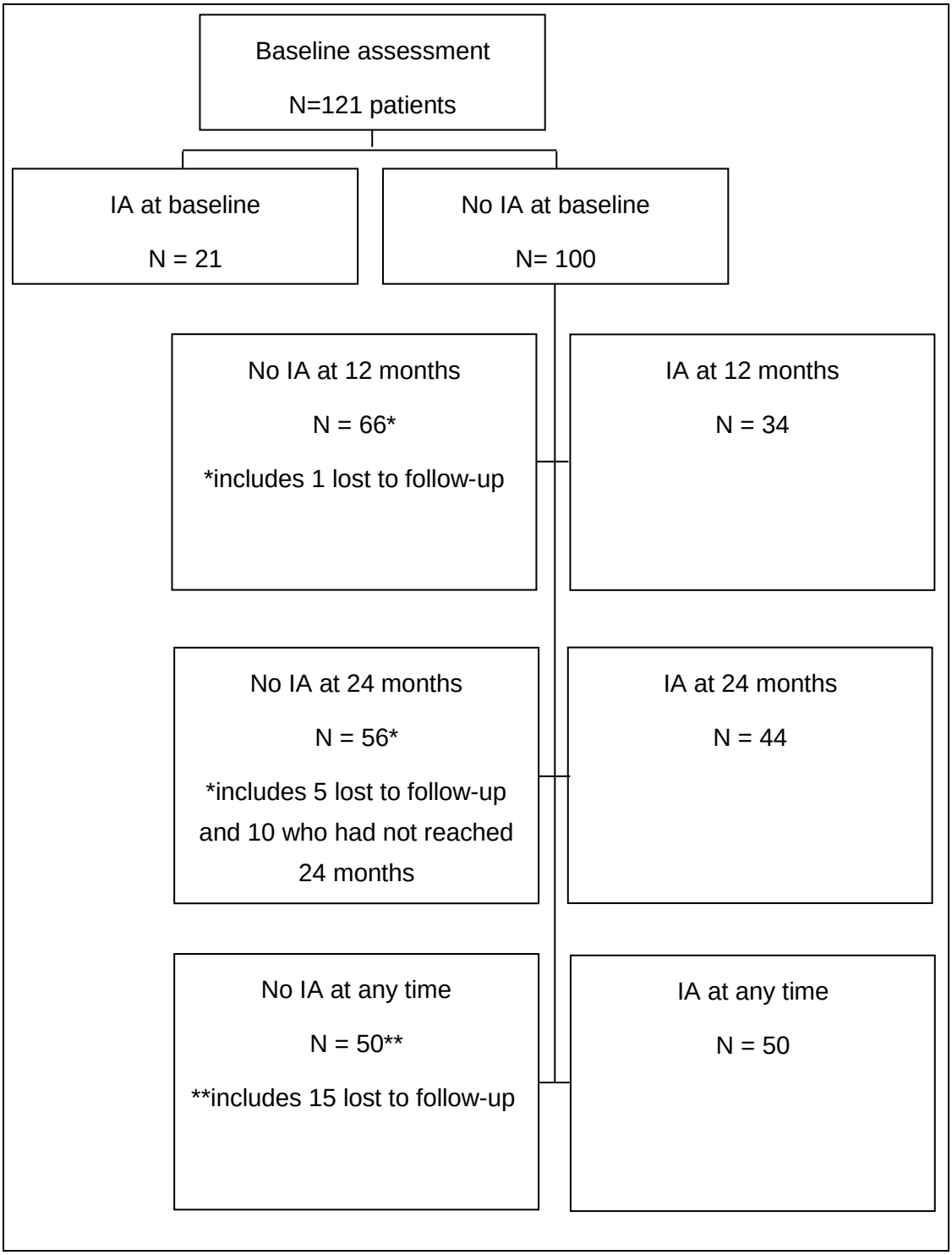


Figure 6.1 Flowchart of the study patients

IA, inflammatory arthritis; **details of the 15 patients lost to follow-up from the research clinic, obtained from their clinical records or with their general practitioners, showed that none had developed IA at their last clinic appointments.

Table 6.2 Associations between baseline demographic, clinical and imaging characteristics and time to development of inflammatory arthritis in anti-CCP positive patients with non-specific MSK symptoms.

Baseline characteristics		**Progression to IA**		
		n/N (%) who developed IA	**Months to IA (mean)**	**HR (95% CI)**
Symptom duration	**<12 months**	15/31 (48)	33.3	reference
	≥12 months	35/66 (53)	35.8	1.05 (0.57, 1.92)
Intermittent symptoms	**absent**	37/77 (48)	37.5	reference
	present	12/20 (60)	31.0	1.27 (0.66, 2.44)
Symptoms in upper and lower extremities	**absent**	28/63 (44)	39.3	reference
	present	22/37 (60)	32.6	1.38 (0.79, 2.41)
EMS	**<30 minutes**	27/61 (44)	38.7	reference
	≥30 minutes	23/39 (59)	32.0	1.70 (0.97, 2.98)
	<60 minutes	37/78 (47)	39.4	reference
	≥60 minutes	13/22 (59)	27.3	1.92 (1.02, 3.63)
FDR with RA	**yes**	11/25 (44)	40.3	reference
	no	37/69 (54)	35.3	1.25 (0.64, 2.46)
Smoker	**never**	12/29 (41)	41.1	reference
	ever	38/70 (54)	35.3	1.26 (0.66, 2.42)
Alcohol consumer	**yes**	30/58 (52)	35.2	reference
	no	9/17 (53)	31.2	1.27 (0.60, 2.69)
BMI	**≥25**	28/54 (52)	36.4	reference
	<25	11/22 (50)	26.5	1.13 (0.55, 2.30)
Tenderness of small joints	**absent**	19/50 (38)	43.9	reference
	present	31/50 (62)	30.9	1.83 (1.03, 3.24)

Pain VAS	**≥50mm**	11/25 (44)	41.6	reference
	<50mm	34/66 (52)	36.0	1.26 (0.64, 2.50)
hsCRP	**<2 mg/dl**	15/31 (48)	35.8	reference
	≥2 mg/dl	24/43 (56)	33.3	1.27 (0.66, 2.42)
Anti-CCP	**+ve**	7/17 (41)	43.7	reference
	++ve	43/83 (52)	35.9	1.43 (0.64, 3.19)
RF	**-ve**	21/54 (39)	45.2	reference
	+ve	9/15 (60)	29.4	1.69 (0.77, 3.69)
	++ve	20/31 (65)	25.9	2.04 (1.10, 3.78)
Autoantibody status	**-ve or +ve RF and +ve anti-CCP**	4/14 (29)	51.1	reference
	++ve RF and/or ++ve anti-CCP	46/86 (53)	35.0	2.17 (0.78, 6.04)
Shared epitope	**absent**	6/23 (26)	20.3	reference
	present	33/63 (52)	15.5	2.47 (1.03, 5.90)
Power Doppler signal	**absent**	28/67 (42)	42.2	reference
	present	22/33 (67)	26.3	1.88 (1.07, 3.29)

-ve, negative; +ve, low positive; ++ve, high positive (3x upper limit of normal); anti-CCP, anti-cyclic citrullinated peptide antibodies; BMI, body mass index; CI, confidence interval; EMS, early morning stiffness; FDR, first degree relative; HR, hazard ratio; hsCRP, high sensitivity C reactive protein; RF, rheumatoid factor; VAS, visual analogue scale.

6.3.1.2 Multivariable Cox regression

Variables were considered for inclusion in the multivariable models of progression if they were substantively associated with progression to IA in the univariable analysis (HR≥1.5) and possibly available in clinical practice. Initially, ultrasound was chosen over the shared epitope due to its wider availability in the UK. The use of shared epitope as a predictive factor however was also explored with and without PD, allowing for differences in the availability of each test in different countries (tables 6.3 and 6.4, and figure 6.2).

The first model of progression to IA (PD model) included 100 patients, 50 of whom progressed over 69 months of follow-up. The independent variables were EMS ≥30 minutes, presence/absence of small joint tenderness, high level RF and/or anti-CCP, and PD. Time-varying covariates were added to each model to test the proportional hazards assumption[392] and found to be satisfied. Harrell's C was used to assess the predictive strength of the model.[393] This assesses whether ordering of the predicted progression times is concordant with the observed data. A value >0.5 indicates predictive ability better than random chance, and a value of 1 represents perfect concordance. Harrell's C for this model was 0.67 (0.59, 0.74). All four variables were substantively associated with risk of progression to IA (HR≥1.5) although none to a statistically significant degree (table 6.2). The model residuals however revealed two unduly 'influential' patients (dfbeta>2/√N). Both had low positive anti-CCP antibody levels and had no PD signal present on ultrasound but progressed to IA. Excluding these two patients, the HRs increased and EMS, antibody levels, and PD were all independently associated with time to progression.

The risk score of this model ranged from 0-5 (table 6.3). The proportion of patients progressing to IA using this risk score suggested that patients could be divided into three risk groups (table 5). Anti-CCP positive patients with none of the four risk factors at baseline could be considered at low risk (0/5 progressed). Those scoring 1-2 points could be pooled into a moderate risk group (31% of 29 patients progressed), and those scoring ≥ 3 could be pooled into a high risk group (62% of 66 patients progressed). Of those who progressed the majority did so within the first 12 months (table 6.4). The 3 different risk groups and their Kaplan-Meier IA-free survival curves over the period up to 69 months of follow-up are shown in figure 6.2A.

Alternative models which included shared epitope were constructed and found to have similar predictive ability (tables 6.3 and 6.4, figures 6.2B - 6.2C). Using shared epitope instead of PD yielded a model with similar predictive ability to that of the PD model (Harrell's C=0.66 (0.58, 0.74)) (table 6.3). The 92 patients with shared epitope available were included in this model, 46 of whom progressed to IA. All four

independent variables were substantively associated with the outcome (HR>1.5). The resulting risk score ranged from 0-4. Fewer patients however were found to be at high or low risk using this model (table 6.4). With both PD and shared epitope, the predictive strength remained moderate (Harrell's C=0.65 (0.58, 0.73)). In this model the adjusted effects of EMS and antibody status were reduced (both HR≈1.5) compared to PD and shared epitope (both HR≈1.8). The resulting risk score ranged from 0-5. None the 11 patients in the low risk group (score 0 or 1) progressed to IA. Follow up of these patients ranged between 18 and 55 months. In the high risk group (score 4 or 5), 72% (18/25) progressed to IA, 56% (14/25) within 12 months of presentation. Excluding both PD and shared epitope, the predictive strength remained moderate (Harrell's C=0.65 (0.58, 0.73)). In this model, antibody status was the dominant predictor (HR=2.46). The resulting risk score ranged from 0-4 (table 6.3). None of the 5 patients in the low risk group (score 0) progressed to IA, compared to 40% (16/40) of those at moderate risk and 62% (24/55) of those at high risk (table 6.4, figure 6.2D). The discriminatory power of model was similar to the model that included shared epitope.

Table 6.3 Results of multivariable Cox regression models of time to progression to inflammatory arthritis

Multivariable Cox-regression predictors	**Excluding outliers HR (95% CI)**	**All subjects (95% CI)**	
		(95% CI)	**B: score**
Power Doppler model	n=98	n=100	
Tenderness of small joints present	1.39 (0.77, 2.53), p=0.277	1.56 (0.87, 2.81)	0.44: 1
EMS ≥ 30 minutes	1.85 (1.02, 3.35), p=0.043	1.75 (0.97, 3.16)	0.55: 1
High level RF and/or anti-CCP	4.52 (1.07, 19.15), p=0.040	1.83 (0.98, 3.42)	0.82: 2
Power Doppler present	1.84 (1.04, 3.27), p=0.037	1.51 (0.83, 2.74)	0.56: 1
Shared Epitope model	n=90	n=92	
Tenderness of small joints present	1.54 (0.83, 2.87), p=0.173	1.68 (0.91, 3.11)	0.52: 1
EMS ≥ 30 minutes	1.61 (0.86, 3.00), p=0.135	1.54 (0.84, 2.84)	0.43: 1
High level RF and/or anti-CCP	3.40 (0.77, 14.96), p=0.105	1.68 (0.57, 5.00)	0.52: 1
Shared epitope present	1.58 (0.72, 3.49), p=0.257	1.87 (0.84, 4.14)	0.62: 1
Power Doppler + Shared Epitope model	n=90	n=92	
Tenderness of small joints present	1.54 (0.82, 2.88), p=0.178	1.69 (0.91, 3.13)	0.52: 1

EMS ≥ 30 minutes	1.56 (0.83, 2.92), p=0.167	1.49 (0.81, 2.77)	0.40: 1
High level RF and/or anti-CCP	3.04 (0.68, 13.6), p=0.147	1.47 (0.48, 4.47)	0.38: 1
Power Doppler present	1.92 (1.06, 3.50), p=0.033	1.89 (0.84, 4.24)	0.63: 1
Shared epitope present	1.57 (0.70, 3.49), p=0.272	1.84 (1.02, 3.32)	0.61: 1
Model without Power Doppler or Shared Epitope	n=98	n=100	
Tenderness of small joints present	1.42 (0.78, 2.57), p=0.252	1.56 (0.87, 2.81)	0.44: 1
EMS ≥ 30 minutes	1.86 (1.03, 3.37), p=0.039	1.75 (0.98, 3.13)	0.56: 1
High level RF and/or anti-CCP	4.86 (1.16, 20.43), p=0.031	2.46 (0.87, 6.99)	0.90: 2

Duration of follow-up = 69 months

Scores for each predictor were derived from the regression coefficients, rounded to nearest 0.5 then multiplied by 2, to give a total risk score ranging from 0-5.

