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The Impact of Moderate Disease Activity Rheumatoid Arthritis and Evaluating the Management of This Cohort

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**THE IMPACT OF MODERATE DISEASE ACTIVITY
RHEUMATOID ARTHRITIS AND EVALUATING THE
MANAGEMENT OF THIS COHORT**

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ABSTRACT

Background

Current management strategies for rheumatoid arthritis (RA) aim to minimise joint inflammation using disease modifying anti-rheumatic drugs (DMARDs), including biologics. Remission, an achievable goal in some patients; however, many patients still fail to achieve low disease activity or remission despite receiving DMARDs. Disease activity is assessed using composite tools such as the disease activity score (DAS) which incorporate both objective and subjective measures. Some measures are influenced by additional factors like pain and may not accurately reflect the inflammatory burden. This makes monitoring disease activity in clinical practice challenging. Patients with high disease activity are likely to have their DMARD therapy increased. However, patients with moderately active disease often have insufficient treatment changes. Guidance on how to treat patients with moderate disease activity is lacking. There is also no international consensus on what is considered an adequate treatment response for these patients. The over-arching aim of this thesis was to evaluate the impact of moderately active RA using existing clinical evidence and to use this information to determine whether there was a reasonable case for treating patients with moderately active disease more intensively.

Methods

The research involved five inter-related studies.

The first study identified changing patterns of disease activity and disability over time based on an analysis of patients seen in routine treatment settings over the previous 20 years.

The second study systematically reviewed current RA guidelines and considered what advice they provided about treating moderately active RA.

The third study explored how reductions in disability and improvements in quality of life were affected by alternative assessments of reductions in disease activity in two trials of intensive treatment strategies in active RA.

The fourth study evaluated RA patients at risk of persistent active disease during conventional treatment. It sought to design a simple algorithm to identify patients with persistent active disease despite DMARDs. It also considered whether patients at higher risk of persistent disease activity would benefit from intensive treatment.

The final study used ultrasound assessments to determine if RA patients with similar clinical disease activity assessed by DAS who also had clinical features of fibromyalgia had lower levels of joint inflammation than similar patients without fibromyalgia.

Results

The five studies provided different types of evidence about the prevalence and impact of persistent moderately active RA. Taken together they make a strong case that some patients with moderately active RA merit more intensive treatment.

Firstly, sequential studies of 1324 RA patients showed that from 1996 to 2014 there were temporal increases in the use of DMARDs. During this time disease activity scores fell and remissions increased. In contrast disability scores were unchanged.

Secondly, the systematic review of 22 RA guidelines showed 20 recommended targeting remission and 16 suggested low disease activity as **an** alternative. All guidelines recommend treating active RA but **only 13 made recommendations specifically** for moderate disease.

Thirdly, in trials in both early and established RA, the magnitude of change in disability, the HAQ and EQ5D, was **greater in both settings in ‘good responders’ where the end DAS28 is in low disease activity or remission, compared with ‘moderate responders’ where some disease activity persists. Patients who achieve a good response should continue on treatment.** However, continuing such treatment strategies is more challenging when only a moderate response is achieved.

Fourthly an analysis of an observational cohort using regression modelling identified three main predictors of persisting active disease; tender joint counts, disability scores and the erythrocyte sedimentation rate. Using these predictors in a four-point prediction score predicted persisting active disease in early and established RA. Patients with high scores were more likely to have persistently active disease at 6 and 12 months.

Finally, an observational study of 47 patients with active RA on DMARDs found those **p**atients meeting criteria for fibromyalgia also had higher scores for disease activity, depression, disability and fatigue. Those meeting both the joint count and classification fibromyalgia criteria had significantly lower levels of grey scale and power Doppler synovitis on ultrasound.

Conclusion

The research presented here demonstrates that RA outcomes have improved over time. Despite significant advances in treatment paradigms and the wider availability of novel targeted drug therapies, many patients fail to achieve remission or low disease activity and continue to suffer disability. There remains a sizeable proportion of patients with moderately active disease. These patients also have poor outcomes. The disease activity and disability measures are also affected by non-inflammatory factors and how these are addressed needs to be better understood. This may be time to revisit existing strategies and the composite tools used in clinical practice if we are to continue to improve outcomes for more patients with RA.

PREFACE

The research studies in this thesis have all been published in peer-reviewed journals. Each paper forms a separate chapter of results. In addition to the results chapters the thesis includes a general introduction, an outline of the methods used in the different parts of the research and a discussion of the findings, which includes recommendations for further research.

Details of all the publications related to the thesis are given in the Appendix, including two general reviews and presentations at meetings such as the British Society for Rheumatology Annual General Meeting.

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Finally I would like to thank my sister Naieela, for her support and encouragement throughout my work on this thesis.

ABBREVIATIONS

ACR	American College Of Rheumatology
ACPA	Anti-citrullinated protein antibodies
ARA	American Rheumatism Association
ATP	Adenosine Triphosphate
bDMARD	Biologic Disease Modifying Anti-Rheumatic Drug
BeST	Behdel Strategieen Treatment Strategy
BMI	Body Mass Index
BROSG	British Rheumatoid Outcome Study Group
BSR	British Society For Rheumatology
CAMERA	Computer-Assisted Management in Early Rheumatoid Arthritis
CARDERA	Combination Anti-Rheumatic Drugs in Early Rheumatoid Arthritis
CASP-UK	Critical Appraisal Skills Programme United Kingdom
CDAI	Clinical Disease Activity Index
CI	Confidence Intervals
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CEAC	Cost-Effectiveness Acceptability Curve
COREQ	Consolidated criteria for reporting qualitative research
CRP	C-Reactive Protein
CSRI	Client Service Receipt Inventory
CTIMP	Clinical Trial of an Investigational Medicinal Product
DARE	Database of Abstracts of Reviews of Effects
DAREA	Disease Activity index for the assessment of Reactive Arthritis
DAS	Disease Activity Score
DAS28	Disease Activity Score For 28 Joints
DAS28-CRP	Disease Activity Score For 28 Joints Based On C-Reactive Protein
DAS28-ESR	Disease Activity Score for 28 Joints based on ESR
DF	Degrees of Freedom
DMARD	Disease Modifying Anti-Rheumatic Drug
DMEC	Data Monitoring and Ethics Committee
EDC	Electronic Data Capture
EQ-5D	EuroQol
ERAN	Early Rheumatoid Arthritis Network
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FM	Fibromyalgia
GA	Global Assessment
GH	Global Health
GWAS	Genome-Wide Association Study
HAQ	Health Assessment Questionnaire
HAQ DI	Health Assessment Questionnaire Disability Index
HCQ	Hydroxychloroquine
HAD	High Disease Activity
HES	Hospital Episode Statistics
HLA	Human leucocyte antigen
HTA	Health Technology Assessment Database
ICER	Incremental Cost-Effectiveness Ratio

Ig	Immunoglobulin
IL	Interleukin
IM	Intensive Management
IQR	Inter-Quartile Range
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention To Treat
JAK	Janus Kinase
LEF	Leflunomide
LDA	Low Disease Activity
LOCF	Last Observation Carried Forward
MBDA	Multi-Biomarker Disease Activity
MCID	Minimal Clinically Important Difference
MCP	Monocyte chemoattractant protein
MDAS	Moderate Disease Activity Score
MHC	Major histocompatibility complex
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Motivational Interviewing
MMP	Matrix metalloproteinase
MREC	Multicentre Research Ethics Committee
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NHS	National Health Service
NICE	National Institute for Health And Care Excellence
NIHR	National Institute For Health Research
NOAR	Norfolk Arthritis Register
NRAS	National Rheumatoid Arthritis Society
NRES	National Research Ethics Service
NS	Not Significant
NSAID	Non-Steroidal Anti-Inflammatory Drug
OPTTIRA	Optimising Treatment With Tumour Necrosis Factor Inhibitors In Rheumatoid Arthritis
PD	Power Doppler
PG	Prostaglandin
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient Reported Outcome
PtGA	Patient Global Assessment
OR	Odds Ratio
QALYS	Quality-Adjusted Life Years
RA	Rheumatoid Arthritis
RAI	Ritchie Articular Index
RAID	Rheumatoid Arthritis Impact of Disease
RAPID3	Routine Assessment of Patient Index Data 3
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REMIRA	Remissions in Rheumatoid Arthritis
RF	Rheumatoid Factor
RISE	Rheumatology Informatics System for Effectiveness
RR	Risk Ratio
SD	Standard Deviation

SDAI	Simple Disease Activity Index
SE	Shared epitope
SF-36	Short Form 36
SIGN	Scottish Intercolleagiate Guidleines Network
SJC	Swollen Joint Count
SLE	Systemic Lupus Erythematosus
SSZ	Sulfasalazine
Subcut	Subcutaneous
TACIT	Tumour Necrosis Factor Inhibitors Against Combination Intensive Therapy
TB	Tuberculosis
TICORA	Tight Control Of Rheumatoid Arthritis
TITRATE	Treatment Intensities and Targes in Rheumatoid Arthritis Therapy
TJC	Tender Joint Count
TNF/TNFi	Tumour Necrosis Factor Inhibitor
TSC	Trial Steering Committee
tsDMARD	Targeted Synthetic Disease Modifying Anit-Rheumatic Drug
UK	United Kingdom
US	Ultrasound
VAS	Visual Analogue Scale
VEDERA	Very Early versus Delayed Etanercept in Rheumatoid Arthritis

Chapter 1 INTRODUCTION

1.1 Background

Rheumatoid arthritis (RA), an immunologically driven long-term condition, is a systemic inflammatory polyarthritis. It is characterised by persistent synovitis of the joints, systemic inflammation and autoantibodies like rheumatoid factor. RA affects approximately 1% of adults (Gibofsky, 2012) and involves women more frequently than men. When inadequately treated it results in disability due to active synovitis, pain and structural joint damage.

1.2 History

The name for rheumatoid arthritis was provided by Alfred Baring Garrod in the late 1850s (Storey, 2001). Before this period there are descriptions of patients who appear to have had the disease which occur from the late 1700s onwards, with more descriptions appearing after 1800 (Short, 1974; Bywaters, 1988; Storey, Comer and Scott, 1994). There are some indications it has a more historic origin. Analysis of portraits from the Flemish school of painters have suggested some of these showed features indicative of rheumatoid arthritis. However, the interpretation of the findings in these paintings is highly subjective (Dequeker, 1977; Appelboom, 1981; Appelboom 2005). There is also some evidence from paleopathological studies that skeletal remains from several thousand years ago in North America showed features suggestive of rheumatoid arthritis (Rothschild, 1992). The interpretation of art and of ancient skeletons are both relatively subjective fields and these very historic findings remain controversial (Buchanan, 1994; Aceves-Avila, 2001). Overall there is substantial evidence that rheumatoid arthritis was definitely present in the nineteenth century and may have existed before them. Whether it is a modern disease or has a long history remains speculative.

1.3 Epidemiology

Worldwide, RA has a prevalence of 0.5-1%. Regional variations have been observed with 6.8% of Chippewa Indians affected (Harvey, 1981) and in contrast <0.5% of patients in the far east (Shichikawa, 1999), suggesting different environmental and possibly genetic factors. It affects women more frequently with a ratio of 3-4:1, suggesting a possible hormonal influence. The prevalence of RA increases with age with a peak age of incidence for women between 50 and 60 years, and >70 for men (Carbonell, 2008).

1.4 Classification and Diagnosis

The diagnosis of RA can be challenging. There is no diagnostic test and a diagnosis is made clinically taking into account the history, examination, serology and radiological findings. The first classification criteria were published in 1958 by the American Rheumatism Association (ARA) (Ropes, 1958). These were updated in 1961 (Rome criteria) when criteria based on histology were dropped due to lack of clinical use and then the New York criteria were devised in 1967 but the format was difficult to use (Sokolove, 2010; MacGregor, 1995). In 1987, the ARA, now the American College of Rheumatology (ACR), published new classification criteria, demonstrating a sensitivity of 91-94%, and a specificity of 89% (Arnett, 1988) (Table 1). Over time, it has become recognised that these criteria are useful for established disease, but lack sensitivity for early RA (Banal, 2009). Further classification criteria were published by ACR and the European League Against Rheumatism (EULAR) in 2010 (Aletaha, 2010) (Table 2), focusing on early recognition and diagnosis of RA and placing emphasis on rapid initiation of disease modifying therapy to prevent joint damage and disability. These criteria include anti-cyclic citrullinated peptide (ACPA) and acute phase reactants; unlike the 1987 criteria which required symptoms to be present for some time, allow a diagnosis to be made much earlier.

The features of joint inflammation include joint swelling, pain and stiffness characteristically most prominent in the mornings. The disease usually presents with polyarticular involvement and predominantly affects the small joints of the hands and feet. Inadequately treated, inflammation in the synovium leads to progressive damage of cartilage and bone.

Table 1. 1987 ACR Criteria for the Classification of Rheumatoid Arthritis

Criterion	Definition
1. Morning Stiffness	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. Serum 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 posteroanterior 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)

For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks.

Table 2. 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis

Target population (Who should be tested?): Patients who:	
1) have at least 1 joint with definite clinical synovitis (swelling)	
2) with the synovitis not better explained by another disease	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of $\geq 6/10$ is needed for classification of a patient as having definite RA)	
A. Joint involvement	
1 large joint	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF <i>and</i> negative ACPA	0
Low-positive RF <i>or</i> low-positive ACPA	2
High-positive RF <i>or</i> high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP <i>and</i> normal ESR	0
Abnormal CRP <i>or</i> abnormal ESR	1
D. Duration of symptoms	
<6 weeks	0
≥ 6 weeks	1

ACPA = anti-citrullinated protein antibody.

Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

“Large joints” refers to shoulders, elbows, hips, knees, and ankles.

“Small joints” refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

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.

1.5 Pathogenesis

Although not fully understood, the aetiology of RA is believed to be multi-factorial, resulting from complex interactions between genetic and environmental factors on the innate and adaptive immune systems (Stahl, 2010; Choy, 2001; Goronzy, 1993).

1.5.1 Genetic Factors

It has become well established that genetic factors play a role in RA risk and disease severity. Twins studies have shown four-fold risk concordance in monozygotic twins compared with dizygotic twins (MacGregor, 2000). Although there are likely to be shared genetic as well as environmental factors amongst twins. The calculated heritability is thought to be 60%.

The most important genetic risk for seropositive RA is found in the human leucocyte antigen (HLA) gene loci (Hill, 2003), in particular the HLA-DRB1 allele. The HLA class II major histocompatibility complex (MHC) molecule plays an important role in antigen presentation.

Several HLA DRB1 molecules share a common amino acid sequence. This sequence is termed the ‘shared epitope’(SE) (Gregerson, 1987). Its association with developing RA has been shown in several populations. This shared epitope most importantly represents a risk factor for ACPA positivity. (Huizinga, 2005; van der Helm-van Mill, 2006; Raychaudhuri, 2012).

Many other genetic risk variants have also been identified including many non-HLA risk loci such as PTPN22, TYK2, ILF3, CTLA4 (Okada, 2013). Developments in genome-wide associated studies (GWAS) has now allowed the identification of more than 100 genetic loci associated with RA (Yarwood, 2016). There is however still a considerable proportion of patients with RA where heritability is unaccounted for (Eyre, 2012).

1.5.2 *Autoantibodies*

RF was first identified in the sera of patients with RA in 1957 (Franklin, 1957) RF antibodies, mostly present as IgM but can also be detected as IgG and IgA (Kunkel, 1966, Dunne, 1979) recognise the Fc portion of Immunglobulin G (IgG). These are thought to form immune complexes which activate complement in the joint and cascade of increased permeability, vascularity and release of chemotactic factors recruiting immune cells.

RFs can also be identified in conditions other than RA such as SLE, Sjogren's syndrome chronic infections and in the healthy population, especially in older age groups (Nell, 2005), hence the presence of RF antibodies alone is insufficient for developing RA, and what role RF plays in initial events triggering RA are not clear.

ACPAs recognise the post-translational modification, citrullination. Citrullination is the conversion of arginine into citrulline by an enzyme reaction. ACPAs were first described in 1964 (Nienhuis, 1964). They can be IgM, IgG and IgA and can recognise multiple citrullinated-antigens such as fibrinogen and type II collagen. ACPA, unlike RF, are rarely found in other diseases or in healthy individuals and therefore have greater sensitivity and specificity for diagnosing RA.

A Dutch observational study found SE encoding HLA alleles to be associated only with ACPA positive RA (van der Helm-van Mil, 2006), and the same has been confirmed in other cohorts of North American and Swedish heritage (Huizinga, 2005; Klareskog, 2006). Although this relationship has not been observed in Chinese patients with RA (Xue, 2008).

Post-translational modification can also occur in other non-enzymatic forms. Anti-hinge antibodies, first described in 1963, recognise proteins that have been modified through the action of proteases (Osterland, 1963). They recognise pepsin-cleaved IgG but not the intact parent IgG. Although pepsin itself is not pro-inflammatory, other proteases including matrix metalloproteinases (MMPs) have been demonstrated in the synovium of patients with RA (Tchetverikov, 2004).

Carbamylation, where isocyanic acid is added to lysine or the N-terminus of a protein (Shi, 2014) is another form of non-enzymatic post translational modification. This can generate an anticarbamylated protein (anti-CarP) antibody response. Although sensitivity for these is low.

The detection of antibodies before disease manifestation and the strong association between antibody positivity and joint destruction suggest that antibodies have a role in the immunopathology of RA, although the precise mechanism is not clearly understood. Antibodies against proteins that have undergone citrullination have been detected in patients with RA 9 years prior to development of clinical features (Rantapaa-Dahlqvist, 1998) and therefore this ‘pre-RA phase’ is now an important area of research to identify if disease development can be modified at an earlier stage.

1.5.3 Environmental Factors

Genetic risk and the presence of antibodies themselves do not constitute RA disease, suggesting that a ‘second hit’ is required to trigger clinical disease.

1.5.3.1 Smoking

Epidemiological studies have shown smoking to be one of the most important environmental risk factors for developing RA (Heliovaara, 1993; Padyukov, 2004; Sugiyama, 2010). The risk

is increased with smoking dose exposure (Di Giuseppe, 2013; Stolt, 2003). The risk is further increased with the presence of the shared epitope and ACPA positivity (Kallberg, 2011). The risk of RA associated with smoking has also been shown to be higher men than women (Hedstrom, 2018).

Although the effects of smoking leading to an increased risk of RA are not fully understood, an increase in oxidative stress and free radicals has been demonstrated (Pryor, 1993; Kalpakoglu, 2007). Cigarettes smoking also has a systemic proinflammatory effect. Raised levels of adhesions molecules and cytokines known to be important in the pathogenesis of RA have been demonstrated in smokers (Sopori, 2002; Arnson, 2010). The risk of developing ACPAs with cigarette smoking, as discussed earlier, has also been shown.

1.5.3.2 Infections

Infections activate the immune system and have been postulated as being the ‘second hit’ in a genetically predisposed individual that triggers the development of RA. Several infections have been of interest the pathogenesis of RA including mycobacteria, Epstein-Barr virus, parvovirus B19, Porphyromonas gingivalis (Meron, 2010; Colmegna, 2009; Rosenstein, 2009).

1.5.3.3 Diet, Coffee And Alcohol

Studies showing the effects of different food types on the risk of developing RA have shown conflicting results (Salliot, 2020). The same is true for coffee and tea consumption. Moderate alcohol consumption has been shown a decreased risk of developing RA (Scott, 2013).

1.5.3.4 *Hormonal effects*

There is a greater incidence of RA in women, suggesting a possible hormonal link. There is also an increased predilection for women with other autoimmune diseases such as SLE, autoimmune thyroid disease and multiple sclerosis (Angum, 2020).

The impact of hormonal changes has been extensively studied. There is an increased risk of developing RA in the first 3 months postpartum (Silman, 1992). In clinical practice, patients with RA often have lower levels of disease activity during pregnancy and flare immediately after. Several studies have shown a reduced risk of RA with parity versus nulliparity (Guthrie, 2010; Karlson, 2004). Oral contraception use is associated with a lower risk (Spector, 1990). Studies exploring an association with breast feeding have shown conflicting results (Karlson, 2004; Brennan, 1994).

1.5.3.5 *Obesity*

Over the last two decades, there has been an increase in the prevalence of obesity worldwide and an increase in the burden of multiple diseases which is considered to be related to this. White adipose tissue has been found to release cytokines such as TNFalpha, IL6 and MCP1, and a number of other adipokines including leptin and adiponectin, thereby leading to a chronic inflammatory state (Gomez, 2011). Case-control studies have demonstrated a significant increase in the risk of developing RA (Symmons, 1997; Pederson, 2006) although other cohort studies have not shown this (Cerhan, 2002).

A cross sectional study looking at body composition in patients with RA found a greater association with obesity and CRP among women with RA, and a similar association was also seen in the non RA sample, suggesting that raised inflammatory markers in women with

obesity and RA may be driven by the presence of adipose tissue and not active joint inflammation (George, 2017). This rise in inflammatory markers still however affects disease activity monitoring indices, patient reported outcomes and response to RA therapies, further complicating the overall management of RA and an area that requires more work.

1.6 Immunopathology

The immunopathology in developing RA is driven by complex interactions in the innate and adaptive immune system. It involves macrophages, neutrophils, T cells, B cells and fibroblasts.

The synovium, usually a few cells in depth serves as a source of nutrients for cartilage. A ‘second hit’ leads to inflammation of the synovium where it undergoes hyperplasia, increased vascularity and infiltration of cells particularly CD4 +T cells, fibroblasts, dendritic cells, macrophages, and monocytes. CD4 T cells are activated by an unknown antigen and also require other co-stimulation signals. This leads to a cascade of inflammatory cytokine production including IL1, TNF alpha, IL6 and IL17, which leads to active synovitis (Goronzy, 1993, Choy, 2001). This process indirectly mediates destruction of cartilage and bone.

B cells also have several possible roles in the inflammatory pathway in RA. B cells can act as antigen presenting cells to T cells and also as a co-stimulatory signal for T cell expansion. B cells themselves are also capable of secreting proinflammatory cytokines such as TNF α and also produce rheumatoid factor and other autoantibodies, which can produce immune complexes and fix complement leading to inflammation. Better understanding of the pathophysiology of RA has lead to the development and clinical availability of newer therapies to patients with severe disease (Fiocco, 2008, Edwards, 2001).

1.7 Measuring Disease Activity

The clinical assessment of a patient, once RA diagnosis is confirmed, includes the number of swollen and tender joints, serological markers of acute phase response, patient and physician global assessment scores, review of function and review of existing damage.

1.7.1 Joint Counts

The importance of assessing the number of joints affected has been stated for several decades. Swollen joints in active RA are a result of synovial inflammation and joint effusion which is detected by assessing for fluctuance around the joint margin. Bony swelling and joint deformities can however also result in the appearance of a swollen joint and may thus affect the count in clinical practice. Particularly when a patient has had long standing RA which has resulted in articular damage, it can be difficult to differentiate swelling from active disease versus swelling from damage.

Tender joints identify pain on joint palpation. In active RA, this is due to the presence of inflammation within the joints but other factors including underlying joint damage and additional contributory causes of chronic pain can also affect this. Sufficient pressure should be exerted when assessing this, of 4kg/cm² (Ritchie, 1968), although the actual pressure exerted in clinical practice is likely to vary considerably.

Several indices measure swollen and tender joint counts. These differ in terms of which joints are assessed, the number of joints assessed and some also grade the amount of tenderness in a joint. Lansbury recommended assessing 86 joints, weighted for surface area and in domains of tenderness, pain on motion, swelling, restriction of movement and deformity (Lansbury, 1956). Since then, different numbers have been proposed from 66/68 joint assessment for tenderness, pain on motion and/ or swelling (ARA)(Mainland, 1965); 53 joint assessment for tenderness

or pain on motion (Ritchie, 1968), 44 joint assessment (Ven der Heijde, 1990; 1993); and 36 joints (Egger, 1985).

Several investigators reported supported evidence that assessing even fewer joints may be sufficient. Fuchs et al carried out longitudinal analyses showing a more simplified 28 joints count assessment provided comparable information compared with traditional more extensive joint counts. (Fuchs, 1989). Prevoo et al also compared a number of different joint counts and indices and found little difference in their validity and reliability (Prevoo, 1995). Smolen et al compared the 28 joint count with the extended ACR 66/68 joint count in a prospective study from which they concluded that the joints chosen in the 28 joint count were those most commonly involved in RA and the two indices were highly correlated (Smolen, 1995). These studies show that the 28 joint count is the preferred method as it is not only as valid and reliable as the 66/68 joint count but is also easier and quicker to perform.

1.7.2 Laboratory Measures

Blood tests are required in the diagnosis and monitoring of RA. The blood tests at diagnosis include rheumatoid factor, ACPA antibodies and acute phase proteins. Rheumatoid factor (RF) is an immunoglobulin directed against the Fc portion of IgG. It is reported as being positive in about 70-80% of RA patients although a negative result does not rule out disease (Wolfe, 1991). The detection of RF also does not in isolation suggest a diagnosis of RA and it may be seen in other rheumatological diseases including Sjogren's syndrome and non-rheumatological conditions such as hepatitis C and low titres can also be seen in the normal population. Hence RF has a low sensitivity and moderate specificity in diagnosing RA (van Zeben, 1992). The more recently discovered ACPA antibody has a sensitivity of about 80% and specificity >98% (van Venrooij, 2002). The presence of RF and ACPA antibodies also have prognostic implications with radiographic progression seen more frequently (Syversen, 2008).

