The Effectiveness of Leflunomide, Etanercept and Infliximab in the Treatment of Rheumatoid Arthritis: A Systematic Review.

Lubna Uppal, BSc (Hons)

MASTER OF PHILOSOPHY

ASTON UNIVERSITY

School of Life & Health Sciences

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SUMMARY

Rheumatoid arthritis (RA) is a systemic inflammatory disorder that mainly affects the diarthrodial (synovial) joint. It has an autoimmune feature, with an unidentified cause, and has a substantial societal effect in terms of cost, disability, and lost productivity. Much emphasis has been geared towards investigating the pathogenesis of RA, and to identify aetiologic markers. Greater insight into the cellular and molecular systems of RA has led to the development of new therapies, and clinical trials have demonstrated the efficacy of such therapies in patients with active disease. Existing management of RA focuses on early use of disease modifying anti-rheumatic drugs (DMARDs), particularly methotrexate and sulfasalazine, to control clinical features and to slow disease progression. However, much of these conventional drugs often produce delayed, inadequate or temporary responses, or troublesome unwanted effects. Several factors are involved in the pathogenesis of RA. T lymphocytes and the cytokines tumour necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) appear particularly important in the development of synovitis and joint destruction. Drugs that target TNF-α, such as etanercept (Enbrel®) and infliximab (Remicade®), and leflunomide (Arava®) that targets proliferating T-cells offer a novel approach. With the approval of marketing these drugs by the Food and Drug Administration (FDA), the safety and efficacy data for these new disease modifying anti-rheumatic agents and combination regimens have come under closer scrutiny.

Objective: To assess the evidence for the effectiveness of etanercept, infliximab and leflunomide in the treatment of rheumatoid arthritis (RA).

Methods: A systematic review of randomised controlled trials (RCTs) investigating etanercept, infliximab and leflunomide in the treatment of adult RA was carried out. Relevant papers were retrieved through Medline, and the main outcome studied was response defined using the American College of Rheumatology 20 (ACR20) criteria. Other outcomes assessed included the health assessment questionnaire (HAQ) scores and radiographic scores. Where appropriate data were pooled.

Results: Twenty-two reports were identified. Seven reports assessed etanercept, six infliximab, and nine leflunomide. Eleven RCTs (fifteen reports) gave data suitable for meta-analysis (5 for etanercept, 1 for infliximab and 5 for leflunomide). All three agents showed significant benefit over placebo in ACR 20 scores, HAQ scores and retardation of joint damage. Anti-TNF therapy appeared to be slightly superior to leflunomide. The differences in efficacy between methotrexate and etanercept or leflunomide were not very considerable. Significant differences, in favour of etanercept (25 mg) were only seen at twenty-four months (RD 0.13 CI: 0.04, 0.22). Leflunomide was also comparable to sulfasalazine. Infliximab mono-therapy was not compared to any other DMARD. Methotrexate combination strategies with all three novel agents resulted in highly significant response rates.

Conclusion: International trials have demonstrated that etanercept, infliximab and leflunomide are very effective in lowering disease activity in RA sufferers. All these agents have tolerable side effects, with common unwanted effects for the anti-TNF agents being infection and injection-site reactions. Liver toxicity is the main concern with leflunomide. Infliximab and etanercept are costly, however recent economic evaluations suggest that these agents may well be cost-effective. All three agents have certainly increased the therapeutic repertoire for RA drug therapy. However their risk-benefit profiles with long-term use have yet to be fully established.

Dedication

To my mother and father

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All glory to Allah (the all knowing), for seeing me through, for making this possible, to Him be all honour and praise forever, Amen.

I would like to thank Professor Alain Li Wan Po for giving me the opportunity to work on this project, and for his help and guidance throughout the course.

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CONTENTS

ABBREVIATIONS

ACR:	American College of Rheumatology
ATTRACT:	Anti-Tumour Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy
DMARD(s):	Disease modifying anti-rheumatic drug(s)
ESR:	Erythrocyte sedimentation rate
EULAR:	European League Against Rheumatism
CI:	Confidence interval
CRP:	C- reactive protein
ERA	Early Rheumatoid Arthritis
FDA:	Food and Drug Administration
HAQ:	Health Assessment Questionnaire
IMAB:	Infliximab
OMERACT:	Outcome Measures in Rheumatoid Arthritis Clinical Trials
RA:	Rheumatoid arthritis
TNFα:	Tumour necrosis factor alpha
ITT:	Intention to treat
IL-1:	Interleukin- 1
MN 301	Phase III multi-centre trial of leflunomide versus sulfasalazine and placebo
MN 302	Phase III trial comparing leflunomide and methotrexate
MTX	Methotrexate
NICE:	National Institute of Clinical Excellence
NSAIDS:	Non-steroidal anti-inflammatory drugs
RA:	Rheumatoid arthritis
RCTs:	Randomised controlled trials
RD:	Risk difference
US301:	Phase III multi-centre trial of leflunomide versus methotrexate and Placebo