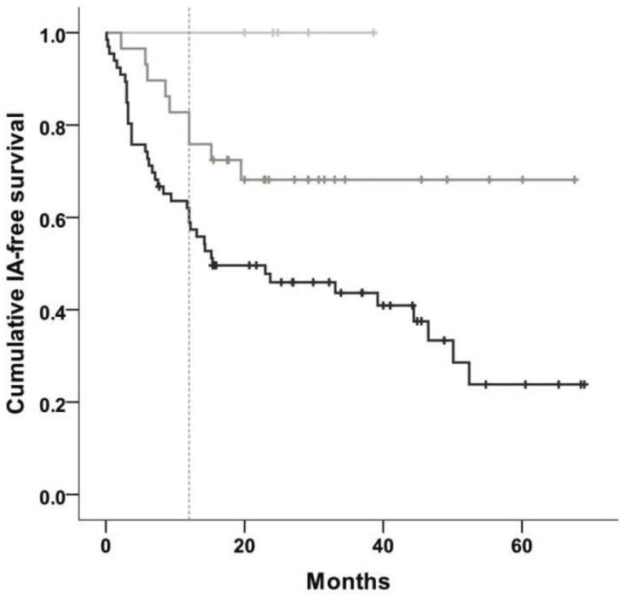
B, regression coefficient; HR, hazard ratio; CI, confidence interval; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide antibodies; EMS, early morning stiffness.

Table 6.4 Proportions of patients progressing to inflammatory arthritis (IA) within 12 or 24 months of referral, or at any time during follow-up, according to their risk score at baseline

Risk score	**Proportion (n/N) of patients who progressed to IA:**			**Risk category:**	**% progressed**
	Within 12 months	**Within 24 months**	**At any time**		
Power Doppler in model					
0	0/5 (0%)	0/5 (0%)	0/5 (0%)	Low:	0%
1	1/3 (33%)	1/3 (33%)	1/3 (33%)	Mod:	31%
2	6/26 (23%)	8/26 (31%)	8/26 (31%)		
3	10/34 (29%)	14/34 (41%)	19/34 (56%)	High:	62%
4	11/23 (48%)	15/23 (65%)	16/23 (70%)		
5	6/9 (67%)	6/9 (67%)	6/9 (67%)		
Shared Epitope in model					
0	0/3 (0%)	0/3 (0%)	0/3 (0%)	Low:	0%
1	0/11 (0%)	1/11 (9%)	2/11 (18%)	Mod:	40%
2	10/32 (31%)	13/32 (41%)	15/32 (47%)		
3	12/33 (36%)	17/33 (52%)	20/33 (61%)	High:	63%
4	8/13 (62%)	9/13 (69%)	9/13 (69%)		

Power Doppler and Shared Epitope in model					
0	0/3 (0%)	0/3 (0%)	0/3 (0%)	Low:	0%
1	0/8 (0%)	0/8 (0%)	0/8 (0%)		
2	7/25 (28%)	9/25 (36%)	11/25 (44%)	Mod:	50%
3	9/31 (29%)	14/31 (45%)	17/31 (55%)		
4	10/19 (53%)	13/19 (68%)	14/19 (74%)	High:	72%
5	4/6 (67%)	4/6 (67%)	4/6 (67%)		
Neither Power Doppler or Shared Epitope in model					
0	0/5 (0%)	0/5 (0%)	0/5 (0%)	Low:	0%
1	1/4 (25%)	1/4 (25%)	1/4 (25%)	Mod:	40%
2	9/36 (25%)	13/36 (36%)	15/36 (42%)		
3	12/35 (34%)	17/35 (49%)	21/35 (60%)	High:	62%
4	12/20 (60%)	13/20 (65%)	13/20 (65%)		

A


Cumulative IA-free survival
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0.8
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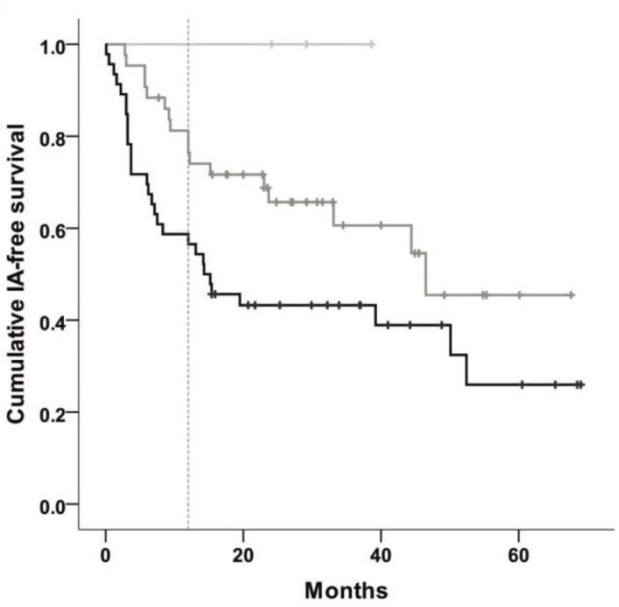
0.4
0.2
0.0
0
20
40
60
Months

B


Cumulative IA-free survival
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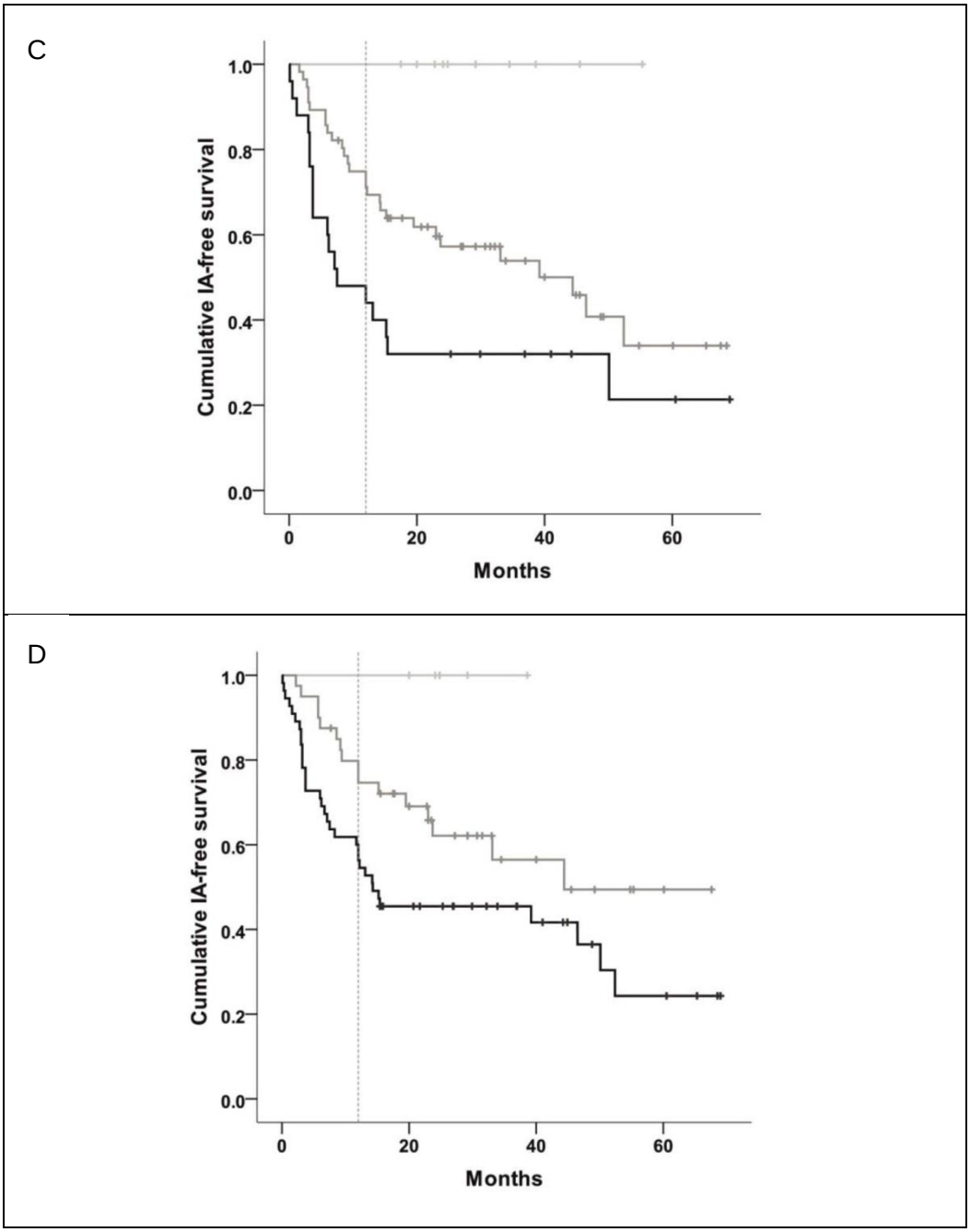


Figure 6.2 Conditional probability of inflammatory arthritis (IA)-free survival over up to 69 months of follow-up, according to categories of risk derived from exploratory risk scores for progression to IA.

Crosses indicate censoring due to loss to follow-up (n=15) or duration of follow-up <69 months without progression to IA (n=35). The majority of those who progressed did so within the first 12 months (dotted line). Four different models are presented (A power Doppler; B shared epitope; C power Doppler & shared epitope; D neither power Doppler nor shared epitope). Black line=high risk of progression to IA; mid-grey=moderate risk; light grey=low risk.

6.4 Discussion

Early identification and treatment of patients with RA is crucial since joint damage occurs early and therapy is most effective during the early stages of the disease. With the wider availability of anti-CCP testing, identifying individuals with disease specific antibodies during the 'at risk' period before the development of clinical IA has become a possibility. Predicting transition to clinical disease in these patients is important to initiate therapy.

In this cohort of anti-CCP positive patients with non-specific MSK symptoms, half developed IA. Most progressed within 12 months of presentation (median 7.9 months) corresponding to what has been labelled imminent RA. Those progressing to IA had some distinctive clinical features and biomarker profiles at baseline. Clinically, they were more likely to report EMS ≥ 30 minutes and to have small joint tenderness at presentation. They were also more likely to have high positive RF and/or anti-CCP and to have a positive shared epitope or PD on ultrasound scan.

The results of this study support the findings of other studies in which the presence of anti-CCP antibodies has been associated with an increased risk of developing IA.[160 378 394 395] The proportion of patients in this cohort progressing to IA (50%) is higher than that reported in another study of individuals at risk (35%).[160] Different inclusion criteria may be one factor accounting for the difference between the studies. In the previous study for example, only 83% of patients were anti-CCP positive.[160] In both cohorts there were some variables that showed similar predictive ability - prolonged EMS, small joint involvement, and antibody status. However, there were other variables that were only reported to predict development of IA in the study by van de Stadt et al – e.g. symptom duration < 12 months, first degree relative with RA, and no alcohol intake.[160] In previous studies, the value of imaging biomarkers to predict the development of IA have been inconsistent**.** In one study, the use of ultrasound was predictive of the development of IA at a joint but not a patient level. Other imaging modalities including MRI have also shown features of subclinical inflammation in patients with ACPA positive arthralgia, [396] with the ability to predict the development of IA in a small cohort of patients with arthralgia and inflammatory symptoms. [134] In a prospective pilot study, subclinical arthritis has also been visualised on macrophage positron emission tomography (PET) in ACPA-positive arthralgia with a subgroup of PET-positive patients developing features of an IA within a two year follow up period.[397]

This study highlights the potential role of biomarkers in patients at risk of developing RA. The simplified risk score which has been developed using variables potentially available in clinical practice may help to identify patients presenting with non-

specific MSK symptoms and a positive anti-CCP. Prolonged EMS, physician-defined tenderness of the small joints of the hands and feet, and a positive RF and anti-CCP antibodies have face validity having previously been shown to be predictors of persistent and erosive arthritis, [79] as well as the transition from UA to RA. [80] Although MSK ultrasound is not available in all rheumatology services, it is becoming more accessible in clinical practice.

In addition, to allow for differences in biomarker availability, the risk scores were performed with and without power Doppler and shared epitope. The predictive performance of the four derived models were similar with regard to the low risk (0% in all models) and the high risk (62 to 72% progression) categories. The model which included both power Doppler and shared epitope, however, allowed a greater number of patients to be classified in the low risk group. The results would suggest that the simplified model using clinical data and antibodies may be used at presentation and those with moderate risk may be referred for additional assessments.

6.5 Limitations

The current study has its limitations. Whilst it is one of the larger prospective cohorts of patients at risk that are followed up from an early phase of non-specific MSK symptoms and anti-CCP positivity and to the development of IA, the number of patients is still relatively small for full multivariable analyses. It has however allowed, for the first time, the development of a potential model incorporating clinical, serological and imaging parameters to determine progression to RA in patients at risk. The ultrasound findings highlights its potential role in the assessment and stratification of patients at risk.

6.6 Conclusions

In summary, this study confirms that patients with nonspecific MSK symptoms and anti-CCP antibodies are at risk of developing RA. The risk score which has been derived from this cohort is a step towards identify these patients at an early stage. This model will need to be confirmed in a larger cohort.

Chapter 7 Use of anti-CCP antibodies in patients with new nonspecific musculoskeletal symptoms to identify patients at risk of early IA in primary care

In this chapter, the use of anti-CCP antibodies has been explored as a tool to identify patients with new, nonspecific musculoskeletal symptoms in primary care at increased risk of developing IA.

7.1 Introduction

From cross sectional studies anti-CCP are present in approximately one percent of the population.[376 398] Their presence has also been associated with a high risk of subsequent development of RA. [367 399] Anti-CCP antibodies however can be found more than 10 years prior to disease onset.[377] The risk of developing RA in anti-CCP positive individuals from the general population has been estimated at 5% over a 5 year period, [376] meaning that this test is unlikely to be of value as a screening tool. However, in retrospective studies, in the years just prior to diagnosis, the predictive value of CCP testing has been found to be much higher, with a positive predictive value (ppv) of 85% noted within 1.5 years of symptom onset.[377]

It is also recognised that people with RA often have MSK complaints which may not be sufficiently suggestive of an inflammatory arthritis (IA) (from herein referred to as 'nonspecific symptoms') in the months or years prior to development of RA. Joint pain, muscle cramps, stiffness, loss of motor control and weakness are described as the first symptoms in people with RA and anti-CCP positive arthralgia.[400] The majority of people present to their general practitioners (GPs) first. It has been estimated that people with RA visited their GPs on average four times before being referred to a specialist for a diagnosis.[401] Identifying individuals with new nonspecific symptoms with the anti-CCP antibody may therefore provide an enriched case selection for imminent RA.

