The development of randomised clinical trials in the treatment of rheumatoid arthritis over 20 years (1991 – 2011) in a single centre

Dr Duncan Porter
MA, BM BCh, MRCP, Diploma Business Administration, BA (theology)

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Institute of Infection, Immunity and Inflammation
College of Medical, Veterinary and Life Sciences,
University of Glasgow

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Summary

Rheumatoid Arthritis (RA) is the commonest inflammatory polyarthritis in the UK, and is associated with significant symptoms, disability and premature mortality. Treatment options in 1980 were restricted to corticosteroids, non-steroidal anti-inflammatory drugs, and a small number of disease modifying anti-rheumatic drugs (DMARDs). There had been few large, well conducted randomised controlled studies such that our knowledge about the relative efficacy and safety of the drugs available was very limited. Trial design also left much to be desired, with inadequate methods of randomisation and/or concealment of allocation being commonplace. There was no consensus about which outcome measures ought to included in trials, and no composite measures of outcome had yet been developed or validated. The limited evidence base and restricted therapeutic armamentarium was reflected in the poor outcome of the disease for many patients: remission was rare, and patients often experienced increasing disability, orthopaedic intervention, work-related unemployment and premature mortality.

Within 20 years, the prognosis for patients with newly diagnosed RA has dramatically improved. Modern management results in the majority of patients achieving low disease activity or even remission. The studies incorporated into this thesis have played an important role in the evolution of these management strategies. Early studies focussed on building the evidence base for the use of DMARD monotherapy, demonstrating that sulfasalazine and methotrexate were both safe and effective treatments. The Sulfasalazine-Auranofin trial contributed to the downfall of auranofin, a drug that is no longer manufactured. Contrary to early concerns, methotrexate was proven to be well tolerated, even in the socially deprived population of Greater Glasgow, and this drug had become the DMARD of first choice in the management of RA. DMARD monotherapy, however, is usually not sufficient to maintain good disease control in the long term. The Gold-Hydroxychloroquine study was one of the first studies to investigate the role of combination DMARD therapy in a well conducted, double blind randomised controlled trial (RCT). The results were negative, but a follow up trial demonstrated the superiority of stepping up to Methotrexate-Sulfasalazine combination therapy when compared to sequential monotherapy in the MASCOT study. The West of Scotland Early RA corticosteroid trial was a double blind RCT investigating the role of low dose oral corticosteroids in addition to sulfasalazine therapy. It failed to demonstrate any benefit of low dose steroids, a finding that is at odds with a growing literature that has established corticosteroids as a proven disease modifying therapy.

The strategy trials (Tight Control of RA [TICORA] and Triple Therapy in Early RA [TEAR] studies) have been the most influential studies to have been performed in Glasgow. They did not primarily address the issue of whether a drug is effective or whether one drug is more effective than another. Rather, they sought to test a hypothesis drawn from observations in other biologic models (principally Type I Diabetes Mellitus): namely, that i) using currently available DMARDs 'tight control' can be achieved if patients are reviewed frequently, their disease assessed formally (using the disease activity score), and their treatment escalated if their disease remained active; ii) that the achievement of tight control would lead to improved outcomes. The studies provided strong evidence that dramatic improvements in symptom control, disability and radiographic progression can be achieved by pursuing this strategy of 'Tight Control'. National and international clinical guidelines, and international consensus statements have embraced the results of TICORA (and subsequent confirmatory studies), such that regular, frequent assessment of the patient, use of composite measures of disease activity and the adoption of a 'treat-to-target' therapeutic strategy have become accepted as 'best practice' throughout the world.

Chapter 1 - Introduction

Epidemiology

Rheumatoid arthritis is the commonest inflammatory polyarthropathy in the UK, affecting 810/100,000 of the population. The annual incidence of newly diagnosed RA is 25/100,000 men and 54/100,000 women, with a peak incidence in the 5th and 6th decades of life (Wiles et al. 1999). Typically, RA causes a symmetrical, inflammatory polyarthropathy affecting large and small joints which results in pain, stiffness, fatigue and loss of function. Persistent inflammation results in joint damage, such that ~20% of patients require orthopaedic intervention (such as joint replacement) over a 20 year period (Scott et al. 1987). Mortality, in patients with established disease, is increased when compared to the general population (Myasoedova et al. 2010). The cost of illness was estimated at £ 1.3 billion pa in England in 1992, comprising both direct NHS costs and societal costs (McIntosh 1996).

Pathogenesis

Our knowledge about the aetio-pathogenesis of RA has expanded significantly over the past twenty years, but the specific cause(s) remain elusive. The heritability of RA has been estimated at 67% indicating a strong genetic component to the aetiology of RA (van der Woude et al. 2009). Genome-wide association scans have identified a number of genetic pre-dispositions to the development of RA (table 1). The strongest association is with the 'shared epitope' (e.g. HLA DR4) which implicates antigen presentation by T-cells to macrophages in the pathogenesis of the disease. Many of the other genetic pre-dispositions identified also code for proteins involved in the immune response (e.g. PTPN22) which is highly suggestive that these genes give rise to an increased risk of disease because of dysregulation of the immune response (Bax et al. 2011, Daha et al. 2009, Padyukov L. Seielstad M. Ong RT. Ding B. Ronnelid J. Seddighzadeh M. Alfredsson L. Klareskog L. Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study group 2011).

Table 1 – susceptibility genes for RA (Bax et al. 2011)

Genes	**Year of Discovery**
HLA-DRw4	1978-1987
PAD14, PTPN22, CTLA4	2003-2005
TRAF1/C5, STAT4, TNFAIP3	2007
KIF5A, PIP4K2C, TNFRSF14, CCL21, PRKCQ, CD40, 1L2RA, 1L2RB	2008
PRDM1, CD2, CD58, FCGR2A, PTPRC, REL, BLK	2009
ANKRD55, IL6ST, C5orf13, GIN1, SPRED2, CCR6, AFF3, IRF5, PXK, RBPJ	2010
TAGAP, DDX6	2011

Studies over the past twenty years have also identified important environmental factors that contribute to the development of RA. Probably the strongest of these is the association with cigarette smoking, but associations with social deprivation and periodontal disease (Hitchon et al. 2010) have also been identified. It is of particular interest that the interaction between environmental and genetic factors have been shown to be of importance. This has been shown most elegantly in studies of patients who develop RA in whom samples had been stored because they had previously been blood donors: the presence of anti-citrullinated protein antibodies (ACPA), shared epitope, certain PTPN22 alleles and smoking interact, leading to substantial variations in the risk of developing RA (Willemze et al. 2011).

Taken together, these findings have led to the current thinking on the likely aetio-pathogenesis of RA: a genetic pre-disposition is present in some subjects (e.g. shared epitope), who may then be exposed to an environmental trigger (such as cigarette smoking); a proportion of these patients respond by producing auto-antibodies such as ACPA. At this stage, there is therefore evidence of B cell immune dysregulation, but no clinical sequelae – and this is often referred to as the 'pre-RA' phase of disease. Over time, a proportion of subjects develop a non-specific prodrome of arthralgia and stiffness, which may lead them to seek help from a rheumatologist. It may be impossible for the clinician to make a specific diagnosis at this stage, because of the lack of overt synovitis (clinical or radiological) but over two years, approximately 40% of patients go on to develop overt inflammatory arthritis that fulfils the American College of Rheumatology Classification Criteria for RA (Bos et al. 2010).

Treatment

Until the mid 1980's, treatment of RA was conservative, and initially followed clinician specific (idiosyncratic) approaches from which emerged the paradigm of a treatment 'pyramid' – at presentation, patients were treated with analgesia and/or non-steroidal anti-inflammatory drugs (NSAIDs). If the patient's symptoms were not controlled, or erosive disease developed, then conventional disease-modifying antirheumatic drugs (DMARD) were introduced. Corticosteroid or immunosuppressive therapy (at the top of the pyramid) was reserved for that sub-group of patients with the most severe disease who failed to respond to other therapy. The rationale for this approach was partly a reaction against the false dawn of the discovery of corticosteroids, and their indiscriminate use at high doses, in which initial dramatic improvements were followed by loss of response and catastrophic, delayed steroid toxicity. Consequently, the principle, 'first do no harm' (*primo non nocere*) came to dominate therapeutic decisions – it was recognised firstly that DMARDs could be

associated with serious drug-related toxicity, and secondly that the evidence base supporting their efficacy was limited.