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CHAPTER 1

INTRODUCTION

Rheumatoid arthritis (RA) is a common form of arthritis, of unknown cause. It is a chronic, multi-systemic, autoimmune disease that largely affects the synovial membranes of multiple joints in the body. Because the disease is systemic, there are many extra-articular features of the disease as well. In addition to the chronic nature of the disease, it can also be a disease of flares (active) and remissions (little to no activity). RA is characterized by the inflammation of the membrane lining the joint, which causes pain, stiffness, warmth, redness and swelling. Inflammatory activity can invade and damage bone and cartilage. The involved joint can lose its shape and alignment, resulting in pain, loss of movement, functional impairment and disability. Inflammation and deformity are most often seen in the hands and feet, giving rise to common RA symptoms such as joint tenderness, stiffness and swelling. Nonetheless, the knees, hips, and shoulders may also be affected. In addition to joint deterioration, people more severely affected may also experience weight loss, low-grade fever, and malaise because of the disease's effects on the whole body. Rheumatoid arthritis usually manifests itself over a period of a few months, for some, the disease may appear over night. However, rapid onset does not mean the individual is at greater risk of disease progression. RA rarely disappears completely although at times the symptoms might temporarily remit; it is thus essential that the RA patient does not stop the treatment program established by experienced health care practitioners. There is no uniform cure for RA but with proper treatment many people newly diagnosed with rheumatoid arthritis can prevent or delay the more disabling and feared complications of the disease.

1.1 EPIDEMIOLOGY

The disease can occur at any age, but it is most common among those aged 40-70 years. Its incidence increases with age. Table 1.1.1, which summarises the incidence rates from seven major population-based epidemiologic studies reveal considerable variation in incidence rates. However, some of the variation is accounted for by the differing age ranges of the various study populations.

Table 1.1.1. Incidence of rheumatoid arthritis. (Adapted from Gabriel SE. Epidemiology of he rheumatic diseases: in Kelley's Textbook of Rheumatology., 2001) Abbreviations: F, Female; M, male, O, overall. * cases per 1000 person years at risk.

Study	Country/ Region	Years of Study	Age Range	Sample Size	Incidence Rate per 100,000
Uhlig, 1998	Oslow, Norway	1988-1993	20-79	550	25.7-O 36.7-F 13.8-M
Symmons, 1994	Manchester, UK	1990-1991	15-85+	104	35.9-F 14.3-M
Kaipiainen-Seppanen, 1996	Finland	1975, 1980, 1985 and 1990 (four 1-Year periods)	16-85+	1321	1975: 29.0 1980: 35.5 1985: 35.0 1990: 29.5
Gabriel, 1996	Olmstead County, Minn., USA	1955-1985	35-85+	425	75.3-O (95% CI: 68.0, 82.5) 98.1-F (95% CI: 87.1, 109.1) 49.7-M (95% CI: 40.5, 58.9)
Jacobsson, 1994	Pima Indians, Ariz, USA	1965-1990	25-65+	78	1966-73 1974-82 1983-90 89-O* 6.2-O* 3.8-O* 11.5-F* 7.5-F* 4.9-O* 5..9-M* 4.6-M* 2.7-M*
Drosos, 1997	Northwest Greece	1987-1995	16-75+	428	24.0-O 36.0-F 12.0M
Dugowson, 1991	Seatle, Wash, USA	1987-1990	18-64	81	23.9-F (women only)

The geographic distribution of rheumatoid arthritis is worldwide, with a notably low prevalence in rural Africa and Caribbean blacks, and a high prevalence in specific tribes of Native Americans (Pima Chippewa) (Silman., 1993). Rheumatoid arthritis affects approximately 1% of the global population (Aho et al., 1998; Gabriel et al., 1999; Drosos et al., 1997), with women affected about two to three times more commonly than men in earlier decades (Gabriel et al., 1999). Studies have presented

strong observations regarding sex hormones, menstrual and reproductive factors, and genetic factors as predisposing elements (Sangha., 2000).

RA not only effects functional status and quality of life but also significantly reduces life expectancy. Earlier studies consistently demonstrate an increased mortality in patients with RA when compared with expected rates in the general population. Two studies suggest that the excess mortality associated with RA has remained unchanged over the past two to three decades (Coste and Jougla., 1994; Gabriel et al., 1999). Thus the findings of these studies indicate that the introduction of newer treatments have had a smaller impact to date on RA in the community. However the effect of a new anti-rheumatic agent may not be apparent for another 5 to 10 years. The high mortality among RA patients compared with controls has been linked with underlying causes such as increased risk from gastrointestinal, respiratory, cardiovascular, infectious and hematologic diseases (Gabriel et al 1999; Prior et al., 1984; Wallberg-Jonsson et al., 1997).