In 2009, the National Audit Office estimated the prevalence of RA in adults in England at 580 000 with an incidence of 26 000 new cases per year.[401] The estimated cost of RA to the UK National Health Service was approximately £560 million a year and the cost of work-related disability and sick leave was estimated at £1.8 billion a year. Delays in treatment have been associated with increased joint damage and poorer function. [8 78]In contrast, early identification has been associated

with improved clinical outcomes, health-related quality of life and work ability.[322] Thus very early identification and targeted treatment of individuals at risk of imminent RA[19] has the potential to be cost effective.

In this study we aimed to show that individuals present with new-onset, nonspecific MSK complaints in the pre-clinical phase of RA, and that these individuals can be identified by performing an anti-CCP antibody test. This should identify anti-CCP positive individuals at risk of rapid progression to RA who would otherwise not be referred, allowing assessment of individuals at risk of IA at the earliest opportunity.

The primary hypothesis was that a higher proportion of individuals with new-onset nonspecific MSK symptoms have anti-CCP antibodies compared to the general population. The secondary hypothesis was that the presence of the anti-CCP antibody in individuals with nonspecific MSK symptoms would help to identify those at risk of rapid progression to RA.

7.2 Patients and methods

This was a longitudinal prospective cohort study adopted by the NIHR CRN.[402] It was initially conducted in West, North and North East Yorkshire and later opened to recruitment across the U.K. Individuals were recruited between July 2007 and March 2015. GPs, MSK physicians, physiotherapists, nurse practitioners and other health professionals were asked to refer individuals aged ≥18 years with any new MSK complaint, whom they were not already planning to refer to a rheumatology unit with an IA, for an anti-CCP test. For purpose of this study, a new MSK complaint was defined as any joint/ MSK symptom, including (but not limited to) rotator cuff tendonitis, subacromial bursitis, carpal tunnel syndrome, tendonitis e.g. epicondylitis, which the patient had not previously reported to their GP. Individuals with documented IA were excluded.

Individuals consenting to study participation were instructed to go to their GPs/ local phlebotomy centres to give a blood sample. The serum was sent to Chapel Allerton Hospital, Leeds for the anti-CCP antibody tests to be performed. This was done using second generation CCP assays. Anti-CCP positivity was determined using machine-specific cut-offs - initially using an Immunocap 250 (Phadia) (reference range <7U/mL) and later a Bioplex 2200 (Bio-rad) machine (reference range <2.99U/mL). They were also asked to complete a questionnaire and provide information on previous or current MSK diagnoses and mark their symptoms on a diagram. The questionnaire was updated during the course of the study to request details for information on family history of RA and smoking.

Individuals with positive anti-CCP antibody test results were contacted by the Rheumatology Department and offered an outpatient appointment at the CCP Clinic at Chapel Allerton Hospital for clinical assessments, blood tests and imaging with X-rays and other imaging modalities. Individuals with negative anti-CCP tests continued to be followed up with their GPs. They were also contacted via telephone/post 12 months after consenting to the study and sent a questionnaire. Follow up was therefore wither after a period of 12 months or until the development of clinical synovitis If necessary, GPs and rheumatology departments were also contacted for relevant diagnoses.

7.2.1 Outcomes

The primary outcome was the proportion of individuals with new-onset nonspecific MSK symptoms who were anti-CCP positive. Secondary outcomes included the number of anti-CCP positive individuals who progressed to IA, in particular RA (according to the 2010 ACR/EULAR RA classification criteria[12]), and the time to IA diagnosis. Other outcomes of interest included the initial presenting complaint of all individuals (anti-CCP positive and negative), as this may help to determine whether there is a symptom complex that would prompt autoantibody testing.

7.2.2 Statistical analysis

Statistical analyses were performed using SPSS 21 and Stata IC 13. For the analyses, the date of the anti-CCP test was used as the baseline date. Demographic characteristics, prevalence of anti-CCP positivity, progression to IA and the associations with joint involvement were calculated using Pearson's chi square tests. A one-sample binomial test was used to assess whether the proportion of individuals with anti-CCP antibodies was higher amongst those presenting with new MSK pain compared to the estimated proportion in the general population (1%). Of the individuals tested, only those who completed the follow up period were included in the analyses addressing time to IA or RA diagnosis. Median time to IA development was compared using a log rank test. Sensitivity and specificity for the anti-CCP antibody test were calculated together with the 95% confidence intervals (Wilson method). Binary logistic regression was used to assess the association between the involvement of specific joint types and the risk of being anti-CCP positive.

7.3 Results

In total 2195 individuals were referred of whom 2028 individuals with new nonspecific MSK symptoms were enrolled (figure 7.1).

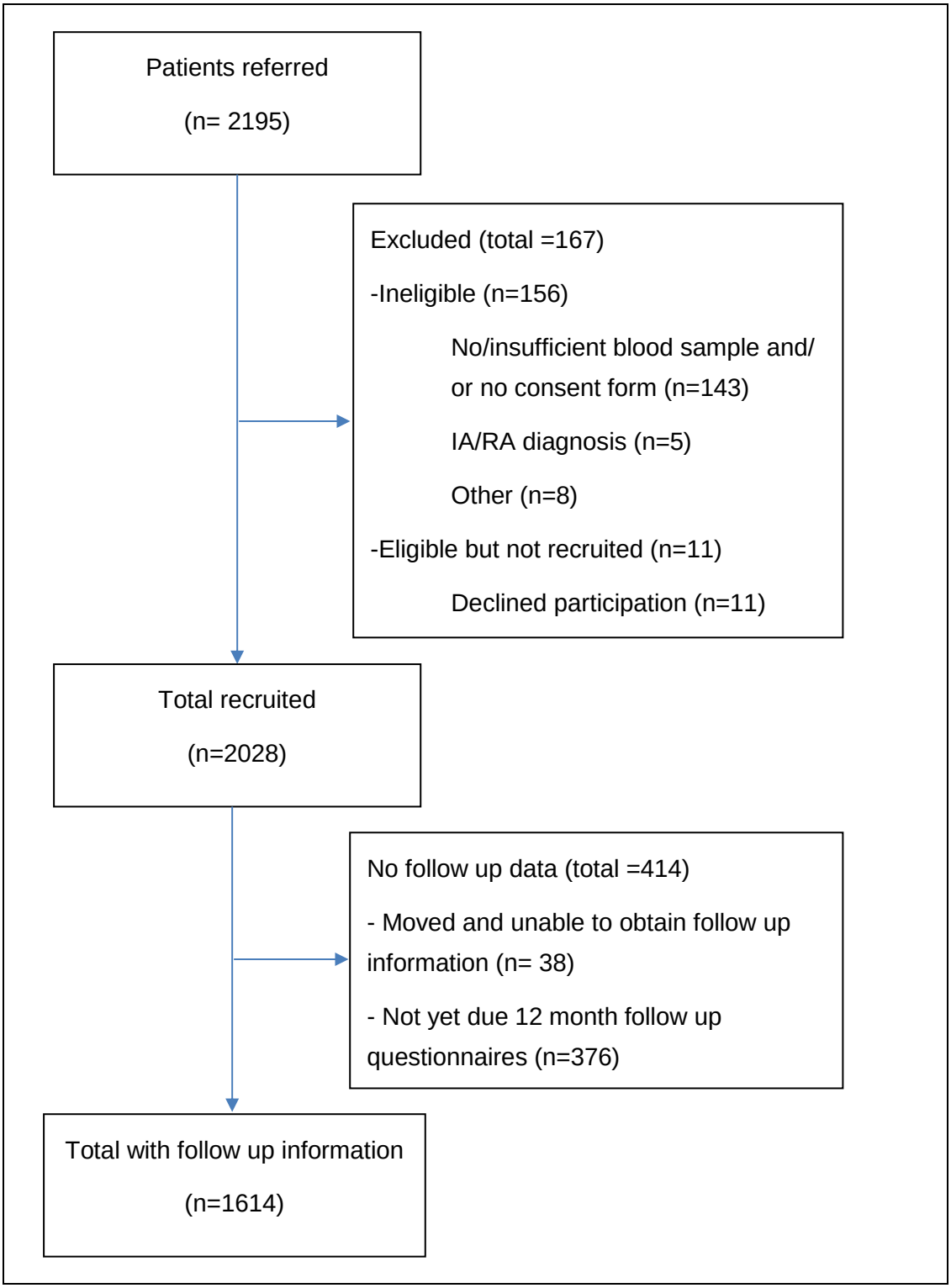


Figure 7.1 Study recruitment

The mean (SD) age was 49.2 (13.6) years and the majority were female (75.9%). Of these, 2.8% (57/2028) were anti-CCP positive, a significantly higher proportion than the estimated 1% for the general population (95% CI 2.1% to 3.6%, p<0.001). There were no differences in demographic features between anti-CCP positive and anti-CCP negative individuals. Individuals had a range of MSK and associated conditions with no significant differences between those who were anti-CCP positive or negative (table 7.1).

Of those who were antibody positive, 47.4% (27/57) were subsequently diagnosed with an IA – 1 with UA, 24 with RA and 2 with polymyositis. Of those who were tested anti-CCP negative and completed at least 1 year of follow up, 1.3% (20/1559) were diagnosed with an IA – 1 with undifferentiated IA, 13 with RA and 6 with psoriatic arthritis (PsA) (table 7.2). The relative risk (RR) (95% CI) for ever developing IA in the anti-CCP positive group was 36.8 (22.0 to 61.7, p <0.001 and the RR for developing RA was 50.4 (27.1 to 93.8), p<0.001) (table 7.2). The sensitivity and specificity for the development of any IA in the anti-CCP positive individuals were 57.4% (43.3% to 70.5%), and 98.1% (97.3% to 98.7%) respectively, and the ppv and negative predictive value (npv) were 47.4% (35.0% to 60.1%) and 98.7% (98.0% to 99.2%). The sensitivity, specificity, ppv and npv for progression to RA were 64.9% (48.8% to 78.2%), 97.9% (97.1% to 98.5%), 42.1% (30.2% to 55.0%) and 99.2% (98.6% to 99.5%) respectively.

Median duration of follow up of anti-CCP positive individuals with MSK symptoms (to IA diagnosis or last assessment) was 11.5 months (IQR 1.5 to 28.2; range: 0.3 to 79.1 months). The median time for progression to IA in the 25 anti-CCP positive individuals was 1.8 months (95% CI: 1.2 to 2.3, IQR 1.0-4.3, range 0.3 to 16.1). The majority (25/27 (92.6%)) were diagnosed within 12 months of the anti-CCP test. In the anti-CCP negative individuals, median time to IA diagnosis or last follow up of was 13.8 months (IQR: 12.5; 21.5, range 1.2 to 84.4 months) and median time to IA diagnosis was 5.1 months (95% CI: 4.2 to 5.8; IQR 2.9; 13.5, range 1.2 to 27.2, p=0.002 for anti-CCP positive vs. anti-CCP negative); 75% (15/20) were diagnosed within 1 year of having the test. The RR for developing IA within 12 months in the anti-CCP positive group was 45.5 (25.4 to 81.6), p<0.001 and RR for developing RA within 12 months: 66.8 (32.2 to 138.4), p<0.001) (figures 7.2 and 7.3).

Table 7.1 Baseline characteristics of individuals with new non-specific MSK symptoms

Characteristic	**Anti-CCP negative (n=1971)**	**Anti-CCP positive (n=57)**	**p**
Female (n)	76.2% (1502)	66.7% (38)	0.097
Age (years) mean (SD; range)	49.2 (13.6; 18-90)	49.2 (13.3; 24-80)	0.986
RA FDR (n (%))	32.0% (369/1153)	28.0% (14/50)	0.552
Smoker **Never smoked** **Ex-smoker** **Current smoker**	 50.6% (171/338) 33.1% (112/338) 16.3% (55/338)	 34.6 % (18/52) 48.1% (25/52) 17.3% (9/52)	0.072
Current or previous diagnoses			
Osteoarthritis/ multiple mechanical joint pain	17.6% (337/1917)	9.1% (5/55)	0.101
Gout	1.0% (20/1917)	1.8% (1/55)	0.581
Hypermobility	0.7% (14/1917)	0% (0/55)	0.525
Arthralgia/ Arthritis NOS/ other joint problems	5.4% (103/1917)	1.8% (1/55)	0.245
Tendinopathies *	24.4 % (468/1917)	21.8% (12/55)	0.658
Nerve entrapment e.g. CTS	13.1% (252/1917)	7.3% (4/55)	0.201
Bone conditions e.g. osteoporosis	0.7% (14/1917)	0% (0/55)	0.525
Polymyalgia rheumatica	0.3% (5/1917)	0% (0/55)	0.705
Fibromyalgia	1.3% (25/1917)	0% (0/55)	0.394
Muscular pain	0.6% (11/1917)	0% (0/55)	0.573
Other conditions**	2.1% (40/1917)	5.5% (3/55)	0.092

Values presented are % (n/N) unless indicated otherwise.

Anti-CCP, anti-cyclic citrullinated peptide; CTS, carpal tunnel syndrome; FDR, first degree relative; MSK, musculoskeletal; NOS, not otherwise specified; RA, rheumatoid arthritis; *include rotator cuff tendonitis, tennis elbow/golfer's elbow and trigger finger; ** other self-reported disease from patient questionnaires which included diagnoses of hypothyroidism, chronic fatigue syndrome, Raynaud's phenomenon, Crohn's disease and vitamin B12 deficiency.