Improved outcome

In the 1980s, the outcome of DMARD therapy remained relatively poor. An editorial published in 1993, entitled 'Gold – standard, sham or substitute?' summed up the prevailing doubts about the risk-benefit profile of the available therapies (Harth 1993). A majority of patients who were commenced on any of the available conventional DMARDs stopped as a result of inefficacy and/or toxicity. The usual pattern was one of slow functional decline over a number of years, with increased mortality (Scott et al. 1987). Even as late as 2000, the Scottish Inter-Collegiate Guideline Network concluded that remission in RA is uncommon. However, a decade later there is a new optimism about the therapy and outcome of RA. The DREAM cohort recently reported that after two years of disease, modern management leads to >60% of patients to be in stable disease remission (Vermeer et al. 2011). What has led to this dramatic improvement in outcome? National and European clinical guidelines on the management of RA have been published and highlight the following developments (Smolen et al. 2010, Smolen et al. 2010):

Early intervention

It has become apparent that not only is the risk-benefit ratio in favour of the use of conventional DMARDs but that delays in the use of DMARD therapy can be associated with long term harm. Consequently, it is recommended that treatment with DMARDs is started as soon as possible in the disease course, preferably within 12 weeks of symptom onset (van der Linden et al. 2010).

Combination DMARD therapy

In the 1980s there was vigorous debate about the safety of DMARDs used singly, and suggestions that two or more DMARDs should be used in combination didn't emerge until the 1990's. Even then, the evidence for the efficacy of combination DMARD therapy was initially conflicting. Better trial design and high quality studies have subsequently proven that some DMARD combinations offer superior efficacy when compared to single DMARDs (Choy et al. 2005, Donahue et al. 2008, Nam et al. 2010).

Biologic therapy

The emergence of targeted biologic therapies has revolutionised the management of RA. The ability to design a treatment that targets a specific protein, pathway or cell type involved in the pathological immune response in RA, has led to a range of novel biological therapies. These therapies have been proven to be effective even in patients who have

failed to respond to multiple conventional DMARDs. Concerns about serious toxicity are slowly abating through the compilation of large national safety databases and registries.

Tight control of RA

Both national and European guidelines now recommend a 'treat-to-target' management strategy, whereby patients are assessed frequently, have their disease activity assessed formally (usually using a composite Disease Activity Score), and treatment adjusted where persistent disease activity is identified (Smolen et al. 2010). The background to these recommendations will be discussed later in this thesis, but suffice to say that the advent of new strategies of care has been at least as important in improving outcomes as the expanding arsenal of new drugs:

> *"... the most important information to be gathered from clinical trials in RA is not necessarily comparison of agents, but rather the strategy of tight control, aiming for remission."* (Sokka, Pincus 2009)

Objective

The objective of this thesis is to review the contribution of randomised controlled trials designed (and largely conducted in) a single centre in Glasgow between 1991 and 2011 (table 2). The author has been involved in the design, execution, analysis or reporting of all the trials discussed. The study will particularly address 1) the contribution of each trial to the emerging evidence base, and 2) the evolution of study design, with special reference to the quality of the studies performed.

Table 2 - Summary of clinical trials performed

Comparators	Study Design	Concealment	Duration	Year of Publication	Role*
Sulfasalazine vs auranofin (SSZ/Aur)	RCT	Open	12 months	1992	A, P
Gold vs Gold + hydroxychloroquine (Gold/HCQ)	RCT	Double blind	12 months	1993	A, P
Gold vs methotrexate (Gold/MTX)	RCT	Open	12 months	2001	D, C, P
Prednisolone vs placebo (WOSERACT)	RCT	Double blind	12 months	2004	D, C, A, P
Methotrexate and Sulfasalazine Combination Trial (MASCOT)	RCT	Double Blind	12 months	2007	D, C, A, P
Routine vs intensive management (TICORA)	RCT and economic evaluation	Blinded assessments	18 months	2004	D, C, A, P
Triple therapy vs Step-up therapy (TEAR)	RCT, strategy	Blinded assessments	12 months	2008	D, C, A, P

* Role – Study design (D), conduct (C), analysis (A), publication (P)

Chapter 2 - Original publications

Porter, D., Madhok, R., Hunter, J.A. & Capell, H.A. 1992, "Prospective trial comparing the use of sulphasalazine and auranofin as second line drugs in patients with rheumatoid arthritis.", Annals of the Rheumatic Diseases, vol. 51, no. 4, pp. 461-464.

Porter, D.R., Capell, H.A. & Hunter, J. 1993, "Combination therapy in rheumatoid arthritis--no benefit of addition of hydroxychloroquine to patients with a suboptimal response to intramuscular gold therapy.", Journal of Rheumatology, vol. 20, no. 4, pp. 645-649.

Hamilton, J., McInnes, I.B., Thomson, E.A., Porter, D., Hunter, J.A., Madhok, R. & Capell, H.A. 2001, "Comparative study of intramuscular gold and methotrexate in a rheumatoid arthritis population from a socially deprived area.", Annals of the Rheumatic Diseases, vol. 60, no. 6, pp. 566-572.

Capell, H.A., Madhok, R., Hunter, J.A., Porter, D., Morrison, E., Larkin, J., Thomson, E.A., Hampson, R. & Poon, F.W. 2004, "Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: results of a randomised controlled trial.", Annals of the Rheumatic Diseases, vol. 63, no. 7, pp. 797-803.

Capell, H.A., Madhok, R., Porter, D.R., Munro, R.A., McInnes, I.B., Hunter, J.A., Steven, M., Zoma, A., Morrison, E., Sambrook, M., Wui Poon, F., Hampson, R., McDonald, F., Tierney, A., Henderson, N. & Ford, I. 2007, "Combination therapy with sulfasalazine and methotrexate is more effective than either drug alone in patients with rheumatoid arthritis with a suboptimal response to sulfasalazine: results from the double-blind placebo-controlled MASCOT study.", Annals of the Rheumatic Diseases, vol. 66, no. 2, pp. 235-241.

Grigor, C., Capell, H., Stirling, A., McMahon, A.D., Lock, P., Vallance, R., Kincaid, W. & Porter, D. 2004, "Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial.", Lancet, vol. 364, no. 9430, pp. 263-269.

Saunders, S.A., Capell, H.A., Stirling, A., Vallance, R., Kincaid, W., McMahon, A.D. & Porter, D.R. 2008, "Triple therapy in early active rheumatoid arthritis: a randomized, single-blind, controlled trial comparing step-up and parallel treatment strategies.", Arthritis & Rheumatism, vol. 58, no. 5, pp. 1310-1317.

Porter, D. 2005, "Targeting Persistent Disease Activity in Early RA: A Commentary on the TICORA Trial", International Journal of Advances in Rheumatology, vol. 3, no. 1, pp. 2-6.

Dale, J. & Porter, D. 2010, "Pharmacotherapy: concepts of pathogenesis and emerging treatments. Optimising the strategy of care in early rheumatoid arthritis", Best Practice & Research in Clinical Rheumatology, vol. 24, no. 4, pp. 443-455.

Chapter 3 – Quality of Clinical Trials

Clinical trials in Glasgow have contributed significantly to our knowledge about how to manage patients with newly diagnosed and established RA. The design of these RCTs has evolved over the years, and issues such as randomisation, choice of outcome measures and the role of strategy trials will be discussed. The quality of clinical trials is of obvious importance if clinicians are to have confidence in their results, and there is a substantial literature that has emerged surrounding the assessment of quality:

Assessment of bias

The Cochrane Handbook defines bias as "a systematic error, or deviation from the truth, in results or inferences" which can "operate in either direction: different biases can lead to underestimation or overestimation of the true intervention effect. Biases can vary in magnitude: some are small (and trivial compared with the observed effect) and some are substantial (so that an apparent finding may be entirely due to bias)" (Higgins, Green 2011).

The risk of bias in a study is related to its' quality – low quality trials introduce a higher risk of bias – but the two dimensions are not identical. For instance, some issues of quality (such as obtaining ethical approval) do not relate to the risk of bias. Some trial designs also introduce a risk of bias, but should not be characterised as being of poor quality, because of impossibility or impracticality – for example, open studies introduce a risk of bias, but it may be impractical to design a double blind study.

Some studies have shown that trial quality, as assessed by the Jadad score (Jadad et al. 1996, Jadad et al. 1996), has an impact on the likelihood of reporting a positive outcome – open (unblinded) studies, those that report inadequate concealment of allocation, and those with a Jadad score ≤ 2 were associated with an increased estimate of benefit (Schulz et al. 1995b, Moher et al. 1998). This conclusion is not universal: for example, Emerson *et al* found no association between quality and the likelihood or magnitude of treatment differences (Emerson et al. 1990).