Raised levels of acute phase proteins which include the Erythrocyte Sedimentation Rate (ESR) and the C-reactive protein (CRP) indicate systemic inflammation and are thus used to monitor disease activity. There is good correlation between raised ESR and CRP and swollen joint counts and no correlation with tender joint counts (Van Leeuwen, 1994). Persistent elevation of ESR and CRP are also associated with more rapid radiological progression compared to those RA patients with a normal ESR and CRP (Hassel, 1993). These acute phase proteins lack specificity however and are used in combination with other clinical assessments to determine level of disease activity.

Patients on immunosuppressive drug treatment also undergo regular blood tests to monitor for adverse effects of therapy including deranged liver biochemistry and bone marrow suppression (Ledingham J, 2017).

1.7.3 Patient and Physician Global Assessment

Patient global assessment is a patient reported outcome (PRO) using a visual analogue scale and is widely utilised in routine clinical practice, in particular as part of composite tools assessing levels of disease activity. This provides an important patient perspective of their disease. The use of this does have some challenges. Including variations in how it is phrased and how patients interpret this. The ACR/EULAR remission criteria specify the following phrase be used relating to disease activity “Considering all the ways your arthritis has affected you, how do you feel your arthritis is today?” (Felson, 2011). The scoring ranges from 0-10cm or 0-100mm, with higher scores representing more active disease or worse overall RA health.

Physician global assessment of disease activity is often not used formally in clinical practice but may inform an overall assessment of disease status by the assessor. Patient global assessment is often scored higher than physician global assessment (Kaneko, 2014).

1.8 Disease activity composite tools

1.8.1 ACR 20/50/70

The American College of Rheumatology (ACR) developed response criteria in 1993 using the extended 66/68 swollen and tender joint counts, (Felson, 1995) defining core disease activity measures for RA clinic trials evaluating differences in response to active treatment versus placebo. This defined the ACR20 as at least 20% improvement in the tender joint count, swollen joint count and at least 3 of 5 core measures: Physician global assessment (GA) and patient global assessment (PGA), patient assessment of pain, patients assessment of physical function and acute phase reactant (ESR or CRP). Trials became standardised quickly using the ACR20 as the primary outcome measure, and became the required outcome measure for FDA approval of new therapies. Over time, an improvement of $\geq 20\%$ has been considered too low and the ACR included newer more stringent improvement outcomes of 50% and 70%. The ACR measures are however dichotomous – a patient achieves it or does not, and they are time consuming to calculate, therefore their utility outside of research is limited. More recently, a hybrid measure has been proposed combining the ACR 20, 50 and 70 (Felson, 2007) to allow a continuous score and to maximise sensitivity to change.

1.8.2 DAS28

The Disease Activity Score (DAS) was developed using data from a large prospective study of patients with early RA (Van der Heijde, 1990; 1993). The original DAS included counting 44 swollen joints, the Ritchie Articular Index (RAI), ESR and a global health visual analogue scale (VAS).

It was later proposed that a 28 joint assessment be used as this provided reasonable information on disease activity status and this was validated and the DAS28 has been in use since (van

Gestel, 1998). A limitation however of the 28 joint count is that the feet are not included and for some patients the feet may be a predominant or significant problem area. The tender joint count also has greater weighting than the swollen joints count, which may therefore be affected by other factors such as chronic pain.

1.8.3 *CDAI and SDAI*

In 2000, Eberl et al developed and validated the Disease Activity index for the assessment of Reactive Arthritis (DAREA), a composite disease activity tool for monitoring reactive arthritis, that was simple to do and clinically relevant (DAREA). This is calculated as the sum of the five components: number of swollen joints (0-5), number of tender joints (0-5), patient's pain and global assessments and CRP (mg/dl). The development of the Simplified Disease Activity Index (SDAI) (Smolen, 2003) was based on this. It includes the sum of swollen joints (0-28), tender joints (0-28), patient global assessment, assessor global assessment and CRP. The SDAI has demonstrated good correlation with the DAS28. Eliminating the CRP seemed to make little difference to the relationship with disability using the Health Assessment Questionnaire (HAQ) tool, when compared with the DAS28 (Lissiane, 2006) which lead to development of the Clinical Disease Activity Index (CDAI) which requires only clinical measures immediately available. Both have been validated in many studies.

These composite measures have stood the test of time and continue to be used as major primary and secondary outcome measures in RA trials for new therapies, with DAS28 and CDAI/ SDAI also being preferred tools in clinical practice. The ACR have recommended recording 28 joint counts (England, 2019) and in the UK, the National Institute for Health and Care Excellence (NICE) guidelines recommend the use of DAS28 regularly to inform treatment decisions (NICE, 2018).

1.9 Comorbidities

Although rheumatoid arthritis predominantly affects the peripheral joints, it is a systemic inflammatory disease. As a result, patients may develop extra-articular features and are at risk of comorbidities from the chronic inflammatory state as well as damage and disability.

It is now well accepted that more effective drug therapies and treatment strategies has led to improved outcomes (Schoels, 2010). There has also been a reduction in the number of patients with RA requiring orthopaedic interventions suggesting better functional status of patients (Shourt, 2012).

Patients have increased mortality rates compared with the general population (van den Hoek et al 2017). There is significantly increased mortality attributed to cardiovascular disease with inflammatory as well as normal risk factors such as smoking, diabetes and hypertension all being contributory factors (Dougados, 2014).

Patients are more susceptible to infection. This is due to dysfunction of the immune system, as a consequence of comorbid conditions or drug therapies (corticosteroids, antiTNF), or a combination of these factors. It is recommended therefore that RA patients are vaccinated against influenza yearly and pneumococcal every 5 years (Van Assen, 2011).

Obesity creates a low grade inflammatory environment and has been linked to the development of RA , as well as poorer outcomes in RA (Schulman, 2017). It also further increases the risk of cardiovascular disease.

Patients with RA at increased risk of osteoporosis and therefore fractures. One Korean study described an 1.9 fold increased risk of osteoporosis compared with non-RA patients (Lee, 2012). The effects of pro-inflammatory cytokines on osteoclast activation, upregulated T cell activation of RANK-ligand, and the frequent concomitant prescribing of corticosteroids all lead to loss of bone mineral density (Romas, 2002; Canalis, 2003).

Malignancy in RA is related to both the disease itself as well as the immunomodulatory treatments. The overall malignancy risk is thought to be the same as the general population, but there is an increased risk of lymphoma and lung cancer in patients with RA (Smitten, 2008).

The prevalence of depression in RA is estimated at 16.8% (Matcham, 2013) but has been reported to be as high as 41.5% (Isik, 2007). RA causes chronic pain and this can have a significant impact on psychological and social health. Patients suffering with depression have poorer health, more severe pain and fatigue and lower quality of life (Katz, 1993) and is associated with lower remission rates (Kekow, 2011).

A systematic review in 2009 found that mental health outcomes were only measured in 4% of RA clinical trials (Kalyoncu, 2009). A more recent systematic review looking at the efficacy of pharmacotherapy on improving mental health outcomes showed that 51% of clinical trials in RA did not measure any mental health outcomes (Matcham, 2018) suggesting there has been a shift in designing studies although there is still a long way to go on addressing this.

1.10 Pain in RA

Pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage”(Merskey, 1994). Sensory fibres known as nociceptors are activated by tissue

damage, resulting in the sensation of pain (Dubin, 2010). Pain in RA is mediated by both inflammatory and non-inflammatory (noniceptive and neuropathic) mechanisms.

Acute inflammation, which causes redness, heat, swelling, pain and reduced function due to recruitment of inflammatory cells and the release of cytokines and pain associated neurotransmitters locally including histamine, nerve growth factors, glutamate, adenosine triphosphate (ATP), prostaglandin, nitric oxide. This results in acutely painful swollen joints clinically and is the hallmark presenting feature of RA. At the joint level, this is due to direct stimulation of primary afferent nociceptors, which include unmyelinated c-fibres and myelinated A-delta fibres, by local tissue damage (Yam, 2018). A-delta fibres are activated under thermal and mechanical stimuli and have relatively fast conduction velocity. C fibres are activated under thermal, mechanical and chemical stimuli and have a relatively slower conduction velocity. Acute inflammation, occurring for a short period of time due to local damage is usually mediated by A-delta fibres. Chronic inflammation lasting beyond the expected healing time, is mediated by C-fibres. These peripheral nerves synapse in the dorsal horn of the spinal cord where inhibitory or excitatory modulation occurs. Secondary spinal neurons then transmit information to the thalamus and the somatosensory cortex (Willis, 1997).

Neuropathic pain is caused by nerve injury in the peripheral or central nervous system. It is often characterised by heightened intensity of pain (hyperalgesia) and pain sensation is felt where it should not (allodynia).

Several cytokines are now known to be involved in the mechanism of pain in RA and this area of research has gathered momentum with particular interest in IL-1, IL-6, and TNF alpha (McInnes, 2007). IL-1B, produced by activated inflammatory cells, has also been found in

nociceptive dorsal root ganglia neurons in animal studies (Coprav, 2001) and expression is increased in peripheral and central nervous system trauma (Yan, 1992). IL-6 has been found to be an important pain mediator in bone cancer pain, neuropathic and inflammatory pain and treatment with IL-6 inhibition reduces allodynia and hyperalgesia (Zhou, 2016). TNFalpha has been identified as playing a key role in peripheral and central sensitization (Leung, 2010).

Cytokines also induce nociceptor sensitization lowering the threshold for nociceptor activation. This is peripheral sensitization. After repeated or chronic peripheral pain stimulus is felt, there is increased excitability of neurons including a lowered threshold. Here the nociceptors usually activated only by noxious stimulus can also be activated by innocuous stimulus leading to allodynia. Studies have shown changes in the central nervous system in this phase (Latremoliere, 2009). This is central sensitization. Neuroimaging such as functional MRI has been of increasing interest in identifying specific areas of the brain responsible for chronic pain. (Martucci, 2014). No single region of brain matter has been implicated in chronic pain and further research is required.

1.10.1 'Fibromyalgic RA'

Fibromyalgia is common, affecting an estimated 1.8 – 2.9 million people in the UK and coexists in 20% of patients with rheumatoid arthritis (Dougadas, 2013). It presents as widespread pain, and was historically diagnosed by identifying 11 or more of 18 tender points on clinical examination (Wolfe, 1990). It has become increasingly recognized as a disorder of polysymptomatic distress and revised criteria take additional somatic symptoms into account these features (Wolfe, 2010).

A cross sectional study by Naranjo et al analysed data from patients with RA and coexisting fibromyalgia, versus patients with RA alone. This study found that patients with coexisting

fibromyalgia received DMARD therapy more frequently and had worse HAQ disability scores, suggesting that the presence of fibromyalgia may highlight a poorer prognosis (Naranjo, 2002).

Several studies have found higher levels of pain, higher patient global scores and higher tender joint counts in patients with RA and fibromyalgia compared with patients without fibromyalgia (Leeb, 2004; Coury, 2009; Pollard, 2010; Ranzolin, 2009). This may lead to an overestimation of disease activity, as these are key components of the composite tools used. Lower remission rates are seen in patients with RA and fibromyalgia (Salaffi, 2017). What this does not account for is quantification of the proportion of the disease activity tool that is due to active inflammation versus other pain signal pathways.

1.10.2 How to Manage Residual Pain in RA

Pain in RA is associated with disability, fatigue, sleep disturbance (Lee, 2011) and chronic pain is associated with depression (Rayner, 2016). Several studies have shown that even patients with well controlled RA in remission and low disease activity may continue to experience pain (Ishida, 2018; Lee, 2011; McWilliams, 2016; Koop et al Arthritis Res Ther 2015). Often patient reported pain does not correlate with the physicians' assessment of disease activity (Khan, 2012; Studenic, 2012). Although pain in established RA may exist due to joint damage, one study by Sarzi-Puttini et al showed that radiographic damage contributes very little to pain (Sarzi-Puttini, 2002).

Given the activation of multiple pain modulating processes, patients are likely to require therapies with different modes of action. Newer Janus Kinase (JAK) inhibitor therapies have shown significantly greater reductions in pain scores compared with TNFi, whilst both treatments have shown similar changes in disease activity measures and inflammatory markers

(Taylor, 2017; Keystone, 2017). This suggests that some drugs may have a two prong effect in managing patients with RA. This may be due to pain modulating mechanisms on reducing inflammation of multiple cytokines or may be due to action on both inflammatory burden as well as central sensitization.

1.11 Disease Progression and Prognosis

It is difficult to map out patterns in terms of disease activity trajectory for patients due to additional contributory factors in each individual. However, ongoing active disease at year one following diagnosis is associated with active disease and poorer functional outcomes at years 2 and 3 (Kiely, 2011).

1.12 Disability and Quality of Life in RA

The World Health Organisation defines disability as “an umbrella term, covering impairments, activity limitations, and participation restrictions”. Early in the disease course, disability largely due is to inflammatory burden. In established disease, radiographic damage is contributory. A number of tools have been devised to measure disability both in clinical practice and in trials. The most widely applied tool to assess function is the Stanford Health Assessment Questionnaire Disability Index (HAQ DI). The HAQ was originally developed in 1978 by James F Fries and colleagues at Stanford University (Fries, 1980). The tool was developed within a Rheumatology setting and is often viewed as a disease specific disability tool in RA, and is frequently utilized in drug therapy cost effectiveness analysis. It has been used in a number of other disease areas. It has been adapted for use in up to 60 languages.

The HAQ DI includes 20 questions organized into 8 categories of dressing, rising, eating, waking, hygiene, grip, reach, chores. Each is scored on a 4 point scale of 0-3 where 0 indicates

no difficulty; 1, some difficulty; 2, much difficulty; and 3, unable to do. The final score is calculated from 0-3 where 0 is no disability and 3 is severely disabled.

Reduced function also leads to impaired ability to work thereby leading to financial implications to self and to society, both due to increased costs of health care utility and additional social support services as well as an inability to contribute to the economy. A third of patients with RA stop working within 2 years of diagnosis and 50% stop working within 10 years of diagnosis due to disability (Isaacs, 2010).

One of the challenges with measuring physical disability in RA with patient reported outcome measures is that it incorporates both reversible and irreversible components. The reversible component in RA is the effect on disability scores from joint inflammation indicating active disease. The irreversible components include irreversible joint damage accrued. Disability also accrues with disease duration. This has been demonstrated in a number of studies. Aletaha et al studied HAQ score in 295 patients achieving SDAI remission (Aletaha, 2006), with the aim to identify the irreversible component of disability. The study found that HAQ progressed with disease duration from 0.19 (< 2 years) to 0.36 (2->5 years) to 0.38 (5-<10 years) to 0.55($\geq$ 10 years). Welsing et al also found a progression of HAQ with disease duration (Welsing, 2001) where HAQ increased by a mean of 0.64 after 9 years.

Relationship between radiographic damage and disability has also been explored by several groups, as has the impact of disease duration. However others have shown that HAQ is not strongly affected by disease duration, but more so by current disease state, pain and psychological factors (Wolfe, 2000).

The HAQ score does have several limitations. It does not take into account psychological and cognitive impairment. It is also patient reported and may therefore be affected by other factors. But it may also be argued that this makes it relevant to patients and is therefore of equal importance to clinician observed objective measures.

Quality of life is distinctly different from monodimensional measures of function, pain severity, fatigue and psychological health. It is patient reported, and likely takes into account many aspects of disease impact on the patient. A number of tools exist to measure quality of life. These include SF-36 and EQ5D. Another tool is the RAID questionnaire (Rheumatoid Arthritis Impact of Disease) which takes into account pain, functional capacity, fatigue, physical and emotional wellbeing, quality of sleep and coping.

1.13 Drug Treatment

Several classes of drugs are now available in the armament for treatment of RA. These can be classified into: analgesics, corticosteroids and disease modifying anti-rheumatic drugs (DMARDs.) These span synthetic DMARDs (sDMARDs), including conventional synthetic DMARDs (csDMARDs) like methotrexate and targeted synthetic DMARDs (tsDMARDs) like tofacitinib; biological DMARDs (bDMARDs), including biological originator DMARDs (boDMARDs) and biosimilar DMARDs (bsDMARDs).

1.13.1 Historical Therapies

The historically used treatment approach for RA consisted of initial ‘first line treatment’ with symptomatic drugs such as analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), then only adding DMARDs later is no longer advocated. This approach was based on the assumption that there was a gradual decline in quality of life and good health over time in RA;

however, it has clearly been shown that there is a rapid decline in health, joint integrity and quality of life soon after the onset of RA (Bukhari, 2003; Goekoop-Ruiterman, 2005; Brinkmann, 2019). Therefore early and intensive treatment with combination DMARDs has now been recommended for many years. (NICE, 2009).

Analgesics are given as adjuncts to reduce the symptoms of pain associated with RA. There are several types of analgesics available including paracetamol, codeine, tramadol and opiate analgesics, and these can be taken in combination with DMARDs.

1.13.2 Corticosteroids

Steroids have a powerful anti-inflammatory effect and are one of the quickest acting drugs used in RA. They are often used early in disease in combination with DMARDs which have a slower onset of action and are frequently prescribed to rapidly suppress inflammation if disease flares. Unfortunately their side effect profile limits their use including cataracts, adrenal suppression, hypertension, fluid retention, musculoskeletal (osteoporosis, myopathy and avascular necrosis) and metabolic (diabetes, hyperlipidaemia and obesity) effects.

1.13.3 csDMARDs

csDMARDs are a group of drugs that slow RA disease progression. These drugs are distinct from anti-inflammatories which simply reduce inflammation without having an effect on the course of disease. csDMARDs are now prescribed earlier in the disease course and there is good evidence that combinations of csDMARDs are better than monotherapy csDMARDs (Verhoeven, 1998). Methotrexate has become the most widely used csDMARD in treating RA. It can be prescribed as monotherapy or in a number of combinations. Frequently used so called ‘triple therapy’ includes methotrexate, sulfasalazine and hydroxychloroquine (O’Dell, 1996).

1.13.4 *bDMARDs*

When csDMARDs are insufficient or cause unacceptable adverse reactions or intolerances for patients who have ongoing active disease, biological therapies are needed. Biological therapies reduce joint inflammation and radiographic joint damage by inhibiting specific cytokines or their receptors.

The first biologic drugs to become available were anti-tumour necrosis factor alpha (TNF- α) drugs, which are usually considered first line biological therapy. Shortly after anti-TNF therapy became available, the drug Anakinra which targets interleukin-1 (IL- 1) was developed. Anakinra has however proven to be less effective and is not recommended in the treatment of RA. Anti-TNF therapy has an increased risk of infection, reactivation of tuberculosis (TB) is possible, and can worsen heart failure.

The current recommendations for the use of biologics by the National Institute for Health and Clinical Excellence (NICE), state that TNF- α inhibitors may be prescribed when a patient has active disease as defined by a DAS28 score of 5.1 or above on at least two occasions one month apart; despite at least two DMARDs, one of which must be methotrexate (NICE, 2013).

A number of newer biologic therapies have come onto the market and are now approved for use in RA after failure of anti-TNF therapy include Rituximab which is a monoclonal antibody directed against CD20 positive B cells, Abatacept which is a co-stimulation blocker that inhibits full activation of T-cells; and Tocilizumab, a monoclonal antibody directed against IL-6. All have shown efficacy in treating RA and are recommended by NICE. Rituximab is recommended as the second line biologic following failure of anti-TNF therapy and abatacept and tocilizumab are recommended for patients who have failed Rituximab (NICE, 2013).

1.13.5 *tsDMARDs*

More recently, the novel JAK inhibitors have been licensed for RA. The JAK inhibitors are involved in intracellular signalling for several important cytokines with the aim of targeting more than one cytokine driving the inflammation. They have the advantage of being an oral preparation, but are also associated with increased herpes zoster infections (Winthrop, 2014) and require ongoing data to understand the impact on cardiovascular disease risk (Yates, 2020).

In the UK, until recently, these higher cost drugs were reserved for patients with highly active disease (DAS28 >5.1), versus other European countries where these can be given to patients with active disease, defined as a DAS28 score >3.2 (moderately active and highly active) or poor prognostic factors. Although it should be noted there is a difference between recommendations from NICE, where cost implications are considered, and those from the BSR.

1.14 Treat To Target Management

Several trials of treatment strategies in RA have established the benefits of using targeted treatments based on aiming to improve composite scores of disease activity. The first of these was the Tight Control of Rheumatoid Arthritis (TICORA) trial (Grigor, 2004) in which patients were randomised to intensive treatment (monthly assessment, combination therapy and escalation according to disease activity); or routine care involving 3 monthly review. After 18 months all assessments of disease activity were significantly better in the intensive active treatment group

Several other strategy trials produced similar results. Most notable were two trials from Holland; the Behandel Strategieën (BeST) or treatment strategy Study (Goekoop-Ruiterman, 2007) and the Computer-Assisted Management in Early Rheumatoid Arthritis (CAMERA) study (Verstappen, 2007).

The “treat to target” initiative in inflammatory arthritis built on these findings in RA. This approach is considered likely to achieve the best outcomes. The primary goal is to fully suppress joint inflammation, which will prevent structural joint damage, reduce long term disability and improve quality of life. “Treat to target” involves using a composite measure to guide treatment. The aim is to achieve remission or low disease activity. An international task force formulated a consensus and published recommendations which could form the basis for using “treatment to target” in routine practice (Smolen, 2010).

Many doubts and uncertainties surround the use of “treat to target”. One challenge is agreeing the best target. There are many different criteria for remission. Although complete remission leads to better overall outcomes for patients, it is only achieved by a small minority of patients (Ajeganova, 2017). Less complete forms of remission are easier to achieve but less beneficial for patients. A second challenge is that there is uncertainty about the optimal treatments to achieve remission. There is a school of thought that the treatment strategy is more important than the agent. In particular there is doubt about the best way to use high-cost biological treatments. Finally in many patients it is not possible to achieve remission or low disease activity. When patients have already developed joint damage, consequent pain and reduced function are unlikely to respond to escalation of DMARDs and immunosuppression. When patients develop significant treatment-related adverse events treatment escalation may be impractical. Co-existing co-morbidities and clinician and patient choice may also limit the use of “treat to target”. As a consequence the best way forward is to develop an individually tailored management plan which is supported by the clinician, the managing team and the patient to achieve the best possible outcome for each individual.

1.15 Moderate Disease Activity

In recent years 'Treat to Target' has provided a widely used management framework for the drug therapy of RA patients. It emphasises that the treatment goal should be achieving remission. There is considerable evidence that this approach is effective in early RA patients, particularly those patients who have high disease activity levels (Schoels et al, 2010; Stoffer et al, 2016; Wailoo et al, 2017; Hughes et al, 2018). A significant proportion of patients seen in clinic do not have a sufficiently high enough DAS score of >5.1 to have their drug therapy escalated to advanced therapies. Additionally, many patients with a high DAS score fit the response criteria of a reduction in DAS of >1.2 to continue advanced therapy, yet continue to have moderately active disease, suggesting inadequate control of inflammation. Thus continued risk of damage and comorbidity. There is uncertainty about what management approaches are appropriate in patients who are receiving csDMARDs who continue to have moderately active established RA. These patients have DAS scores between 3.2 and 5.1.

1.16 Research Aims And Objectives

A large proportion of patients seen in clinic have insufficient control of disease activity and remain have a DAS28 3.2 – 5.1. There needs to be a better understanding of the consequences of persistent moderately active disease and how these patients should be optimally treated to improve outcomes. A proportion of patients may benefit from increased immunosuppression, but other interventions may be required and better defined. The over-arching aim of this thesis was to evaluate the impact of moderately active RA using existing clinical evidence and to use this information to determine whether there was a reasonable case for treating patients with moderately active disease more intensively. There were five individual objectives linked to this overall aim, and these are outlined below.

The first objective involved identifying changing patterns of DAS28 and HAQ scores over time based on an analysis of patients seen in routine treatment settings to determine whether these had changed over the last 20 years. In particular to describe the change in proportions of patients with moderately active disease over the period where RA treatment paradigms have shifted to include tighter targeted disease control, combination therapy and the availability of biologics. The evaluations were undertaken in two adjacent English rheumatology units over two decades. They examined the changes in treatment, disease activity and disability levels over time in sequential cross-sectional studies.

The second objective involved systematically reviewing current RA guidelines and considering what specific advice if any they provided about treating moderately active RA. It involved evaluating the range and nature of guidelines currently available, assessing variations in their recommendations about RA management, and highlighting divergences in their perspectives.

The third objective involved exploring how reductions in disability and improvements in quality of life scores were affected by alternative assessments of reductions in DAS28 scores in two trials of intensive treatment strategies in active RA. This was to explore if a treatment response to therapy, with an end DAS28 remaining in the moderately active disease group was a sufficiently good enough response to reduce disability and improve quality of life.

The fourth objective evaluated assessing RA patients at risk of persistent active disease with conventional treatment to explore if patients can be risk stratified to identify those that would benefit from additional intervention. The research sought to design an algorithm to identify patients with persistent active disease ($\text{DAS28} \geq 3.2$) at 6 and 12 months despite DMARDs. It

also considered if patients at higher risk of persistent disease activity would benefit from intensive treatment.