Table 7.2 Outcomes of anti-CCP positive and negative individuals with new nonspecific MSK symptoms

	Anti-CCP negative (n=1557)*	**Anti-CCP positive (n=57)**
No IA % (n)	98.7% (1537)	52.6% (30)
UA % (n)	0.1% (1)	1.8% (1)
RA % (n)	0.8% (13)	42.1% (24)
PsA or IA with Psoriasis % (n)	0.4% (6)	0% (0)
CTD % (n)	0% (0)	3.5% (2)

IA, inflammatory arthritis; RA, rheumatoid arthritis; PsA, psoriatic arthritis; UIA, undifferentiated inflammatory arthritis; *patients who had reached their 12 month follow-up time point (1557/1971)

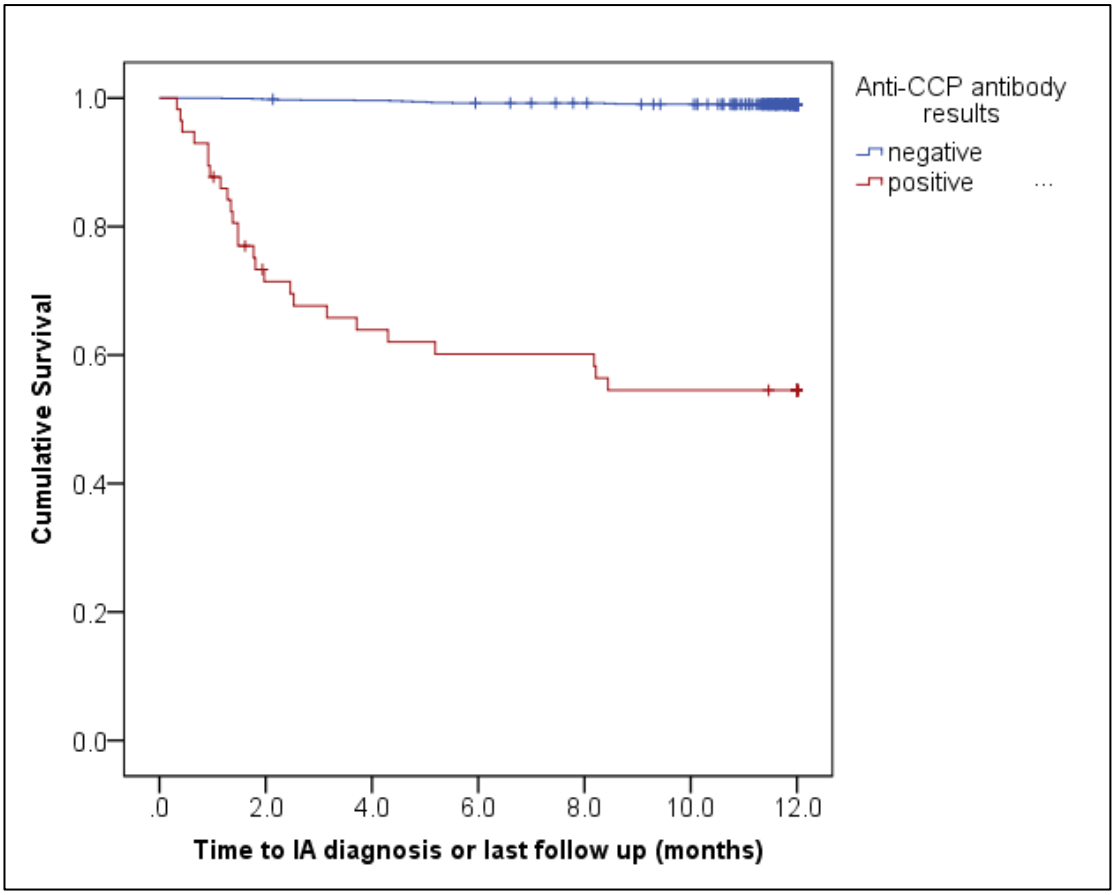


Figure 7.2 Kaplan-Meier graph: Time to IA progression in anti-CCP positive and anti-CCP negative individuals with MSK symptoms

anti-CCP, anti-cyclic citrullinated peptide antibody; IA, inflammatory arthritis; MSK, musculoskeletal symptoms

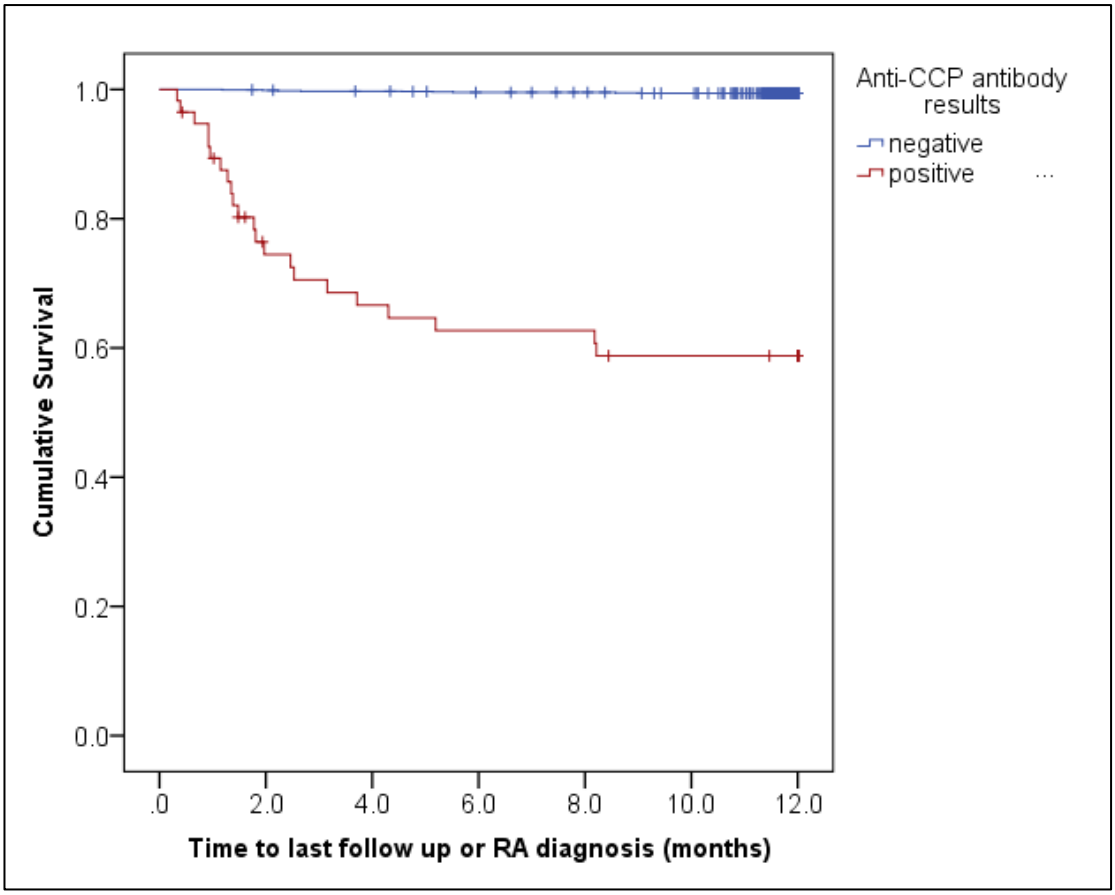


Figure 7.3 Kaplan-Meier graph: Time to RA progression in anti-CCP positive and anti-CCP negative individuals with MSK symptoms

anti-CCP, anti-cyclic citrullinated peptide antibody; RA, rheumatoid arthritis; MSK, musculoskeletal symptoms

Analyses of location of symptoms, showed that individuals with pain affecting the regions of the wrists and/or hands or the feet were more likely to be anti-CCP positive (RR 2.9 (1.2 to 7.3, p=0.024) for wrists and/or hands and RR 2.1 (1.2 to 3.6, p=0.008) for feet). Those with shoulder symptoms were also more likely to have a positive anti-CCP result (RR 2.1 (1.2 to 3.7, p=0.010)) (table 7.3). The association between the location of symptoms and progression to RA was not analysed as the number of patients per variable would be too small.[403 404]

Table 7.3 Associations between joint symptoms and anti-CCP positivity in individuals with new nonspecific MSK symptoms

Joint involved		**% (n/N) who are anti-CCP positive**	**RR (95% CI), p**
Neck	**Absent**	2.9% (40/1364)	reference
	Present	2.5% (15/608)	0.9 (0.5, 1.6); p=0.627
Back	**Absent**	3.6% (48/1352)	reference
	Present	1.1% (7/620)	0.3 (0.1, 0.7);p=0.008
R or L shoulder	**Absent**	2.2% (25/1116)	reference
	Present	3.5% (30/856)	2.1 (1.2, 3.8);p=0.010
R or L elbow	**Absent**	3.1% (40/1297)	reference
	Present	2.2% (15/675)	0.7 (0.4, 1.2);p=0.184
R or L wrist and/or hand	**Absent**	1.0% (5/483)	reference
	Present	3.4% (50/1489)	2.9 (1.2, 7.3);p=0.024
R or L hip	**Absent**	3.4% (41/1208)	reference
	Present	1.8% (14/764)	0.6 (0.3, 1.1); p=0.075
R or L knee	**Absent**	3.3% (28/836)	reference
	Present	2.4% (27/1136)	0.8 (0.5, 1.4);p=0.442
R or L ankle	**Absent**	3.1% (41/1333)	reference
	Present	2.2% (14/639)	0.8 (0.4, 1.4);p=0.377
R or L foot	**Absent**	2.2% (27/1224)	reference
	Present	3.7% (28/748)	2.1 (1.2, 3.6); p=0.008

L, left; MSK, musculoskeletal symptoms, R, right

7.4 Discussion

At the time of performing this work, this was the first prospective cohort study addressing the prevalence of anti-CCP in individuals with new non-specific MSK symptoms without clinical synovitis and the progression to IA. In this cohort of individuals referred from primary care, 2.8% were anti-CCP antibody-positive with 47% progressing to IA mainly RA, the majority within one year or antibody testing.

Several retrospective studies have identified the presence of RA associated autoantibodies in individuals with RA prior to disease onset with a rise in prevalence in the years just prior to diagnosis. [376 377] In a large population study, the prevalence of RA was found to be 19% in RF positive individuals.[405] Findings from the Nurses' Health Study showed a sensitivity and specificity of 28% and 100% respectively in a single pre-RA diagnosis serum sample tested for anti-CCP antibodies. Higher antibody levels were associated with a shorter time to diagnosis. [394] In another cohort of 147 individuals with arthralgia without IA, of whom 50 were CCP positive, 52 RF positive and 45 positive for both antibodies, 45% developed RA after a median 28 months. The presence of ACPA, but not RF or shared epitope, was associated with disease progression. [395]

In recent years, there has been increasing focus on work addressing individuals at risk of developing RA.[13] Other methods have also been evaluated for identifying these individuals early. Liang et al. have explored the possibility of an internet-based method for identifying people with symptoms of an inflammatory polyarthritis of less than 12 weeks. In this study, 43 244 people took the online questionnaire.[406] Of these 60 took a self-scoring algorithm for IA, 48 screened positive, 24 were evaluated and 3 diagnosed with IA. Of the 24 people, 17 completed a follow up questionnaire at 1 year – 3 were diagnosed with RA and were on methotrexate.

An important question that would need careful consideration prior to implementing any case finding strategy is that of cost–effectiveness. On the one hand, there is the cost of the disease, which is associated with irreversible joint damage and increased morbidity, the cost of treatment and societal costs including potential job loss.[401] This needs to be balance against the cost of performing investigations in order to finding early treatable RA and preventing disease progression.

Testing of individuals with nonspecific symptoms for anti-CCP provides a relatively easy and simple method for identifying individuals at risk at an early stage. Another possibility would be to refine the group to be tested and referred. Hand involvement has been reported to be more common in individuals who progress to RA. [400] In our cohort, symptoms involving the wrists and/or hands, feet and the shoulders were

associated with anti-CCP positivity. In the previous chapter, a history of EMS, the presence of polyarticular pain, RF or inflammatory markers has been reported to increase the positive predictive value of anti-CCP in individuals with early RA.[407] In another cohort, anti-CCP positive individuals with symmetric arthralgia of small joints and EMS, 60% progress to RA.[395] The presence of anti-CCP together with inflammatory symptoms, the presence of shared epitope and imaging with ultrasound have been shown to enable identification of individuals with RA at an early stage.[19]

Whilst the majority of anti-CCP positive individuals who progressed to IA in this study were classified as RA, two individuals were later diagnosed with Jo-1 polymyositis, one with high level anti-CCP antibodies and one with a borderline result. Studies suggest that the autoimmune process in ACPA-associated diseases may begin at mucosal sites e.g. the lung.[408] These two individuals may have an overlap of RA and polymyositis. The possibility of a pathogenic link between polymyositis and ACPA with lung involvement in both, however, is an interesting one.

7.5 Limitations

The study has its limitations. These findings have been compared to an estimated 1% based on blood donor cohorts.[376 398] Whilst this may be a reasonable approximation of anti-CCP positivity in the general population, it is known that screening of donors exclude individuals with medical conditions and may therefore underestimate the population prevalence of the antibody. Despite this, findings from this study suggest that individuals with rapid progression to IA may be identified. Another limitation is that participants in this study have mainly been recruited from Yorkshire, U.K. The antibody prevalence may differ in other populations and ethnic groups. Of the individuals who progressed to RA, approximately one third were anti-CCP negative. Whilst anti-CCP positivity has been associated with more severe destructive disease, the study confirms the need for additional biomarkers for the diagnosis of seronegative RA and other inflammatory arthritides e.g. PsA. The joint symptoms and associated conditions were all self-reported from patient questionnaires. It is possible that there may be a bias towards under-reporting as patients may have only reported what they may have perceived as relevant to the study.

7.6 Conclusions

In this study selecting individuals with new nonspecific MSK symptoms without clinical synovitis enriched the prevalence of anti-CCP positivity to 2.8%, with anti-CCP positive individuals being found to be at high risk of rapidly developing an inflammatory arthritis, in particular RA. The cost-effectiveness of this approach will need to be determined.

Chapter 8 Discussion, future directions and conclusions

This final chapter presents a summary of the findings from this thesis, discussing the results in context of the recent literature and potential research questions arising from the thesis.