Assessing quality of Randomised Controlled Trials

Assessing the quality of randomised controlled trials is challenging. Moher *et al* reviewed 25 published scales and 9 checklists, and noted considerable heterogeneity in these, and obvious shortcomings in most (Moher et al. 1995). The evidence concerning the question of whether the use of different scales alters the assessment of quality is

mixed, but in some circumstances applying a different scale is associated with changes in the assessment of quality (Detsky et al. 1992, Moher, Jadad & Tugwell 1996). The uncertainty surrounding the usefulness of using scales and checklists have led the Cochrane Collaboration to recommend that these are not used, in favour of a descriptive tool. Indeed, the use of the Jadad score is explicitly discouraged partly because concealment of allocation (one of the few factors consistently associated with an increased estimate of benefit if it is lacking) is not included in the scale (Higgins, Green 2011). Nonetheless, the Jadad score remains the most widely used scale in methodological reviews of study quality (Dechartres et al. 2011), and so the Glasgow studies' Jadad score is shown in Appendix 1. In place of the Jadad score, the Cochrane Collaboration recommends the descriptive assessment of the following domains:

a. Random sequence generation
b. Allocation concealment
c. Blinding of participants and personnel
d. Blinding of outcome assessment
e. Completeness of outcome data
f. Evidence of selective reporting
g. Other sources of bias

These domains have formed the basis of the 'Assessment of Risk of Bias' table for each study (Appendix 2).

Randomisation and Concealment of Allocation

The methods used for allocation of participants to their therapy in the various studies are summarised in Table 3.

Table 3 – Method of randomisation and allocation concealment

Trial	Allocation	Method of randomisation and concealment
SSZ/Aur	Partial randomisation	Sealed envelopes
Gold/HCQ	Random	Not stated
Gold/MTX	Random	Sequential allocation to therapies determined by random number tables, which were not concealed.
WOSERACT	Random	In pharmacy
MASCOT	Random	In pharmacy
TICORA	Random	Telephone to study co-ordinator using randomisation software
TEAR	Random	Telephone to study co-ordinator using randomisation software

Over 20 years, there has been an improvement in the study design, partly explained by the advances in information technology. The earliest studies used two different methods of randomisation. In the SSZ/Aur study, an equal number of cards marked with each drug name were placed into opaque envelopes which were then shuffled and numbered. Sequential patients recruited to the study were then allocated their therapy according to the drug in the next envelope. However, a significant proportion of the patients were allocated their treatment because they had already received the comparator drug. Study records are no longer extant, and it is not clear how this was handled by the 'randomisation' process – possibly, if the opened envelope indicated the 'wrong' drug that allocation was held over for the next patient. What is clear is that 1) the process fell substantially short of full randomisation 2) the methodology was poor and 3) the fact that not all the patients' therapy was randomised is clear from the study report.

In the Gold/MTX study, a different but also sub-optimal methodology was used. In this study, random number tables were used to generate a random order of drug allocation. This order was recorded in a master study file; when a patient was recruited to the study, the next study number (and its allocated treatment) was assigned to the patient. However, the master study file was not concealed such that potentially 1) the next treatment to be allocated could be ascertained in advance 2) if two patients needed to be allocated at the same time, the next two treatment could be allocated to the patients (rather than randomised). It is not known if the lack of concealment led to any flaws in the randomisation process, but it certainly raises the possibility of potential bias. Importantly, this flaw in study design is not discernible from the published report.

The double blind studies (WOSERACT, Gold/HCQ, MASCOT) all had full randomisation and concealment which can confidently be assumed to have eliminated allocation bias, The most recent studies have been open label, with blinded assessments of outcome (TICORA, TEAR) but have all used off-site randomisation, either by a trial co-ordinator using randomisation software. Again, a lack of allocation bias can be confidently relied upon.

In summary, there has been an evolution in study methodology over twenty years, with a definite improvement leading to increased confidence in the elimination of allocation bias.

Outcome Measures

The outcome measures employed in RA clinical trials has evolved significantly over the last twenty years:

1. The individual variables employed to assess disease activity and outcome has changed such that some are now rarely employed, if ever (e.g. the measurement of grip strength) whereas others have become much more widely used (e.g. generic measures of health-related quality of life such as SF36).

2. International consensus has been sought through the auspices of the Outcome Measures in RA Clinical Trials (OMERACT) initiative leading to recommendations about which outcome measures should be utilised in all clinical trials (Felson et al. 1993).

3. The use of composite outcome measures has been the most significant development (Table 4). The process has taken twin tracks on either side of the Atlantic. In the USA, the American College of Rheumatology developed the ACR20% response criteria, which was specifically designed to maximise the statistical power in discriminating between active drugs and placebo in RCTs. Later iterations of the process have led to the development of the nACR response criteria, and the hybrid ACR response criteria (Felson, American College of Rheumatology Committee to Reevaluate Improvement Criteria 2007). The latter add further ability to distinguish active response from placebo response, but have not yet been widely employed as primary outcome measures in clinical trials.

   In Europe, the disease activity score (DAS) (van Gestel et al. 1996) was subsequently developed, and followed by several alternatives including the DAS28 (Prevoo et al. 1995) (based on a smaller number of joints being assessed), clinical disease activity index (CDAI, which does require any laboratory results to score), and the simplified disease activity index (SDAI) (Smolen et al. 2003). DAS can also be used to categorise patients according to EULAR response by defining remission, good response, moderate response, or no response.

Table 4 – Composite outcome measures

Outcome measure	Abbreviation	Components
ACR Response Criteria	ACR20/50/70, nACR, ACR Hybrid	SJC, TJC, ESR/CRP, PS, PGA, AGA, HAQ
Disease Activity Score	DAS	SJC, RAI, ESR, PGA
28 joint count Disease Activity Score	DAS28	SJC, TJC, ESR, PGA
Simplified Disease Activity Index	SDAI	SJC. TJC, PGA, AGA, CRP
Clinical Disease Activity Index	CDAI	SJC. TJC, PGA, AGA

SJC – Swollen Joint Count; TJC – tender joint count; PS – visual analogue pain score; PGA – patient global assessment of disease activity; AGA – assessor global assessment of disease activity; HAQ – health assessment questionnaire; RAI – Ritchie articular index

It is now almost inconceivable that a RCT between two DMARDs or DMARD strategies would not use one of these composite measures as an outcome measure. In Glasgow, the outcome measures used are shown below:

Table 4 – Outcome Measures used

Trial	Primary Outcome	Secondary outcome measures
SSZ/Aur	-	Ritchie AI, VAS pain score, duration of morning stiffness, ESR, CRP, platelet count
Gold/HCQ	-	Ritchie AI, VAS pain score, duration of morning stiffness, grip strength, ESR, CRP, Global wellbeing (Likert scale, 1-5), Health Assessment Questionnaire.
Gold/MTX	-	Ritchie AI, VAS pain score, duration of morning stiffness, ESR, CRP, Global wellbeing (Likert scale, 1-5), Health Assessment Questionnaire, modified Paulus response and Menninger response.
WOSERACT	Total Sharp Score	Ritchie AI, VAS pain score, ESR, CRP, Physician Global assessment (Likert scale, 1-5), Patient Global assessment (Likert scale, 1-5), Health Assessment Questionnaire
MASCOT	DAS	EULAR good response, remission, ACR20/50/70, HAQ
TICORA	DAS	EULAR good response, remission, ACR20/50/70, HAQ score, SF36, Total Sharp Score, Economic evaluation
TEAR	DAS28	EULAR good response, remission, ACR20/50/70, HAQ score, SF12, Total Sharp Score

The use of composite outcome measures has become the norm in clinical trials, but there has been an interesting development that has grown out of this, namely, that their use has become increasingly widespread in routine clinical practice. This has been in no small part due to the positive findings in the TICORA study whereby the routine and systematic use of DAS to guide therapeutic decisions (within the context of a tight control strategy) led to far better clinical outcomes. Consequently, national and international guidelines recommend the use of composite outcome measures in routine clinical practice (National Institute for Health and Clinical Excellence 2009).

Chapter 4 –Scientific Contribution of studies

Only a small number of DMARDs were in routine use in the management of RA in the 1980's. Rational prescribing decisions were limited by a lack of high quality evidence from randomised controlled trials. Those studies that had been performed tended to be small without validated outcome measures, which limited their usefulness.

- Intramuscular gold had been shown to have disease modifying properties in 1960 (Anonymous1960) but inefficacy and serious toxicity were common such that only a small proportion of patients remained on therapy for longer than 5 years (Sinclair, Duthie 1949) (Maetzel et al. 2000).