The final objective was undertaking a pilot study to determine if RA patients with similar clinical disease activity assessed by DAS28 who also had clinical features of fibromyalgia (FM), as defined by the tender joint criteria, have lower levels of joint inflammation compared with RA patients without FM as determined by ultrasound (US). This was to explore if patients that may benefit from additional intervention other than increased immunosuppression can be identified in clinic.

Chapter 2 METHODS

2.1 Background

The research in this thesis included observational studies, secondary analyses of previously published trials and a systematic review. It has all been published a peer-reviewed papers and the methods used is explained in detail in each of these papers. This chapter provided a synopsis of the methods which were used.

2.2 Temporal Changes Study

Cross-sectional observational data were collected from routine clinical practice outpatient from two rheumatology centres: King's College Hospital London and University Hospital Lewisham. Data were collected from visits over four time periods: 1996-97; 2001-03; 2009-10; 2012-13. All these patients were diagnosed with RA by the 1987 or 2010 ACR classification criteria. The patients were consecutive outpatient attenders during these time periods. The first three time periods collected data using paper records; the final time period used a custom-built database linked to the electronic patient record system.

Data collated included demographic details including age, gender and disease duration. Disease specific data including DAS28 with the individual components and RA immunosuppressive therapy taken at the time of data collection were also collated. Disability outcomes using the HAQ, pain score using 0-100mm VAS and fatigue scores using 0-100mm VAS were also collected for the first, second and fourth cohorts.

Statistical analysis used STATA software (version 13) to describe mean and standard deviation for normally distributed data, or median and inter-quartile range (IQR) for non-normally distributed data. Number of patients and percentages were used to describe the proportion of patients in each DAS28 group. Ethical approval was obtained prior to conducting the study through the Kings College Hospital Local Ethics Committee.

2.3 Systematic Review of RA Guidelines

A systematic literature search was carried out of Embase and Medline databases using the terms ‘clinical practice guidelines’ and ‘rheumatoid arthritis’. A further search was carried out of any guidance published by national bodies in the UK including NICE and the Scottish Intercollegiate Guidelines Network (SIGN). A secondary reference search was also done from guidelines identified.

Inclusion criteria included: publications identified by the authors as guidelines, guidance on the general management of RA, guidance including a range of different pharmacological therapies. Only publications in the English language were included. Guidance on specific disease area management of RA were excluded, as were guidelines of a single drug.

Two independent researchers assessed publication for eligibility and extracted information required for comparative review. This included year of publication, how the guidance was developed, quality method used, systematic review of evidence, patient population considered, area of management included, composite disease activity indices, prognostic assessments, treatment targets, the range of treatments considered. Any discrepancy between the two researchers resulted in joint assessment and decision making about guidance.

Due to the considerable heterogeneity between published guidelines, a narrative review of the recommendations was carried out.

2.4 Optimal Responses In Disease Activity

Data from two published trials was used to evaluate this question. The first trial, Combination Anti-Rheumatic Drugs in Early Rheumatoid Arthritis (CARDERA) evaluated synthetic DMARDs and steroids in early untreated active RA. The second trial, Tumour necrosis factor

Inhibitors Against Combination Intensive Therapy (TACIT), evaluated intensive treatment strategies in established active RA. The methodology for the trials has been published previously. The patients met existing NICE criteria for biologic treatments. They received either a combination of conventional synthetic DMARDs or biologic DMARDs (tumour necrosis factor inhibitors in this study).

At the end of each trial (24 months for CARDERA and 12 months for TACIT), patients who had completed the trial and had experienced changes in DAS28 scores >1.2 were identified. These patients were considered irrespective of which treatment they received. These patients were then divided into two groups: (a) good EULAR responders (final DAS28 ≤ 3.2); (b) moderate EULAR responders (final DAS28 >3.2). Comparisons in changes in HAQ and EQ-5D (EuroQol) scores and final HAQ and EuroQol between the two groups scores were also carried out.

Statistical analysis was carried out using IBM SPSS statistical software (version 22). DAS28 scores, HAQ and EQ5D scores were recorded at baseline and trial endpoint. Descriptive statistics was used to show mean and standard error values. Comparative analysis of HAQ and EQ5D scores between good and moderate responders was then carried out for each trial using independent sample t-tests.

2.5 Predicting Responses

Data was analysed from the Early Rheumatoid Arthritis Network (ERAN) observational cohort and from two clinical trials, CARDERA and TACIT to explore if there are predictors to identify patients who suffer with persistently active disease despite DMARD therapy, and if these patients benefit from intensive therapy.

The observational data were collected from 2002 – 2007 in patients with newly diagnosed RA from the ERAN observational cohort. Patients were recruited into the inception cohort from 19 UK centres, and this reflects routine care. Details of this cohort have been previously published.

The trial data used were from the CARDERA trial and the TACIT trial. These trials have been previously reported. Local ethics approval was obtained for the observational cohort and for the clinical trials. All patients provided written, informed consent.

Age, sex and disease duration, DAS28 and its components, and information on drug therapy were collected. The ERAN cohort in addition also collected data on rheumatoid factor and smoking status. Persistently active disease was defined as patients with a DAS28 score of >3.2 at 6 and 12 month visits. Statistical analysis was carried out using SPSS statistical software (version 17). Predictors of persistent disease activity were assessed using logistic multiple regression and reported as odds ratios (OR) with 95% confidence intervals (CI).

2.6 The Role Of Ultrasound In Determining Disease Activity

RA patients with ongoing active disease defined by DAS28 >2.6 were recruited from clinical attendances. A previously reported study found a joint count of 28 joints where the number of tender joints minus the number of swollen joints was at least 7, had a high sensitivity and specificity for indentifying patients with fibromyalgia as per the 1990 ACR criteria. Patients identified in clinic with a DAS28 >2.6 were divided into two groups: meeting or not meeting the tender joint minus swollen joint criteria.

Local ethics committee approval was obtained prior to commencing the study. All patients provided written informed consent. Each patient underwent clinical examination for the components of the DAS28, and fibromyalgic tender points. Patients completed a series of

questionnaires. A second assessor, who was blinded to the clinical joint assessment, carried out musculoskeletal ultrasound of the hands and wrists.

Statistical analysis was carried out using SPSS (version 22) statistical software. Descriptive statistics were reported for patient characteristics. Grey scale and power doppler scores between the two groups were compared using Mann Whitney U test.

Chapter 3 CHANGES IN RA OUTCOMES OVER TIME

**This chapter is presented as a published paper and is a copy of the following
journal publication:**

Mian AN, Ibrahim F, Scott IC, Bahadur S, Filkova M, Pollard L, Steer S, Kingsley GH, Scott DL, Galloway J. Changing Clinical Patterns in RA management over two decades: sequential observational studies. BMC Musculoskeletal Disord 2016; 17(1):44.

RESEARCH ARTICLE

Open Access



Changing clinical patterns in rheumatoid arthritis management over two decades: sequential observational studies

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Abstract

Background: Rheumatoid arthritis (RA) treatment paradigms have shifted over the last two decades. There has been increasing emphasis on combination disease modifying anti-rheumatic drug (DMARD) therapy, newer biologic therapies have become available and there is a greater focus on achieving remission. We have evaluated the impact of treatment changes on disease activity scores for 28 joints (DAS28) and disability measured by the health assessment questionnaire scores (HAQ).

Methods: Four cross-sectional surveys between 1996 and 2014 in two adjacent secondary care rheumatology departments in London evaluated changes in drug therapy, DAS28 and its component parts and HAQ scores (in three surveys). Descriptive statistics used means and standard deviations (SD) or medians and interquartile ranges (IQR) to summarise changes. Spearman's correlations assessed relationships between assessments.

Results: 1324 patients were studied. Gender ratios, age and mean disease duration were similar across all cohorts. There were temporal increases in the use of any DMARDs (rising from 61 % to 87 % of patients from 1996-2014), combination DMARDs (1 % to 41 %) and biologic (0 to 32 %). Mean DAS28 fell (5.2 to 3.7), active disease (DAS28 > 5.1) declined (50 % to 18 %) and DAS28 remission (DAS28 < 2.6) increased (8 % to 28 %). In contrast HAQ scores were unchanged (1.30 to 1.32) and correlations between DAS28 and HAQ weakened (Spearman's rho fell from 0.56 to 0.44).

Conclusions: Treatment intensity has increased over time, disease activity has fallen and there are more remissions. However, these improvements in controlling synovitis have not resulted in comparable reductions in disability measured by HAQ. As a consequence the relationship between DAS28 and HAQ has become weaker over time. Although the reasons for this divergence between disease activity and disability are uncertain, focussing treatment entirely in suppressing synovitis may be insufficient.

Keywords: Rheumatoid arthritis, Disease activity, Disability, Epidemiology, Clinical outcomes

Background

Rheumatoid arthritis (RA) management paradigms have changed over the last two decades. There is now greater emphasis on intensive suppressive treatment with greater use of disease modifying anti-rheumatic drugs

(DMARDs), including combinations of DMARDs, and the use of biologic treatments when standard DMARDs are insufficient [1]. The impact of treatment can be assessed using standard methods such as the Disease Activity Score for 28 joints (DAS28) [2] and the Health Assessment Questionnaire Disability Index (HAQ) [3]. In recent years 'Treat to Target' has provided a management framework. It emphasises that the treatment goal should be achieving remission [4]. Several groups have shown that the frequency of severe disease is declining and there are growing numbers of patients with

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moderate or low DAS28 scores [5–8]. Despite these findings, studies from the Netherlands have suggested that although disease activity levels have improved over time, levels of disability may actually be increasing [9]. We consider further information is needed about the changing patterns of DAS28 and HAQ scores in RA patients seen in routine treatment settings over the last 20 years. We have undertaken such an evaluation in two adjacent English rheumatology units over two decades examining the changes in treatment, disease activity and disability levels over time in sequential cross-sectional studies.

Methods

Setting

Cross-sectional data were collected at four time points from secondary care rheumatology departments at King's College Hospital and University Hospital Lewisham; these are two adjacent centres in South London. The data were collected prospectively by different trained clinicians using standardised clinical assessments in: (i) 1996-97; (ii) 2001-3; (iii) 2009-10; (iv) 2013-14. The surveys assessed consecutive consenting outpatients attending specialist rheumatology clinics within routine clinical care settings.

Patients

The hospitals serve ethnically diverse inner city populations with broad ranges of social and financial status. Patients included had a consultant diagnosis of RA by the 1987 criteria of the American College of Rheumatology. Disease duration was calculated from date of rheumatologist diagnosis.

Data for the first three cohorts were collected as surveys undertaken as part of routine care evaluations; these have been previously published [10–12]. The patients were consecutive outpatient attenders; there were no exclusion criteria. Only patients in whom full data for DAS28 components had been collected were studied; this meant excluding 3 % of the previously reported patients. Data for the fourth cohort were extracted from routinely captured clinic attendance electronic patient records; full data was available during the survey period in 520 RA patients from 1200 attenders with inflammatory arthritis.

Assessments

The data collected comprised demographic details (age, sex and disease duration), information about disease activity including the disease activity score for 28 joints (DAS28) and its component parts with ESR, and the use of synthetic DMARDs, biologic DMARDs and oral steroids. We also collected information about disability scores using the Health Assessment Questionnaire

(HAQ), pain (100 mm visual analogue scores) and fatigue (100 mm visual analogue scores) completed by the patients were collected in the first, second and fourth cohorts (for pain) and second and fourth cohort (for fatigue). HAQ scores, pain VAS and fatigue measures were not collected in the third cohort. Patients were assessed prospectively by medical and nursing staff who had been trained in RA assessments.

Analysis

Statistical analysis used STATA statistical software (version 13). Age, disease duration, disease activity assessments and other outcomes were described using means and standard deviations (SD) or medians and interquartile ranges (IQR) for non-normal data. DAS28 category proportions were given as raw figures and percentages. DAS28 remission was defined as a score of <2.6, low disease activity 2.6 – 3.2, moderate disease activity 3.2 – 5.1, severe disease >5.1. Spearman's correlations were used to assess relationship between the DAS28 and HAQ.

Local approvals

Collecting data for the first cohort received approval from King's College Hospital Local Research Ethics Committee; patients provided written informed consent. The third and fourth cohorts utilised data collected through departmental audits. Approval for these collections was obtained from the Trust audit division. All data was anonymised before analysis. No additional data were collected from patients for the purpose of the current study. As the analysis was the secondary use of existing anonymised data our local research and development office approved its use in line with current national research governance arrangements.

Results

The four cohorts of RA patients seen between 1996 and 2014 ranged in size from 189 to 520 patients. Overall 1324 patients were studied. The groups had similar demographic features (Table 1): 76-80 % were female; their mean ages were 58-60 years; and their mean disease durations were 9.1-10 years.

Over time more patients received suppressive therapy: in 1996-97 only 61 % of patients received one or more DMARDs; by 2013-14 87 % of patients were receiving them (Table 1). The intensity of suppressive treatment increased over time, with rising numbers of patients receiving combination DMARDs and biologics. Combination DMARD use was 1 % in 1996-97 and increased to 41 % by 2013-14. No biologics were available in 1996-97; their use increased from 4 % in 2001-03, 17 % in 2009-10 and further still to 32 % in 2013-14. In contrast, systemic steroid use was unchanged.

Table 1 Characteristics of patient cohorts

Characteristic	1996-97 <i>n</i> = 189	2001-03 <i>n</i> = 310	2009-10 <i>n</i> = 304	2012-14 <i>n</i> = 520*
Female gender, <i>n</i> (%)	140 (74 %)	237 (76 %)	244 (80 %)	413 (79 %)
Age, mean (SD)	59 (14)	60 (13)	59 (15)	58 (15)
Disease duration in years, median (IQR)	8 (13)	9 (10)	10 (9)	10 (9)
Any DMARD, <i>n</i> (%)	115 (61 %)	199 (64 %)	242 (80 %)	420 (87 %)
Combination DMARDs, <i>n</i> (%)	1 (1 %)	31 (10 %)	65 (21 %)	199 (41 %)
Biologic users, <i>n</i> (%)	0	11 (4 %)	53 (17 %)	155 (32 %)
Oral steroids, <i>n</i> (%)	23 (12 %)	70 (23 %)	30 (10 %)	56 (12 %)
DAS, mean (SD)	5.2 (1.6)	4.7 (1.6)	3.8 (1.5)	3.7 (1.6)
Tender joint count, mean (SD)	10.1 (9.2)	7.5 (7.3)	4.1 (5.6)	4.2 (6.2)
Swollen joint count, mean (SD)	7.1 (5.5)	4.8 (4.1)	2.9 (4.2)	1.5 (2.7)
Patient global, mean (SD)	50 (25)	50 (29)	40 (25)	35 (28)
ESR, mean (SD)	35 (26)	33 (27)	26 (21)	19 (21)
HAQ score, median (IQR)	1.30 (1.52)	1.52 (0.79)	Not available	1.32 (0.84)
Pain, Mean (SD)	50 (24)	48 (28)	Not available	44 (28)
Fatigue, Mean (SD)	Not available	50 (28)	Not available	51 (26)

Legend: SD standard deviation, IQR interquartile range, **n* = 484 for DMARD data

Disease activity fell over time, with the proportion of patients in remission increasing from 8 % in the earliest cohort to 28 % in the most recent (Table 2). In parallel, the proportion with severe disease fell from 50 % in the earliest cohort to 18 % in the most recent, whilst the proportion with moderate disease remained constant. There are differences in the relative contribution of the individual components of DAS28 across disease activity strata (Table 2). Most noticeable are the reductions in swollen joint counts in all strata compared with the increases in patient global scores in most strata. The mean pain VAS improved with each consecutive cohort from 50 in 1996-97, 48 in 2001-03, and 44 in 2013-2014 but mean fatigue scores did not fall (see table).

In contrast to measures of disease activity, there was no evidence of a fall in disability levels over time. Mean HAQ scores were 1.30 in 1996-97 and 1.32 in 2013-14, with a slightly higher mean HAQ of 1.52 in 2001-03. Comparing disability change over time across the disease activity groups, mean HAQ scores in patients in remission and low disease activity states were higher in 2013-14 compared to 1996-97 (Table 2). Associated with this finding the overall correlation between disease activity and disability became weaker over time; in 1996-97 Spearman's rho was 0.56, in 2001-03 it was 0.55 and in 2013-14 it was 0.44.

Discussion

Our consecutive cross-sectional surveys across two collaborating adjacent specialist units in London between 1996 and 2014 showed the changing pattern of RA treatment and disease severity. The key changes were: increases in

the use of DMARDs, combination DMARDs and biologics; falls in mean DAS28; and increases in DAS28 remissions. However, HAQ scores were unchanged and correlations between DAS28 and HAQ weakened. The age, gender and disease duration of the four cohorts were similar and consequently changes in DAS28 could not be explained by differences in demographic factors.

There are several possible explanations for the decline in disease severity: RA may be becoming a milder disease; milder cases of RA may be attending outpatient clinics; or RA treatments are becoming more effective. We noted a minor non-significant difference in disease durations in the last two cohorts compared with earlier cohorts (increasing from 8 years to 10 years). We cannot be certain that this did not have some impact on disability levels but it is unlikely to have been substantial.

Our findings suggest a trend towards milder RA. This has been highlighted in studies of inception cohorts of RA patients [13–16]. Similar reduction in disease activity levels have also been described in established RA, and these reductions preceded the introduction of biologic agents [6]. There are several possible explanations for these observed declines in disease severity. Firstly RA may be becoming a milder disease. Secondly, milder cases of RA may be attending outpatient clinics. Finally RA treatments may be becoming more effective. A North American analysis of patients seen over three consecutive decades from 1970 suggested the reduction in disease severity could be explained entirely by adjusting for DMARD exposure, indicating increased treatment accounts for the improvement [8]. Irrespective of why

Table 2 Comparison of DAS28 components and disability status across disease activity strata

DAS28 Group	<2.6	2.6 – 3.2	3.2 – 5.1	>5.1
<i>1996-97 Cohort</i>				
Number of patients, (%)	15 (8 %)	8 (4 %)	72 (38 %)	94 (50 %)
Tender joint count, mean (SD)	0.7 (1.4)	0.8 (1.4)	4.9 (4.8)	16.4 (8.5)
Swollen joint count, mean (SD)	0.3 (0.9)	4.0 (3.6)	4.5 (3.3)	10.5 (5.1)
Patient global, mean (SD)	14 (7)	26 (16)	42 (20)	64 (21)
ESR, mean (SD)	12 (7)	15 (8)	30 (27)	44 (25)
HAQ, mean (SD)	0.3 (0.4)	0.8 (0.8)	1.0 (0.8)	1.7 (0.8)
<i>2001-03 Cohort</i>				
Number of patients, (%)	29 (9 %)	32 (10 %)	115 (37 %)	135 (43 %)
Tender joint count, mean (SD)	0.4 (0.7)	1.3 (1.6)	4.6 (4.2)	12.9 (7.1)
Swollen joint count, mean (SD)	0.8 (1.4)	2.3 (2.6)	3.5 (2.8)	7.5 (4.0)
Patient global, mean (SD)	15 (19)	28 (22)	42 (22)	70 (22)
ESR, mean (SD)	9 (7)	20 (19)	26 (21)	48 (28)
HAQ, mean (SD)	0.7 (0.7)	1.0 (0.7)	1.4 (0.7)	1.9 (0.6)
<i>2013-14 Cohort</i>				
Number of patients, (%)	148 (28 %)	67 (13 %)	212 (41 %)	93 (18 %)
Tender joint count, mean (SD)	0.7 (1.6)	1.6 (2.4)	4.7 (4.7)	15.2 (7.9)
Swollen joint count, mean (SD)	0.2 (0.7)	1.0 (1.6)	1.9 (2.3)	5.3 (3.6)
Patient global, mean (SD)	24 (17)	24 (17)	50 (21)	73 (16)
ESR, mean (SD)	9 (7)	22 (17)	26 (18)	34 (23)
HAQ, mean (SD)	0.9 (0.8)	1.2 (0.8)	1.4 (0.8)	1.9 (0.6)

Legend: SD standard deviation

fewer patients have highly active RA, its impact is reflected by declining rates of hand and foot surgery for RA [17].

Studying the DAS28 strata in the different cohorts showed differences over time between subjective and objective components of DAS28. Swollen joint counts fell but patient global responses did not. Composite measures like DAS28 are influenced by many factors in addition to the inflammatory burden of RA. These other factors include comorbidity, especially psychological problems such as depression, and other features of the disease such as pain [18]. The fact that swollen joint counts have fallen so substantially across all disease activity strata implies that the control of synovitis by modern treatment is more effective than would appear to be the case from DAS28 scores alone. The most prevalent RA state under follow up in contemporary practice is moderately active disease, which accounted for 41 % of the most recent cohort, and an evidence-based management strategy is needed for this group.

Throughout the time of the four cross sectional surveys, there was greater emphasis on the use of DMARDs, DMARD combinations and biologics. There has also been an increase in the involvement of specialist nurses. We consider these developments are the most likely explanation of these changes. The greater emphasis on seeing

RA patients early may also have influenced the findings. However, the introduction of formal early arthritis clinics in both centres did not occur until after the last survey was completed.

The relationship between disease activity and disability has been studied in detail in historic cohorts, where it was apparent that disease activity was the key driver of disability in early disease, whilst erosive damage became more important in established disease [19]. However, in an era of diminishing erosive damage, the relationship between disease activity and disability may have changed. A longitudinal analysis of the Nijmegen inception cohort actually revealed increasing levels of disability over time [9]. UK data from the Norfolk Arthritis Register (NOAR) revealed similar findings, with increasing levels of reported disability over time, despite reductions in measured disease activity [13]. Of even more relevance is an analysis combining the NOAR cohort with another UK inception cohort that explored HAQ progression over time [16]. Several distinct trajectories were noted; these were predicted by older age, female sex, longer symptom duration, higher DAS28 and lower social class.

Our findings help contextualise the changes in HAQ over time. Whilst we observed an overall reduction in disability, this was possibly driven by a decline in patients

with severe disease. In contrast, HAQ scores increased within the lower DAS28 groups. This corresponds to the rise in the subjective components of DAS28, which predictably correlate better with patient reported disability. One explanation for these findings is that background levels of disability might be rising, perhaps due to external factors such as the climbing levels of obesity in the general population. However, this is at odds with data from non-RA populations that have reported reductions in disability in the general population [20]. An alternative explanation is that way patients complete HAQ scores may be changing: patients might report disability differently using the HAQ due to higher expectations. The HAQ tool is also limited by floor and ceiling effects. Irrespective of the reason for the changing pattern of HAQ score, it remains a core metric by which effectiveness of RA treatments are judged [21].

Our study has several strengths. We have reported real time data with no exclusion criteria which is likely to be highly representative of RA patients seen in outpatient clinics at the time of each survey. It was also sufficiently large to provide robust assessments of treatment and disease activity. Our study does however have some limitations. The data were collected at consecutive cohorts was cross sectional and did not capture the same patients. As the data collected were anonymized we were uncertain if some patients contributed to more than one cohort. The assessments were carried out by a number of different physicians over the four time periods and there might have been variations in the way individual clinicians assess joint counts. It is also possible that the pattern of follow up in clinics has changed with RA patients who have milder disease being more frequently. Another possibility is that there may have been changes in the level of background disease activity in patients seen in specialist clinics. These are inherent problems in all studies that evaluate temporal changes in disease activity.

Conclusions

Over the last two decades the management of rheumatoid arthritis has changed. Patients are treated more intensively with both conventional DMARDs and biologics. Disease activity levels have fallen and more patients achieve remission; however, as only a minority of patients are in remission there is still substantial room for improvement. The failure to substantially reduce disability levels is of some concern. It is possible that focusing on reducing disease activity has less impact on disability than was previously considered. It may be particularly important to focus on reducing tender joint counts and patient global assessments, which may be related to non-inflammatory aspects of RA. Finally, further work is needed to understand how

to best manage moderate RA, the phenotype that now makes up the largest burden of clinic attenders.

Abbreviations

DAS28: Disease activity score for 28 joints; DMARD: Disease modifying anti-rheumatic drug; HAQ: Health assessment questionnaire; IQR: Interquartile range; NOAR: Norfolk arthritis register; RA: Rheumatoid arthritis; SD: Standard deviation.

Competing interests

The authors have no conflicts of interest to declare.

Authors' contributions

ANM had the main responsibility of writing the paper and overseeing the submission. FI contributed to the data analysis and editing of the paper. ICS, SB, MF, LP were involved in data collection. SS, GHK and JG were involved in the study design and editing of the paper. DLS proposed the idea of the study and contributing to the editing of the paper. All authors have seen and approved the final version of the paper before submission.

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Chapter 4 GUIDANCE ON MANAGING PATIENTS WITH RA

**This chapter is presented as a published paper and is a copy of the following
journal publication:**

Mian A, Ibrahim F, Scott DL. A Systematic Review of Guidelines for Managing
Rheumatoid Arthritis. BMC Rheumatol 2019; 3: 42.

RESEARCH ARTICLE

Open Access

A systematic review of guidelines for managing rheumatoid arthritis



Aneela Mian*, Fowzia Ibrahim and David L. Scott

Abstract

Background: We systematically reviewed current guidelines for managing rheumatoid arthritis (RA) to evaluate their range and nature, assess variations in their recommendations and highlight divergence in their perspectives.