8.1 Overview

Review of the literature and evidence from clinical practice have shown that outcomes of patients with IA are significantly improved when treated early[8 78] with effective DMARD therapies,[187] followed by regular monitoring and, where necessary, DMARD escalation to achieve a treatment target (ideally remission).[222] In a recent study of patients with early inflammatory polyarthritis, early sustained remission was associated with lower all-cause mortality.[409]

Notably, of the DMARDs, use of bDMARDs[178] have been highly effective in achieving disease control in patients with IA. Their use is supported by a wealth of evidence from clinical trials confirming their efficacy. [187 223] With the cost of these drugs remaining an important point of consideration,[207] however, many treatment guidelines place them after failure of one or more csDMARDs.[188 410] Questions regarding the benefit of bDMARD therapy in the early phases of the disease also remained unanswered.

The importance of early treatment has in turn placed increasing emphasis on the need for early diagnosis. Several biomarkers have been identified in patients in the early stages of the disease. The genetic marker, shared epitope, has long been associated with patients with RA. Serological markers including RF and ACPA have been shown to be present in the preclinical phase of the disease. Imaging with ultrasound has also been shown to be more sensitive than clinical examination for detecting synovitis. Use of these biomarkers in clinical practice in patients at-risk of IA, however, have not yet been well established.

This thesis has addressed the management of RA across the IA disease continuum, looking at (1) the treatment of IA, particularly focusing on the role of bDMARD in early disease, and (2) the diagnosis of IA, focusing on the identification of patients at-risk before developing clinically apparent disease (figure 8.1).

First the thesis provided an up-to-date systematic review of the literature of RCT evidence of the efficacy of all available bDMARDs and emerging bsDMARDs along the IA continuum, from patients with UA to those with established RA, to underpin

guidance for treatment recommendations for the use of these agents.[209] Two RCTs then addressed the use of bDMARDs in patients with early DMARD naïve IA, an area in which the evidence for their use was less clear. One of the RCTs was in patients with early RA and the other included patients with UA. Both incorporated a treat-to-target approach within their study designs.

The thesis also aimed to explore the use of biomarkers available in clinical practice for the early identification of patients with IA in secondary care and the specific use of anti-CCP in primary care to identify a cohort of patients at greater risk of developing IA (with the eventual aim of enabling earlier intervention).

8.1.1 Thesis synopsis

Chapter Three: Systematic literature review of the efficacy of biological DMARDs in patients along the inflammatory arthritis disease continuum

This SLR confirmed the efficacy of bDMARDs particularly in combination with methotrexate. With studies showing superior long-term clinical and radiographic outcomes using combination therapy with a bDMARD and a csDMARD, this remains the optimal treatment approach. In situations where patients may not tolerate methotrexate or another csDMARD, bDMARD monotherapy may be considered. In general, studies also showed earlier improvement in signs and symptoms with more intensive initial treatment strategies compared to step-up approaches. In patients with insufficient response to methotrexate or other csDMARDs, however, outcomes were similar once bDMARDs were added. Radiographic progression was also lower with therapies that included a bDMARD. High clinical response rates and less radiographic progression were also seen in clinical trials which incorporated treat-to-target type strategies - many of these also included glucocorticoids. Biological DMARD- and drug-free remission was achievable in some patients with IA, particularly with early bDMARD use. Newer therapies have also begun to emerge, with the first published RCT showing efficacy of CT-P13, the first infliximab bsDMARD in RA.

Chapter Four: Infliximab vs. intravenous methylprednisolone with methotrexate as induction therapy in DMARD naïve early RA

Results from this chapter (the IDEA study) showed that first-line therapy with methotrexate and high dose IV steroid in early DMARD naïve RA, together with a treat-to-target approach, resulted in little damage progression. Methotrexate and infliximab was not superior to methotrexate and high dose IV steroid in inhibiting radiographic progression, however there was a trend towards earlier clinical

responses, with significantly earlier achievement of DAS28 remission and greater reduction in synovitis on ultrasound in the bDMARD group.

Chapter Five: Etanercept with methotrexate vs. methotrexate monotherapy in DMARD naïve early IA

In this RCT of DMARD naïve early IA, almost a third of patients had no tender and no swollen joints after one year of treatment. A high proportion also achieved DAS28-CRP<2.6 and low levels of ultrasound synovitis. Combination therapy with methotrexate and etanercept was not superior to methotrexate monotherapy in achieving the primary outcome, however clinical responses were more rapid in the methotrexate and etanercept combination therapy group.

Chapter Six: Use of clinical, genetic, serological and imaging biomarkers in anti-CCP positive patients with nonspecific musculoskeletal symptoms to identify early IA in the secondary care

This longitudinal cohort study confirmed that patients with nonspecific MSK symptoms and anti-CCP antibodies are at risk of developing IA with 50% of patients having progressed to IA, the majority within the first year of follow-up. A risk score was derived using a combination of clinical features, serology and ultrasound imaging or shared epitope as a genetic marker to risk stratify patients with the potential to develop IA.

Chapter Seven: Use of anti-CCP antibodies in patients with new nonspecific MSK symptoms to identify patients at risk of early IA in primary care

In this prospective cohort study of patients in primary care, 2.8% of patients with new nonspecific MSK symptoms were found to be anti-CCP positive. Of these a significant proportion (47%) developed IA, the majority within one year of having the blood test done.

8.2 Discussion

The following section will discuss the work from this thesis in context of the recent literature especially work that was done contemporaneously or since the thesis studies were completed. It will also address areas related to, but outside the scope of this body of work. These will be discussed under two main headings: (1) update of IA treatment and (2) update of early IA diagnosis.

8.2.1 Update of IA treatment

Since the work of this thesis, several new therapies have emerged. All thus far have only been examined in clinical trials in established RA. A few new studies have also been published on treatment strategies in early IA/RA. This section will therefore seek to examine the literature that may give clues on therapies and new strategies that will impact the early disease continuum regimens. This will be discussed under three main subheadings (1) new therapies, (2) treatment strategies in early IA and (3) how should IA be treated, in the light of the body of work arising from this thesis.

8.2.1.1 New therapies

8.2.1.1.1 Emerging Biological DMARDs

Despite current treatment options, some patients continue to have refractory disease, leaving scope for newer therapies. Sarilumab, a fully human anti-IL-6Rα monoclonal antibody, can bind both soluble and membrane-bound IL-6Rα thereby inhibiting IL-6 mediated inflammatory signalling. Following an initial dose-ranging portion of a two-part phase II/III RCT,[411] the second part of the study was conducted comparing subcutaneous sarilumab 150mg, 200mg or placebo every two weeks with methotrexate in patients with moderate to severe MTX-IR RA.[412] Both sarilumab groups met their co-primary endpoints, showing significantly greater improvements than placebo: ACR 20 responses at week 24: 58%, 66.4% vs 33.4%, $p<0.0001$), HAQ-DI at week 16: -0.53,-0.55 vs -0.29, $p<0.0001$ and mTSS at week 52: 0.90, 0.25 vs 2.78, $p<0.00001$ in the sarilumab 150mg, 200mg and placebo groups respectively. Serious infections were documented in 2.6%, 4.0% and 2.3% of the three groups. Laboratory abnormalities were similar to those reported in other studies of IL-6 blockade, with neutropaenia, elevated liver transaminases and increases in fasting cholesterol in a proportion of patients.[413 414]

Newer therapies targeting other sites along the inflammatory cascade have also been investigated. One such therapy is granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF is a pro-inflammatory cytokine that is involved in the differentiation and survival of macrophages and neutrophils. In a phase 2 double blind RCT, treatment with mavrilimumab, a fully human monoclonal antibody targeting GM-CSF receptor-α, resulted in significantly greater reduction in DAS28-CRP ≥ 1.2 at 12 weeks (primary outcome) than placebo.[415] No significant adverse events were noted. In the phase 2b EARTH-EXPLORER 1 study of moderate to severe csDMARD-IR RA, groups receiving mavrilimumab 30mg, 100mg and 150mg every other week. The study met its co-primary endpoints of mean change in

DAS28-CRP from baseline at 12 weeks and ACR 20 at 24 weeks.[416] The safety profile was acceptable. There were no serious infections in the mavrilimumab 100mg and 150mg groups but two cases of pneumonia – one in each of the mavrilimumab 30mg and placebo groups.

8.2.1.1.2 Biosimilar DMARDs

The drug armamentarium continues to grow with the emergence of the biosimilar [224] DMARDs.[315] Since the introduction of the first bsDMARD, CT-P13, [346] several others have come to the fore. These include two rituximab biosimilars, CT-P10[417] and PF-05280586.[418] In a phase 1 trial in TNFi-IR RA, CT-P10 has showed equivalent pharmacokinetic and pharmacodynamic properties to rituximab. Efficacy, in terms of the ACR 20, 50 and 70 and EULAR responses, and safety profiles were also similar up to 24 weeks. Studies of PF-05280586 have shown similar in vitro structure and functionality to rituximab. A phase I/II clinical trial in TNFi-IR RA (NCT 01526057) is underway. For the etanercept biosimilar, GP2015, in vitro binding to TNFα, and pharmacokinetic properties and efficacy in animal models were similar to the innovator product.[419]

Several bsDMARDs have undergone phase 3 clinical trials. In a double blind RCT, 189 RA patients with active RA (2010 ACR/EULAR classification criteria) on stable dose methotrexate with a CRP ≥10 mg/L were randomized to BOW015 or innovator infliximab.[420] Therapeutic equivalence was seen between the biosimilar and the innovator compounds (ACR 20 at week 16: 85.0% and 85.5% in the ITT populations (95% CI for the difference: -11.2% to 10.3%). The pharmacokinetics, proportion of anti-drug antibodies and adverse events were also similar between the two groups. Another infliximab biosimilar, SB2, also demonstrated equivalence to infliximab in terms of ACR20 responses to week 30 in patients with moderate to severe MTX-IR RA. Its pharmacokinetics, immunogenicity and safety profile were also similar to infliximab.[421] In an RCT evaluating the efficacy of an etanercept biosimilar, HD203, 294 RA patients were randomized to receive HD203 or Enbrel ®, both in combination with methotrexate. The ACR20 at week 24 of 83.5% and 81,4% in the HD203 and Enbrel® groups respectively (difference (95% CI) 2.12 (-7.65, 11.89), p=0.67), demonstrating equivalence in efficacy. There was no significant between group difference in adverse events.[422] Another etanercept biosimilar, SB4, also showed equivalent ACR responses to its reference etanercept at week 24. The safety profile was comparable between the two groups.[423]

At present only one bsDMARD – the infliximab biosimilar CT-P13 (Remsima ® or Inflectra ®) - is approved by the European Medicines Agency. The similarities in

efficacy, safety and immunogenicity between this and other bsDMARDs and their innovator products in the clinical trials is promising.

Due to the complex nature of these compounds and their production, bsDMARDs are not identical to the originator product. Registry data and ongoing pharmacovigilance will therefore be vital to provide long-term information on the efficacy and safety of these drugs. The questions around starting a bsDMARD or switching between a bsDMARD and its innovator also still need to be addressed. A large RCT, the NOR-SWITCH study, is currently underway to evaluate the impact of substituting the originator infliximab for the biosimilar compound across several indications including RA, psoriatic arthritis, spondyloarthropathy, Crohn's disease, ulcerative colitis and chronic plaque psoriasis.[424] Initial reports of its use in clinical practice suggest that its efficacy profile is similar to infliximab.[425]

8.2.1.1.3 Small molecules

Whilst the biological and biosimilar DMARDs look to target extracellular signaling, there have also been advances in research into novel small molecules directed at intracellular pathways.[426] The focus of these therapies in RA have mainly been on inhibiting intracellular protein tyrosine kinases which include JAKs and spleen tyrosine kinase (SYK). These enzymes are responsible for protein phosphorylation thereby modifying downstream protein signaling and nuclear protein transcription.

There are four members of the JAK family – JAK1, JAK2, JAK3 and tyrosine kinase 2 (Tyk2). JAK2 is mainly expressed on haematopoetic cells while the other three are more widely expressed. JAKs are associated with cytokine receptors. Cytokine binding causes signaling through their associated signal transducer and activator of transcription factors (STATs) – the JAK-STAT pathway. Tofacitinib is the first and only JAK inhibitor that has been approved for the treatment of RA. It preferentially inhibits JAK3 and/ or JAK1, down-regulating several cytokines including interleukins 2, 4, 7, 9, 15 and 21. The main advantage of this drug is its availability in an oral form. Several published RCTs have confirmed clinical efficacy of tofacitinib in combination with methotrexate or other csDMARDs in MTX- naïve, DMARD-IR and TNFi-IR RA.[317 427-429] As monotherapy, in DMARD-IR RA, higher ACR responses and greater improvement in function was achieved with tofacitinib than placebo. The proportion of patients achieving DAS28-4variable(ESR) remission was similar in the tofacitinib 5mg and 10mg groups.[427] Inhibition of radiographic progression, however, has been demonstrated in MTX-IR RA with the tofacitinib 10mg but not the 5mg dose.[430] The drug has been approved for use by the United States (US) food and drug administration[431] as well as in several other countries including

Switzerland, Russia and Japan for the treatment of adults with moderate to severe active RA who have had inadequate response or are intolerant to methotrexate.

Long-term efficacy and safety profiles need to be established. Thus far, pooled data from phase 2 and 3 clinical trials and long-term extension studies in moderate to severe RA has shown the overall risk of infection and mortality to be similar to that of the biological therapies (serious infections (95% CI) 3.09 (2.37-2.39) per 100 patient-years and all-cause mortality (95% CI) 0.30 (0.20-0.44) per 100 patient-years.[432] Serious infections were higher in patients with low lymphocyte counts (<0.5 $x10^3/mm^3$). Whilst it was unclear whether this was the cause or due to the infection, regular monitoring of lymphocyte counts has been advised whilst on treatment. Higher rates of herpes zoster infection has also been documented with this agent (239 cases of 4879 tofacitinib-treated patients; 4.4 per 100 patient-years (95% CI 3.2-6.0) compared to 1.5 per 100 patient years (95% CI 0.5-4.6) in the placebo treated patients in the phase 3 trials).[433] Complicated herpes zoster, however, was rare.