- Sulfasalazine (SSZ) had originally been developed in the 1930's but was not re-discovered until the early 1980's when two studies rekindled interest in the drug for the treatment of RA (Pullar, Hunter & Capell 1983, McConkey et al. 1980); even then, the evidence remained relatively weak, for instance, with no direct evidence that SSZ therapy was associated with reduced radiographic progression.

- Penicillamine was also used widely as a DMARD, as the result of a double blind placebo controlled trial reported in 1973. This demonstrated improvements in clinical symptoms (such as pain), acute phase response (ESR) and function (grip strength). Once again, modification of radiographic progression was not demonstrated, and significant toxicity was recorded (Golding et al. 1973)(Bunch et al. 1984a)

- Chloroquine and hydroxychloroquine were widely used in the management of RA (Clark et al. 1993, Freedman 1956). At the time, anti-malarials were believed to be less efficacious, but safer, than the other DMARDs available, an impression that has subsequently been confirmed in RCTs (van der Heijde et al. 1990).

- Methotrexate was just becoming available in the mid 1980's with placebo controlled RCTs demonstrating superiority over placebo (Williams et al. 1985). Initial concerns about the potential for hepatotoxicity led to caution in its widespread use, particularly in Europe, but over time its safety record, tolerability and efficacy have resulted in it becoming the most widely prescribed DMARD (Criswell, Henke 1995).

The challenge facing the rheumatology community was to establish which DMARDs were effective, to evaluate their relative efficacy, and to identify drug combinations and/or

strategies that would optimise patient outcomes. The studies performed in Glasgow over two decades have contributed to the pursuit of these goals:

Sulfasalazine and auranofin

SSZ was first developed and used in the treatment of inflammatory arthritides by Nana Svartz in Sweden in the 1930's. At the time, there was a belief that RA may have an infective aetiology and her rationale was to combine an anti-inflammatory agent (5-aminosalicylic acid) with an antibiotic (sulfapyridine). The original reports were encouraging; the patients included had a number of diagnoses, which with hindsight did not necessarily negate her results (Svartz 1948). Nevertheless, interest in the drug diminished when a negative report of a study in RA was published in the UK (Sinclair, Duthie 1949). Interest in the use of SSZ was not re-kindled until the 1980s when two positive trials were reported (Pullar, Hunter & Capell 1983, McConkey et al. 1980).

Auranofin (Aur), a water soluble gold salt, was developed as an oral alternative to the injectable gold salts that had been in use since the 1950s. Placebo controlled RCTs have demonstrated the superiority of Aur over placebo with improvements in clinical and laboratory markers of disease activity (Johnsen et al. 1989, Ward et al. 1983, Williams et al. 1984)(Menard et al. 1982, Schattenkirchner et al. 1982, Smith, Brown & Meyers 1982). Interestingly, considering that it has subsequently fallen out of favour because of a poor risk-benefit profile, Aur was one of the few drugs in the 1980s to be proven to slow radiographic progression in RA (Katz et al. 1982). Small comparative RCTs suggested that Aur was probably better tolerated than injectable gold, but was somewhat less efficacious (Menard et al. 1982, Schattenkirchner et al. 1982, Smith, Brown & Meyers 1982).

At the time the Glasgow trial was performed, very few head to head comparisons between two DMARDs had been published. It was important for rheumatologists and their patients to elucidate if one DMARD was preferable over another, to maximise the likelihood of clinical response and minimise the risk of toxicity. The study was designed to answer the question of whether SSZ or Aur had a better risk-benefit profile. The choice of an active comparator study, rather than a placebo controlled trial, is important. Placebo controlled trials had already shown superiority of both agents when compared to placebo, and it was deemed inappropriate to expose patients to a prolonged period without active treatment through the inclusion of a placebo arm in the study. There are several significant limitations and weaknesses in the study design and reporting, which are an indication of how many improvements have been made over the past 20 years in this regard:

- ethical approval – the study had ethical approval but there is no mention of this in the study report

- exactly 200 patients were recruited, and this is an indication that there were no power calculations performed, and that the sample size was arbitrary

- randomisation – that the study was not truly randomised has already been discussed above (p14)

- no primary outcome measure was selected

Patients dropped out from their assigned therapy over the course of the trial such that 63/50% of patients continued on SSZ/Aur respectively by the end of the trial. This design, whereby only patients who continued on their assigned therapy are analysed for efficacy, militates against a positive result – patients with a sub-optimal response could have their treatment changed to an alternative, thereby leaving the trial. Essentially, responding (at least partially) to therapy becomes a pre-requisite for staying on the trial, and hence for being included in the analysis. Consequently, it is unsurprising, if only responders are analysed, that differences between groups disappears with time.

Analysis of disease activity at 12 weeks demonstrated that patients assigned to SSZ had significantly lower median ESR (28 vs 36, p=0.04 Mann-Whitney) and articular index (8 vs 12, p=0.04 Mann-Whitney), but there were no significant differences in median CRP, duration of early morning stiffness or visual analogue pain score. There was a larger mean improvement with SSZ therapy in ESR (figures not provided, p=0.04, Students t-test) and CRP (p=0.026, Students t-test) between 0 and 12 weeks, but not between 0 and 24 or 0 and 48 weeks. Various possible interpretations can be placed on these findings:

1) SSZ is a more effective DMARD than Aur – the findings are consistent with this interpretation. However, the lack of positive findings in all measures of disease activity, or at subsequent time points needs to be explained. The convergence of the groups at 24, 36 and 48 weeks may be explained as above, namely, that the trial design (analyzing only 'responders') militates against finding a difference between the groups as follow up gets longer. In some regards, it is no surprise that comparisons between groups showed no significant differences between groups for individual variables. The magnitude of change expected with DMARD therapy in individual variables is small, compared with the variance of these variables; whilst these variables continue to be included in the EULAR 'core set' of outcome variables (Felson et al. 1993) it has been

amply demonstrated that composite outcome measures are much more sensitive at identifying differences in efficacy between different treatments.

2) SSZ works faster than Aur – the findings are also consistent with the possibility that whilst SSZ works faster, it is ultimately no better than Aur. The data show that after 48 weeks the patients remaining on therapy were as well controlled as those remaining on SSZ, indicating that in many patients (50% Aur vs 63% SSZ) Aur proved to be as effective a DMARD as SSZ. The difference in the number of patients remaining on therapy after 48 weeks were not statistically different, and the numerical difference between the groups can be largely explained by a very high drop out rate from the Aur group in patients who had previously received intramuscular gold (19/26 patients).

3) SSZ and Aur are equally effective DMARDs – the statistical superiority of the SSZ group in a small number of variables after 12 weeks might be explained as follows:

    a. Multiple testing – the p values for the differences are only just less than 0.05, and in the absence of any adjustment for multiple comparisons might not be considered 'significant'. However, 3 out of 18 hypotheses tested were significant, and all favoured SSZ, which is more than would be expected by chance.

    b. Confounding – this is a significant concern with this trial: >20% of patients were not randomized but had their therapy assigned because of their previous treatment. An attempt to mitigate this was made by performing a sub-group analysis, excluding patients who had been previously treated with intramuscular gold; this found that the superior benefit in the SSZ group after 12 weeks was still found, and was 'statistically significant in more parameters'. However, ideally, this analysis would have excluded all patients who had not been randomised, thereby also excluding patients who had previously been treated with SSZ and who were assigned to the Aur group.

    c. Bias – the method and effectiveness of allocation concealment for those patients who were randomised is uncertain, which has been shown to be associated with larger estimates of treatment effects (Schulz et al. 1995a).

In conclusion, whilst it is possible that the findings of this trial demonstrate that SSZ works significantly faster as a DMARD than Aur, the study design was associated with a significant risk of bias that would indicate that caution should be exercised in reaching definite conclusions. Over time, further evidence has accumulated that Aur is less well

tolerated that SSZ – after five years, a follow up reported that very few patients continued on Aur (McEntegart et al. 1996) – and the drug is no longer manufactured.

Gold and hydroxychloroquine combination therapy

In the early 1990's the role of DMARD therapy was not yet fully established, although there was increasing evidence for the efficacy and safety of DMARD monotherapy. The role of combination DMARD therapy was even more uncertain, although there were its protagonists (Healey, Wilske 1991, Wilske, Healey 1989). In some parts of the world (Australia and Canada), combination therapy was quite commonly used and yet it was acknowledged that the evidence base was weak (Paulus 1990). Some uncontrolled, observational studies had been published, but few randomised controlled trials had been performed. A meta-analysis performed in 1994 concluded that combination therapy did not offer any substantial improvement in efficacy but was associated with higher toxicity (Felson, Anderson & Meenan 1994). However, the limitations of DMARD monotherapy were also acknowledged, particularly that relatively few patients responded well to therapy, and most patients continued to experience disease progression, leading to increasing joint damage and physical disability. The Gold/HCQ study was the first large, double blind placebo controlled studies to investigate the efficacy of adding a second DMARD (HCQ) to the treatment of patients with persistent disease activity despite the use of another (Gold).