Methods: We searched Medline and Embase databases using the terms 'clinical practice guidelines' and 'rheumatoid arthritis' from January 2000 to January 2017 together with publications of national and international bodies. We included guidelines providing recommendations on general RA management spanning a range of treatments and published in English. We undertook narrative assessments due to the heterogeneity of the guidelines.

Results: We identified 529 articles; 22 met our inclusion criteria. They were primarily developed by rheumatologists with variable involvement of patient and other experts. Three dealt with early RA, one established RA and 18 all patients. Most guidelines recommend regular assessments based on the Outcome Measures in Rheumatology core dataset; 18 recommended the disease activity score for 28 joints. Twenty recommended targeting remission; 16 suggested low disease activity as alternative. All guidelines recommend treating active RA; 13 made recommendations for moderate disease. The 21 guidelines considering early RA all recommended starting disease modifying drugs (DMARDs) as soon as possible; methotrexate was recommended for most patients. Nineteen recommended combination DMARDs when patients failed to respond fully to monotherapy and biologics were not necessarily indicated. Twenty made recommendations about biologics invariably suggesting their use after failing conventional DMARDs, particularly methotrexate. Most did not make specific recommendations about using one class of biologics preferentially. Eight recommended tapering biologics when patients achieved sustained good responses.

Conclusions: Five general principles transcend most guidelines: DMARDs should be started as soon as possible after the diagnosis; methotrexate is the best initial treatment; disease activity should be regularly monitored; give biologics to patients with persistently active disease who have already received methotrexate; remission or low disease activity are the preferred treatment target.

Keywords: Rheumatoid arthritis, Systematic review, Management guidelines

Background

Guidelines for the management of rheumatoid arthritis (RA) produced by expert groups based on assessments of the research evidence have been produced for over 25 years [1–4]. They provide explicit recommendations to influence practice through a formal process of disseminating advice on effective management. Guidelines can help minimise unnecessary care. Many guidelines for managing RA have been published over recent years; many of them have been updated to take into account

new treatments and novel research evidence about existing treatments.

The existence of multiple guidelines raises several questions. First, as they have all had access to the same research data, albeit at different time-points, are there recommendations similar or are there substantial differences between them? Second, why are there different guidelines dealing with the same issue – how best to treat RA? Thirdly, what is the impact of these guidelines on clinical practice? Finally, what guidelines will be needed in future years?

We have systematically reviewed current RA guidelines. Our overall aims were to evaluate the range and

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nature of guidelines currently available, to assess the variations in their recommendations about RA management, and highlight any divergence in their perspectives. The specific questions we considered were: (a) to examine their recommendations about composite assessments of disease activity; (b) to identify their management targets with drug therapy; (c) to define the categories of drug treatments considered. As a consequence of these assessments we sought to provide insights into the value and relevance of different guidelines.

Methods

Literature search

We searched Medline and Embase databases using the terms 'clinical practice guidelines' and 'rheumatoid arthritis'. We also searched national bodies including the Scottish Intercollegiate Guidelines Network (SIGN) and the National Institute For Health and Care Excellence and national and international specialist societies including the British Society for Rheumatology, the American College of Rheumatology and the European League Against Rheumatism. Finally we searched lists of references from identified guidelines.

Inclusion and exclusion criteria

Our inclusion criteria comprised: (a) publications that identified themselves as guidelines; (b) guidelines that provided recommendations on the general management of RA; (c) guidelines that included a range of different drug treatments; (d) guidelines published from January 2000 to January 2017; (e) guidelines published in English. Our exclusion criteria comprised: (a) guidelines and appraisals that dealt with specific areas of management, such as safety monitoring of drugs; (b) guidelines or appraisals of single drugs or technologies. When there were several versions of guidelines from the same organisation, only the latest guideline was included.

Screening and data extraction

Two researchers (AM, DLS) independently assessed studies for eligibility and extracted data onto a predefined template. The data included: (a) year of publication; (b) format (who was involved); (c) quality method followed; (d) systematic review of evidence; (e) patient groups considered; (f) area of management included; (g) composite activity assessments; (h) prognostic assessments; (i) treatment targets; (j) and range of treatments considered. When there were differences between assessors, they reviewed the reports together and came to a joint conclusion.

Assessment of quality methods

We sought evidence that individual guidelines had followed nationally or internationally accepted quality

methods in their development; we did not assess their quality as part of this report. Firstly, we recorded who had been involved in developing the guideline, including the involvement of specialists, other experts and patients. Secondly we evaluated whether they had used recognised quality methods such as Agree and Agree II [5], Adapte [6], Grade [7], and National Institute for Health and Clinical Excellence (NICE) [8] methods. Thirdly we sought evidence whether they had used systematic reviews of published evidence to develop their recommendations. We did not specifically examine the quality of individual guidelines because we anticipated this would be highly variable because some guidelines were developed by large organisations such as the American College of Rheumatology whilst others were developed by smaller groups with far less resources making substantial variations in the quality of the guidelines inevitable.

Methodological approaches

We followed the general PRISMA recommendations [9] and other approaches for systematic reviews [10], although none of these specifically deal with reviews of guidelines. We also followed methods recommended for reviews of systematic reviews [11] and approaches taken in previous systematic reviews of guidelines [12, 13]. As PRISMA does not specifically include systematic reviews of guidelines we did not pre-register our protocol; this was omitted in other systematic reviews of guidelines [12].

Methods of analysis

The guidelines were very heterogeneous in terms of the areas covered, the approaches taken in their development and the presentation of their recommendations. Consequently we undertook narrative assessments of their recommendations. Initially we assessed the areas covered by the guidelines, whether they included statements of principles and needs, their intended audiences and their overall structure, including whether they dealt with specific questions or recommendations. We then focussed on three predefined areas related to our specific aims. These comprised: (a) recommendations about composite assessments of disease activity and other assessments; (b) management targets with drug therapy including the impact of prognostic assessments; (c) and the categories of drug treatments considered. We considered this approach would enable us to assess the variations in their recommendations about RA management and identify divergences in their perspectives. We did not set out to produce any single optimal set of recommendations for RA management from our analyses of these guidelines. We considered management from the perspective of conventional disease modifying anti-rheumatic drugs (DMARDs) like methotrexate, biologic

Table 1 Features of clinical guidelines included in review

Guideline	Year	Format			Quality Method	Systematic Review Of Evidence		Patients	Areas Covered		
		Specialists	Other Experts	Patients		In Guideline	Separate		Diagnosis	Drugs	MDT
1. American [14]	2015	Yes	Yes	Yes	Grade	Yes	–	All	–	Yes	–
2. APLAR [15]	2015	Yes	–	Yes	Agree II	Yes ^a	–	All	–	Yes	–
3. Australian [16]	2009	Yes	Yes	Yes	Agree	Yes ^a	–	< 2 years	Yes	Yes	Yes
4. Brazilian [17]	2012	Yes	–	–	–	Yes	–	All	–	Yes	Yes
5. British Columbia [18]	2012	Not Specified			–	–	–	All	Yes	Yes	Some
6. British Society For Rheumatology: Established [19]	2009	Yes	Yes	Yes	–	–	–	> 2 years	–	Yes	Yes
7. British Society For Rheumatology: Early [20]	2010	Yes	Yes	Yes	–	–	–	< 2 years	Yes	Yes	Yes
8. Canadian [21]	2011	Yes	Yes	Yes	Adapte	Yes ^a	–	All	–	Yes	–
9. EULAR [22]	2016	Yes	Yes	Yes	Agree II	–	Yes	All	–	Yes	–
10. French [23]	2014	Yes	Yes	Yes	–	–	–	All	Yes	Yes	Some
11. German [24]	2013	Yes	–	Yes	–	Yes	–	All	–	Yes	–
12. Hong Kong [25]	2010	Yes	Not Specified		–	–	–	All	Yes	Yes	–
13. Indian [26]	2008	Yes	Not Specified		–	–	–	All	Yes	Yes	Yes
14. Latin American [27]	2006	Yes	Not Specified		–	–	–	All	Yes	Yes	Yes
15. Mexican [28]	2014	Yes	Not Specified		Agree II	Yes ^a	–	All	–	Yes	–
16. England [29]	2009	Yes	Yes	Yes	NICE	Yes	–	All	Yes	Yes	Yes
17. Scotland [30]	2011	Yes	Yes	–	Grade	Yes ^b	–	< 5 years	Yes	Yes	Yes
18. South African [31]	2013	Yes	Yes	Yes	–	–	–	All	Yes	Yes	Yes
19. Spanish [32]	2007	Yes	Yes	–	–	Yes	–	All	Yes	Yes	Yes
20. Swedish [33]	2011	Yes	Not Specified		–	–	–	All	–	Yes	–
21. Treat to Target [34]	2010	Yes	–	Yes	–	–	Yes	All	–	Yes	–
22. Turkish [35]	2011	Yes	Yes	–	–	Yes	–	All	–	Yes	Yes

MDT Multidisciplinary team

^aSystematically reviewed other guidelines^bused existing published systematic reviews

were intended to amend existing international guidelines for local circumstances.

The approaches to assessing clinical research evidence supporting the guidelines also varied. The two EULAR guidelines [22, 34] commissioned detailed systematic reviews which were published separately [36, 37]. The American College of Rheumatology (ACR) guideline commissioned [14] detailed systematic reviews that were published as an appendix. The English (Royal College of Physicians) guideline [29] commissioned detailed systematic reviews for each question which were published within the guideline itself. Eight other guideline guidelines included some systematic reviews [15–17, 21, 24, 28, 30, 32, 35, 38] within them, including systematically assessing other guidelines, and one other guideline formally used existing published systematic reviews to assess each question they considered [30].

Two guidelines dealt with early RA under 2 years duration [16, 20] and one under 5 years duration [30]; one guideline dealt with established RA over 2 years [19] duration; the other guidelines dealt with all RA patients.

Areas covered

All the guidelines dealt with drug treatment, though they did not all cover the same aspects of drug therapy. Eleven guidelines also covered diagnosis [16, 18, 23, 25–27, 29–32] and 13 covered some or many non-drug treatments [16–20, 23, 27, 29–32, 35]. Those guidelines which considered non-drug treatments by multidisciplinary teams outlined a range of supportive treatment options. Some of these guidelines, such as the Spanish guidelines [32], provided extensive details about these non-drug treatments. Others, such as the Scottish guidelines [30], give more general recommendations.

Statements of principles and needs

Guidelines often included a range of statements of general principles, the specific need for the guideline and the audience the guideline was intended to inform. These statements were so diverse that it is not possible to provide a succinct summary of them.

The EULAR guidelines [22] provided the most extensive global statements which were mainly related to ethical issues and philosophical principles such as the central role of patients, the role of specialist rheumatologists and the high costs of the disease burden in RA. The ACR guideline [14] had more disease specific general principles and included statements about the need for payers not to influence some treatment decisions. The English (Royal College of Physicians) [29] guideline was most specific about its audience, but it was designed to be part of the government-funded National Health Service. Other guidelines, such as the APLAR guideline [15] highlighted the diversity of patients managed in the areas they represent and the potential differences from Western countries.

Intended audiences

Twenty guidelines outlined, to a greater or lesser extent, their intended audience [14–17, 19–31, 33–35]. All 20 indicated they were mainly aimed at clinicians; the Australian (Royal Australian College of General Practitioners) indicated their guidelines [16] were specifically intended for GPs. Other guidelines included broader ranges of medical specialists and other health care professionals involved in the management of RA. Guidelines were sometimes intended to provide information for a broader range of readers: 6 guidelines [19–21, 23, 29, 34] included a range of administrative staff including commissioners and payers of healthcare; 7 guidelines [14, 19–21, 23, 29, 34] included patients and in some cases patient groups. An example of a guideline with a broad audience is English (Royal College of Physicians) guidance [29] which spanned all healthcare professionals, people with RA and their carers, patient support groups, commissioning organisations and service providers.

Structure

13/22 guidelines dealt with specific questions or recommendations [14, 16, 17, 19, 21–25, 28, 29, 34, 35]; the average number was 20 (range 10–37). Some of these guidelines had specific structures which were replicated across questions; for example the Canadian guideline [21] for each question included the recommendation, the supporting evidence and the barriers to implementation. The other 9/22 guidelines focused on different themes or areas [15, 18, 20, 26, 27, 30–33] which incorporated a number of related issues; the average number

was 6 (range 3–12). Some of these guidelines also had specific structures replicated across themes; for example the English (Royal College of Physicians) guideline [29] had summaries of the evidence, sections from evidence to recommendations and then one or more recommendations for each of the themes it considered.

Assessments

18/22 guidelines [14, 15, 17, 21–35] recommend regular assessments using a variety of clinical assessments based on the Outcome Measures in Rheumatology (OMER-ACT) core dataset [39] using composite indices. These all recommended using the disease activity score for 28 joints (DAS28) [40]. In addition 14 also recommended simple disease activity index (SDAI) and 13 recommended Clinical Disease Activity Index (CDAI) [41]. Two guidelines recommended other assessments – the Patient Activity Scale (PAS) [42] and Routine Assessment Of Patient Data Index (RAPID3) [43]. None of the guidelines specifically recommended one composite index over another. The importance of assessing disability was considered by most guidelines. The recommendations varied more widely on how to do this and 10/22 guidelines recommended regularly assessing disability [15, 17, 21, 25–27, 29, 31–33]; 9 of these recommended using the Health Assessment Questionnaire (HAQ) [44]; the Canadian guidelines did not specifically suggest assessing HAQ regularly [21].

The importance of frequent assessment is stressed in most guidance. Some guidelines gave relatively specific suggestions. For example EULAR guidelines recommend assessing patients every 1 to 3 months, at least in the early stages of their RA. Many guidelines indicated patients should be assessed by rheumatologists at least annually. The English (Royal College of Physicians) guideline gives a very specific recommendation for annual review. The ACR guideline recommended annual assessments of function.

Remission and other targets

Twenty guidelines recommended remission as a treatment target and 16 guidelines recommended using low disease activity as an alternative target (Table 2). Two guidelines recommend aiming to suppress inflammation: the British Columbia guideline [18] concluded that the objective of treatment is to “suppress all inflammation”, implying this is joint inflammation; the British Society For Rheumatology established RA guideline [19] recommended “suppressing inflammation” indicating this was to limit disease progression.

Remission was defined in various ways, in keeping with current international criteria [45]. DAS28-defined remission was recommended in 13 guidelines, SDAI in 9, CDAI in 7 and Boolean in 6. There were 6 guidelines

Table 2 Recommended treatment targets

Guideline	Treatment Target			Remission Definitions				Treat Moderate Disease
	Remission	LDA	Suppress Inflammation					
1. American [14]	Yes	Yes	–	SDAI	Boolean			Yes
2. APLAR [15]	Yes	Yes	–	DAS28	SDAI	CDAI	Boolean	Yes
3. Australian [16]	Yes	–	–	–	–	–	–	Yes
4. Brazilian [17]	Yes	Yes	–	DAS28	SDAI	CDAI	–	Yes
5. British Columbia [18]	–	–	Yes	–	–	–	–	–
6. British Society For Rheumatology: Established [19]	Yes	–	Yes	–	–	–	–	–
7. British Society For Rheumatology: Early [20]	–	–	–	–	–	–	–	–
8. Canadian [21]	Yes	Yes	–	DAS28	SDAI	CDAI	Boolean	Yes
9. EULAR [22]	Yes	Yes	–	SDAI	Boolean	–	–	Yes ^a
10. French [23]	Yes	Yes	–	DAS28	SDAI	CDAI	Boolean	Yes
11. German [24]	Yes	Yes	–	DAS28	–	–	–	Yes ^a
12. Hong Kong [25]	Yes	–	–	DAS28	–	–	–	Yes ^a
13. Indian [26]	Yes	–	–	–	–	–	–	Yes
14. Latin American [27]	Yes	Yes	–	DAS28	–	–	–	–
15. Mexican [28]	Yes	Yes	–	DAS28	–	–	–	Yes
16. England [29]	Yes	Yes	–	DAS28	–	–	–	–
17. Scotland [30]	Yes	Yes	–	DAS28	–	–	–	Yes
18. South African [31]	Yes	Yes	–	SDAI	–	–	–	Yes
19. Spanish [32]	Yes	Yes	–	DAS28	CDAI	Boolean	–	Yes ^a
20. Swedish [33]	Yes	Yes	–	DAS28	SDAI	CDAI	–	Yes
21. Treat to Target [34]	Yes	Yes	–	DAS28	SDAI	CDAI	Boolean	Yes
22. Turkish [35]	Yes	Yes	–	–	–	–	–	Yes

LDA Low disease activity

^aTreatment of moderate RA is implied rather than definitively stated

which did not give any criteria for assessing the presence of remission. In addition many guidelines emphasised the importance of minimising disability, minimising progressive joint damage and maximising quality of life, though these were less explicit management goals.

All guidelines recommend treating active RA. There was less unanimity about treating moderately active disease. Thirteen guidelines made specific recommendations about treating moderate disease. Four guidelines gave implied guidance about treating moderate disease in that they indicated what treatment policies were needed until patients achieved remission. Five guidelines made no recommendations about treating moderate disease.

Prognostic assessments to guide treatment decisions

Sixteen guidelines specifically included assessments of prognostic factors to help guide management decisions about treatments [15–18, 21–28, 31–33, 35]. All these 16 guidelines recommended using anti-citrullinated protein antibodies (ACPA); 14 guidelines recommended using rheumatoid factor (RF) [15–17, 21–28, 31–33]; 15

guidelines recommended using x-ray erosion [15, 16, 21–27, 31–33, 35]; and 9 guidelines recommended using high disability or extra-articular disease [21, 25–28, 31–33, 35]. These recommendations are summarised in Table 3. The guidelines including prognostic assessments all recommended considering more intensive treatment with conventional DMARDs and biologic DMARDs in those patients with poor prognostic features. They gave variable details of exactly how this should be achieved.

Initial conventional DMARD recommendations

Twenty one guidelines dealt with the management of early RA; all of these recommended starting conventional DMARDs as soon as possible after diagnosis. Methotrexate, which is often described as the “anchor” drug for RA, was recommended for most patients in 19/22 guidelines [14–17, 20–29, 31–35] (Table 4). In 13/22 guidelines there was consideration of the relative benefits and risks of oral and subcutaneous methotrexate [14, 17, 20–24, 27, 29, 31–33, 35]; however, the approach taken to this issue varied considerably and there was no

Table 3 Recommended composite disease activity assessments and prognostic assessment to guide treatment

Guideline	Composite Disease Activity Assessments					Prognostic Assessments				
	PAS	RAPID3	CDAI	SDAI	DAS28	RF	ACPA	X-ray Erosions	Poor Function	Extra-Articular Disease
1. American [14]	Yes	Yes	Yes	Yes	Yes					
2. APLAR [15]	–	–	Yes	Yes	Yes	Yes	Yes	Yes		
3. Australian [16]	–	–	–	–	–	Yes	Yes	Yes		
4. Brazilian [17]	–	–	Yes	Yes	Yes	Yes	Yes	Yes		
5. British Columbia [18]	–	–	–	–	–		Yes	Yes		
6. British Society For Rheumatology: Established [19]	–	–	–	–	–					
7. British Society For Rheumatology: Early [20]	–	–	–	–	–					
8. Canadian [21]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. EULAR [22]			Yes	Yes	Yes	Yes	Yes	Yes		
10. French [23]			Yes	Yes	Yes	Yes	Yes	Yes		
11. German [24]	–	–	–	–	Yes	Yes	Yes	Yes		
12. Hong Kong [25]	–	–	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Indian [26]	–	–	Yes	Yes	Yes	Yes	Yes	Yes		Yes
14. Latin American [27]	–	–	–	–	Yes	Yes	Yes	Yes	Yes	Yes
15. Mexican [28]			Yes	Yes	Yes	Yes	Yes			Yes
16. England [29]	–	–	–	–	Yes					
17. Scotland [30]	–	–	Yes	Yes	Yes					
18. South African [31]	–	–	–	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19. Spanish [32]	–	–	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
20. Swedish [33]	–	–	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
21. Treat to Target [34]	–	–	Yes	Yes	Yes					
22. Turkish [35]	–	–	–	–	Yes		Yes	Yes	Yes	

RF Rheumatoid factor, ACPA Anti-citrullinated protein antibody

obvious consensus across guidelines about when best to use parenteral methotrexate.

When there are contraindications to methotrexate or if there are clinically significant adverse events to methotrexate all 19 guidelines that suggested methotrexate as initial treatment recommend considering alternative conventional DMARDs. Sulfasalazine, leflunomide and hydroxychloroquine were all considered potentially appropriate; there was no consistent pattern in these recommendations. Other rarely used conventional DMARDs, such as azathioprine, though not excluded were not specifically recommended.

Three guidelines considered DMARDs generically without giving recommendations about which drugs to use; these were the British Guidelines for established [19] and early RA [20] and the EULAR treat to target guidance [34]. These three guidelines focussed on the overall strategy for managing RA rather than the best individual treatment options and so consequently did not provide recommendations about specific drugs.

The way individual guidelines outlined the initial treatment for RA varied considerably. EULAR guidelines recommend that methotrexate should be part of the first treatment strategy. ACR guidelines recommend that DMARD monotherapy is generally more acceptable and better tolerated than combination DMARD therapy and that methotrexate should be the preferred initial DMARD for most early RA patients. Canadian guidelines recommend that initial combination therapy with traditional DMARD should be considered, particularly in patients with poor prognostic features, moderate-high disease activity and in patients with recent-onset disease. English (Royal College of Physicians) guidelines recommended that in people whose RA is active, patients should be offered a combination of DMARDs (including methotrexate, at least one other DMARD, plus short term glucocorticoids) as first-line treatment.

Combinations of conventional DMARDs

Twenty guidelines considered the use of combinations of conventional DMARDs; 19 of these guidelines

Table 4 Drug treatment recommendations

Guideline	DMARDs					Biologics			Symptomatic Treatments	
	MTX	Others	Combinations	JAK Inhibitors	Glucocorticoids (steroids)	First	Subsequent	Tapering	NSAIDs	Pain
1. American [14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–	–
2. APLAR [15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–
3. Australian [16]	Yes	Yes	Yes	–	Yes	Only for specialists			Yes	Yes
4. Brazilian [17]	Yes	Yes	Yes	–	Yes	Yes	Yes	Yes	Yes	–
5. British Columbia [18]	Yes	Yes	Yes	–	Yes	Only for specialists			Yes	Yes
6. British Society For Rheumatology: Established [19]	Generic DMARDs		–	–	–	Generic biologics			Yes	Yes
7. British Society For Rheumatology: Early [20]	Generic DMARDs		Yes	–	Yes	Generic biologics		Implied	Yes	Yes
8. Canadian [21]	Yes	Yes	Yes	–	Yes	Yes	Yes	Yes	–	–
9. EULAR [22]	Yes	Yes	–	Yes	Yes	Yes	Yes	Yes	–	–
10. French [23]	Yes	Yes	Yes	–	Yes	Yes	Yes	Yes	–	–
11. German [24]	Yes	Yes	Yes	–	Yes	Yes	Yes	–	–	–
12. Hong Kong [25]	Yes	Yes	Yes	–	Yes	Yes	Yes	–	–	–
13. Indian [26]	Yes	Yes	Yes	–	Yes	Yes	Yes	–	Yes	Yes
14. Latin American [27]	Yes	Yes	Yes	–	Yes	Yes	Yes	–	Yes	Yes
15. Mexican [28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–	Yes	Yes
16. England [29]	Yes	Yes	Yes	–	Yes	Yes	Yes	–	Yes	Yes
17. Scotland [30]	Yes	Yes	Yes	–	Yes	Yes	Yes	–	Yes	Yes
18. South African [31]	Yes	Yes	Yes	–	Yes	Yes	Yes	–	Yes	Yes
19. Spanish [32]	Yes	Yes	Yes	–	Yes	Yes	Yes	–	Yes	Yes
20. Swedish [33]	Yes	Yes	Yes	–	Yes	Yes	Yes	Yes	–	–
21. Treat to Target [34]	Generic DMARD treatments			–	Yes	Generic biologics		Implied	–	–
22. Turkish [35]	Yes	Yes	Yes	–	Yes	Yes	Yes	Yes	–	–

recommended using them in some patients [14–18, 20, 21, 23–33, 35]. They were recommended when patients failed to respond fully to DMARD monotherapy and that biologics were not necessarily indicated. Specific Combinations of conventional DMARDs were recommended by 12/22 guidelines [14, 15, 17, 21, 23–28, 31, 33]: these combinations comprised methotrexate with sulfasalazine and hydroxychloroquine or methotrexate with leflunomide in 9 guidelines; 2 guidelines omitted leflunomide from combinations [23, 33] and one guideline recommended chloroquine instead of hydroxychloroquine [31]. One guideline, from England, recommended initial combinations of conventional DMARDs [29], though it did not specify which drugs to use.

The one exception was the EULAR guidelines which do not specifically recommend using them. However, EULAR did not exclude their use, and mention them briefly. The EULAR guidelines also provide an extensive commentary on the divergence of expert opinion on this issue, highlighting potential toxicities and difficulties dissociating the impact of methotrexate, short-term

glucocorticoids (steroids) and other conventional DMARDs in combinations.