Several other JAK kinase inhibitors are also undergoing phase 2 and 3 clinical trials.[434] One of these is the JAK 1 and JAK 2 inhibitor, baricitinib. In a phase IIb study in MTX-IR RA, the proportion of patients in the combined baricitinib 4mg and 8mg groups achieved significantly higher ACR20 responses than placebo at week 12 (76% vs. 41%, p<0.001).[435] ACR 50 and 70 responses and DAS28, SDAI and CDAI remission were also higher in the baricitinib groups. Serious infections were described in two patients receiving baricitinib. There were no reported cases of opportunistic infections, tuberculosis, herpes zoster or death. Recently, results from two phase 3 RCTs, RA-BUILD and RA-BEACON, have been published in patients with moderate-to-severely active csDMARD-IR RA, and in TNFi-IR RA in patients continuing background csDMARD therapy.[436 437] In RA-BUILD, there were significantly greater improvement in clinical responses and function at weeks 12 and 24 with baricitinib 2mg and 4mg compared to placebo, with responses seen as early as one week after starting. Radiographic progression was also significantly lower in both baricitinib groups, with least progression in the baricitinib 4mg group. In RA-BEACON, improvements in clinical outcomes and function were also higher in the baricitinib groups compared to placebo, with greatest benefits seen in the baricitinib 4mg group. Whilst there were numerically more reported cases of Herpes zoster in the baricitinib 4mg group in this study, the proportion of serious adverse events including serious infections in both studies was not significantly higher than in those receiving placebo.

SYK, another group of cytoplasmic tyrosine kinases, is expressed in most haematopoetic cells, including macrophages, neutrophils, B cells, naïve T cells and

mast cells. It is also found on platelets and some other non-haematopoetic cells including osteoclasts.[438 439] It acts downstream to B cell receptors and Fc receptors. Though intracellular signaling, SYK can affect cell survival, proliferation, differentiation and cytokine release in immune cells[440] and in non-immune cells e.g. osteoclasts has a role in cell differentiation and function. In two phase 2 clinical trials in MTX-IR RA, fostamatinib a SYK-inhibitor, showed significantly higher ACR 20, 50 and 70 responses and DAS28 responses compared to placebo,[441 442] however in another, in bDMARD non-responders, the primary endpoint (ACR20 at week 12 for fostamatinib and methotrexate vs. placebo and methotrexate) was not met.[443] In early DMARD-IR or DMARD-naïve RA, fostamatinib monotherapy was superior to placebo but less effective than adalimumab monotherapy in achieving clinical responses. [444] In a phase 3 trial of MTX-IR RA, ACR responses at week 24 were higher in the two fostamatinib groups that placebo but improvements were not as great as in the phase 2 trials. Radiographic progression was similar between the groups. [445] A phase 3 trial of a single TNFi-IR RA showed significantly higher ACR20 responses at week 24, but only in the group receiving fostamatinib 100mg bd compared to placebo.[446] Diarrhoea, hypertension and headache were frequently reported adverse events. Following the results of these trials, the companies developing this drug has decided to put further studies on hold.[444-446]

8.2.1.2 Treatment strategies

Since the SLR in chapter 3, there have also been new strategies trials in early and established IA.

8.2.1.2.1 Treatment strategies in established RA

The multicenter non-inferiority TACIT trial compared combination csDMARD therapy to TNFi in patients with csDMARD-IR RA who would be eligible to bDMARD therapy according to UK NICE guidelines[162].[447] In this pragmatic open-label RCT, 214 patients were randomised to receive additional csDMARD therapy followed by TNFi therapy at 6 months in cases of nonresponse, or immediate TNFi therapy switching to another TNFi at 6 months in cases of nonresponse. The study met its primary endpoint with a ΔHAQ-DI at 12 months of -0.45 in the csDMARD group and -0.3 in the TNFi group, mean difference (95% CI) -0.14 (-0.29 to 0.01). This was below the pre-specified non-inferiority margin of 0.22. Clinical responses were achieved earlier in patients in the TNFi group, but at 12 months there were no significant between group differences, findings similar to those of the RACAT trial.[242] There were 28 serious events (10 in the csDMARD group and 18 in the TNFi group. The number of patients with infections involving several body systems

were also higher in the TNFi group (54 vs. 30). Overall, however, number of adverse events was higher in the csDMARD group (635 vs. 465 in the csDMARD vs TNFi groups respectively). This study therefore highlights the benefits of treat-to-target. Whilst there was a higher number of infections with bDMARD use, multiple csDMARD use was also associated with an increase in adverse events.

Studies have also looked at bDMARD-free remission in established disease. In the open-label non-randomised HONOR trial, 75 patients with disease duration approximately 7.5 years, in DAS28-ESR remission (<2.6) for ≥ 6 months on stable dose methotrexate and adalimumab (without glucorticoids or NSAIDs) could choose to withdraw or continue adalimumab.[448] At 12 months, 48 % who withdrew adalimumab (n= 52) maintained DAS28 remission vs. 83% in those who continued treatment (n=23). Greater depth of remission (DAS28-ESR ≤1.98) at treatment discontinuation was the main factor for remission maintenance. Of importance, control of disease activity could be re-established on restarting adalimumab and there was no radiographic progression and no loss of function with bDMARD withdrawal. This study adds to the body of evidence that bDMARD-free remission is achievable, even in patients with established disease. It also highlights the importance of achieving tight control of disease activity to enable bDMARD withdrawal – a treatment goal which is more easily attained in early disease.

8.2.1.2.2 Treatment strategies in early IA

There have also been several RCTs looking at remission induction strategies in early disease. In the U-ACT-EARLY strategy study, 317 patients with early DMARD naïve RA were randomised to receive tocilizumab and methotrexate, tocilizumab monotherapy and methotrexate monotherapy. Patients were seen monthly and treatment escalated if remission was not achieved. If in sustained remission (defined by a DAS28 <2.6 and SJC ≤4, sustained for ≥23 weeks, with the exception of ≤2 visits where the DAS28 could be ≥2.6 but <3.2) treatment was tapered and reintroduced at flare (DAS28 >2.6). Sustained remission was achieved in 86%, 84% and 44% in the tocilizumab and methotrexate, tocilizumab monotherapy and methotrexate monotherapy groups respectively (p <0.002 for the tocilizumab and methotrexate vs the methotrexate and tocilizumab vs methotrexate, p=0.62 for tocilizumab and methotrexate vs. tocilizumab).

In the SLR in Chapter 3, several studies showed that, in patients in whom remission or low disease activity was achieved, bDMARD therapy may be successfully withdrawn. This was particular so in early disease.[2 449 450] Since then, the AVERT trial of MTX-naïve anti-CCP positive early RA, has been published.[451] In this RCT, the first to address drug free remission as a primary endpoint, a small but

significant proportion of patients were able to successfully stop all therapy. Drug free remission after 12 months of DMARD therapy (DAS 28 (CRP) < 2.6 at 12 and 18 months) was achieved in 7.8%, 12.4% and 14.8% in the methotrexate, abatacept, and methotrexate and abatacept groups respectively (OR (95% CI) for methotrexate and abatacept vs. methotrexate: 2.51 (1.02, 6.18), p=0.045 and for abatacept vs. methotrexate : 2.04 (0.81, 5.14)). Factors predicting sustained remission on treatment withdrawal were lower mean symptom duration at baseline, DAS28(CRP), HAQ-DI and DAS28 (CRP) < 2.6 over time during the treatment period – features once again highlighting the importance of early treatment.

Tapering csDMARDs has also been addressed in the tREACH trial.[452] In this RCT which incorporated a treat-to-target strategy, patients receiving combination csDMARDs with glucocorticoids achieved earlier control of disease activity than those receiving methotrexate monotherapy with glucocorticoids however outcomes in both groups were similar at two years. Function, measured by the HAQ-DI score, however, was significantly better in the combination csDMARD group. In both, approximately 50% of patients achieved sustained remission but those in the combined csDMARD group required less TNFi therapy (21% vs. 38%). Those achieving sustained remission, a DAS < 1.6 at two consecutive visits, were eligible to taper DMARD therapy. Of those who did, 43% in both groups had a flare of disease activity (defined as an increase in DMARD therapy after tapering had commenced). Approximately 19% achieved drug free remission at the end of the two year period. Radiographic progression was low in both groups.

8.2.1.3 How should IA be treated

Findings from the SLR in chapter 3 together with the recently published studies, confirm the efficacy of bDMARDs in patients across the IA disease continuum from patients with UA to those with established RA and from DMARD-naïve through to those that had failed previous bDMARDs, in particular the TNFi therapies.

With evidence highlighting the importance of treating patients at the earliest opportunity, several clinical trials have addressed the impact of bDMARD use as first-line therapy. These have compared combination therapy with methotrexate and a bDMARD to methotrexate monotherapy, [182 230] to other treatment combinations e.g. triple csDMARD therapy[241] and to methotrexate with high dose oral or IV steroid. The more recent trials have also incorporated some form of treat-to-target strategy. [183 293 296 337] Overall, these have shown more rapid clinical responses with the use of bDMARD therapy but ultimately similar results in the non-bDMARD groups when treatment was escalated in the non-responders. This was seen

particularly in patients with early disease and when adopting a treat-to-target approach, escalating therapy when a treatment target (remission or low disease activity) was not met. These findings were supported by the results from the IDEA and EMPIRE studies (chapters 4 and 5 respectively).[17] [18] Furthermore, the ability to de-escalate bDMARD therapy is greatest in patients who achieve disease control early.

The data therefore, first and foremost, support the need for early effective treatment. In addition, clinical and radiographic outcomes are improved with regular monitoring of disease activity and escalating therapy as part of a treat-to-target type approach. Regarding treatment choice, bDMARDs are highly effective therapies and have the potential for earlier clinical responses, lower radiographic progression, and the possibility of tapering and stopping therapy. A proportion of patients however will respond to csDMARD therapy and bDMARD therapies are still relatively costly. In the main, therefore, bDMARDs are only available to patients with active disease following failure of one or more cs-DMARD (depending on the governing body authorising their use).[162]

The results from the SLR on bDMARD efficacy (Chapter 3),[16] together with one on DMARD safety[189] and the efficacy of sDMARDs and glucocorticoids, [453] were used to inform the 2013 EULAR recommendations on DMARD therapy for patients with RA. These are summarised in table 8.1. [209] The guidelines advocate the use of early treatment with csDMARDs and glucocorticoids, regular monitoring of disease activity, and treating-to-target. In patients in whom response to csDMARD therapy is inadequate, timely commencement of bDMARD therapy are advocated. With less data on the infliximab biosimilar DMARD, CT-P13 and the tsDMARD, tofacitinib, recommendations for their use are following treatment failure of the more established cs- and bDMARDs.[209]

Over the past two decades, the treatment and treatment principles of IA have undergone many changes. It is likely that treatment strategies will continue to evolve with the newer emerging therapies and the work being done to gain further insights into the disease and treatment responses. These will be discussed in section 8.3.1 on future directions on the treatment of early IA.

Table 8.1 2013 update of the EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological DMARDs (from Smolen et al. ARD 2014[209])

1. Therapy with DMARDs should be started as soon as the diagnosis of RA is made
2. Treatment should be aimed at reaching a target of remission or low disease activity in every patient
3. Monitoring should be frequent in active disease (every 1-3 months); if no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted
4. MTX should be part of the first treatment strategy in patients with active RA
5. In case of MTX contraindications (or early intolerance), sulphasalazine or leflunomide should be considered as part of the (first) treatment strategy
6. In DMARD-naïve patients, irrespective of the addition of glucocorticoids, csDMARD monotherapy or combination therapy of csDMARDs should be used.
7. Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible
8. If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another csDMARD strategy should be considered; when poor prognostic factors are present, addition of a bDMARD should be considered
9. In patients responding insufficiently to MTX and/or other csDMARD strategies, with or without glucocorticoids, bDMARDs, (TNF inhibitors, abatacept or tocilizumab, and, under certain circumstances, rituximab) should be commenced with MTX
10. If a first bDMARD has failed, patients should be treated with another bDMARD; if a first TNF inhibitor therapy has failed, patients may receive another TNF inhibitor or a biological agent with another mode of action
11. Tofacitinib may be considered after biological treatment has failed
12. If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs, especially if this treatment is combined with a csDMARD
13. In cases of sustained long-term remission, cautious reduction of the csDMARD dose could be considered, as a shared decision between patient and physician

14. When therapy needs to be adjusted, factors apart from disease activity, such as progression of structural damage, comorbidities and safety issues, should be taken into account

DMARD, disease-modifying antirheumatic drug; EULAR, European League against Rheumatism; MTX, methotrexate; RA, rheumatoid arthritis; TNF, tumour necrosis factor

8.2.2 Update of early IA diagnosis

Early treatment requires early disease identification. There are several stages along the IA disease continuum at which this may be achieved. Much work thus far has been done to determine the progression from UA to RA.[80 210 367] The development of the 2010 ACR/EULAR RA classification criteria were developed to identify, among patients with IA, those with early RA, in particular those at greatest risk of developing persistent and /or erosive disease. These criteria have been shown to be more sensitive, although somewhat less specific, than the 1987 ACR criteria for the classification of RA.[454-458] They have also enabled earlier identification of patients starting DMARD therapy.[454 455 459] In a recent study, the use of these criteria have been assessed as a potential tool to help triage patients referred from primary care with possible IA.[460] In this eight month prospective study, 143 referrals were included - 71 met the triage criteria and 72 did not. Of the patients whose referrals met the triage criteria and attended their rheumatology clinic appointments, 40% (25/63) were diagnosed with RA, compared to 2% (1/49) where the triage criteria were not fulfilled. The median wait time for a rheumatology appointment in each of the two groups was 7.9 weeks and 45.4 weeks respectively.