One of the strengths of this study was the careful characterisation of the study cohort. Concerns about the potential for increased toxicity associated with combination DMARD therapy, and the realisation that some patients responded well to DMARD monotherapy led to a study design that delineated a sub-group of patients who had made a sub-optimal response to IM gold therapy over a six-month period. This eliminated the risk of unnecessary use of combination therapy in patients who would respond well to a single drug. It is a study design that has prevailed, being employed in some modern trials of conventional and biologic DMARD management (van Vollenhoven et al. 2009). The study therefore recruited 440 patients with RA who were starting on IM gold therapy. Over the first 6 months, 25% responded well to IM gold and so did not need combination therapy. 140 patients stopped their IM gold within 6 months, predominantly because of drug-related toxicity. A further 48 patients were not offered or declined the option of taking part in the trial, leaving 142 (32%) of the original cohort to be randomised.

The analysis of the outcome measures suffered from the usual difficulties encountered commonly at that time, in that composite outcome measures had not been developed,

leading to very poor statistical power. Nonetheless, the lack of any improvement between 0 and 6 months of combination therapy in most outcome measures argued against a large benefit from Gold/HCQ combination therapy. In retrospect, this finding may now be surprising – HCQ used in combination with MTX (+/- SSZ) has been proven to be more effective than MTX monotherapy, and has become the mainstay of many patients' therapy (O'Dell et al. 1996, O'Dell et al. 2002). Of course, it is possible that there is drug specific synergism between MTX and HCQ that does not exist between HCQ and IM gold. The possibility, however, that the Gold/HCQ study gave a negative result as the result of a Type 2 error must also be borne in mind.

The study emphasises the importance of a careful assessment of the value of different combinations of DMARDs. It should not be assumed that two DMARDs that are both effective as monotherapy will inevitably work together additively or synergistically. A recent example includes the observations that TNF inhibitors are more effective when co-prescribed with methotrexate, but that adding methotrexate to tocilizumab appears to afford no additional benefit.

Gold and methotrexate

Methotrexate had emerged in the mid 1980s as a safe and effective DMARD. The popularity of MTX grew quickly in the USA whereas in Europe IM gold remained a mainstay of DMARD therapy, second only to SSZ in popularity. In many centres, including Glasgow, SSZ was the DMARD of first choice. In patients who failed to respond, or who developed drug-related toxicity, the question arose as to which drug to use next. There was concern in the West of Scotland, that methotrexate toxicity may be more common in the local population because of social derivation, poor nutrition, smoking and high alcohol intake. On the other hand, it was widely recognised that IM gold is poorly tolerated in the long term, and in the USA continuation rates with methotrexate were substantially higher (Maetzel et al. 2000). The Gold/MTX study set out to compare the efficacy and safety of IM gold and methotrexate in the West of Scotland in a prospective, open label, randomised controlled trial.

There were significant limitations in the trial design:

1) the method of allocation concealment was inadequate and could have introduced allocation bias. It is not possible to ascertain whether this occurred, or if it would have affected the results of the study (or in which direction, in favour of MTX or IM gold).

2) there were no power calculations performed to determine the sample size. It is important to consider whether the lack of any significant difference in clinical response, between groups, was the result of inadequate sample size leading to a Type 2 error.

3) dose of comparator drugs – in hindsight, the initial dose of methotrexate (5mg/wk) and rate of dose escalation (2.5mg/wk/month) was unnecessarily cautious. The caution was understandable, given that the rationale for the trial included a concern that the study population in the West of Scotland would be particularly susceptible to MTX toxicity. However, time has taught us that MTX can be started at a higher dose (7.5 – 15mg/wk) and escalated rapidly to 20 mg/wk within 4-8 weeks. In the study, it would have taken 6 months to reach a dose of 20mg/wk; it is notable that the only statistically significant difference between the groups in any efficacy outcome variable at any time point was a lower ESR in the IM gold group after 12 weeks. Almost certainly, this resulted from the slower dose escalation rather than an intrinsically slower treatment response with MTX. The average dose of MTX at the end of the trial was also considerably lower (10mg/wk) than in other reports (Grigor et al. 2004), which might have limited the clinical response.

Despite these limitations, the study yielded useful information for UK rheumatologists. Far from confirming concerns about higher toxicity with MTX, the results showed that more patients withdrew from IM gold treatment for any reason ($p=0.014$) or for toxicity ($p=0.0026$).

The choice of clinical efficacy outcome assessment in the Gold /MTX trial is interesting, being the first in Glasgow to use a composite outcome measure – the Paulus 50% response criterion was a composite outcome measure using ESR, duration of early morning stiffness, patient global assessment of wellbeing and joint tenderness (Paulus et al. 1990). This was adapted for the use in the Gold/MTX trial, and a numerically greater number of patients made a good (50%) response to MTX than IM gold (27 vs 19), which approached statistical significance (Chi squared $p=0.069$). Clearly this raises the possibility of a type 2 error, and that a caveat should be added to the conclusion reached at the time, which was that there were no differences in efficacy between IM gold and MTX. However, other comparative trials have reached broadly similar conclusions of similar efficacy, but more toxicity with IM gold (Lehman et al. 2005).

Low dose oral corticosteroid

The use of corticosteroids in the treatment of RA has always been controversial (Myles 1985). Very early reports of miraculous improvements in disease activity promised a new dawn in the therapy of this previously intractable disease. Early promise soon evaporated in the face of the development of serious corticosteroid toxicity, and the role of steroid therapy diminished. Despite early evidence that corticosteroids may be disease-modifying, most rheumatologists viewed corticosteroids as (ideally) short term symptomatic therapy. The prevalence of corticosteroid use varied quite dramatically: in Glasgow, it was used very sparingly as oral therapy, with a preference for intra-articular or intra-muscular triamcinolone used to treat acute flares of disease. Elsewhere in many parts of the world, low dose oral prednisolone was used in 40-60% of the RA population to control symptoms. However, the safety of this approach has been questioned in view of the association between corticosteroid use and adverse long term outcomes (Saag et al. 1994). Protagonists maintained that the association is not causal, but attributable to confounding by indication – namely that it is patients with severe disease that experience poor outcomes, and who also require corticosteroids. Antagonists to widespread corticosteroid use remain unconvinced, and concerned about infection, cardiovascular morbidity, osteoporosis and mortality.

In 1995, the ARC Low Dose Corticosteroid Group published a well conducted, prospective, double blind randomised controlled trial comparing prednisolone 7.5mg daily with placebo in the treatment of early RA (Kirwan 1995). The study found that there was a significant reduction in the radiographic progression in patients treated with prednisolone. One limitation of the study rests in the fact that the use of DMARDs was left to the discretion of the attending rheumatologist. Given that these drugs are known to retard radiographic progression, an imbalance in their use between the study groups would have been a confounding factor. Whilst the study report documents that there were no significant differences in the use of DMARDs, only overall percentage use (not split for groups) of DMARDs was recorded. Perhaps more importantly, however, is the observation that only ~2/3 of patients were prescribed DMARDs at all. The precise figure is not deducible from the study report and may be lower than this if some patients received more than one DMARD during the study follow up. It is not known if the radiographic progression occurred predominantly in those patients not treated with DMARDs.

The West Of Scotland Early RA Corticosteroid Therapy study (WOSERACT) was designed to test whether the findings of Kirwan *et al* could be replicated in a group of patients who were all being treated with the same DMARD therapy, namely, sulfasalazine.

The results did not replicate the findings of the earlier ARC Low Dose Corticosteroid Group study. It is possible that this was because the steroid was prescribed in combination with sulfasalazine in all patients. However, there are reasons to suspect that this might not be the case. Foremost among these are that there have been a number of subsequent trials that have confirmed the benefit of low dose corticosteroids in early RA, even when prescribed in combination with other DMARDs. A meta-analysis has confirmed that there is good evidence of disease-modification with corticosteroids, and the WOSERACT study appears to be an outlier (Saag et al. 1996). Why might this be? The first possibility is that assessors and/or participants could have become aware of treatment allocation due to unfortunate circumstances (the placebo tablet had to changed from pyridoxine to ascorbic acid following MHRA advice to avoid long term pyridoxine use) which could have introduced bias. However, it is difficult to explain how unblinding of treatment allocation could influence radiographic progression, or the scoring of the radiographs by assessors who were undoubtedly still blinded to treatment group.