Janus Kinase inhibitors

Only 4 guidelines consider the use of Janus Kinase inhibitors; this mainly reflects whether they were developed after these drugs became available. Those guidelines that consider them recommend their use as an alternative to biologics in some patients with established RA. They are usually recommended to be used in combination with methotrexate.

Glucocorticoids (steroids)

Twenty guidelines recommended using glucocorticoids in some RA patients; these were usually patients with early RA who were starting DMARD treatment. In the main only short-term courses of low dose glucocorticoids (steroids) were recommended. The EULAR treat to target guideline implied glucocorticoids (steroids) should be used within the treatment strategy in some patients but did give any recommendations about

specific therapies. The British guidelines for established RA did not consider glucocorticoids (steroids). In addition some guidelines gave advice about the role of glucocorticoids (steroids) in specific clinical settings, particularly in the management of some comorbidities.

Biologic DMARD

Twenty guidelines made recommendations about using biologics. Three guidelines made generic recommendations about biologics and the other 17 that dealt with them considered individual biologics and classes of biologics. The 2 guidelines that did not were for primary care clinicians who should not usually prescribe these treatments. All the guidelines that dealt with biologics recommended their use in patients who had failed to respond to conventional DMARDs, particularly methotrexate. They also recommended using them in combination with methotrexate whenever possible. Most guidelines did not make specific recommendations about using one class of biologics preferentially. However, some guidelines such as the Canadian ones, recommend using tumour necrosis factor inhibitors as an initial biological treatment. In patients who have continuing disease activity despite biologic treatment or adverse events to biologics starting an alternative biologic was recommended. In most instances no particular sequences of biologics were recommended in the different guidelines.

Biologic DMARD tapering

Eight guidelines recommended considering tapering biologic treatment in patients who had achieved sustained good responses and remissions. A further two guidelines implied this was appropriate without giving detailed recommendations.

Symptomatic treatment

Thirteen guidelines made recommendations about the use of NSAIDs and 12 about using analgesics to control symptoms. Those guidelines which consider the use of NSAIDs invariably focus on minimising exposure to these treatments. For example the Scottish Guidelines suggest using the lowest NSAID dose compatible with symptom relief, and indicate that treatment should be reduced and if possible withdrawn as soon as possible and that gastro-protection should be included when using them. When analgesics such as paracetamol were mentioned for symptom relief though the evidence supporting their use is noted to be minimal by current standards.

Discussion

Our overview of 22 different RA management guidelines shows that several general principles transcend the majority of them. Firstly DMARDs should be started as

soon as possible after the diagnosis has been established. Secondly disease activity should be regularly monitored using composite indices such as DAS28, which relates to our initial aim which was our initial specific question. Thirdly methotrexate is the best initial treatment, and that this can be usefully supplemented with short-term glucocorticoid (steroid) therapy. Fourthly biologic DMARDs should be given to patients with persistently active disease who have already received methotrexate and, in some instances another conventional DMARD. These principles relate to another of our specific questions. Fifthly remission or low disease activity is a suitable target and that treatment can be tapered in patients who have achieved sustained remissions. This principle relates to our final specific question. We consider that applying these general principles to RA management in all clinical settings is likely to achieve good overall clinical outcomes.

There is considerable uncertainty about the value and place for using combinations of conventional DMARDs. The most recent EULAR guidance is particularly uncertain about its value. Other guidance including the ACR guidance is more definite in its perspective. The reasons for this difference are unclear. In part it may be presentational; EULAR guidance does not exclude using such combinations and ACR guidance does not explicitly recommend them; consequently much of the apparent difference may represent the way in which the information is presented. There has been correspondence about this particular aspect of the EULAR guidelines [46, 47]. However, the balance of opinion in these various guidelines favours the use of combinations of conventional DMARDs in some patients. Interestingly, recent guidance from NICE in a multiple technology appraisal (a type of assessment we excluded from this systematic review) recommended only starting biologics in patients with disease that had not responded to intensive therapy with a combination of conventional DMARDs [48]. These perspectives were from expert groups who had considered the same evidence in detail and they show the divergence of expert views when assessing clinical research findings.

There is also relatively little overall consensus about treating moderately active RA. The ACR guidance makes the strongest recommendation on this point. Other guidance has either not considered it or may have been published prior to much evidence becoming available. Despite the limitations of explicit recommendations, those guidelines which consider moderate disease recommend treating it intensively.

The guidelines differ in the formality of their approach and in the extent of systematic reviews commissioned specifically for them. The EULAR, ACR and Royal College of Physicians guidelines were the most detailed

and involved the greatest amount of preparatory work including a number of detailed systematic reviews. Specialist rheumatologists were involved in almost all guidelines; varying numbers of other experts and patients were involved. The impact that these non-rheumatologists would be able to make to the guidelines was uncertain.

The limitations of clinical guidelines have been described in detail [49–52]. We do not intend to consider the relative strengths and weakness of guidelines in general. However, one particular challenge with the current published guidelines is that only 8/22 specifically followed a nationally or internationally agreed approach to ensure they were of high quality. Future guidelines ought to explicitly adopt one of these quality methods. In RA the overall the degree of agreement between the guidelines is striking and exceeds the differences between them. As health care is not universally uniform it is inevitable national groups would wish to have their own local guidelines, which reflect the arrangements of their medical systems. The overall impact of the guidelines is difficult to establish. As the various updates of ACR and EULAR guidelines have high citation rates on bibliometric systems it seems likely they are used by many groups. Some guidelines have immediate practical implications. For example technology appraisals by NICE, though outside our remit, have been crucial for ensuring patients have access to high cost therapies. It is likely guidelines achieve this goal more globally, and the appearance of many guidelines reflects the major changes in drug therapy for RA in recent years.

Our own assessment of RA guidelines has its own limitations. Firstly, some of the guidelines were developed over 10 years or longer and the older ones cannot have included the more recent clinical evidence. Therefore comparisons need to take this into account. Secondly, there are different types of guidelines. We have included general ones. Many others focus on single drugs or treatment modalities including surgery. It is difficult to draw a clear line between which ones to include and which to omit. Not all experts would necessarily agree with our approach to inclusion. Thirdly, we have only provided a narrative assessment of them. They are too diverse in their approaches to allow any synthesis of their various conclusions and recommendations. Fourthly we have focussed on issues in the guidelines we consider to be of most importance. Other experts may have considered different aspects of the guidelines in more detail and overlooked some of the matters we have dealt with. Finally, systematic reviews of guidelines are not one of the current PRISMA extensions [53] though we anticipate they will be included in subsequent updates. Consequently we did not register our protocol; however, several other recent systematic reviews have

evaluated different guidelines using similar approaches to our own, such as the report by Jolliffe et al. on stroke rehabilitation guidelines [13]. Systematic reviews of guidelines differ from both scoping [54] and umbrella reviews [55].

Our analysis shows several things. Firstly, the recommendations in the guidelines are broadly similar, though they differ in some points of detail; for example the use of combinations of conventional DMARDs. Such minor variations most likely reflect the challenges in balancing evidence of benefits against evidence of risks. Secondly, although guidelines deal with the same issue, they bring together different groups of experts and it is likely the production of guidelines enhances clinical practice. Consequently multiple guidelines appear to be needed. Thirdly, although it is difficult to judge accurately the impact of guidelines on clinical practice, there is evidence that RA outcome have improved significantly during the last 10–20 years and in part this is likely to reflect the impact of guidelines in improving the quality of clinical practice. Finally, as new treatments are introduced, particularly new JAK inhibitors, guidelines will need to be continually updated and, potentially produced by different groups.

We anticipate that many of the existing guidelines will be updated in future years. We believe it important to do so to maintain their relevance to clinical practice. The frequency of review will reflect the timing of new clinical information. Looking back at the earliest guidelines from the 1990s [1–3] shows just how much clinical practice has changed over the years, indicating the need for guidance to be updated. We consider there are two ways in which the process of developing guidelines could be improved. Firstly, there guideline development should conform with one of the published quality standards; whilst there is no reason to prefer one standard over another, it seems worthwhile to adopt one of them. Secondly, guidelines should incorporate divergent views, when there is no universally agreed answer. The controversy about the value of combinations of conventional DMARDs highlights this issue.

One important role of guidelines is to suggest potential future research questions. Our own research in the TITRATE research programme, of which this systematic review in a single component, was based on the absence of evidence on the benefits of intensive management in moderately active RA [56]. Interestingly, though the clinical research evidence has changed little on this aspect of treat to target, current guidelines often recommend treating moderately active RA intensively, showing the way in which guidelines interpret the evidence in very different ways.

Conclusions

Although a number of differences exist between guidelines, there are some general principles. These include starting DMARDs soon after diagnosis; methotrexate should be used first line; disease activity should be monitored regularly; biologics therapies should be used where there is persistently active disease; and remission or low disease activity is the preferred target.

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Authors' contributions

AM and DLS conducted the literature search and screening and selection for relevant guidelines. AM, FI and DLS analysed the final guidelines included. AN, FI and DLS all contributed to the writing of the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

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Chapter 5 OPTIMAL RESPONSES IN DISEASE ACTIVITY

**This chapter is presented as a published paper and is a copy of the following
journal publication:**

Mian AN, Ibrahim F, Scott DL, Galloway J; TITRATE study group. Optimal responses in disease activity scores to treatment in rheumatoid arthritis: Is a DAS28 reduction of >1.2

RESEARCH ARTICLE

Open Access



Optimal responses in disease activity scores to treatment in rheumatoid arthritis: Is a DAS28 reduction of >1.2 sufficient?

Aneela N. Mian^{1,2*}, Fowzia Ibrahim^{1,2}, David L. Scott^{1,2}, James Galloway^{1,2} and On behalf of the TITRATE study group

Abstract

Background: The overall benefit of intensive treatment strategies in rheumatoid arthritis (RA) remains uncertain. We explored how reductions in disability and improvements in quality of life scores are affected by alternative assessments of reductions in disease activity scores for 28 joints (DAS28) in two trials of intensive treatment strategies in active RA.

Methods: One trial (CARDERA) studied 467 patients with early active RA receiving 24 months of methotrexate monotherapy or steroid and disease-modifying anti-rheumatic drug (DMARD) combinations. The other trial (TACIT) studied 205 patients with established active RA; they received 12 months of treatment with DMARD combinations or biologic agents. We compared changes in the health assessment questionnaire (HAQ) and Euroqol-5D (EQ5D) at trial endpoints in European League Against Rheumatism (EULAR) good and moderate EULAR responders in patients in whom complete endpoint data were available.

Results: In the CARDERA trial 98 patients (26 %) were good EULAR responders and 160 (32 %) were EULAR moderate responders; comparable data in TACIT were 66 (35 %) and 86 (46 %) patients. The magnitude of change in the HAQ and EQ5D was greater in both trials in EULAR good responders than in EULAR moderate responders. HAQ scores had a difference in of -0.49 (95 % CI -0.66, -0.32) in the CARDERA and -0.31 (95 % CI -0.47, -0.13) in the TACIT trial. With the EQ5D comparable differences were 0.12 (95 % CI 0.04, 0.19) and 0.15 (95 % CI 0.05, 0.25). Both exceeded minimum clinically important differences in HAQ and EQ5D scores.

Conclusions: We conclude that achieving a good EULAR response with DMARDs and biologic agents in active RA results in substantially improved mean HAQ and EQ5D scores. Patients who achieve such responses should continue on treatment. However, continuing such treatment strategies is more challenging when only a moderate EULAR response is achieved. In these patients evidence of additional clinically important benefits in measures such as the HAQ should also be sought.

Keywords: Rheumatoid arthritis, DAS28, Response criteria

Background

A key goal in treating rheumatoid arthritis (RA) with conventional disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents is reducing inflammatory synovitis, which reduces disability and maximises quality of life. Reductions in synovitis with treatment are

assessed using the disease activity score for 28 joints (DAS28) [1]. The European League Against Rheumatism (EULAR) classifies good responders as having DAS28 scores of 3.2 or less with reductions in DAS28 of more than 1.2 [2]. Patients with DAS28 scores over 3.2 who have reductions in DAS28 scores of more than 1.2 have moderate responses. Patients with reductions in DAS28 of less than 0.6 are non-responders. The treat-to-target initiative recommends increasing treatment until patients achieve remission or low disease activity [3].

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High-cost biologic treatments such as tumour necrosis factor inhibitors are used within agreed guidelines. When patients achieve good EULAR responses there is strong rationale for maintaining treatment. Similarly, when patients do not respond there is no reason to continue treatment. However, there is uncertainty in patients with incomplete responses. The British Society for Rheumatology (BSR), recommends patients with active RA, who have not responded to methotrexate and another DMARD, should be considered for biologic therapy [4]. Provided they achieve reductions in DAS28 of over 1.2 by 6 months they should continue receiving biologic treatments. This approach was accepted by the National Institute for Health And Care Excellence (NICE) in its health technology appraisals of biologic treatments for RA [5, 6]. Initially NICE recommended only continuing treatment if DAS28 is reduced by 1.2 or more [5], though recent guidelines recommend patients achieve at least a moderate EULAR response for treatment to continue [6].

The impact on disability and quality of life of reducing disease activity are assessed using the Health Assessment Questionnaire (HAQ) [7] and EuroQol-5D (EQ5D) [8]. There are doubts about the value both to patients and the funders of healthcare from maintaining high-cost treatments if patients only achieve moderate EULAR responses. We hypothesised that patients with good EULAR responses have substantially larger improvements in HAQ and EQ5D scores than patients with moderate EULAR responses, who do not achieve low disease activity or remission, and in whom the final DAS28 scores remain over 3.2. We tested our hypothesis in secondary analyses of two published randomised controlled trials (RCTs). One trial, cost-effectiveness of treatment strategies using combination of disease modifying anti-rheumatic drugs and glucocorticoids in early rheumatoid arthritis (CARDERA), studied intensive DMARD treatment in early RA [9]. The other trial, tumour necrosis factor inhibitors against combination intensive therapy (TACIT), studied intensive treatment with DMARDs and biologic agents in established RA [10]. In both trials we compared changes in HAQ and EQ5D scores in patients achieving good EULAR responses with patients achieving reductions in DAS28 scores over 1.2, and who had only moderate EULAR responses.

Methods

Patients

We undertook secondary analyses using data from two completed randomised controlled trials in RA. Details of the patients and treatments used have been published [8, 9]. The CARDERA trial randomised 467 patients to monotherapy or combination therapy with conventional DMARDs and steroids in early untreated active RA. The

TACIT trial randomised 205 patients to intensive conventional DMARDs or biologic treatment strategies in established active RA. In TACIT all patients met the current NICE criteria for biologic treatments.

Assessments

Both trials used the DAS28 calculated with erythrocyte sedimentation rate (ESR) to assess disease activity. We studied patients at the predefined final endpoints of each trial: 24 months for CARDERA and 12 months for TACIT. Both trials measured disability using the HAQ and quality of life using the EQ5D. We applied reported minimal clinically important differences (MCID) to assess benefits from reducing DAS28 scores. For the HAQ we used an MCID of 0.22 [11]. For the EQ5D we used an MCID of 0.07 [12]. We used the DAS28 to assess remission, which was defined by $\text{DAS28} < 2.6$; this definition has been widely used [13].

Analyses

We used IBM SPSS statistical software (version 22). Descriptive statistics described means, standard error and confidence intervals. We studied patients with all data available at the trial endpoints. We divided patients into EULAR non-responders, moderate responders and good responders. We compared changes in HAQ and EQ5D scores between good and moderate EULAR responders for each trial using the independent samples *t* test. We also subdivided moderate and good EULAR responders by their final DAS28 scores. In addition, we used the previous NICE criterion for remaining on treatment (change in DAS28 score > 1.2) to categorise patients, replicating EULAR response criteria by dividing patients into those who also achieved DAS28 low disease activity scores at the trial endpoint and those who did not. Finally, we assessed the numbers of patients who achieved different levels of improvement in HAQ and EuroQol scores in both trials in relation to moderate and good EULAR responses.

Results

Patients studied

In the CARDERA trial 121 patients (32 %) were EULAR non-responders, 160 (42 %) moderate responders and 98 (26 %) good responders. In the TACIT trial 34 patients (18 %) were EULAR non-responders, 86 (46 %) moderate responders and 66 (35 %) good responders. The trial designs differed, with all patients in TACIT but not CARDERA receiving intensive therapy; consequently, differences in response rates were expected. In both trials demographic characteristics, clinical variables like DAS28 scores and components of the DAS28, HAQ and EQ5D scores were similar across groups. As this

secondary analysis does not assess treatment effects no comparative data between groups are presented.

Baseline and endpoint scores

Baseline and final endpoint data for DAS28 and HAQ and EQ5D scores in both trials for different EULAR responses are shown in Table 1. In the CARDERA trial there were no significant differences between baseline scores in any EULAR responder groups. In the TACIT trial the good EULAR responders had lower baseline HAQ scores and higher baseline EQ5D scores.

Differences in disability between EULAR moderate and good responders

Only patients with either moderate or good EULAR responses had significant reductions in HAQ scores at the trial endpoints (Table 2). Moderate responders had reductions in HAQ scores of 0.39 and 0.33 in the CARDERA and TACIT trials, respectively. Good responders had reductions of 0.88 and 0.64, respectively. In both trials the difference between moderate and good responders exceeded the MCID for HAQ scores (0.22) with differences in reductions of 0.49 and 0.30, respectively. These differences were significant ($p < 0.01$, unpaired t test).

Changes in quality of life

The mean EQ5D scores had a similar pattern. Only patients with moderate or good EULAR responses had significant improvements in EQ5D scores at the trial endpoints (Table 3). Moderate responders had increases in EQ5D scores of 0.18 and 0.15 in the CARDERA and TACIT trials, respectively. Good responders had increases of 0.30 in both trials. The difference between moderate and good responders exceeded the EQ5D MCID (0.07) in both trials with differences in increases in EQ5D scores of 0.12 and 0.15, respectively. These differences were significant ($p < 0.01$, unpaired t test).

Alternative assessments of response

Similar analyses based on patients achieving reductions in DAS28 > 1.2 , subdivided by whether or not they also achieved low DAS28 at the trial endpoints, were similar in relation to both HAQ and EQ5D scores. Patients who did not achieve low disease activity scores had only modest improvements in both scores (detailed results not shown).

Additional benefits of achieving remission

Another analysis subdivided patients achieving good EULAR responses into those who were also in remission and those who were not at the trial endpoints. In the CARDERA trial 70/98 patients (71 %) with good responses were in remission and 28/98 (29 %) were not. There were non-significant benefits for both HAQ scores and EQ5D scores with remission; mean differences between groups were -0.29 (95 % CI $-0.61, 0.02$) for HAQ scores and 0.11 ($-0.02, 0.24$) for EQ5D scores. In the TACIT trial 41/66 patients (62 %) with good responses were in remission and 25/66 (38 %) were not. There were also non-significant benefits for both HAQ scores and EQ5D scores with remission. The mean differences between the groups were -0.13 ($-0.41, 0.14$) for HAQ and 0.08 ($-0.07, 0.24$) for EQ5D.

Categories of HAQ and EQ5D change with EULAR responses

In the CARDERA trial 63 % of patients with moderate EULAR responses had improvements in HAQ exceeding the MCID (0.22) compared with 79 % of patients with good EULAR responses. In the TACIT trial 57 % of patients with moderate EULAR responses had improvements in HAQ exceeding the MCID compared with 80 % of patients with good EULAR responses. On more detailed analysis (Fig. 1) there was a wide range in HAQ score improvements in both trials in moderate and good EULAR responders; more patients with large improvements in

Table 1 Baseline and endpoint assessments in completers in the TACIT and CARDERA trials (mean scores (95 % confidence intervals))

EULAR Response	Number	DAS28		HAQ		EQ5D	
		Initial	Endpoint	Initial	Endpoint	Initial	Endpoint
CARDERA trial							
None	121	5.45 (5.22, 5.68)	5.67 (5.45, 5.89)	1.43 (1.30, 1.56)	1.53 (1.39, 1.67)	0.46 (0.40, 0.51)	0.48 (0.43, 0.53)
Moderate	160	6.08 (5.89, 6.27)	4.21 (4.07, 4.35)	1.70 (1.60, 1.80)	1.31 (1.20, 1.42)	0.42 (0.37, 0.46)	0.60 (0.56, 0.63)
Good	98	5.57 (5.33, 5.80)	2.17 (2.04, 2.30)	1.47 (1.35, 1.60)	0.60 (0.48, 0.72)	0.47 (0.42, 0.52)	0.77 (0.73, 0.80)
TACIT trial							
None	34	6.40 (6.08, 6.71)	6.34 (6.06, 6.63)	2.15 (2.00, 2.29)	2.11 (1.94, 2.28)	0.22 (0.11, 0.33)	0.23 (0.13, 0.34)
Moderate	86	6.30 (6.11, 6.49)	4.23 (4.07, 4.38)	1.91 (1.78, 2.04)	1.58 (1.42, 1.73)	0.41 (0.35, 0.47)	0.56 (0.51, 0.61)
Good	66	6.13 (5.96, 6.30)	2.29 (2.14, 2.44)	1.64 (1.47, 1.81)	1.00 (0.81, 1.19)	0.40 (0.32, 0.47)	0.69 (0.64, 0.75)

TACIT tumour necrosis factor inhibitors against combination intensive therapy, CARDERA cost-effectiveness of treatment strategies using combination of disease modifying anti-rheumatic drugs and glucocorticoids in early rheumatoid arthritis, EULAR European League Against Rheumatism, DAS28 twenty-eight joint disease activity score, HAQ Health Assessment Questionnaire, EQ5D Euroqol-5D

Table 2 Changes in disability (HAQ scores) by EULAR response mean scores (95 % confidence intervals)

	None	Moderate	Good	Difference moderate and good
CARDERA	0.10 (-0.01, 0.21)	-0.39 (-0.48, -0.30)	-0.88 (-1.02, -0.73)	-0.49 (-0.66, -0.32)
TACIT	-0.04 (-0.15, 0.08)	-0.33 (-0.44, -0.22)	-0.64 (-0.77, -0.51)	-0.30 (-0.47, -0.13)

EULAR European League Against Rheumatism, CARDERA cost-effectiveness of treatment strategies using combination of disease-modifying anti-rheumatic drugs and glucocorticoids in early rheumatoid arthritis, TACIT tumour necrosis factor inhibitors against combination intensive therapy

HAQ scores exceeding 1.0 had good EULAR responses, particularly in the early RA trial (CARDERA). In this trial 41 % of patients with good EULAR responses had improvements in HAQ over 1.0.

Changes were similar with the EQ5D scores. In the CARDERA trial 59 % of patients with moderate EULAR responses had improvements in EQ5D scores exceeding the MCID (0.07) compared with 80 % of patients with good EULAR responses. In the TACIT trial 59 % of patients with moderate EULAR responses had improvements in EQ5D scores exceeding the MCID compared with 79 % of patients with good EULAR responses. On more detailed analysis (Fig. 2) there was a wide range in improvement in the EQ5D scores in both trials in moderate and good EULAR responders; more patients with good EULAR responses had large improvements in EQ5D scores. The benefits from achieving good EULAR responses were less marked with improvements in EQ5D scores.

Discussion

Our secondary analyses of two large English RCTs in early and established active RA shows that patients with good EULAR responses have larger clinically meaningful improvements in disability and quality of life than patients with moderate EULAR responses. These findings support the concept of treat-to-target. They indicate that achieving low disease activity or remission states should be the treatment goal. The benefits of good EULAR responses are seen in both early and established RA. The findings were similar if we used the earlier NICE criterion of an improvement in DAS28 of more than 1.2.

The reliance of current NICE guidance on changes in DAS28 of more than 1.2 has been criticised by Jerram et al [14], who point out that this threshold was not used in clinical trials. This concern is ameliorated by the new NICE guidance. Judging patients' responses to DMARDs and biologic therapy is challenging. EULAR response criteria were designed for use in individual patients and trials. The other major composite response criteria, the

American College of Rheumatology (ACR) criteria, are only intended for trials. These two validated response criteria have been compared in several studies [15, 16]; they measure similar changes. However, their use in routine clinical practice and relating their findings to patients' perceived responses requires more research. Gulfe et al. showed that when response criteria are used at the individual patient level the results are difficult to interpret [17]. Ward et al. [18] found patients' perceptions of improvement may differ from conventional assessments like ACR20 responses, and that thresholds of minimal clinically important improvement may be larger than previously thought, including the need for a DAS28 improvement of at least 1.2 [19]. Among patients receiving treatment for active RA, three months may be the optimal time point to increase the intensity of treatment [20]. However, when assessing response to biologic therapy, real-world evidence suggests a six-month time point is needed to optimise patients' responses [21].

Low disease activity optimises key patient-related outcomes like HAQ and EQ5D scores [22–24]. Our own findings mirror these previous reports. Remission is one potentially important outcome, although only a minority of our patients achieved this. Interestingly some other trials in early RA, such as the FIN-RACo trial [25], reported higher remission rates; the reasons for this heterogeneity are uncertain. When patients achieve sustained remission, they have less long-term work disability [26]. Some patients with moderate EULAR responses in our trials had good reductions in disability and improvements in quality of life. However, many did not and the best management of such patients is uncertain. Continuing to prescribe high-cost biologic therapy for patients with modest improvements in disease activity and little or no reduction in disability seems questionable. It may be preferable to continue biologic treatments in patients with moderate EULAR responses who have also had clinically meaningful reductions in disability.