Work from this thesis had addressed the earlier phases along the disease continuum - in patients with systemic autoimmunity associated with RA and symptoms without clinical arthritis (groups c+d[13] using terminology proposed by the EULAR study group for risk factors for RA (table 8.2)).[13]

Table 8.2 Phases up to the development of RA [13]

(a) Genetic risk factors for RA (b) Environmental risk factors for RA (c)Systemic autoimmunity associated with RA (d) Symptoms without clinical arthritis (e) Unclassified arthritis (f) RA
The term 'arthritis' is used to denote clinically apparent soft tissue swelling or fluid (not bony overgrowth alone). (a) to (e) can be used in a combinatorial manner for example, an individual may have (a)+(b), or (a)+(b)+(c) or (a)+(b)+(d) etc.

Initial estimates suggested that approximately 1% of the general population are anti-CCP positive, with progression to IA occurring over a variable period of time, possible more than 10 years after initial antibody detection.[376] In clinical practice, screening asymptomatic individuals for serological markers (group d)[13] for the development of RA would therefore not be feasible.

In a recent analysis from the European Perspective Investigation of Cancer in Norfolk (EPIC-Norfolk) UK cohort study, 18628 individuals aged 40-79 years were tested for anti-CCP. [461] Anti-CCP positivity in this population sample was 2.1%, with previous or current smokers (OR (95% CI) 1.29 (1.02 to 1.55) and 1.6 (1.95 to 2.13)) and older age (OR (95% CI) 1.01 (1.00 to 1.03)) associated with antibody positivity. There was a 10 fold increase of anti-CCP positive individuals progressing to IA within the following 3-10 years compared to those who were anti-CCP negative, supporting evidence for the role of anti-CCP in identifying an at-risk population.

The results from chapter 7 showed that testing for anti-CCP in patients presenting with new nonspecific MSK symptoms in primary care enable the identification of an anti-CCP positive cohort at high risk of rapid progression to IA. Overall, there was a 2.8% anti-CCP positivity in patients with new nonspecific MSK symptoms with approximately 45% developing IA, the majority within 12 months.

Requesting anti-CCP tests has become more widely used in secondary care and in some primary care centres. In Alberta, Canada, for example, some patients are

referred for rheumatology assessment on the basis of a positive anti-CCP test.[462] Over a three year period, it was noted that 11614 referrals were received and accepted for a rheumatology consultation via the Central Referral and Triage service in the Calgary Heath Region. Of these, 4.5% (568/11614) were referrals for a positive anti-CCP test. A proportion were thought to have RA by the referring clinician and in the majority (81.3% (61/75)), the diagnosis was confirmed. In addition, RA was diagnosed in half (120/239) of those that were termed unresolved or non-RA.

The cohort study described in chapter 6 was one of the first prospective studies to address the role of anti-CCP in early IA diagnosis in secondary care. In this study of anti-CCP positive patients with MSK symptoms, half developed IA over a 6 year follow-up period, with a third showing disease progression within the first year. The clinical findings together with the use of serological markers, shared epitope, ultrasound scans of the wrists and hands and/or the genetic marker, enabled further risk stratification for disease progression.

The number of patients in this study however was relatively small. Findings from the study will therefore need to be validated in a larger cohort.

Improved understanding of the pathogenesis of the IA has led to the discovery of several new antibodies. The role of these and other biomarkers in this patient group also needs to be explored. Some of these will be discussed below.

8.2.2.1 Anti-CarP antibodies

The identification of antibodies to citrullinated proteins has improved our understanding of the RA. The presence of ACPAs, often measured using the anti-CCP2 test, has been associated with disease progression[19 367 395] and a more severe disease course, thus assisting with RA diagnosis and prognosis.

Since its discovery, antibodies to other neo-self epitopes generated though processes of post-translational modification have been described.[463] Antibodies to carbamylated proteins have also been found in patients with IA.[464] Through the non-enzymatic process of carbamylation, cyanate reacts with lysine to produce homocitrulline.[465] Interestingly, whilst homocitrulline and citrulline are structurally very similar, not all ACPA and anti-CarP antibodies have been found to be cross-reactive.[466] Anti-CarP antibodies have been documented in both anti-CCP positive (49%-73%) and in anti-CCP negative (8%-14%) RA patients.[467]

Anti-CarP antibodies have also been detected in the sera of symptomatic blood donors prior to RA diagnosis, evidence for their presence during the preclinical

phase of the disease[468] and may therefore play an important role in identifying ACPA negative patients at risk of disease progression. Presence of this antibody has also been associated with a greater risk of joint damage.[98]

8.2.2.2 Malondialdehyde-acetaldehyde

More recently, antibodies to a new post-translationally modified protein, malondialdehyde-acetaldehyde (MAA) have been described in RA.[469] Reactive oxygen species can cause membrane lipid peroxidation, with the formation of highly reactive aldehydes that can modify peptides, in particular the amine of lysine residues, resulting in the formation of MAA products. Alterations in proteins by these MAA adducts can have deleterious effects on protein function and can alter inflammatory processes. These are produced during oxidative stress and may be associated with inflammation.[470]

These antibodies have been seen in several conditions including diabetes mellitus and coronary artery disease.[471] [472] Thiele et al also found an increased concentration of MAA-modified proteins in the synovial tissue of patients with RA compared to OA.[469] In RA synovium they co-localised with citrullinated proteins.

Levels of antibodies to MAA have been found to be significantly higher in RA patients than in controls. They have been associated with RF and ACPA positivity and some measures of disease activity. No cross-reactivity has been seen between anti-MAA antibodies and ACPAs, suggesting that these are different antibody systems. IgG anti-MAA antibodies have been detected in 88% of ACPA-negative patients. Whilst they are not specific for RA, they may be another clinically useful biomarker for the disease.

8.2.2.3 Magnetic resonance imaging

Preliminary work has been done evaluating the use of MRI as an imaging biomarker in patients with symptoms but without clinical synovitis. One of the first studies looked at synovial histology and compared dynamic contrast-enhanced knee MRI scans of 13 arthralgia patients who were positive for IgM RF and/or ACPA and six healthy controls. Synovial volume, maximal enhancement and rate of enhancement and enhancement shape curve distribution of the knees were found to be similar between the two groups.[473]

A subsequent cross-sectional study looked at MRI changes in small joints of the wrists, hands and feet. The mean combined inflammation scores (synovitis plus bone marrow oedema using the rheumatoid arthritis magnetic resonance imaging

score (RAMRIS)) of painful MCP and PIPs, wrists and MTPs were found to be higher in patients with anti-CCP positive arthralgia than those of asymptomatic controls but lower than anti-CCP positive RA patients (mean combined scores of the MCPs and PIPs: 0.1, 0.7 and 3.7 ($p<0.001$) in controls, anti-CCP positive arthralgia and anti-CCP positive RA patients respectively; mean scores of the wrists: 0.9, 2.3 and 10.3 respectively ($p<0.001$) ; and of the MTPs: 0.5, 0.9 and 3.8 respectively ($p=0.10$)). In this study, however, relatively small number of joints per region were scanned (in the anti-CCP-positive patients: MCPs (n=4), PIPs (n=3), wrist (n=3) and MTPs (n=10)), and whist the patients received contrast-enhanced scans, the controls were scanned without contrast.[396]

A longitudinal study of 28 anti-CCP positive arthralgia patients with three years of follow-up addressed the predictive value of MRI for progression to IA. MRI synovitis was found in the majority of patients (93%).[474] Surprisingly, the median (IQR) cumulative MRI score in those who progressed was significantly lower than those who did not (9.0 (6.3-13.8) vs. 20.0 (10.8-21.8), OR (95% CI) 0.87 (0.76-0.99, $p=0.03$) although at a joint level, there was a trend towards earlier progression to IA in patients with a RAMRIS synovitis score of 2. Of note, low levels of imaging synovitis was also found in the four controls, and in both patients and controls, those who were older tended to have higher total MRI scores.

In another study in patients with arthralgia and inflammatory symptoms (irrespective of autoantibody status), MRI scans were perform on the unilateral wrist, MCP joints 2-4 and MTP joints 1-5 of 93 patients.[134] MRI inflammation was defined by a combined RAMRIS score of synovitis, bone marrow oedema and tenosynovitis ≥3. In total, 44% were found to have subclinical inflammation. Patients with MRI inflammation were more frequently anti-CCP antibody positive than those without MRI inflammation (anti-CCP positivity: 22% (9/41) vs. 7.7% (4/52), $p= 0.049$). Ten out of 29 patients (34.5%) with MRI inflammation developed an IA within at least two months of follow-up.

Overall these studies, all of which have been performed using 1.5T MRI scanners, have demonstrated the presence of subclinical synovitis and tenosynovitis in patients with symptoms without clinical synovitis, particularly in those who were auto-antibody positive. Longer follow-up in large cohorts however are needed to determine the role of MRI in identify patients at risk of IA disease progression. Positive findings in patients who did not progress and in controls[475] also highlights the need for further work in determining cut-off's of MRI scores for defining synovitis. Preliminary work in this regard has recently been presented on a cohort of 193 individuals without joint symptoms who underwent contrast enhance 1.5T MRI of the dominant wrist, MCTs and MTPs. Using a RAMRIS score ≥1, MRI-

detected synovitis was seen in 48%, bone marrow oedema in 58% and tenosynovitis in 17%. In most individuals scores were low but a correlation between anatomical site and age was seen. Reference values have been calculated based on these.[476]

8.2.2.4 Positron emission tomography

Whilst ultrasound and MRI are able to detect synovial thickening, they are not always able to determine the metabolic activity of the tissue. Grey scale on ultrasound, for example, is not able to differentiate active from chronic synovitis, and enhancement on contrast MRI may be due to capillary permeability and hypervascularisation rather than synovial inflammation.

Positron emission tomography (PET) is another modality that has been investigated for imaging arthritis. The radioligand ^{18}F-fluorodeoxyglucose (^{18}F-FDG) accumulates in metabolically active cells and can visualise synovitis in established RA.[477] Macrophage-specific tracers, e.g. (R)-^{11}C-PK11195 (1-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3-isoquinoline carboxamide), which may be more specific for inflammation, has also been shown in one study, to detect subclinical synovitis in patients with RA.[478] PET tracer uptake correlated significantly with CD68 staining of macrophages from synovial biopsies of the affected joint. In another study of 22 ACPA-positive arthralgia patients, increased uptake of (R)-^{11}C-PK11195 was seen in the hand or wrist of four patients. Two RA control patients also had increased tracer uptake in clinically inflamed joints but none of the six healthy volunteers had enhanced uptake. After two years, nine developed synovitis including all four patients who had baseline PET-positive findings.[397] Further work in this area in larger cohorts will help determine whether this may be another tool to aid early IA diagnosis.

8.3 Future Directions

Whilst there has been a rapid expansion of knowledge and understanding in the field of early IA, there are still areas for further research to improve management of this disease. These will be discussed under three main headings, addressing (1) the treatment of early IA, (2) diagnosis of early IA and the potential for (2) prevention in early IA.

8.3.1 Treatment of early IA

Over the past two decades there has been a surge of new therapies for the treatment of IA including bDMARDs, bsDMARDs and small molecules (discussed in section 8.2.1.1). All have undergone clinical trials in patients with RA who have failed one or more csDMARD or TNFi. Information from open-label extension studies following these trials and from registries will be important to provide long-term efficacy and safety data on these drugs. Their efficacy in early IA, in particular DMARD-naïve IA, still need evaluation.

With the number of new therapies, in particular the bsDMARDs, it is likely that the cost of these highly effective therapies will decrease. Whilst bsDMARDs are not identical to their originator bDMARD, their efficacy and safety profiles from clinical trial data look promising. It is possible that, in time to come, bDMARD or bsDMARD induction strategies followed by treatment reduction and maintenance with fewer drugs may become more cost-effective options for treating IA.

The newer drugs also target different sites in the immune system, increasing the types of therapies available. Routes of administration also differ, with the small molecules offering the possibility of oral therapy. The increasing number of options raises the question regarding the optimal choice of DMARD for an individual patient. Ideally treatment should be tailored such that the right drug is given to the right patient at the outset. Evidence from clinical trials and experience in clinical practice highlight the fact that response to treatment in patients with IA is variable. Thus whilst csDMARD therapy, including methotrexate monotherapy, may be the treatment of choice in a sizeable proportion of patients (approximately 40%),[183 240] others may benefit from early bDMARD therapy or other combinations of DMARD therapies. Identifying patients who will respond to a particular DMARD or DMARD strategy would allow for safer, more effective treatment, and potentially the achievement of bDMARD free - or even drug-free remission.

One study addressing the immunological changes in early RA has shown that baseline T-cell analysis may predict response to methotrexate.[375] In this group of patients with DMARD naïve early RA, higher naïve T cell frequency was associated with remission. Analyses of synovial tissue samples in patients with established RA looking at gene expression, histology and cellular analysis, have also been done.[479 480] Several histological phenotypes - lymphoid, myeloid, low inflammatory and fibroblast patterns – have been described in patients with RA. Synovial histology findings, together with analyses of serum biomarkers in patients from the ADACTA trial which compared adalimumab and tocilizumab monotherapy in MTX-IR RA,[275] suggest that molecular and cellular differences may enable prediction of response to therapy. Patients with a so-called ‘myeloid phenotype’ have been found to have high levels of intracellular adhesion molecule (ICAM) 1. The presence of both

‘myeloid phenotype’ and ICAM 1have associated with a better clinical response to TNFi therapy. The lymphoid and fibroid phenotypes, however did not show correlation with response to treatment. Further research of large cohorts in early RA e.g. the Pathobiology of Early Arthritis Cohort (PEAC)[429] will be helpful in providing further insights into the early phases of the disease and possibly the identification of synovial and systemic biomarkers to predict treatment responses in different patient groups.[481]

One may also learn from other areas of medicine where one condition may have several treatment options but where individual responses differ and a need for so-called ‘personalised’ medicine is required. In the field of oncology, a new approach to clinical trial design has been suggested in which novel treatment evaluation occurs alongside the evaluation of a biomarker within a phase II/III study setting.[482] This type of study would answer three questions (1) does the new therapy provide a signal of response in different biomarker-defined populations, (2) if so, are outcomes definitively improved and (3) is this restricted to the biomarker-defined populations. Because this study design would allow the evaluation of multiple treatment and biomarkers, a large number of patients would fulfil study inclusion criteria. As an adaptive trial design, any new treatment which proved ineffective could be stopped and new biomarkers that appeared promising could be added and patients restratified. New treatments would be compared to placebo or standard care. Patients who do not wish to receive new therapies would therefore also be able to participate in the study and receive conventional therapy and be stratified according to whether they were biomarker positive or not. The FOCUS4 study of patients with metastatic colorectal cancer is the first multicenter parallel biomarker-stratified RCT which is currently underway.