An alternative possible explanation lies in the scoring of the radiographs: the radiographs were scored by two readers using slightly different techniques. One read the films in chronologically ordered pairs whereas the other read the films unaware of the order of the films. The scores from both readers showed no significant differences in radiographic progression between the groups, but there was a five-fold difference in the average scores recorded. Such differences are not explicable by the reported differences in methodology, and must reflect fundamental differences in what radiographic appearances were recorded as erosions or joint space narrowing (the two components that comprise the Total Sharp Score). However, despite the methodological differences, neither scorer found a significant difference in radiographic progression between groups.

One finding that WOSERACT and the ARC Low Dose Corticosteroid Group studies both found was the lack of efficacy of low dose corticosteroids on acute phase response. This was somewhat surprising given the widespread use of corticosteroids to treat symptoms or flares of disease activity, but might suggest that the role of chronic low dose corticosteroids should be restricted to reducing radiographic progression. However, other recent reports have shown that within the context of a treat-to-target management strategy, the addition of low dose prednisolone not only reduces radiographic progression but also increases the rate of clinical remission (Bakker et al. 2012). Moreover, there are other appropriate uses of corticosteroid therapy – the COBRA (Boers et al. 1997) and BeSt (Goekoop-Ruiterman et al. 2005) studies show that high dose oral steroid can contribute to

rapid, early disease control, and the TICORA and TEAR trials used intra-articular and intra-muscular steroid as 'bridge' therapy in the early stages of DMARD therapy.

Methotrexate and sulfasalazine combination therapy

The acceptance of the need to treat patients with DMARD therapy gained very widespread acceptance over the 1980's and 1990's with the advent of high quality RCTs that demonstrated unequivocally that MTX, SSZ and leflunomide all have disease modifying properties (Scott et al. 2001, Strand et al. 1999). This enthusiasm for therapy was tempered by the observation that despite the use of DMARDs, the prognosis of RA remained poor. There were two main concerns: firstly, patients on DMARD monotherapy often continued to have persistent disease activity, and clinical remission was rare; secondly, a minority of patients continued on any DMARD long term as the result of a combination of poor efficacy and drug toxicity.(Maetzel et al. 2000, Felson, Anderson & Meenan 1990) The rise in popularity of MTX as the DMARD of first choice was largely the result of better long term continuation rates (compared to IM gold or sulfasalazine), rather than superior efficacy, but even MTX monotherapy fails to control most patients' disease activity.

The upshot was a growing interest in the use of combination DMARD therapy, to investigate whether such an approach would yield additional benefits at acceptable levels of toxicity. The results were mixed: some small studies suggested a modest increase in efficacy at the expense of a similarly modest rise in adverse effects (Bunch et al. 1984b); other studies failed to demonstrate any superiority of combination therapy (Porter, Capell & Hunter 1993). The two DMARDs most commonly prescribed at this stage were SSZ and MTX, with HCQ being used in patients will milder disease. Important evidence started to emerge in the 1990's about the value of using combinations of these three DMARDs. Two studies showed that triple therapy resulted in better clinical outcomes and increased rates of remission (O'Dell et al. 1996, Mottonen et al. 1999). However, two well conducted RCTs failed to show any superiority of MTX/SSZ therapy over monotherapy with either drug in early disease (Haagsma et al. 1994, Dougados et al. 1999). How were the results of these studies to be reconciled? Was dual therapy ineffective, but triple therapy effective? Questions were also being raised about the wisdom of using combination DMARD therapy in *all* patients when a proportion (approximately 30-40%) of patients respond well to monotherapy.

The Methotrexate and Sulfasalazine Combination Therapy (MASCOT) trial was designed to explore these issues further. The trial design excluded patients with a good response (or early toxicity) from the study population, thereby enriching it for patients who might be

more likely to benefit from combination therapy. The results of the study supported the use of 'step-up' strategies of care, whereby patients with a sub-optimal response to their initial DMARD have a second DMARD added, rather than using sequential monotherapy. There are alternative combination strategies that can be pursued (parallel or step-down) but the results of MASCOT provided valuable confirmation of the step-up strategy, which has been endorsed by SIGN guidelines:

> *A combination DMARD strategy, rather than sequential monotherapy, should be considered in patients with an inadequate response to initial DMARD therapy* (Scottish Intercollegiate Guidelines Network 2011)

Tight control of rheumatoid arthritis

Evidence was emerging from other biological models that 'tight control' of disease may result in superior clinical outcomes. Foremost among these was Type 1 diabetes mellitus (DM) – the Diabetes Control and Complications Trial randomised patients to routine care or tight glycaemic control using multiple daily insulin injections. The results were a striking reduction in the development of micro-vascular complications such as retinopathy – for instance there was a 75% reduction in new episodes of retinopathy (primary prevention), and a 50% reduction in further deterioration of retinopathy (secondary prevention) (The Diabetes Control and Complications Trial Research Group 1993). Both RA and Type 1 DM are chronic auto-immune diseases in which severe complications arise insidiously over many years, resulting in significant morbidity and premature mortality. Following the publication of the results of the DCCT, a hypothesis emerged that similar improvements in outcome could be achieved in RA patients through 'tight control' of synovial inflammation. The Tight Control in RA (TICORA) study was designed to test this hypothesis.

It is important to reflect that evidence from other biological models indicates that caution is wise before assuming that tight control will invariably or inevitably lead to superior outcomes. Firstly, the positive benefits of tight control may need to be weighed up against negative effects. For example, studies of primary and secondary prevention of cardiovascular events have clearly demonstrated that cholesterol lowering therapy (for instance with statins) results in improved cardiovascular outcomes. But emerging data shows that these improvements come at the cost of an increased incidence of Type 2 DM. Thus, the use of high dose atorvastatin (80mg daily) delivers a substantial reduction in cholesterol but for every three cardiovascular events that are saved, one new case of diabetes emerges (Sattar et al. 2010).

Secondly, not all tight control studies have demonstrated any effect. For instance, attempts to translate the tight control strategy of DCCT into the treatment strategies for the management of Type 2 DM have not delivered the expected reductions in macro-vascular complications (Hemmingsen et al. 2011). Thus, the TICORA study was needed to assess whether 1) tight control could be achieved 2) if so, whether this would lead to improved medium term outcomes 3) and if so, whether this benefit would be offset by significant costs, either financial ("would intensive management cost too much?") or clinical ("would there be too many drug-related side effects?").

The strength of a strategy trial, is that it is not tied to the assessment of the efficacy of a single drug or drug combination. Rather, TICORA integrated the latest developments in clinical disease assessment (using DAS) with all drugs and drug combinations known to be efficacious into an all-embracing strategy that focussed on optimising care irrespective of which drug(s) were utilised.

It is notable that the improvement in clinical outcome with intensive management was much more striking than the reduction in radiographic disease progression. Experience from trials of anti-TNF drugs has shown that, in established disease, radiographic damage in the hands and feet can be almost entirely halted (Maini et al. 1999). These results are seen despite the fact that the clinical response rates, while good, are not dramatically so. In TICORA, the reverse seemed to be true – the remission rates exceed those reported in trials of anti-TNF therapy, but the impressive stabilization of radiological damage is not seen. Why should this be so? Firstly, it must be remembered that the patient populations in these trials differ. The anti-TNF trials quoted above were conducted in patients with established RA, not in those with early disease. When anti-TNF therapy has been studied in early RA, continuing joint damage is seen, albeit at a reduced rate when compared with methotrexate therapy (Genovese et al. 2002). Secondly, it took several months to induce remission in most patients, and it is likely that radiological damage was progressing apace in this period. Thirdly, it was noted that there was a significant reduction in erosive damage, but no impact on joint space narrowing, and that the vast majority of the increased Sharp score consisted of deterioration in the joint space narrowing component of the score. It is possible that the pathological processes of cartilage loss and erosive damage are distinct, and that conventional DMARDs are more effective at ameliorating the latter.

The finding that intensive outpatient management, often using multiple DMARDs, was associated with fewer drug related side effects is, on the face of it, surprising. However, similar findings were reported in the COBRA trial. It seems likely that the improved

general well-being of the patient contributes to a reduction in perceived (or actual) side effects. In TICORA, the frequent clinical review may also have facilitated additional patient education (perhaps reducing inappropriate drug cessation during intercurrent, but unrelated episodes), reassurance, and appropriate adjunctive therapy.