Our report has several strengths. The two trials were large, there was reasonable patient retention on treatment,

Table 3 Changes in health-related quality of life (EQ5D scores) by EULAR response mean scores (95 % confidence intervals)

	None	Moderate	Good	Difference moderate and good
CARDERA	0.02 (-0.03, 0.07)	0.18 (0.14, 0.23)	0.30 (0.24, 0.35)	0.12 (0.04, 0.19)
TACIT	0.00 (-0.13, 0.14)	0.15 (0.08, 0.21)	0.30 (0.22, 0.37)	0.15 (0.05, 0.25)

EQ5D EuroQol-5D, EULAR European League Against Rheumatism, CARDERA cost-effectiveness of treatment strategies using combination of disease-modifying anti-rheumatic drugs and glucocorticoids in early rheumatoid arthritis, TACIT tumour necrosis factor inhibitors against combination intensive therapy

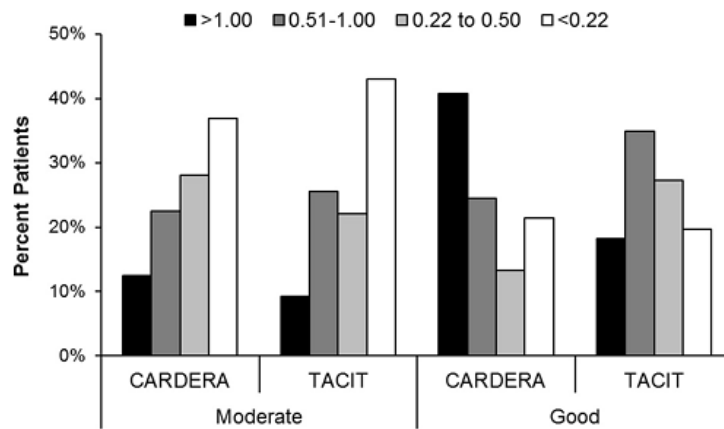


Fig. 1 Changes in Health Assessment Questionnaire (HAQ) scores in four categories in moderate and good European League Against Rheumatism (EULAR) responders in both the cost-effectiveness of treatment strategies using combination of disease-modifying anti-rheumatic drugs and glucocorticoids in early rheumatoid arthritis (CARDERA), and tumour necrosis factor inhibitors against combination intensive therapy (TACIT) trials

and they were based across many English specialist centres with a broad geographic spread. We found similar effects in trials of early and established RA. Our findings are therefore likely to be generalisable in guiding clinical practice decisions.

Our analyses also have limitations. First, we only considered differences at the trial endpoints. Different effects would have been seen by evaluating all time points. Second, choosing specific cutoff points, such as DAS28 of 3.2 or less may have over done similarly well. Third, some of the treatments used, particularly ciclosporin, which was used in the CARDERA trial, are not commonly prescribed in routine practice. Fourth, we combined the

effects of a range of different treatments, and the relationship between disease activity and HAQ and EQ5D scores may be different across drug classes. Finally, our inference that patients who do not achieve low DAS28 scores with one treatment strategy may do better with another could be incorrect; some patients may achieve poor outcomes with all treatment strategies.

Conclusions

Achieving good EULAR responses to treatment with DMARDs and biologic agents leads to substantial improvements in HAQ and EQ5D scores. Patients who achieve such responses should continue on treatment.

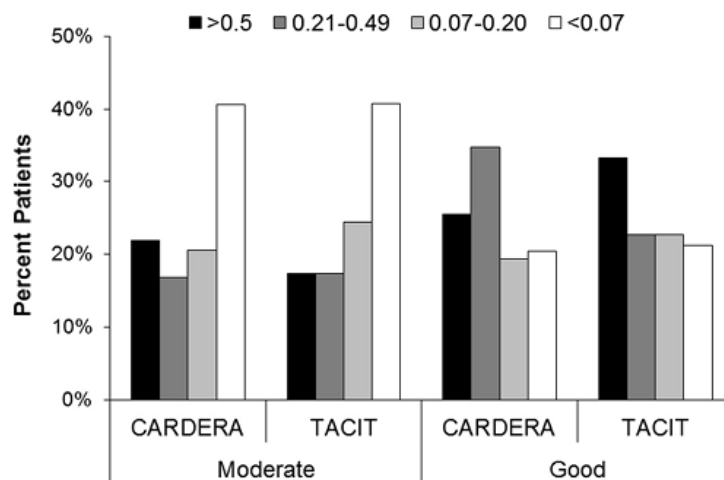


Fig. 2 Changes in EuroQol-5D (EQ5D) scores in four categories in moderate and good European League Against Rheumatism (EULAR) responders in both the cost-effectiveness of treatment strategies using combination of disease-modifying anti-rheumatic drugs and glucocorticoids in early rheumatoid arthritis (CARDERA), and tumour necrosis factor inhibitors against combination intensive therapy (TACIT) trials

However, continuing patients on intensive treatment regimens, particularly using high-cost biologic agents, is more challenging if they only achieve moderate EULAR responses. Evidence of additional clinically important benefits in measures such as the HAQ should also be sought to justify continuing treatment in these patients.

Abbreviations

ACR, American College of Rheumatology; CARDERA, Cost-effectiveness of treatment strategies using combination of disease-modifying anti-rheumatic drugs and glucocorticoids in early rheumatoid arthritis; CI, confidence interval; DAS28, twenty-eight joint disease activity score; DMARD, disease-modifying anti-rheumatic drug; EQ5D, Euroqol-5D (a standardized instrument for measuring generic health status); EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; MCID, minimal clinically important difference; NICE, National Institute of Health and Care Excellence; RA, rheumatoid arthritis; RCT, randomized controlled trial; TACIT, tumour necrosis factor inhibitors against combination intensive therapy

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Authors' contributions

AM and FI carried out the analysis and drafted the manuscript. DS and JG conceived the study, participated in the design and coordination and helped draft the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The CARDERA trial was approved by the South East Multicentre Research Ethics Committee ((MREC(1)99/04)). The TACIT trial was approved by University College London Hospital research ethics committee (MREC Ref: 07/Q0505/57). All patients gave written informed consent.

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Chapter 6 PREDICTING TREATMENT RESPONSES IN RA

**This chapter is presented as a published paper and is a copy of the following
journal publication:**

NJ Gullick, **A Mian**, F Ibrahim, D Walker, A Hassell, PDW Kiely, R Williams,

David A Walsh, A Young, DL Scott and TITRATE Programme Investigators.

Predicting responses in patients with rheumatoid arthritis to disease modifying
agents using baseline clinical data. Clin and Exp Rheumatol, 2017; 35(5):810-815.

Predicting responses in patients with rheumatoid arthritis to disease-modifying agents using baseline clinical data

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Abstract Objective

The optimal treatment for active rheumatoid arthritis (RA) is unresolved, particularly in early RA. We used data from an observational cohort to develop the simple predictor algorithm and evaluated its application in two completed clinical trials in early and established RA. We assessed whether using a simple algorithm can identify patients who have persisting active disease despite treatment with disease-modifying drugs (DMARDs). We also examined if patients who have lower likelihoods of persisting active RA are likely to benefit from intensive treatment.

Methods

We developed a simple predictive score for persisting disease activity using conventional clinical assessments in an observational cohort of patients with early RA (ERAN). It was tested in two trials in early (CARDERA) and established (TACIT) RA. Persistent disease activity was defined as disease activity score for 28 joints (DAS28) >3.2 at both 6 and 12 months.

Results

Regression modelling identified three main predictors of persisting active disease in ERAN; tender joint counts, health assessment questionnaire (HAQ) scores and ESR. We dichotomised these predictors (≥ 6 tender joint counts, ≥ 1.0 HAQ ≥ 20 mm/h ESR) in a four-point prediction score. This simple prediction score predicted persisting active disease in the ERAN cohort and both CARDERA and TACIT trials. Patients with high scores were more likely to have persistently active disease at 6 and 12 months. The relationship was weaker in TACIT because no patients were without any predictive factors.

Conclusion

Combining tender joint counts, ESR and HAQ in a simple predictive score prospectively identifies patients with higher risks of persistent disease activity over the next 12 months. More patients with all three risk factors had persistent active disease than those with none or one risk factor.

Key words

outcome, early rheumatoid arthritis, treatment response, health utility

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Introduction

The optimal treatment for active rheumatoid arthritis (RA) is unresolved, particularly in early RA. Monotherapy with methotrexate and other disease-modifying anti-rheumatic drugs (DMARDs) is often insufficient. Initial intensive management with either combination DMARDs or DMARD monotherapy with biologics like tumour necrosis factor (TNF) inhibitors, though more effective, risks over-treating some patients (1). The uncertainty about which RA patients need intensive treatment is reflected in divergent advice from management guidelines (2-4).

One way to minimise uncertainty is to use response predictors to judge if intensive treatment is needed. Several clinical variables predict poor treatment outcomes, including longer disease durations, female gender, high disability and disease activity levels, rheumatoid factor positivity and smoking (5-8). Treatment response predictors have been studied in detail in early RA. Studies show responses to methotrexate and other DMARDs are predicted by rheumatoid factor and anti-citrullinated peptide antibody positivity, female gender, disease activity, disability scores, genetic risks and smoking status (9-14).

Clinical trials in RA usually enrol patients with active disease identified with simple assessments, like 6 or more tender and swollen joints and ESRs of 28mm/h or more (15). Not all early RA patients need intensive treatment and a simple algorithm using commonly recorded clinical assessments may identify early RA patients likely to respond poorly to initial DMARD monotherapy. The goal using DMARDs is sustained low disease activity. We therefore designed an algorithm to identify patients with persistent active disease (DAS28 ≥ 3.2) at 6 and 12 months despite DMARDs. Data from an observational cohort (16) helped develop a simple predictor algorithm. We evaluated it using published clinical trials in early (17) and established RA (18). We asked two specific questions. Firstly, can a simple algorithm identify patients who with persisting active disease despite DMARDs? Secondly, will patients at higher risk of persistent disease activity benefit from intensive treatment?

Methods

Observational study

We studied data collected from 2002–2007 in patients from the Early RA Network (ERAN) observational cohort. This inception cohort of patients with newly diagnosed RA was recruited from 19 UK centres. It reflected contemporary routine care. 62% fulfilled four or more ACR criteria for RA at first visit. Most patients (97%) received DMARDs; 91% received initial DMARD monotherapy (usually sulfasalazine or methotrexate); 9% received DMARD combinations; details of these ERAN patients have been previously reported (21).

Clinical trials

We studied patients in two trials. The first, in early RA, was the combination anti-rheumatic drugs in early RA (CARDERA) trial. The second, in established RA, was the tumour-necrosis-factor inhibitors against combination intensive therapy with conventional disease-modifying anti-rheumatic drugs in established RA (TACIT) trial. CARDERA recruited active RA patients of less than 24 months' duration meeting the 1987 ACR classification criteria. They had active disease with three of the following: ≥ 3 swollen joints, ≥ 6 tender joints, ≥ 45 minutes morning stiffness and an erythrocyte sedimentation rate (ESR) > 28 mm/h. It compared methotrexate monotherapy, methotrexate with cyclosporine, methotrexate with steroid or all three drugs (17). The trial lasted 24 months.

TACIT recruited patients with active RA (18). Patients met the 1987 ACR classification criteria for RA and had active disease (two DAS28 scores over 5.1 at least one month apart). They received combination DMARDs, with tumour necrosis factor inhibitors given to non-responders after 6 months, or initial tumour necrosis factor inhibitors with DMARD monotherapy. The trial lasted 12 months.

Approval

Ethical approval was obtained for ERAN from the Trent Research Ethics Committee (ref. 01/4/047) for CARDERA from the South East Multicentre Research Ethics Committee (ref.

MREC (1) 99/04) and for TACIT from the University College London Hospital research ethics committee ref. 07/Q0505/57). All patients gave written, informed consent.

Data analysed

Patient demographics (age, sex, disease duration), Disease Activity Score for 28-joints (DAS28) and its components, disability using the health assessment questionnaire (HAQ), treatments with disease-modifying drugs (DMARDs), biologics and steroids were available for analysis in all studies. In ERAN rheumatoid factor and baseline smoking status was also analysed.

Persistent disease activity

Persistent disease activity was defined as a DAS28 of greater than 3.2 at both 6 and 12 month visits (19).

Statistical analysis

Predictors of persistent disease activity in ERAN were assessed using logistic multiple regression and expressed as odds ratios (OR) with 95% confidence intervals (CI). The baseline explanatory variables considered were sex, tender joint count, swollen joint count, ESR, DAS28 and HAQ. As DAS28 was strongly associated with all other variables it was not included in the model. Chi-squared tests compared the proportion of patients with low disease activity scores. Statistical analyses were performed using SPSS v. 17 (SPSS Inc). *P*-values of less than 0.05 were considered statistically significant.

Results

Patient cohorts

We studied 155 patients in the observational cohort (ERAN) who had completed 12 months' follow-up and who had had clinical data collected at 0, 6 and 12 months. The CARDERA trial enrolled 465 patients with early RA; we evaluated 377 patients where complete data were available. The TACIT trial enrolled 205 patients with established RA; we evaluated 179 patients with all data available. Baseline characteristics of each group are shown in Table I.

Table I. Baseline patient characteristics in the ERAN and CARDERA studies.

Characteristics	ERAN cohort (n=155)	CARDERA trial (n=465)	TACIT trial (n=205)
Mean age (SD)	56 (14)	54 (13)	57 (12)
Women (%)	101 (65%)	325 (70%)	152 (74%)
Tender joints	8 (7)	11.8 (7.6)	17 (7)
Swollen joints	6 (6)	9.9 (6.3)	11 (6)
ESR	30 (25)	41 (29)	32 (25)
Health Assessment Questionnaire	1.1 (0.8)	1.6 (0.7)	1.8 (0.6)
DAS28	4.7 (1.6)	5.8 (1.3)	6.3 (0.9)

Table II. Overall predictors of persistently active disease in ERAN patients.

Predictor	Unadjusted		Adjusted	
	OR (95% CI)	Significance	OR (95% CI)	Significance
Tender joint count	1.16 (1.09, 1.23)	<0.01	1.11 (1.04, 1.19)	<0.01
HAQ	3.83 (2.23, 6.54)	<0.01	2.10 (1.16, 3.81)	<0.02
ESR	1.06 (1.03, 1.08)	<0.01	1.05 (1.02, 1.08)	<0.01
Swollen joint count	1.13 (1.05, 1.21)	<0.01	-	NS

Developing simple predictive model using observational data

Regression modelling assessed the effects of individual predictors of persisting active disease (DAS28 >3.2 at 6 and 12 months) using ERAN data. An unadjusted regression model showed initial tender joint counts, HAQ, ESR and swollen joint counts were all predictive factors (Table II). Age, gender, smoking and rheumatoid factor status did not show significant relationships. Variables which remained significantly associated at 5% level with persisting active disease in univariate analysis were subsequently included in a multivariable logistic regression model. This adjusted model showed the three key predictors of persisting active disease comprised tender joint counts, HAQ and ESR (Table II). This regression model was subsequently transformed into a simple practical score by dichotomising these three key predictors. We used cut-offs of ≥ 6 tender joint counts, ≥ 1.0 HAQ and ≥ 20 mm/h ESR as simple predictors, based on clinical utility. All three dichotomised variables showed significant associations in unadjusted and adjusted models (data not shown). We combined these three simple predictors into a four point prediction score (0–3). It showed strong relationships to all patients in the ERAN cohort and also those patients in the ERAN cohort who had been treated with methotrexate (Table III).

Confirmatory studies using clinical trial data

The simple predictors score developed in the observational cohort showed similar relationships in patients in the CARDERA trial (Table IV); only 20% of patients with no initial predictors had persistent active disease, compared with 80% of patients with all three initial predictors. There was a similar, though weaker relationship in the TACIT trial; this was mainly because no TACIT patients fell into the lowest prediction category without any predictive factors. In both trials, patients with high scores were more likely to have persistently active disease at 6 and 12 months (Table IV).

We also evaluated the impact of treatment type. In CARDERA 90% of patients with all three poor predictive factors who received methotrexate monotherapy had persistently active disease. This was reduced to 76% in the triple therapy group (Table IV). There was no difference in the predictive capacity for different treatment strategies in TACIT.

Initial predictors, remission, and treatment intensities in clinical trial patients

In both the CARDERA and TACIT trials there were significant overall relationships between remissions at trial end-points (24 and 12 months, respectively) and initial predictive factors.

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Table III. Simplified predictors of persistently active disease at 6 and 12 months in the ERAN cohort.

Patients	DAS28 at 6 and 12 months	Combination of TJ ≥ 6 , HAQ ≥ 1.0 and ESR $\geq 20^*$				Significance
		0	1	2	3	
All treatments	≤ 3.2	21	27	9	4	$\chi^2=51.2$; DF=3; $p<0.01$
	>3.2	5	16	38	36	
	Percent with active disease	19%	37%	81%	90%	
Methotrexate monotherapy	≤ 3.2	5	7	5	2	$\chi^2=11.6$; DF=3; $p<0.01$
	>3.2	3	7	15	20	
	Percent with active disease	38%	50%	75%	91%	

*These variables were measured at baseline.

Table IV. Applying simplified predictors of persistently active disease to clinical trial patients.

Trial	DAS28 at 6 and 12 months	Combination of TJ ≥ 6 , HAQ ≥ 1.0 and ESR $\geq 20^*$				Significance
		0	1	2	3	
CARDERA (All treatments)	≤ 3.2	8	25	40	24	$\chi^2=41.1$; DF=3; $p<0.01$
	>3.2	2	29	99	150	
	Percent with active disease	20%	54%	71%	86%	
CARDERA (Methotrexate monotherapy)	≤ 3.2	2	2	10	3	$\chi^2=14.9$; DF=3; $p<0.01$
	>3.2	0	8	26	41	
	Percent with active disease	0%	80%	72%	93%	
CARDERA (Triple therapy)	≤ 3.2	1	11	14	9	$\chi^2=8.9$; DF=3; $p<0.05$
	>3.2	0	7	26	28	
	Percent with active disease	0%	39%	65%	76%	
TACIT (All treatment)	≤ 3.2	-	8	31	40	$\chi^2=5.9$; DF=2; $p=0.05$
	>3.2	-	2	38	60	
	Percent with active disease	-	20%	55%	60%	

*These variables were measured at baseline

When different treatments were evaluated, these relationships were not seen with methotrexate monotherapy in the CARDERA trial and the DMARD strategy in the TACIT trial. They only occurred with triple therapy in CARDERA and the biologic strategy in TACIT.

Discussion

Our results show combining three initial clinical assessments before a new treatment is started in RA patients – tender joint count, ESR and HAQ – produce a simple algorithm which prospectively identified patients with higher risk of persistent disease activity over 12 months. The predictive value was similar in ERAN and CARDERA patients and comparable in TACIT patients. Substantially more patients with all three risk factors had persisting active disease than those with none or one risk factor. Our approach falls within the framework for prognostic studies recommended by the Progress Partnership (20).

Previous research shows genetic predictors appear important in determining responses to methotrexate and other DMARDs in early RA, particularly genes associated with methotrexate metabolism (21). There has also been extensive interest in identifying general prognostic indicators in early RA (22) and predictors of erosive progression (23, 24), functional disability (25, 26), extra-articular disease (27) and remission (28, 29). A different approach is using synovial pathobiology, but this is at a more developmental stage (30). None of these previous studies have focused on simple clinical algorithms of the sort we have developed.

A critical issue when treating patients with active RA is whether all patients are likely to benefit from intensive treatment. Although we were able to identify patients likely to fail to have their RA controlled with current treatment strategies, there was evidence that patients with all risk profiles benefitted from intensive treatment. TAC-

IT showed patients with only one risk predictor had substantial benefit from the biologic strategy with 75% achieving remission at the trial end-point. Interestingly, Markusse *et al.* (31) suggested that benefits from intensive treatment should be extended to all patients and not restricted to poor prognosis patients. However, this perspective is controversial (32).

Our study has several strengths. In particular we studied large numbers of patients and replicated our findings across two clinical trials in both early and established RA. It also has a number of limitations. We did not include genetic predictors, which may be crucial predictors of response. Second, we did not evaluate rheumatoid factor isotypes or anti-citrullinated peptide antibodies, which may also be important response predictors. Third, using simple predictors failed to identify all patients with persistently active disease. This is partly because intensive treatments used in CARDERA and TACIT trials did not

prevent a substantial proportion of persistently active disease. Finally, our patients were enrolled before the introduction of new diagnostic criteria for the classification of early RA (33), although there is uncertainty about the impact of these criteria when used to prospectively identify patients with early RA (34, 35). However, there is growing evidence the new criteria change the exact nature of patients classified as having RA, particularly patients with seronegative disease (36, 37). In addition the clinical phenotype and frequency of RA may also be changing over time (38). It is possible these changes in classification and disease phenotype could alter the impact of our prognostic criteria. We conclude RA patients have variable outcomes to treatment with DMARDs and biologics, which can in part be predicted using a simple algorithm. This concept builds on previous research about the predictive value of high DAS28 scores (38) and high HAQ scores [39]. This indicates that patients may not need identical treatment regimens; treatments should be individualised. However, the ability of the treatments used in this study to control RA, given in a range of settings during the last 10–15 years, seems incomplete. There is substantial supportive evidence in studies of biologics in a range of routine clinical practice settings (41, 42). Consequently, we consider most patients with active RA need to follow an intensive treatment regimen. Our findings suggest treatment intensities are still sub-optimal and there is a need to identify more effective treatment modalities and combinations of new and existing agents.

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Chapter 7 ULTRASOUND AND DETERMINING DISEASE ACTIVITY

**This chapter is presented as a published paper and is a copy of the following
journal publication:**

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Rheumatoid arthritis patients with fibromyalgic clinical features have significantly
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RESEARCH ARTICLE

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Rheumatoid arthritis patients with fibromyalgic clinical features have significantly less synovitis as defined by power Doppler ultrasound

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Abstract

Background: In patients with rheumatoid arthritis (RA) clinical measures of disease activity may not reliably discriminate between patients with active inflammatory disease and those with concomitant fibromyalgia (FM). Recent work has shown RA patients with a 28 tender joint count (TJC) minus swollen joint count (SJC) of 7 or more (joint count criteria) are more likely to meet classification criteria for FM. This study aimed to determine whether RA patients meeting clinical criteria for FM had lower levels of joint inflammation as determined by ultrasound (US).

Methods: RA patients with DAS28 > 2.6 were recruited. Patients underwent clinical assessment including ultrasound examination of the hands and wrists with quantification of grey scale (GS) and power Doppler (PD) synovitis. Patients completed questionnaires to assess pain, fatigue, disability and psychological comorbidity.

Results: Patients meeting either of the FM criteria had higher scores for disease activity, depression, disability and fatigue. Those meeting both the joint count and classification FM criteria had significantly lower levels of GS and PD inflammation on US.

Conclusions: RA patients with concomitant FM, as determined by widespread soft tissue tenderness but fewer clinically inflamed joints, have higher disease activity scores but may have lower levels of synovial inflammation on US. This has implications for the identification and management of these patients who may not respond to conventional therapy and hence be more suitable for alternative approaches to treatment.

Keywords: Rheumatoid arthritis, Fibromyalgic rheumatoid, Ultrasound

Background

Rheumatoid Arthritis (RA) is a chronic inflammatory arthritis which, if untreated, can lead to progressive joint damage, disability, and reduced quality of life. Evidence suggests that the a 'treat to target' approach achieves better outcomes [1]. The frequently used twenty-eight joint disease activity score (DAS28) includes both objective and subjective measures and hence non-inflammatory

factors contribute to patient-reported measures, pain and tenderness.

Fibromyalgia (FM) is a condition characterized by chronic widespread pain and tender points on clinical examination. In the majority of patients, it is associated with psychological comorbidity, sleep disturbance, fatigue and other somatic symptoms which are reflected in recently proposed diagnostic criteria [2]. An estimated 20 % of patients with RA have co-existing fibromyalgia [3]. The presence of concomitant FM can make treatment decisions challenging, as disease activity scores can be high despite limited clinical evidence of active synovitis [4]. As the DAS28 cannot distinguish these two groups of patients who require different treatment pathways, it is

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important to ascertain other discriminatory measures. It is unknown whether clinical criteria, including those for FM, are sufficient to discriminate those with active from those with inactive disease.

Recent work [5] has suggested that a tender joint count from 28 (TJC) minus swollen joint count (SJC) of at least 7 (joint count criteria) predicts with high sensitivity and specificity RA patients who also meet 1990 ACR FM classification criteria (tender point criteria). It is currently unknown whether the joint count or tender point count can differentiate patients with RA with genuinely lower inflammatory disease activity and hence be used to guide treatment decisions.

The aim of this pilot study was therefore to determine if RA patients with similar clinical disease activity assessed by DAS28 with clinical features of FM, as defined by the tender joint criteria have lower levels of joint inflammation compared with RA patients without FM as determined by US.

Methods

Participants

Patients meeting either the 1987 ACR or the 2010 ACR/EULAR 2010 RA classification criteria with DAS28(ESR) > 2.6 were recruited. Patients were categorized into those meeting or not meeting the joint count criteria i.e., TJC minus SJC ≥ 7 , or TJC minus SJC < 7. Patients were recruited sequentially until approximately equal numbers were recruited to each group.