Extrapolating this biomarker-stratified trial design to clinical trials in IA may be a method that would help evaluate novel therapies and biomarkers to determine optimal individual treatments. Alternatively the active arms may compare different treatment strategies (e.g. bDMARD and methotrexate vs. triple therapy with methotrexate, sulphasalazine and hydroxychloroquine) rather than a new therapy to standard therapy or placebo. An example of a biomarker stratified RCT is illustrated in figure 8.1.

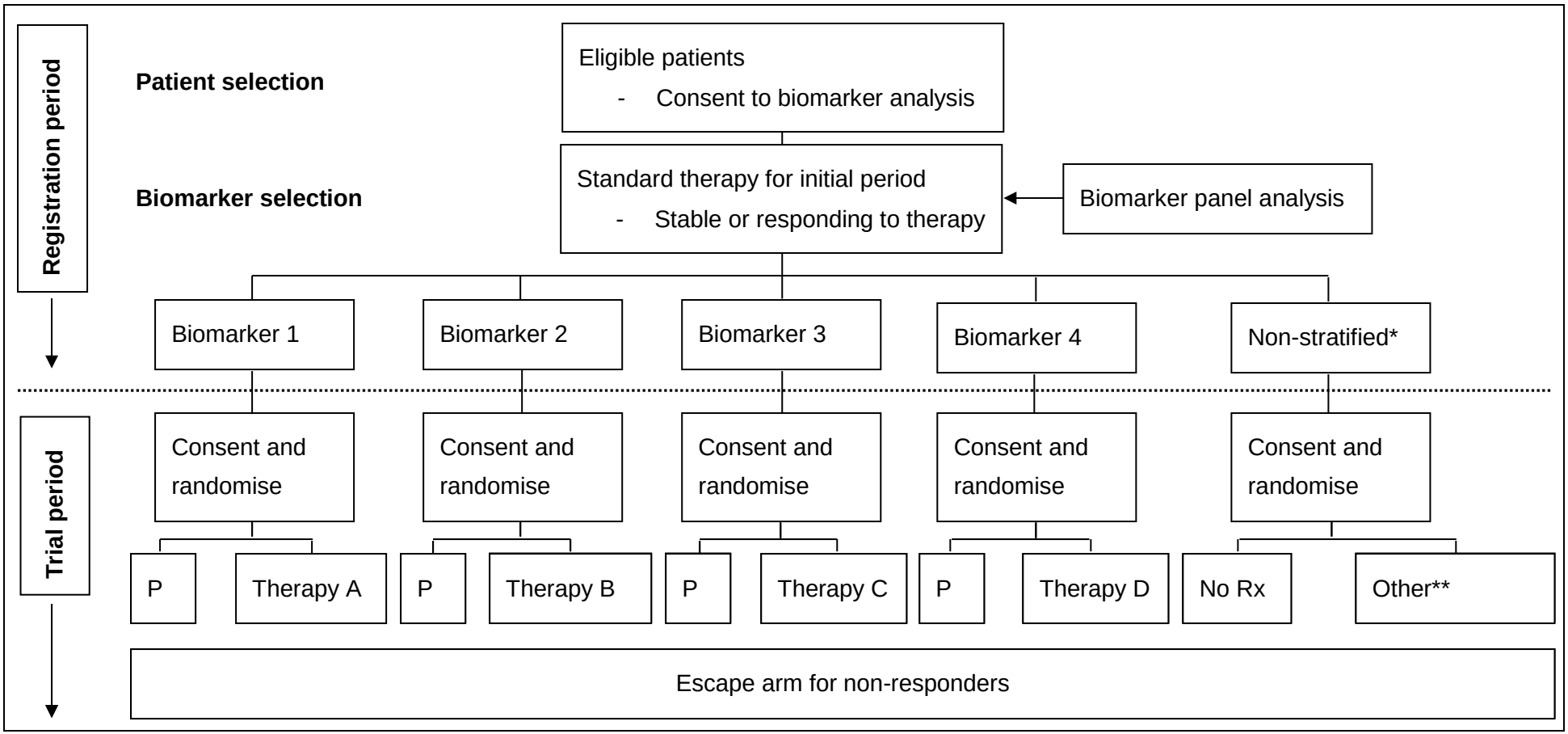


Figure 8.1 Biomarker stratified randomized controlled trial, adapted from Kaplan et al., Journal of Clinical Oncology 2013[482]

Rx, treatment, *unclassified or when stratifications refused or unavailable, **another therapy as decided by the chief investigator(s)

8.3.2 Diagnosis of early IA

The work on early diagnosis in this thesis (chapters 6 and 7) highlights the need for a cost-effective care pathway to identify patients with IA early. Delays in treatment have been associated with increasing joint damage and function.[8 78] In 2009, the U.K. National Audit Office estimated that the cost of RA to the NHS was approximately £560 million per annum and that of work-related disability and sick leave approximately £1.8 billion a year.[401] Identifying at-risk individuals during an early treatable stage has the potential to reduce the long-term costs (both health related and those due to work-related disability). It may be health-service dependent, and therefore differ in different countries. In places where primary care is the main first point of patient contact, further work in this area will need to continue fostering close collaboration with GPs and health professionals to identify patients at risk of IA in the earliest stages.[483] Expanding on the research outlined in chapters 6 and 7 and the use of additional biomarkers described in section 8.2 may further refine the means to identify and stratify patients at risk of IA in both primary and secondary care, working towards the development of a cost-effective clinical decision tool.

Thus far, most of the discussion in patients at risk has focused on patients with symptoms without clinical arthritis. Family members of patients with RA form another at-risk group. Twin studies suggest that genetic factors contribute about 60% to the development of RA,[51 53] and over 100 genetic loci have been associated with the condition.[484] The risk of RA in FDRs has been estimated be 3-9 time higher than that of the general population.[485] Whilst population screening would not be cost-effective, studying family members, a group at increased risk of developing RA, [486-488] may provide further insights into early disease diagnosis. In a large US multicentre prospective cohort study of RA FDRs, 55% (538/1058) had one or more copies of the shared epitope and 15.9% were autoantibody positive (anti-CCP 1.7%, IgM-RF 4.7%, IgG-RF 6.2% and IgA-RF 3.8%).[489] During the initial follow up period, four FDRs developed RA (6.7 cases per 1000 person-years), an incidence rate for RA similar to that described in previously evaluated FDR cohorts.[486] Work similar to that described in chapter 7 is currently underway testing FDRs for the presence of anti-CCP antibodies. A larger national study (PReVeNT RA) is also being undertaken to establish a national register of FDRs of patients with established RA.[490] The study aims to assess various factors including genetic and lifestyle and other biomarkers of the disease.

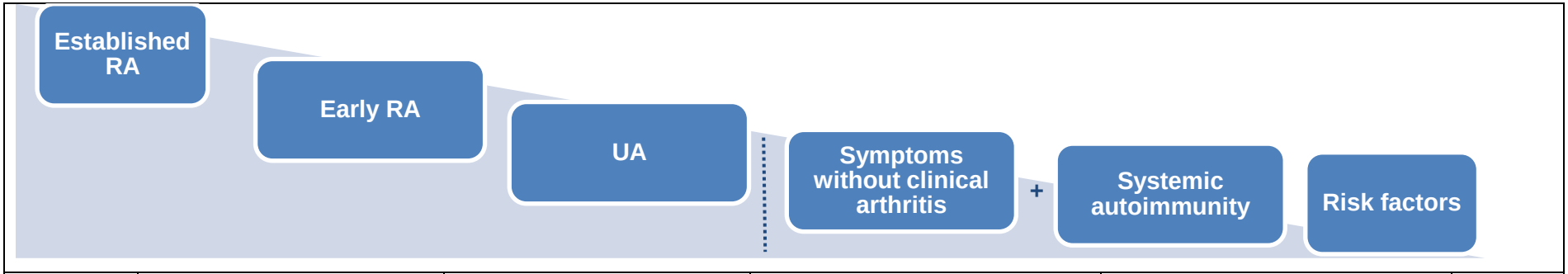
8.3.3 Prevention of early IA

Whilst clinical trials of DMARD therapy in early IA have shown good clinical and radiographic results, [236 238 288 289] a proportion of patients will continue to have ongoing disease. Earlier therapy has been associated with improved clinical outcomes, less joint damage, a higher chance of achieving remission and lower mortality rates.[8 26 78 491] Not only is earlier treatment important for clinical response, but is has been hypothesised that there may be a period very early on in which the disease process may be altered or even reversed.[148] A recent study of two early arthritis cohorts showed that the effect of time of treatment initiation on achieving drug-free free remission was non-linear with the highest change of achieving this being early in the disease course, [492] suggesting that there may be a 'window of opportunity' for IA treatment.

Immunological findings also suggest a window in the pre-clinical period during which a number of changes occur. In at-risk cohorts have demonstrated that ACPA and RF levels rise during the phase just before the development of clinical disease.[376 377] Abnormal IgG galactosylation has also been shown prior to RA disease onset, possibly suggesting a process of post-translational modification rendering these antibodies more pathogenic.[493] Rise in antibody levels has been associated with an increase in cytokine and chemokines, including some which are targeted by current RA therapies, including TNFα, IL-1 and ILF-6, just before disease onset. High antibody levels have also been associated with an epitope spreading (an increase in the number of citrullinated epitopes) [386 494] and isotype switching, resulting in greater diversity in antibody structures and function. Notably, whilst many ACPA isotypes are present before diagnosis, isotype distribution does not seem to expand significantly from progression from UA to RA[381] suggesting that most of the changes occur during the preclinical phase.[495] Avidity maturation has also been shown to occur before disease onset with stabilisation at disease onset.[496 99]

It is likely, therefore, that if a window of opportunity for intervention truly exists for modifying the disease, that it would be at a very early stage, possibly within the pre-clinical phase. Clinical trials have begun to address the potential for IA prevention. In 2010 Bos et al. treated 83 anti-CCP or IGM-RF positive patients with arthralgia with two dose of IM dexamethasone or placebo. Whilst the glucocorticoid reduced ACPA and RF levels, progression to clinical IA was not prevented.[497] The first RCT addressing the use of bDMARDs in IA prevention was initiated in 2009. In the PRAIRI study (prevention of clinically manifest rheumatoid arthritis by B cell directed therapy in the earliest phase of the disease), RF or ACPA positive patients

without clinically apparent IA and either elevated CRP or evidence of synovitis on imaging were randomised to receive a single dose of rituximab or placebo The primary outcome is the difference in number of patients who develop RA at 4 years.[498] In the U.K., the APIPPRA (Arthritis Prevention In the Pre-clinical Phase of RA with Abatacept) trial, a multicentre RCT comparing abatacept to placebo in patients, seropositive for RF and/or anti-CCP at risk of RA, has just begun.[499] The results of these trials will be of value not only in their primary outcomes but also to further the understanding of the immunological changes of the disease and help to inform future studies.



	Chapter 4	Chapter 5	Chapter 6	Chapter 7	
	Therapy in DMARD-naïve early RA - long-term outcomes of initial bDMARD therapy -DMARD de-escalation -Treatment with novel therapies - Biomarker responses to DMARD therapy	Therapy in DMARD-naïve early IA - long-term outcomes of initial bDMARD therapy -DMARD de-escalation -Treatment with novel therapies - Biomarker responses to DMARD therapy	Validation of the prediction model using clinical, serological and imaging biomarkers (with ultrasound) in anti-CCP positive patients with MSK symptoms to detect early IA Use of other biomarkers e.g. MRI Treatment in at-risk patients	Cost effective clinical decision tools for early identification of patients at risk of IA	

Figure 8.2 Addressing the inflammatory arthritis disease continuum- potential areas for research arising from this thesis

8.4 Conclusions

Work undertaken in this thesis has focused on the diagnosis and treatment of early inflammatory arthritis, particularly with the use of bDMARDs.

Early effective DMARD therapy and the use of treat-to-target strategies (with regular monitoring of disease activity and treatment escalation if disease control is not achieved) are two important principles in the management of patients with IA. In terms of therapies, bDMARDs have transformed patient outcomes in early IA. Studies identified in a SLR of bDMARDs in IA, and two RCTs - one in early RA (the IDEA study) and the other in early IA (the EMPIRE study) - have demonstrated rapid induction of clinical responses, improvement in function and prevention of joint damage with bDMARD therapy. Induction with bDMARDs has also enabled the potential for treatment de-escalation and DMARD-free remission. Whilst the effects of csDMARDs were somewhat slower, their use has been associated with similar long-term clinical outcomes, particularly within a treat-to-target approach in early disease. At present, the majority of guidelines therefore still place bDMARDs after failure of one or more csDMARD(s).

The emergence of novel therapies, however, including newer biological and biosimilar DMARDs and small molecules, continue to increase the armamentarium of therapy. It is possible that with the number of available therapies, the cost of these highly effective drugs will fall and that bDMARD induction strategies may become a possible treatment option. With the increasing number of available therapies, research addressing biomarker responses to treatment are also becoming increasingly important to enable a more tailored treatment approach for an individual patient.

The importance of early treatment has also placed greater emphasis on early diagnosis. Cost-effective clinical decision tools for early diagnosis are needed. The use of anti-CCP antibodies in patients with new MSK symptoms has enabled the identification of individuals at risk of rapid progression to IA. Together with biomarkers available in clinical practice including MSK ultrasound, patients may be further risk stratified for the development of clinical IA.

Studies addressing treatment during the very earliest phase of the disease - in at-risk individuals will improve the understanding of pathogenesis of the disease. These may have the potential to alter and in future possibly lead to the prevention of inflammatory arthritis.

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