The health economics assessment that was performed is reassuring. Before the trial, it was thought that there might be a trade off between improved clinical results and increased cost. In fact, the trial demonstrated no increase in overall costs, although it has to be noted that the confidence intervals for the estimates of cost were wide. Nonetheless, the trial suggests that the increased outpatient costs of intensive management are offset by reduced community healthcare costs, and, most importantly, reduced inpatient costs. This results in a cost-neutral intervention, with far superior clinical results, which suggested that this form of intensive intervention ought to find a place in routine clinical practice.

It was important to establish whether the results of the trial were robust and reproducible. The trial was relatively small, and the impact of the intervention was greater than might have been predicted. Subsequently, however, other strategy trials have been published:

1. CAMERA – this Dutch study used computerised algorithms to direct therapy in the intervention group, and found that this resulted in superior outcomes when compared to traditional physician directed care.(Verstappen et al. 2007)

2. Fransen et al published the results of a study that randomised centres (rather than patients) to deliver ‘treat-to-target’ care or routine management, and again found that directing therapy according to the patients’ DAS delivers significant improvements of outcome.(Fransen et al. 2005)

These three studies are the only ones that have sought to compare ‘treat-to-target’ or intensive management strategies with ‘routine’ care and their findings are consistent. Other studies (TEAR (Saunders et al. 2008), BeST (Goekoop-Ruiterman et al. 2005), SWEFOT (van Vollenhoven et al. 2009), CAMERA-II (Bakker et al. 2012)) have incorporated different elements of a ‘treat-to-target’ strategy but have focused on the comparison of the use of different drug regimens within that context. A systematic review has concluded that the evidence is ‘compelling’ and ‘unanimous’ that the use of a treat to target strategy of care is effective (Schoels et al. 2010). These conclusions are reflected in international consensus statements (Smolen et al. 2010) and clinical guidelines that recommend that patients are reviewed frequently, have their disease assessed using a composite measure of

disease activity, and have treatment escalated until the patient is in low disease activity or remission:

> *Treatment should be aimed at reaching the target of remission or low disease activity as soon as possible, in every patient; as long as the treatment target has not been reached, treatment should be adjusted by frequent (every 1-3 months) and strict monitoring* (Smolen et al. 2010)

Triple therapy in Early RA

The results of the TICORA study raised as many questions as it answered. Because the intensive management strategy comprised many different components, it wasn't possible to tease out which are the most important. For instance, the improved outcomes might be the result of: frequent assessments with appropriate adjustment of therapy; or the liberal use of IA/IM steroid early in the disease course; the use of combination therapy; the close doctor-patient relationship that developed; or any combination of these or other factors. At the end of the study (after 18 months of follow up), 56% of patients in the intensive group were receiving triple therapy with MTX/SSZ/HCQ. O'Dell *et al* had already published on the superiority of triple therapy over MTX monotherapy (O'Dell et al. 1996) and it was possible that this was a major contributor to the success of the TICORA strategy. If so, would the use of triple therapy from the outset lead to still greater response rates? Because of the complex nature of the treatment strategy, the ideal study design to address this issue was to compare two groups, both treated with an identical intensive treatment strategy, with a single difference: one group would start on triple therapy whilst the other group would be treated with a step-up regimen (as in TICORA).

The results of the TEAR provided valuable information to complement the results of TICORA. Firstly, it was reassuring to have the effectiveness of intensive management confirmed in a second cohort of patients. At the end of 12 months ~40% of patients were in clinical remission; whilst this is less that the 65% remission rate reported in TICORA, this study was conducted over 18 months, and the remission rate at 12 months was very similar (unpublished data). Secondly, the results strongly suggested that treating all patients with newly diagnosed RA with triple therapy affords no advantages over employing a 'step-up' strategy whereby patients only move on to combination therapy if and when their disease is poorly controlled despite a three month trial of monotherapy. This has proved to be somewhat contentious, and requires further evaluation:

1. Several studies have shown that 30-40% of patients with newly diagnosed RA make a sustained good response to MTX monotherapy (van Vollenhoven et al. 2009, Goekoop-Ruiterman et al. 2005). Most patients and clinicians would prefer to avoid unnecessary combination therapy on the grounds of convenience, cost and safety. The TEAR study is encouraging evidence that patients do not suffer any ill effects from delaying combination therapy while a therapeutic trial of MTX monotherapy is undertaken *within the context of an intensive management strategy*. This rider is necessary because the frequent assessments (e.g. to address minor side effects, to ensure rapid escalation of therapy), use of bridging IM corticosteroid, and targeted use of IA steroid into swollen joints may be important in securing the efficacy of a step-up approach.

2. There are discrepancies between UK national and European guidelines: the NICE Clinical Guidelines recommends that all patients with newly diagnosed, active RA should receive initial combination DMARD therapy, unless there are reasons not to (National Institute for Health and Clinical Excellence 2009). In contrast, EULAR guidelines indicate that initial monotherapy should be the norm unless there are poor prognostic indicators (although the evidence for using combination therapy in patients with adverse prognostic features (which are not defined) is lacking) (Smolen et al. 2010).

3. Some of the evidence cited for the superiority of initial combination therapy is drawn from trials comparing monotherapy with combination therapy, such as the FinRACo study (Mottonen et al. 1999) but outwith the context of a 'treat-to-target' or intensive strategy – i.e. patients on monotherapy were not given step-up therapy if they had persistent disease activity despite monotherapy. The BeSt study directly compared step-up therapy with initial combination therapy, and found a faster (but ultimately no greater) clinical response with reduced radiographic progression in the initial combination group (Goekoop-Ruiterman et al. 2005). However, there are some important features of the trial that should lead to caution before reaching a conclusion that initial combination therapy should be considered superior to monotherapy: firstly, the combination group received high dose oral corticosteroids (tapered to low dose over a few weeks) which is almost certainly the explanation for the rapidity of the response, and very likely to be the explanation for the reduced radiographic progression (because corticosteroid therapy has been demonstrated to reduce erosive change). Secondly, the step-up group did not receive intensive therapy in two regards:

the frequency of assessment was only quarterly (rather than monthly), and the use of intramuscular corticosteroid as 'bridge therapy' during the first three months of DMARD therapy was not allowed.

In conclusion, the evidence suggests that a significant proportion of patients (up to 30-40%) will respond well to MTX monotherapy. It's not necessary to treat all patients with combination therapy from the outset, because delaying treatment to establish which patients require combination therapy leads to no long term ill effects. Rapidity of onset can be achieved by co-prescribing high dose oral corticosteroids or bridge IM steroid, and long term radiographic progression will be minimised by using low dose oral corticosteroids although this benefit must be offset against the potential deleterious effects of chronic steroid use.

Some important issues that remain unresolved. Firstly, studies to date have mostly used DAS or DAS28 as the target for tight control. Other clinical/laboratory indices could be used, and the use of biomarkers has also been explored (van Tuyl et al. 2008). The use of musculoskeletal ultrasound as an adjunct to clinical examination is being studied, in view of its increased sensitivity to sub-clinical synovitis. Secondly, the decision about how low to aim is important: recent consensus statements have suggested that aiming for clinical remission is appropriate in most patients, although the evidence base is mainly drawn from studies like TICORA and TEAR in which low disease activity was the target (Smolen et al. 2010).

Conclusions

The clinical trial programme in Glasgow has contributed significantly to our knowledge of how to treat newly diagnosed RA: the disease-modifying properties of DMARDs, the role of combination therapy, low dose oral corticosteroids and, especially, the advantages of employing an intensive management strategy have been elucidated. The early trials (SSZ/Aur, Gold/MTX and Gold/HCQ) were not, perhaps, as individually influential as TICORA but it is important to remember that at the time the debate about the risk/benefit of DMARDs continued to be brisk. These trials played a significant part in that debate by demonstrating that many DMARDs were both safe and effective. Nonetheless it is the later studies which have made a bigger international impact. The findings of the TICORA study have been endorsed in other studies, and national and European guidelines draw on the results directly in their recommendations for best practice. Early RA clinics have become increasingly widespread with the aim of delivering an intensive management strategy in all RA patients. Typically, after diagnosis, patients are reviewed monthly. At each visit, their

disease is formally assessed using the 28 joint disease activity score and management is guided by this. In most UK centres of excellence, patients are given combination therapy or are offered a step-up approach to drug therapy: starting with MTX, stepping up to triple therapy, and biologic therapy as required by the persistence of disease activity

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Appendix 1 - Jadad Scores

Study	Randomisation	Double Blind	Withdrawals & Dropouts	Total
SSZ-Auranofin	0	0	1	1
Gold-HCQ	2	2	1	5
Gold-MTX	1	0	1	2
WOSERACT	2	1	1	5
MASCOT	2	2	1	5
TICORA	2	0	1	3
TEAR	2	0	1	3

1 point is scored for each "Yes" or 0 points for each "No."