Ethical approval

Research ethics committee approval was obtained from the Greenwich REC (# 234567) prior to commencing the study. The study was carried out according to the principles of Good Clinical Practice. All participants provided written informed consent.

Assessments

Patients underwent clinical assessment including 28 tender/swollen joint count with ESR (DAS28) and assessment of soft-tissue tender points. The examining physician recorded the Symptom Severity Score (SSS). Patients completed a series of questionnaires including PHQ9 (depression), GAD7 (anxiety), PHQ15 (somatisation), FACIT-fatigue (fatigue), HAQ (disability), global assessment visual analogue scale, and the Widespread Pain Index (WPI).

Patients underwent ultrasound examination by a second physician blinded to the results of the clinical assessment. US was carried out in a darkened room, in a seated position with hands prone. Scanning was performed using Logic 9 (GE Healthcare) scanner with an 14 MHz transducer. US views were taken using standardised transducer orientation, taking longitudinal images of the MCPs, PIPs, and wrists (radiocarpal, ulnar carpal and intercarpal). PRF

was set at 1.4KHz and PD gain was set to just below the threshold where PD signal disappeared. Grey scale (GS) still images and 3 s PD images were recorded. A semi quantitative score was used to grade GS and PD for each joint (0 no GS or PD signal, 1 = minimal, 2 = moderate, 3 = severe) according to validated criteria [5] and a total derived for each patient for each of GS and PD.

Analysis

Statistical analysis was carried out using SPSS version 22 (IBM). Descriptive statistics (mean, standard deviation and confidence intervals) were used for patient characteristics. PD and GS ultrasound score differences between groups were tested using the Mann–Whitney *U* test. Significance was set at $p < 0.05$. Mann–Whitney *U* tests were used to compare difference between patient reported outcome measures between the two groups.

Results

Forty-seven patients with active RA on disease-modifying therapy were recruited. The patient characteristics are shown in Table 1. The mean age of the patients was 61; 81 % were women, and 70 % were positive for rheumatoid factor. Mean DAS28 of the patients was 4.5, with 43 % with moderate disease activity (DAS28 > 3.2 and < 5.1), and 36 % with high disease activity (DAS28 > 5.1). The mean HAQ was 1.5 (range 0.25–2.5).

Forty percent of patients fulfilled the ACR 1990 Classification Criteria (CC) and/or the 2010 preliminary diagnostic criteria (DC) for fibromyalgia with 25 % meeting both criteria. 53 % of patients had TJC minus SJC ≥ 7 thus meeting the 'joint count' criteria and 36 % of patients met both 'joint count' and 'classification' criteria.

Mean DAS28 scores were significantly higher for patients meeting versus those not meeting FM classification criteria, with scores of 5.23 (SD 0.75) and 4.11 (1.0) respectively ($p < 0.001$). Mean DAS28 scores were also significantly higher for patients meeting versus not meeting the tender joint count with scores of 4.99 (0.97) and 4.03 (1.0) respectively ($p = 0.002$). Tender joint counts were also significantly higher in patients meeting the FM classification criteria versus those not meeting criteria 15.66 (5.84) and 7.39 (5.40) respectively ($p < 0.001$). Tender joint counts were also higher in patients meeting the tender joint count criteria versus those not meeting criteria with mean tender joint counts of 15.15 (5.21) and 5.24 (4.17) respectively. Patient global scores were numerically higher for patients meeting FM classification criteria versus those not meeting criteria with scores of 57.05 (18.31) and 49.50 (20.52) respectively, however these did not reach significance ($p = 0.23$). The same was true for patient global scores for patients meeting versus not meeting the tender joint criteria with scores of 56.42 (18.45) and 47.76 (20.82) ($p = 0.13$). There were no significant

Table 1 Patient characteristics

	TJC minus SJC ≥ 7 (TJC criteria) <i>n</i> = 26	TJC minus SJC <7 <i>n</i> = 21	<i>P</i>	TP ≥ 11 (ACR 1990 criteria) <i>n</i> = 19	TP <11 <i>n</i> = 28	<i>P</i>	Fulfil both ACR 1990 and TJC criteria <i>n</i> = 17	Do not meet both TJC and ACR criteria <i>n</i> = 30	<i>P</i>
Age (SD)	57	66		57	63		57	63	
Sex F (%)	22 (85)	16 (76)		16 (84)	22 (79)		15 (88)	24 (80)	
RF ^a (%)	16 (62)	17 (81)		10 (53)	23 (82)		9 (53)	24 (80)	
DAS28 (SD)	4.99 (0.97)	4.03 (1.00)	0.002	5.23 (0.75)	4.11 (1.00)	<0.001	5.27 (0.68)	4.16 (1.07)	<0.001
TJ (SD)	15.15 (5.21)	5.24 (4.17)	<0.001	15.663 (5.84)	7.39 (5.40)	<0.001	16.47 (5.52)	7.47 (5.26)	0.002
SJ (SD)	1.50 (1.99)	3.52 (3.82)	0.67	1.84 (2.29)	2.79 (3.51)	0.44	1.71 (2.14)	2.80 (3.48)	0.457
ESR (SD)	18.96 (14.79)	20.67 (18.53)	0.94	20.53 (14.44)	19.18 (17.84)	0.38	18.35 (10.99)	20.50 (18.92)	0.157
PG (SD)	56.42 (18.45)	47.76 (20.82)	0.13	57.05 (18.31)	49.50 (20.52)	0.23	59.65 (17.50)	48.53 (20.18)	0.487

^amissing data for one patient

Figures given as means and SD

DAS28 twenty-eight joint disease activity score, SJC swollen joint count, SJ swollen joints, TP tender points, TJC tender joint count, TJ tender joints, PG patient global, RF rheumatoid factor

differences in swollen joint counts or ESR. These results are shown in Table 1.

GS US scores were significantly lower in patients meeting either the FM classification or joint count criteria and for patients that fulfilled both criteria. PDUS scores for patients meeting either of these criteria were numerically lower but did not meet significance. However, patients who met both FM classification and joint count criteria had significantly lower PDUS scores (2.94, FM group vs 8.33, non-fibromyalgic group, $p = 0.028$) than those meeting a single fibromyalgia criteria or none. When the 2010 ACR preliminary diagnostic FM criteria were used, no differences were seen in US scores or other objective or subjective clinical measures except higher DAS28 scores and tender joint counts.

Significantly higher levels of fatigue (GAD7), depression (PHQ9) and disability (HAQ) were also seen in patients meeting either the joint count or classification criteria (Table 2). Scores for somatic symptoms and fatigue were not significantly different.

Discussion

Around 20 % of patients with RA may have concomitant fibromyalgia [3]. A number of studies have shown that RA patients with comorbid fibromyalgia, in most cases as defined as widespread pain with soft tissue tenderness, tend to have higher disease activity scores despite less objective evidence of active inflammatory disease [4]. This suggests that conventional disease activity scores may not be able to differentiate patients with differing causes of high DAS28 scores to allow selection of optimal treatment strategies. Patients with generalized pain driven by non-inflammatory mechanisms are unlikely to respond to therapies focused on suppressing inflammation. In our study median DAS28 scores were higher in patients meeting all definitions of fibromyalgia, an effect mainly driven by differences in the tender joint count.

It has been reported that a TJC minus SJC score greater than ≥ 7 ('joint count' criteria) identifies RA patients who are more likely to meet the 1990 ACR classification criteria for fibromyalgia, who score highly for disability, depression and fatigue [3]. This is supported by further data showing psychological distress and poor quality sleep, reduce pain thresholds in people with RA [3]. Psychological distress is predictive of the development of FM in patients with early inflammatory arthritis [6, 7]. Within the group of RA patients with concomitant FM and active disease defined by DAS28, but limited objective evidence of joint inflammation, it is unclear whether clinical measures can differentiate those with active synovial inflammation from those without.

PDUS is more sensitive than clinical examination for the presence of inflammation [8]: it is predictive of outcomes in RA and is hence increasingly used in clinical practice to inform treatment decisions [9]. It therefore has the potential to help to differentiate patients with joint pain secondary to generalised widespread pain from those with active synovial inflammation.

In this study we did not find a significant difference in PDUS scores between the FM versus non FM patients when the tender joint criteria were used. It is well-established that active synovitis can be demonstrated by PD in joints which are not clinically swollen [10] and so this may not be surprising. Furthermore, no significant differences were seen when either the 1990 classification or 2010 diagnostic criteria were used alone. Neither of the latter have been validated in the RA patient population. The identification of widespread non-inflammatory pain does not preclude the presence of active synovial inflammation so this is not an unexpected finding. A recent study comparing GS and PDUS findings in RA patients meeting or not meeting the 2010 diagnostic criteria for FM found no difference in total GSUS or PDUS scores of a panel of 7 joints [11]. The diagnostic criteria for FM

Table 2 Patient reported outcome measures: FACIT-fatigue (FF), GAD7 (anxiety), Health Assessment Questionnaire (HAQ), PHQ9 (depression), PHQ15 (somatization), Symptom Severity Score (SSS), Widespread Pain Index (WPI)

	TJC minus SJC ≥ 7 (joint count criteria) <i>n</i> = 26	TJC minus SJC < 7 <i>n</i> = 21	<i>P</i>	TP ≥ 11 (ACR 1990 classification criteria) <i>n</i> = 19	TP < 11 <i>n</i> = 28	<i>P</i>	Fulfil both ACR 1990 and joint count criteria <i>n</i> = 17	Do not meet both joint count and ACR criteria <i>n</i> = 30	<i>P</i>
GAD7	7.58	3.62	0.005	7.84	4.43	0.001	7.71	4.73	0.020
PHQ9	9.27	4.52	0.017	10.89	4.61	0.000	10.59	5.20	0.027
PHQ15	10.77	6.90	0.019	11.79	7.18	0.226	11.88	7.43	0.230
HAQ	1.70	1.27	0.070	1.84	1.29	0.002	1.85	1.32	0.005
FF	25.85	15.81	0.461	27.47	17.21	0.332	28.29	17.43	0.725
WPI	7.15	4.81	0.145	9.47	4.25	0.073	9.41	4.62	0.886
SSS	7.50	4.95	0.699	7.53	5.14	0.316	7.65	5.23	0.494

SJC swollen joint count, TJC tender joint count, TP tender points

include assessment of fatigue, cognitive symptoms, sleep quality and somatization. However, RA patients score higher for poor sleep quality, fatigue, cognitive and somatic symptoms than controls [12, 13], which are predictive of worse symptoms overall in RA patients regardless of the presence of FM [14]. It is therefore not surprising that the FM diagnostic criteria alone lack sensitivity for FM in a population with RA. Our findings support the view that the DAS28 may lack sensitivity for inflammatory activity where there is little or no joint swelling, and therefore there may be a role for the use of US to guide treatment decisions.

We showed that FM classification criteria or joint count criteria alone did not differentiate patients with higher vs. lower PDUS scores, but when combined they were able to differentiate patients with lower ultrasound scores. This supports our suggestion that more rigorous composite criteria, defining both the presence of widespread pain and limited clinical inflammatory disease activity, are necessary to differentiate patients with lower US scores. Our findings that RA patients meeting the FM classification or joint count criteria scored more highly for depression, fatigue, somatic symptoms and disability, replicates that of previous studies. We suggest that patients with fibromyalgia, RA and high DAS28 scores could be identified by more a comprehensive assessment incorporating clinical examination, serology and patient-reported outcome measures.

More accurate stratification of the subgroup of patients with RA and non-inflammatory widespread pain could help optimise treatment decisions. If the causes of symptoms and signs in this difficult to define group can be clearly identified, it will allow the increasingly useful therapies for fibromyalgia or inflammatory arthritis to be used with greater precision [15]. Importantly, therapies for FM are also effective in RA patients [16] and these strategies may thus help more sophisticated stratification of patients into different treatment regimens.

Our study has several limitations. Only the hands and wrists were assessed by US whereas inclusion of other joints may provide additional information. It is unclear how many and which joints should be included and it may be that a larger panel of joints would have produced different results. The number of patients included in this study was relatively small and these findings need to be replicated in a bigger sample. A larger study is underway in our centre to determine whether multiple clinical measures of disease activity and patient-reported measures of other factors which may be associated with widespread non-inflammatory pain can better differentiate these groups.

Conclusion

This preliminary study has shown that composite clinical tools may help to differentiate patients with RA and concomitant fibromyalgia with DAS28 > 2.6 who have lower ultrasonographic disease activity. These patients are less likely to respond to escalation of inflammation-suppressing therapy and may be more suitable for other forms of treatment including alternative means of pain control and psychological support. Further work is needed to determine whether clinical criteria can be used as predictive tools to identify these patients or whether imaging is necessary for accurate stratification. We are currently undertaking a larger study exploring correlation between multiple clinical parameters and ultrasonographic measures of inflammation.

Abbreviations

DAS28: 28 joint disease activity score; FM: Fibromyalgia; FMRA: Fibromyalgic rheumatoid arthritis; GS: Grey scale; HAQ: Health Assessment Questionnaire; MCP: Metacarpo-phalangeal joint; PD: Power Doppler; PG: Patient global; PIP: Proximal Interphalangeal joint; RA: Rheumatoid arthritis; SJC: Swollen joint count; SSS: Symptom severity scale; TJC: Tender joint count; WPI: Widespread pain index

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Availability of data and materials

Requests for further detail on the dataset and queries relating to data sharing arrangements may be submitted to the corresponding author.

Authors' contributions

AM, BK and TG devised the study design. AM, KC, JW and SS were involved in data collection. Data analysis was carried out by AM, NG and TG. All authors were involved in writing and agreed the final manuscript. All authors read and approved the final manuscript.

Competing interests

Bruce Kirkham has received consulting fees from Novartis (less than \$10,000) and speaking fees from Abbvie and Bristol-Myers Squibb (less than \$10,000). All other authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics and consent to participate

Research ethics committee approval was obtained from the Greenwich REC (# 234567) prior to commencing the study. The study was carried out according to the principles of Good Clinical Practice. All participants provided written informed consent.

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Chapter 8 DISCUSSION

8.1 Overview Of Main Findings

The five studies in this thesis considered different types of evidence about the impact of moderately active RA. Taken together they make a strong case that some patients with moderately active RA merit intensive treatment. Key findings in each study are outlined below.

8.1.1 Study On Changing Patterns Of DAS28 And HAQ Scores

Sequential studies of 1324 RA patients showed that from 1996 to 2014 there were temporal increases in the use of DMARDs including combination DMARDs and biologic DMARDs. During this time mean DAS28 scores fell, active disease ($\text{DAS28} > 5.1$) declined and DAS28 remission increased. In contrast HAQ scores were unchanged and correlations between DAS28 and HAQ weakened. Although treatment intensity has increased over time and disease activity has fallen and there are more remissions these improvements in controlling synovitis have not resulted in comparable reductions in disability measured by HAQ. As a consequence the relationship between DAS28 and HAQ has become weaker over time. Although the reasons for this divergence between disease activity and disability are uncertain, focussing treatment entirely in suppressing synovitis may be insufficient.

8.1.2 Systematic Review Of RA Guidelines

The systematic review of 22 RA guidelines showed 20 recommended targeting remission and 16 suggested low disease activity as alternative. All guidelines recommend treating active RA but only 13 made recommendations for moderate disease. The 21 guidelines considering early RA all recommended starting DMARDs as soon as possible; methotrexate was recommended for most patients. Nineteen recommended combination DMARDs when patients failed to respond fully to monotherapy and biologics were not necessarily indicated. Twenty made recommendations about biologics invariably suggesting their use after failing conventional

DMARDs, particularly methotrexate. Most did not make specific recommendations about using one class of biologics preferentially. Eight recommended tapering biologics when patients achieved sustained good responses. These guidelines showed five general principles: DMARDs should be started as soon as possible after the diagnosis; methotrexate is the best initial treatment; disease activity should be regularly monitored; give biologics to patients with persistently active disease who have already received methotrexate; remission or low disease activity are the preferred treatment target.

8.1.3 Impact Of Different Reductions In DAS28 On Disability And Quality Of Life

In early RA 26 % patients were good EULAR responders and 32 % were EULAR moderate responders; in established RA comparable results were 35 % and 46 % patients respectively. The magnitude of change in the HAQ and EQ5D was greater in both settings in EULAR good responders than in EULAR moderate responders. Achieving a good EULAR response with DMARDs and biologic agents in active RA results in substantially improved mean HAQ and EQ5D scores. Patients who achieve such responses should continue on treatment. However, continuing such treatment strategies is more challenging when only a moderate EULAR response is achieved. In these patients evidence of additional clinically important benefits in measures such as the HAQ should also be sought.

8.1.4 Patients At Risk Of Persistent Active Disease

In an observational cohort regression modelling identified three main predictors of persisting active disease; tender joint counts, HAQ scores and ESR. These predictors were dichotomised (≥ 6 tender joint counts, ≥ 1.0 HAQ ≥ 20 mm/h ESR) to produce a four-point prediction score. This simple prediction score predicted persisting active disease in one early and one established RA clinical trials. Patients with high scores were more likely to have persistently active disease

at 6 and 12 months. The relationship was weaker in established RA because no patients were without any predictive factors. Importantly, more patients with all three risk factors had persistent active disease than those with none or one risk factor.

8.1.5 Impact Of Fibromyalgia On RA Assessments

An observational study of 47 patients with active RA on DMARDS found those patients meeting criteria for fibromyalgia also had higher scores for disease activity, depression, disability and fatigue. Those meeting both the joint count and classification fibromyalgia criteria had significantly lower levels of grey scale and power Doppler synovitis on ultrasound. RA patients with concomitant fibromyalgia, as determined by widespread soft tissue tenderness but fewer clinically inflamed joints, have higher disease activity scores but may have lower levels of synovial inflammation on ultrasound. This has implications for the identification and management of these patients who may not respond to conventional therapy and hence be more suitable for alternative approaches to treatment.

8.2 Implications For Current Clinical Practice

There have been substantial shifts in RA treatment paradigms. RA is a different disease in 2022 from that seen in the clinic twenty years ago. Patients are identified, referred and treated earlier, there is a wider armament of drug therapies available, patients are monitored using composite tools and treated to target, and there are now fewer surgical referrals and an improved life expectancy. This thesis has explored and brought together these changes and demonstrated the impact and where the unmet need remains.

8.2.1 *DAS28 And HAQ Changes Over The Last Two Decades*

The publication on temporal changes highlights these changes seen in clinical practice in the UK with an increase in prescribing of DMARD therapy as a whole from 6.1% to 87%, with increased prescribing of combination therapy of csDMARDs from just 1% in 1996-97 to 41% in 2012-14. bDMARDs were not widely available until early 2000s, and the use in clinic was seen to increase from 4% in 2001-03 to 32% in 2014.

Disease activity scores have improved over this time with the mean DAS28 falling with each consecutive cohort from 5.2 (SD 1.6) in 1996-97, 4.7 (SD 1.6) in 2001-03, 3.8 (SD 1.5) in 2009-10, and 3.7 (SD 1.6) in 2012-14. Although the proportion of patients with highly active disease fell over time and the proportion of patients with low disease activity and remission increased, there remained a sizeable and stable proportion of patients with moderately active disease at each time period. Interestingly, the swollen joint and tender joint counts improved with consecutive cohorts as did pain VAS, ESR measures, and the patient global VAS (although this was a smaller reduction). Fatigue and HAQ scores did not improve. This highlights that these aspects of the patients disease continue to be potentially driven by other factors, not just the inflammatory burden of the disease. Given that pain and tender joint scores also improved, although pain VAS improved to a lesser degree points to disability and fatigue although may in part be driven by pain, this also does not explain the entire picture.

The DAS28 has several limitations. There can be considerable inter-assessor variability in joint assessments despite training (Pincus, 2008). Furthermore, the way it is calculated gives a different weight to each component contributing to the overall score, for example, the tender joint count (TJC) score is more heavily weighted than the swollen joint count (SJC) score (Prevoo, 1995). Each component may be driven by a number of different factors. Chronic RA

can result in synovial thickening and joint damage, which in the absence of active inflammation, may still be deemed swollen. ESR can vary by BMI, age and sex. TJC may be driven by pain sensitization, and the patient GH VAS can be driven by a number of factors including depression and fatigue. Patient VAS may be interpreted differently by patients to mean how much pain are they suffering, how are they coping, their perception of how effective their treatment is (Hewlett, 2012). The TJC and patient GH VAS may also be affected by age and disease duration where patients may have underlying joint damage or osteoarthritis. Depression, anxiety and fatigue are common in RA and patients with depression have a poorer response to anti-TNF treatment and smaller reductions in RA disease activity (Hider, 2009;). Each component of the DAS28 can clearly present a challenge. Therefore the DAS28 score itself does not help discriminate between patients where the score is driven by active inflammation, versus patients with little or no inflammation. There is often a mismatch between the objective and subjective components of the DAS28. A recent study found better association with the objective SJC out of 28 and CRP with inflammation confirmed on imaging and a new scoring tool of these two components only, excluding the subjective TJC and patient GH VAS has been proposed (Hensor, 2019).

There may be a number of possible reasons for these observations in DAS28 trends. It has been suggested that RA is becoming a milder disease (Welsing, 2005), although the trend coincides with an increase in the prescribing of immunosuppressive therapies (Finckh, 2006;). A study analysing patients seen over serial time periods from the Norfolk Arthritis Register (NOAR) cohort, a primary care inception cohort recruiting patients with recent onset disease, showed a general trend towards a lower baseline DAS28 score with time. This may have been due to wider awareness and recognition in primary care (Diffin, 2014).

Radiographic damage has been shown to have improved over time between 1985 and 2000 (Pincus, 2005). The biggest change seen here in 2000 was an increased numbers of patients receiving methotrexate in combination with other DMARDs or corticosteroids. The dose of corticosteroids had also reduced. bDMARDs were still not widely available and very few patients received these. This suggests the increasing use of methotrexate has significantly reduced joint damage. This was also seen in the Finland Rheumatoid Arthritis Combination Trial (FinRACo)(Korpela, 2004) and the TICORA trial (Grigor, 2004). A study by Finckh et al also reported a trend towards less radiographic progression between 1970s and 1990s, and attributed this to more patients receiving immunosuppressive csDMARD therapy and corticosteroids (Finckh, 2006). Hand and foot surgery rates have also declined between 1986 and 2011 (Nikhiporou, 2014).

There has recently been a greater emphasis on earlier identification, referral and treatment of inflammatory arthritis, although this is very recent and unlikely to have been the main factor in the studies mentioned and the advent of early arthritis services in the UK is very recent (BSR best practice). An analysis of a more recent dataset from the King's Cohort may help capture this and the impact this has had on outcomes.

There are of course limitations to the study included in this thesis. This was two geographically linked hospitals in the same city with possibly similar populations, although this was not formally analysed. The patients would have been seen by a number of different clinicians through their time at the centre and the joint counts would have been affected by assessor variability. Although assessing patients longitudinally over the same period of time would not be possible in a more robust trial setting.

The study using the NOAR cohort found an increase in HAQ scores over time despite an improvement in DAS28 scores (Diffin, 2014). This is not in keeping with the research reported in this thesis or in other cohorts such as Nijmegen inception cohort (Kievit, 2013).

Welsing et al (Welsing, 2001) analysed data from recent onset RA, with follow up for six years from 1985 at the University Medical Center Nijmegen. This study found that functional capacity was most affected by disease activity in early disease and by joint damage later in disease. Norton et al explored functional trajectories in 1460 patients with early RA between 1986 and 1998 from the Early Rheumatoid Arthritis Study (ERAS) cohort. The results showed a decline in HAQ over the first two years, possibly due to improved disease activity with treatment. After three years, the HAQ score increased in a linear pattern. A sample analysis of 20 randomly selected patients with little missing data from this cohort, found that the linear rise in HAQ scores was not seen in all patients, and described four trajectory patterns: 46% followed a J shaped trajectory with initial improvement and then gradual decline; 28% showed a moderate HAQ that improved initially but then slowly worsened over time; 20% had a persistently high HAQ; and 6% mildly disability initially which then improved and remained low and stable (Norton, 2013). There was no difference between the four pattern groups for BMI, erosion scores, RF or smoking status. The low stable group were younger, male, had lower pain VAS at baseline, and fewer tender joints and lower use of corticosteroids in the first year. The persistently high HAQ group, were female, had lower education levels, higher pain VAS, DAS and swollen, tender joints at baseline. This group also had higher ESR at baseline, but not at later timepoints. A larger data set analysis may help identify predictors better although real world data sets often have many missing data points an HAQ scores are often poorly completed.

8.2.2 RA Treatment Guidelines And The Guidance For Managing MDAS

The review of published guidelines recognises that many principles of RA management are now widely accepted and universally recommended. These include starting DMARD therapy soon after a diagnosis is made, and that disease activity should be monitored using a composite tool such as the DAS28. Methotrexate should be used in first line DMARD therapy, and patients should be offered bDMARD therapy soon where patients continue to have severe uncontrolled disease. Remission and low disease activity have been demonstrated as being an achievable goal and should be the treatment target for all patients. Although radiographic progression has been seen in patients with low as well as moderately active disease (Klooster, 2019). Other studies have also observed significant radiographic progression in the MDAS group (Fautrel, 2015; Combe, 2015).

Patients with persistent moderately active disease, experience ongoing disability, poor quality of life and pain despite therapy, with functional impairment reported in 13 – 25% of patients (Conaghan, 2010; Scott, 2020; Combe, 2015; Kiely, 2011). Large inception cohort data has also demonstrated that patients with MDAS having a significantly higher prevalence of major orthopaedic surgery compared with patients in remission (Nikhiporou, 2016).

Managing patients with moderately active disease was until recently, a unique problem in the UK. In many countries, this has for some time been considered to require treatment escalation in the same way as a DAS28 >5.1. Published literature for moderate disease activity has been relatively sparse. The guidance for this group was found to be limited in the review, specifically only addressed by the ACR guidelines.

Indeed, where a patient has failed to reach low disease activity or remission, therapy should continue to be escalated. Interestingly, Yun et al analysed data from Rheumatology Informatics System for Effectiveness (RISE), a large registry of 27,274 patients with longitudinal data from Jan 2016 to June 2017 and found that only 54.6% of patients with moderate or high disease activity added/ switched csDMARDs or bDMARDs. Of those patients with ongoing moderate or high disease activity already receiving combination csDMARDs, only 45.9% had changes made to their medication, and this was as low as 35.6% for patients already receiving bDMARDs with csDMARDs (Huifeng, 2020). Fewer older patients, those already receiving combination DMARD therapy or bDMARDs had their treatment changed despite active disease. The reasons for this including both physician and patient factors warrant further exploration and understanding.

Improved disease activity was observed in the prospective cohort MODERATE study with anti-TNF therapy in moderately active disease in patients previously anti-TNF naïve patients with 21% achieving remission status at 1 year and an improvement in DAS28 of >1.2 in 58% (Ceccarelli, 2017). Although remission was only achieved by 21% at one year. Several other studies have also demonstrated the benefits of anti-tnf therapy (Keystone, 2009; Ceccarelli, 2017; Hobbs et al., 2015; Yamanaka et al., 2016; Hyrich, 2009; Van Der Heijde, 2009). The number of work days lost for these patients has been found to be similar to that of patients with high disease activity (DAS28 >5.1) (Olofsson, 2016) and data from the Swedish biologics registry has shown no difference in healthcare costs between the two groups (Johansson, 2015). Moderate RA, where advanced therapy has not been available in the UK, has been associated with increased healthcare resource utilisation, impaired quality of life and function with total work productivity loss of 29% in one study, and considerable impact on the lives of caregivers (Galloway, 2021).

Until recently, access to advanced therapies including bDMARDs and tsDMARDs was not available on the National Health Service (NHS) due to the cost effectiveness estimates determined by NICE. These patients therefore continued to receive combination of csDMARDs, even where these were deemed insufficiently effective at managing active inflammation. Advanced therapy has now been made available to patients with moderately active RA in the UK, in an unprecedented technology appraisal (NICE, 2021). It is likely that other advanced therapies will also become available for these patients in the future. Longitudinal data analysis of the treatments prescribed and outcomes in these patients will provide further insights into long term outcomes for this group.

8.2.3 What Is An Acceptable Treatment Response?

As described earlier, patients with moderate disease activity also have poor outcomes. The NHS in the UK recommends an improvement in DAS28 of >1.2 denotes adequate response to continue advanced, higher cost therapies. The EULAR criteria for response allows further division into what is considered a moderate response versus a good response, which requires not only an improvement in DAS28 of 1.2 but also an end DAS28 of <3.2 , low disease activity or remission. The study described in this thesis demonstrated that a greater proportion of patients achieved the minimal clinically important difference (MCID) in HAQ and EQ5D compared with patients achieving a moderate EULAR response.

The NICE DAS28 improvement threshold of 1.2 has been criticised for being not used in clinical trials, as being too high, and the three month time point of assessing response has also been deemed as too early. Jerram et al analysed data from clinic attendances of 271 patients which showed 7.7% of NICE non-responders would have met a moderate EULAR response and that this improved to 23.7% at 6 months (Jerram, 2008). The challenge faced in the UK is

of the treatment being withdrawn altogether and switching to an alternative agent, or where several switches have already occurred, to stop high cost therapy altogether. A study by Kievit et al (2009) also suggests that a response needs to be assessed at 6 months and not 3 months. In reality these patients may require a combination of therapies including but not solely focussing on immunosuppression.

Predicting which patients will have poorer outcomes may help identify those that would benefit from a highly stringent treat to target approach. Longer disease duration, female sex, RF and ACPA positivity, baseline ESR, presence of radiographic damage and current smoking have been established as being associated with poorer outcomes for some time (Anderson, 2000; Courvoisier, 2008; Saevarsdottir, 2015). The wealth of research on predictors historically reported, although well recognised and multifactorial, are difficult to use and interpret for individual patient assessments and decision making.

The predicting responses analysis carried out for this thesis identified $TJC \geq 6$, $HAQ \geq 1$ and an $ESR \geq 20$ as highly predictive of persistently active disease. Gender, smoking and RF positivity were not found to be predictors. This analysis found the simple scoring tool incorporating these predictors as being highly predictive of achieving or not achieving low disease activity or remission. This requires validation in several different and larger datasets, but may be an important step to risk stratification in the clinic.

Female sex, older age, higher functional class and longer morning stiffness have been reported as being and has been reported as more prevalent in patients with RA and fibromyalgia (Ranzolin, 2009). These patients also had worse scores in DAS28, HAQ and SF-36. Ultrasound can detect active inflammation in subclinical disease (Wakefield, 2004) and has been shown to

have a high sensitivity similar to Magnetic Resonance Imaging (MRI) for detecting synovitis (Szkudlarek, 2001; Terslev, 2003). It is being increasingly utilised by rheumatologists in the clinical setting to aid diagnosis and therapeutic decision making. The purpose of the study carried out for this thesis was to determine if a greater number of tender joints compared with swollen joints would be consistent with lower power Doppler (PD) signal on ultrasound.

8.3 Pain Sensitisation

The study identified that 43% of the total 47 patients with active disease, had MDAS. 40% of the patients met either the ACR FM classification or diagnostic criteria; 53% of the patients met the 'joint count criteria' of TJC minus SJC count of ≥ 7 ; and 36% met both the tender joint count criteria and the FM classification criteria. The DAS28 was higher for patients meeting the FM classification criteria versus those that did not, with mean scores of 5.23 (SD 0.75) and 4.11 (1.0) respectively, ($p < 0.001$). This was also true for those meeting the TJC criteria compared with those that did not; DAS28 4.99 (0.97) and 4.03(1.0) ($p = 0.002$).

Interestingly, the PD ultrasound scores, although numerically different between the two groups, did not meet statistical significance. This suggests that the presence or absence of pain sensitization does not tell determine whether or not a patient has ongoing synovitis or not. The findings suggest that even where clinically there may be deemed to be little joint inflammation, this may in fact not be the case, suggesting the 'fibromyalgic RA' terminology is too simple. Similar findings were reported by a recent study by Ghib et al (2015). The presence of persistent PD signal has been demonstrated in patients in clinical remission, and can predict relapse. (Saleem, 2012; Scire, 2009). There is a clearly a role of ultrasound in the clinic, however scanning a patient can take 30-60 minutes, requires significant time dedicated to formal training, and needs to be carried out frequently to ensure competency can be maintained.

With a national shortage of rheumatologists and already strained services, it may be some time before this is routinely available contemporaneously in clinic.

There are currently no drugs licensed specifically for pain in RA. Recent tsDMARD, JAKi data suggests this group of drugs may have more than one mode of action in patients with RA with not only improvements in disease activity but also greater improvements in pain scores with baricitinib versus adalimumab or placebo (Taylor, 2019). More data including longitudinal outcomes and a better understanding is needed on the role of JAKi in active RA with pain sensitization.

There is compelling evidence of a strong relationship between FM and fatigue, sleep and cognitive problems that can be severe, affecting function and quality of life (Wolfe, 2014). In a cross sectional study exploring the relationship between disease activity, sleep, psychiatric distress and pain sensitivity in patients with RA in 59 patients, CRP was not correlated with pain thresholds, tender joint count inversely correlated with pain thresholds, sleep problems were associated with lower pain thresholds (Lee, 2009). Depression is prevalent in RA. Matcham et al published a systematic review and meta-analysis of 72 studies including 13189 patients (Matcham, 2013). The prevalence of major depression was 16.8% of patients with RA. The estimates were similar to those observed in diabetes, Parkinson's disease and cancer.

8.4 Is More Intensive Treatment The Approach For All Patients With MDAS?

The Treatment Intensities and Targets in Rheumatoid Arthritis Therapy (TITRATE) trial assessed whether patients with moderate disease activity would benefit from intensive treatment (Martin, 2017). Participants were randomised to standard care or intensive therapy (with monthly review optimised drug treatment and psychosocial support in the form of

motivational interviewing also addressing pain, fatigue and adherence). The trial showed the intensive treatment was effective and more patients achieved remission and greater improvements in fatigue (Scott, 2020). However, disease activity scores were higher at baseline in obese patients with a BMI $>35\text{kg/m}^2$ (Lee, 2021). Fewer obese patients achieved remission over twelve months, and had higher overall pain and fatigue.

The impact of earlier etanercept in combination with methotrexate versus methotrexate treat to target and delayed addition of etanercept in the MDAS group was explored in the Very Early versus Delayed Etanercept in Rheumatoid Arthritis (VEDERA) Trial. After 24 weeks of treatment, 43% and 35% of patients were in still in MDAS in the two groups respectively. This suggests that escalating all patients with MDAS to advanced therapies may not be appropriate (Shukla, 2022).

8.5 Strengths And Limitations

8.5.1 Strengths Of Different Studies

Although the individual studies had different strengths, a number of common factors are evident. Firstly, many of the observational studies reported real time data with no exclusion criteria; this made them likely to be highly representative of RA patients seen in outpatient clinics at the time they were undertaken. Secondly, most of them were sufficiently large to provide robust assessments of treatments and disease activity. Those studies involving secondary analyses of clinical trials used trials that were large and were based across many English specialist centres with a broad geographic spread. Finally, there were similar effects seen in early and established RA. As a consequence the findings are likely to be generalisable in guiding clinical practice decisions.

8.5.2 *Limitations Of Different Studies*

The limitations of the different studies are specific to them and have therefore been considered separately for each study.

8.5.3 *Study On Changing Patterns Of DAS28 And HAQ Scores*

There were five main limitations to this study had several limitations. Firstly, the data were collected at consecutive cohorts was cross sectional and did not capture the same patients. Secondly, as the data collected were anonymized it is uncertain if some patients contributed to more than one cohort. Thirdly, the assessments were carried out by a number of different physicians over the four time periods and there might have been variations in the way individual clinicians assess joint counts. Fourthly, it is also possible that the pattern of follow up in clinics has changed with RA patients who have milder disease being more frequently. Finally, another possibility is that there may have been changes in the level of background disease activity in patients seen in specialist clinics. These limitations are inherent problems in all studies that evaluate temporal changes in disease activity.

8.5.4 *Systematic Review Of RA Guidelines*

This study had five main limitations. Firstly, some of the guidelines were developed over 10 years or longer and the older ones cannot have included the more recent clinical evidence. Therefore comparisons need to take this into account. Secondly, there are different types of guidelines. Only the general ones were included. Many others focus on single drugs or treatment modalities including surgery. It is difficult to draw a clear line between which ones to include and which to omit. Not all experts would necessarily agree with our approach to inclusion. Thirdly, only a narrative assessment was provided. They are too diverse in their approaches to allow any synthesis of their various conclusions and recommendations. Fourthly

the analysis focussed on issues in the guidelines considered to be of most importance. Others may have considered different aspects of the guidelines in more detail and overlooked some of the matters we have dealt with. Finally, systematic reviews of guidelines are not one of the current PRISMA extensions though they may be included in subsequent updates. Consequently the protocol was not registered. Systematic reviews of guidelines differ from both scoping and umbrella reviews.

8.5.5 Impact Of Different Reductions In DAS28 On Disability And Quality Of Life

This study also had five limitations. Firstly, the analyses only considered differences at the trial endpoints. Different effects would have been seen by evaluating all time points. Secondly, choosing specific cutoff points, such as DAS28 of 3.2 or less may have over done similarly well. Thirdly, some of the treatments used, particularly ciclosporin, which was used in the CARDERA trial, are not commonly prescribed in routine practice. Fourthly, the studies combined the effects of a range of different treatments, and the relationship between disease activity and HAQ and EQ5D scores may be different across drug classes. Finally, the inference that patients who do not achieve low DAS28 scores with one treatment strategy may do better with another could be incorrect; some patients may achieve poor outcomes with all treatment strategies.

8.5.6 Patients At Risk Of Persistent Active Disease

This study had four limitations. Firstly, it did not include genetic predictors, which may be crucial predictors of response. Secondly, it did not evaluate rheumatoid factor isotypes or anti-citrullinated peptide antibodies, which may also be important response predictors. Thirdly, using simple predictors failed to identify all patients with persistently active disease. This is partly because intensive treatments used in CARDERA and TACIT trials did not prevent a

substantial proportion of persistently active disease. Forthly, the patients were enrolled before the introduction of new diagnostic criteria for the classification of early RA, although there is uncertainty about the impact of these criteria when used to prospectively identify patients with early RA.

8.5.7 Impact Of Fibromyalgia On RA Assessments

Our study had two main limitations. Firstly, only the hands and wrists were assessed by US whereas inclusion of other joints may provide additional information. It is unclear how many and which joints should be included and it may be that a larger panel of joints would have produced different results. Secondly, the number of patients included was relatively small and the findings need to be replicated in a bigger sample.

8.6 Unmet Need And Recommendations For Future Research

8.6.1 Predicting Poor Responders

The reasons why some patients have less favourable outcomes despite appropriate DMARD therapy remains unclear. A recent systematic review by Edwards et al (2019) evaluated 30 studies of RA patients in MDAS states of activity. It identified several key prognostic factors with consistent evidence for progression and poor outcome prediction. These predictors comprised: DAS28 scores ≥ 4.2 ; the presence of ACPA antibodies and power Doppler ultrasound scores ≥ 1 . They suggested combining two or more of these factors might enhance their predictive potential.

An alternative approach to predicting patients with poor outcomes involves using multi-biomarker disease activity (MBDA) scores to identify patients at higher risk of progression. Li et al (2016) found that in a study of 163 RA patients assessed over 271 visits MBDA scores

improved the ability of conventional risk factors to predict radiographic progression in patients with established RA receiving non-biologic DMARDs. Another study of predicting outcomes using MBDA scores by Ma et al (2020) found that in 148 patients with initially stable low disease activity scores or remission, MBDA scores predicted those patients who remained in sustained remission. Other studies also report positive predictive findings using MBDA scores; an example is the analysis by Brahe et al (2019) of a completed trial which shows MBDA scores predict radiographic progression and remission.

Taken together these various studies provide a compelling case for undertaking more research on clinical predictors and the use of assessments such as MBDA scores, which have yet to become established in routine practice settings.

8.6.2 Difficult To Treat RA

EULAR have proposed a definition for difficult-to-treat RA for use in clinical practice and research. Their criteria include failure of at least two advanced therapies with a different mode of action after failing csDMARDs; signs of active or progressive disease; the management of the signs and symptoms of disease is perceived as being problematic in the patient and or clinician (Nagy, 2021). The EULAR task force involved in defining difficult-to-treat RA believe it may help improve the management of patients in who, the goal of achieving remission cannot be delivered. It suggests these patients need a different treatment approach which will be identified by new research studies.

An alternative approach to risk stratification suggested by Astorri et al (2015) is to focus on histopathological risk stratification and tailored personalised drug therapy. In a review of the existing evidence for this approach they highlighted the potential value of synovial

histopathology as a potential prognostic biomarker for patient stratification in RA, and in particular for determining the use of specific biologic therapies. This concept has been extended by Lewis et al (2019) who suggested there may be divergent pathogenic pathways in early RA. Pro-myeloid inflammatory synovial gene signatures are associated with clinical response to initial drug therapy while plasma cell genes identified a poor prognosis subgroup with progressive structural damage. This is an area in which further research is justified.

8.6.3 Alternatives To DAS28 And Other Assessments

The DAS28, and other composite disease activity tools such as SDAI and CDAI, have been incredibly important in the RA research journey and resulted in better disease control in patients and thus significant improvements in outcomes. However, given the observations described in this thesis and the challenges and limitations of these tools, it is possible they need to now be revisited and modified. Using this two component DAS28 Dagliati et al (2020) studied 2,991 RA patients in whom treatment with a biologic disease-modifying antirheumatic drug was being initiated within the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate cohort. They found the two component DAS28 defines important biologic and clinical phenotypes associated with treatment outcome and characterises potential underlying response mechanisms to biologic drugs.

A more recent study by Gwinnutt et al (2022) analysed 2500 RA patients followed for 8-10 years in three different observational cohorts. Within each cohort, some trajectories had comparable two components DAS28 scores but different HAQ scores. They found higher pain, fatigue and depressive symptoms were associated with being in the high HAQ trajectories. They argue that in some patients, disability will most likely be reduced by focussing on alternative treatments for pain, fatigue and abnormal mood. There is consequently a strong case

for extending and amending the measures used in the routine assessment of RA in clinical practice and more research is needed on this issue.

There are also challenges with the HAQ. It is self-reported and hence describes subjective, perceived disability. It does not discriminate between impaired function due to structural joint damage, weakness, pain or fatigue. A recent study of HAQ in 2,701 RA patients from two UK prospective cohorts over 10 years found that high end-point HAQ scores were associated with sociodemographic factors such as increased age at disease onset, female gender and minority ethnicity (Busby, 2022). Consequently such sociodemographic factors may need to be taken into account when assessing clinical status in RA. This area also needs further ongoing research studies before changes are made to clinical practice.

8.6.4 Using Biologics And Other Innovative Treatments

Access to advanced therapies in the UK is an important issue for patients with MDAS. There is accumulating evidence that the treat to target approach should be followed aiming for remission in all patients. A disease activity score above this should be considered suboptimal and inadequate. Patients predicted to have persistently active disease and poorer outcomes should continue to have treatment escalated. However there are complexities about the access to such therapies in many countries including the UK.

A recent editorial by McKenna (2022) highlighted the protracted dilemma in England about access to biological treatments for patients with MDAS. Since 2020 EULAR has recommended that MDAS patients should have access to these treatments if poor prognostic factors are present and treatment with methotrexate alone is insufficient (Smolen et al 2020). An evaluation of the impact of exclusion of EULAR-eligible RA patients on the basis of national

reimbursement criteria found a considerable number of RA patients would be excluded from receiving biologics (Kaló et al 2017). McKenna highlighted the finding that when treated with a biologic patients with moderate disease have similar response compared with those with active disease, which has been shown in an analysis of patients in the British Society for Rheumatology biologics register (Hyrich et al, 2009). Fortuitously, the most recent guidance from NICE (2021) indicates that adalimumab, etanercept and infliximab, all with methotrexate, are recommended as options for treating active rheumatoid arthritis in adults provided that: intensive therapy with two or more conventional DMARDs has not controlled the disease well enough; the disease is moderate (DAS28 of 3.2 to 5.1); and the drugs can be provided at approved costs. Adalimumab and etanercept can also be used as monotherapy when methotrexate is contraindicated or not tolerated provided the other criteria are met. Patients need to achieve at least a moderate response 6 months after starting therapy if therapy is to be maintained. It appears that concerns over limited access for biologics in moderate RA are largely resolved in England.

The analyses in this thesis have examined the impacts of drugs, particularly DMARDs, but have not explored in any detail the effects of non-drug treatments. There is extensive evidence that these approaches may be useful in many RA patients (Forestier et al, 2009; Gossec et al, 2006; Vliet Vlieland et al, 2011). The findings on fibromyalgia and RA in the final research study in this thesis suggest that at least some RA patients may benefit from more non-drug therapy and there needs to be more research on this theme.

Finally, the research on predictors of poorly responding RA in this thesis showed that RA is likely to be a heterogeneous disorder. A recent systematic review by focussed on the heterogeneity of difficult to treat RA (Roodenrijs, 2021). It would therefore be sensible to

undertake more research on predicting responders in active and moderate RA. The interaction of disease activity with obesity and depression merits further research.

Increased immunosuppressive therapy is unlikely to be the only intervention that is required for many patients. The increasing armament of drugs with different mode of action, and tighter disease control using existing composite tools have improved, but it is possible the impact of these for the RA population has plateaued. RA management has come a long way but clearly continued efforts are needed to understand how to get more patients into remission, reduce disability and improve quality of life.

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APPENDIX

Papers In Peer Reviewed Journals Included In Thesis

1. **AN Mian**, F Ibrahim, DL Scott. A systematic review of guidelines for managing Rheumatoid Arthritis. BMC Rheumatol. 2019 Oct 22; 3: 42. doi: 10.1186/s41927-019-0090-7.
2. NJ Gullick, **A Mian**, F Ibrahim, D Walker, A Hassell, PDW Kiely, R Williams, David A Walsh, A Young, DL Scott and TITRATE Programme Investigators. Predicting responses in patients with rheumatoid arthritis to disease modifying agents using baseline clinical data. Clin Exp Rheumatol. 2017 Sep-Oct; 35(5): 810-815.
3. **AN Mian**, K Chaabo, J Wajed, S Subesinghe, N Gullick, B Kirkham, T Garrood. Rheumatoid Arthritis patients with fibromyalgic clinical features have significantly less synovitis as defined by power Doppler ultrasound. BMC Musculoskelet Disord. 2016 Sep 23; 17 (1): 404. doi: 10.1186/s12891-016-1258-6.
4. **AN Mian**, F Ibrahim, J Galloway, DL Scott. Optimal responses in disease activity scores to intensive treatment in rheumatoid arthritis. Arthritis Res Ther. 2016 Jun 16; 18 (1): 142. doi: 10.1186/s13075-016-1028-8.
5. **AN Mian**, IC Scott, S Bahadur, F Ibrahim, M Filkova, L Pollard, S steer, G Kinglsey, DL Scott, J Galloway. Changing clinical patterns in rheumatoid arthritis: less active disease but more functional disability. BMC Musculoskelet Disord. 2016 Jan 27; 17 (1): 44. doi: 10.1186/s12891-016-0897-y.

Other Papers Related To Thesis

1. **AN Mian**, DL Scott. Treat to Target in managing inflammatory arthritis. Br J Hosp Med 2015 76:31-34

2. **AN Mian**, DL Scott. People need to learn to recognise early signs of Rheumatoid Arthritis. Guidelines In Practice, May 2014,
<https://www.guidelinesinpractice.co.uk/musculoskeletal-and-joints-/people-need-to-learn-to-recognise-early-signs-of-rheumatoid-arthritis/348608.article>

Abstracts Presented at Meetings Related To Thesis

1. NJ Gullick, F Ibrahim, **A Mian**, A Vincent, DL Scott, B Tom, BW Kirkham. Intensive treatment for rheumatoid arthritis reduces disease activity over time. British Society For Rheumatology Annual Conference, 2016
2. **Mian A**, Ibrahim F, Scott IC, Bahadur S, Filkova M, Pollard L, Kingsley GH, Steer S, Scott DL, Galloway J. Has the Relationship Between Disease Activity and Disability in Rheumatoid Arthritis Changed? American College of Rheumatology Annual Meeting, 2015.
3. **Mian A**, Chaabo K, Wajed J, Kirkham BW, Garrood T. Clinical Features of Fibromyalgia in Patients with Rheumatoid Arthritis Predict Lower Power Doppler Scores on Ultrasound American College of Rheumatology Annual Meeting, 2015.
4. **A Mian**, K Chaabo, J Wajed, B Kirkham, T Garrood. Rheumatoid Arthritis patients with fibromyalgic clinical features have significantly less synovitis as defined by power Doppler ultrasound. EULAR Annual Congress, 2015
5. H Lempp, F Ibrahim, **A Mian**, J Galloway. Changes in DAS28 by age and ethnicity among patients attending one rheumatology clinic in London UK. EULAR Annual Congress, 2015
6. **A Mian**, K Chaabo, B Kirkham, T Garrood. Ultrasound findings in ‘fibromyalgic’ rheumatoid arthritis: a pilot cross-sectional study. British Society For Rheumatology Annual Conference, 2015.

7. S Bahadur, **A Mian**, I Scott, J Galloway, L Pollard, GH Kingsley, DL Scott. Comorbidities And Treatment Intensity In Rheumatoid Arthritis. British Society For Rheumatology Annual Conference, 2015
8. **A Mian**, DL Scott, GH Kingsley, F Ibrahim. Impact of achieving low disease activity on general health status. British Society For Rheumatology Annual Conference, 2015.
9. F Matcham, **A Mian**, S Steer, N Gullick, D Scott, M Hotopf, J Galloway. Psychological Comorbidity In Rheumatoid Arthritis (RA): Relationship to disease activity scores. British Society For Rheumatology Annual Conference, 2015.
10. **Mian**, J. Galloway, S. Steer, I. Scott, G. Kingsley, D. L. Scott. Changing patterns in prescribing in Rheumatoid Arthritis. EULAR Annual Congress, 2014.
11. **Mian A**, Galloway J, Steer S, Scott I, Kingsley G, Scott D. Changing patterns in Rheumatoid Rheumatoid Arthritis Disease Activity. British Society For Rheumatology Annual Conference, 2014