Q1. Was the study described as randomised (this includes the use of the words such as randomly, random, and randomisation)?

*Give an additional point if the method to generate the sequence of randomisation was described **and** it was **appropriate** (table of random numbers, computer generated, etc). Deduct a point if the method to generate the sequence of randomisation was described **and** it was **inappropriate** (patients were allocated alternately, according to date of birth, hospital number, etc).*

Q2. Was the study described as double blind?

*Give an additional point if the method of double-blinding was described **and** it was **appropriate** (identical placebo, active placebo, dummy, etc). Deduct a point if the method of blinding was **inappropriate** (e.g., comparison of tablet vs, injection with no double dummy).*

Q3. Was there a description of withdrawals and dropouts?

Appendix 2 – Assessment of Risk of Bias

SSZ/Aur trial

Trial - SSZ vs Aur		Comments	
Random Sequence Generation	Method of randomization not stated; not all patients randomised	1. Patients previously treated with SSZ [n=25] or Aur [n=4] were assigned to other drug 2. Patients who stopped IM gold for inefficacy or 'serious' toxicity (proteinuria, leucopaenia, thrombocytopaenia) were assigned to receive SSZ. The number of patients previously treated with IM gold and assigned to SSZ group is not stated, but overall 40 patients in SSZ group and 26 in the Aur group had previously been treated with IM gold.	
Allocation Concealment	Not stated	Potential for randomisation bias	
Blinding of participants and personnel	Participants – not blinded; personnel - not blinded	Potential for bias	
Blinding of assessment	Not blinded	Potential for assessment bias	
Completeness of outcome data		No consort diagram provided; drop outs not included in the analysis - % analysed = 63% [SSZ] and 50% [Aur]	
Evidence of selective reporting	None		
Other sources of bias		None identified	
Statistical analysis	Power calculations – not reported	Primary outcome – not stated	Adjustment for multiple comparisons – none

Gold/HCQ trial

Trial – Gold/HCQ		Comments	
Random Sequence Generation	Yes	Methodology not reported	
Allocation Concealment	Yes	Methodology not reported	
Blinding of participants and personnel	Yes, double blind	Yes; HCQ 400mg or matching placebo were prescribed to patients. neither participants nor personnel were aware of treatment allocation.	
Blinding of assessment	Yes, double blind		
Completeness of outcome data	'Completer' only analysis was performed	Consort diagram provided complete information on the cohort of 440 patients who started on IM gold, and the reasons for not being randomised into the study after 6 months are provided. Drop outs – only patients completing 6 months of therapy were included in the analyses, thereby excluding 50 patients (25 in each group). No intention to treat analysis was performed	
Evidence of selective reporting	None		
Other sources of bias		None identified	
Statistical analysis	Power calculations – not reported	Primary outcome – not stated	Adjustment for multiple comparisons – none

Gold/MTX trial

Trial – IM gold vs MTX		Comments	
Random Sequence Generation	Random number tables		
Allocation Concealment	Inadequate	There was inadequate concealment of the allocation process – treatments were allocated using random number tables to sequential study numbers that were then assigned to sequential patients. These were recorded in a trial master file that was not concealed; potentially the next treatment to be allocated could have been ascertained, could have influenced recruitment, and could have introduced allocation bias	
Blinding of participants and personnel	Participants – not blinded; personnel - not blinded	Potential for bias	
Blinding of assessment	Not blinded	Potential for bias - the published report almost certainly contains an error, stating that "patients, medical and metrology staff were *unaware* [emphasis added] of treatment allocation" but the abstract clearly states that this was an open label trial (confirmed by personal communication).	
Completeness of outcome data	Complete	Consort diagram – none, but the number of patients who declined to take part, and their stated reasons for so doing are recorded. Drop outs – patients who stopped their allocated therapy were included in some of the analyses using intention to treat. Within group analyses only used patients who remained on therapy without any 'last observation carried forward' (LOCF) analyses.	
Evidence of selective reporting	None		
Other sources of bias		None identified	
Statistical analysis	Power calculations – not reported	Primary outcome – not stated	Adjustment for multiple comparisons – none

West of Scotland low dose corticosteroid trial

Trial – WOSERACT		Comments	
Random Sequence Generation	Randomisation software	Randomisation used a minimisation technique to control for rheumatoid factor, age, gender, and the presence of erosions on baseline radiographs	
Allocation Concealment	Good	Performed by remote study co-ordinator using randomisation software	
Blinding of participants and personnel	Yes	The study was double blind, but the placebo tablets did not match the prednisolone in appearance. Moreover, during the study, the appearance of the steroid tablets changed because of a change in supplier. In addition, the composition of the 'placebo' tablet changed mid-trial from pyridoxine to ascorbic acid as a result of an MHRA warning about the avoidance of long term pyridoxine. Together, these factors indicate a significant possibility that some patients or staff did not remain blinded to treatment allocation.	
Blinding of assessment	Blinded	The primary outcome measure for the trial was the change in the total Sharp Score and the readers of the radiographs were blinded to treatment allocation.	
Completeness of outcome data	Complete	Consort diagram – provided. Drop outs – the primary analysis was by intention to treat, and drop outs were accounted for.	
Evidence of selective reporting	None		
Other sources of bias		None identified	
Statistical analysis	Power calculations – yes	Primary outcome – Change in Total Sharp Score	Adjustment for multiple comparisons – N/A

MTX and SSZ combination therapy trial

Trial – MASCOT		Comments	
Random Sequence Generation	Randomisation software	Randomisation used a minimisation technique to control for the presence of rheumatoid factor, erosions and disease duration.	
Allocation Concealment	Good	Performed by remote study co-ordinator using randomisation software	
Blinding of participants and personnel	Yes	The study was double blind. Matching placebo tablets were provided by Wyeth (MTX placebo) and Pharmacia (SSZ placebo)	
Blinding of assessment	Blinded		
Completeness of outcome data	Complete	Consort diagram shown, including documentation of those patients who started Phase 1 on SSZ but were not randomised to the placebo controlled Phase 2. Drop outs – an intention to treat analysis was undertaken with the last observation carried forward. The number of patients completing Phase 2 in each group is recorded.	
Evidence of selective reporting	None		
Other sources of bias		None identified	
Statistical analysis	Power calculations – the study had >95% to detect a difference of one DAS unit at the 2.5% significance level assuming a SD of 1.2 in change from baseline.	Primary outcome – Mean reduction in DAS	Adjustment for multiple comparisons – none

Tight Control of RA trial

Trial – TICORA		Comments	
Random Sequence Generation	Randomisation software		
Allocation Concealment	Good	Performed by remote study co-ordinator using randomisation software	
Blinding of participants and personnel	None	Neither participants nor personnel were blinded to patient allocation – the nature of the strategy trial in which one group were followed up more frequently, and assessed more thoroughly renders this impossible. This introduces the potential for bias.	
Blinding of assessment	Blinded	Attempts were made to mitigate the risks of bias associated with the open study design: 1) the inclusion of objective outcome measures such as radiographic progression that might be less affected by any bias 2) the use of an assessor who was blinded to allocation for measuring all clinical outcomes	
Completeness of outcome data	Complete	Consort diagram shown, and intention to treat analyses were undertaken where appropriate.	
Evidence of selective reporting	None		
Other sources of bias		None identified	
Statistical analysis	Power calculations – yes	Primary outcome – mean change in DAS	Adjustment for multiple comparisons – none

Triple Therapy in Early RA trial

Trial – TEAR		Comments	
Random Sequence Generation	Randomisation software		
Allocation Concealment	Good	Performed by remote study co-ordinator using randomisation software	
Blinding of participants and personnel	None	Neither participants nor personnel were blinded to patient allocation. This introduces the potential for bias.	
Blinding of assessment	Blinded	Attempts were made to mitigate the risks of bias associated with the open study design: 1) the inclusion of objective outcome measures such as radiographic progression that might be less affected by any bias 2) the use of an assessor who was blinded to allocation for measuring all clinical outcomes	
Completeness of outcome data	Complete	Consort diagram shown, and intention to treat analyses were undertaken where appropriate.	
Evidence of selective reporting	None		
Other sources of bias		None identified	
Statistical analysis	Power calculations – yes	Primary outcome – mean change in DAS28	Adjustment for multiple comparisons – none