1.2 AETIOLOGY

Despite intensive work, only modest progress has been achieved in determining the cause of RA and the specific cause of RA is simply not known. Many studies suggest that a combination of environmental and genetic factors is responsible, in that the contribution of one is necessary but not sufficient for full expression of the disease. Although the immunogenetics is incompletely understood, perhaps the most dominant risk factor is the class II major histocompatibility complex (MHC) haplotype of an individual.

Class II MHC genes that account for these disease associations lie within the human leukocyte antigen (HLA) locus. HLA molecules are divided into two major types. Each class has three types of antigens:

Class I: HLA-A, HLA-B, HLA-C

Class II: HLA-DR, HLADP, HLA DQ

At each locus one of several alleles can be inherited (i.e. HLA-A1, HLA-A2, HLA-A3, etc.). The observation that HLA-DR4 occurred in 70 percent of patients compared with 28 percent of controls (Stastny., 1978) led to the idea of a genetic link between RA and HLA-DR. Specific RA-associated alleles have been identified using techniques such as PCR (polymerase chain reaction) and site specific probes. Complementary DNA (cDNA) probes directed against specific α- and β- chains of the DR loci reveal 'susceptibility cassettes' or shared epitopes on the β-chains of DR that predispose to the development of RA. The susceptibility to RA is associated with the third hypervariable region of DRβ chains, from amino acid 70 through 74 (Gregersen et al., 1986; Nepom et al., 1989). This susceptibility epitope is a sequence found in the β1 chain of HLA-DR4 and also on β1 chains encoded by other DR genes (DR1, DR6, DR10) (Ollier and Thomson., 1992). It is not certain as to what role this sequence plays in the initiation of RA. The specific roles of the HLA-DR products (MHC molecules, present on antigen presenting cells) and T cell receptors in initiating RA remain controversial.

The important genetic determinant for RA resides within the groove of the MHC molecule that binds antigen and presents it to T-cells (Salmon., 1992). The allele

encoded MHC can bind an environmental factor (toxin or infectious agent). However through several investigations no such factors have been identified. Alternatively, the molecule can bind to a self-peptide (auto antigen) resulting in activation and proliferation of T-cells. T-cells that cannot recognise the endogenous MHC antigens, bind to self-antigen, or bind tightly to the MHC itself are eliminated in foetal development via thymic deletion. MHC molecules are largely involved in this process of selection. It is thus also possible that the disease-associated allele somehow causes a positive selection of those T-cells that bind the disease associated molecule tightly (Smith and Haynes 2002).

These class II MHC associations primarily implicate cellular immune responses. There are some associations noted in the humoral system, not as prevalent, however. Autoantibodies to the immunoglobulin IgG Fc region known as rheumatoid factors are the hallmark of the disease. However, rheumatoid factor are not specific for RA, since RF producing B-cells are an important effector of the normal immune response. Deficient galactosylation of immunoglobulin may be a risk factor for the development of autoimmune diseases, including RA (Perdriger and Chales., 1997). The IgG glycosolation defect is present before the onset of RA and is especially prominent on the IgG_1, IgG_2 and IgG_4 isotypes of rheumatoid factor. The cause might be reduced galactosyl transferase activity in RA B cells (Rademacher et al., 1994).

It is not understood why RA, one of many chronic inflammatory diseases predominates in women. The disease is thought to be associated with the effects of the hormonal milieu on immune function. Pregnancy is usually associated with the suppression of RA (Persellin 1977). More than 75 percent of pregnant patients

improve, but 90 percent of these experience a flare of disease associated with a rise in rheumatoid factor titres in the week or months after delivery (Quinn et al., 1993). This defensive mechanism is not yet recognized, it could be the result of the production of large amounts of anti-inflammatory agents during pregnancy or alterations in cell-mediated immunity (Lin et al., 1993).

Although there is abundant evidence that RA is immune mediated, it is still not clear whether it is primarily an autoimmune disease, for example, whether the initiating agent is infectious, self antigen, or both; to what extent the course of the disease depends on systemic or joint specific events; or how the cells within the rheumatoid joint interact to produce the invasive and destructive environment observed in the disease. The next section discusses the pathogenesis of RA, and what function it plays in the progression of the disease.

1.3 PATHOGENESIS

RA is characterised by infiltration of the synovium with lymphoid cells, formation of new blood vessels, synovial proliferation, and joint destruction. The current view is that chronic inflammation is initiated by antigen induced activation of T-cells, which accumulate within the joint. Whether the perpetuation of the inflammatory process depends on T cells remains highly contentious, but vascular and synovial cell proliferation as well as cytokine production seem to sustain chronic synovitis and play an important part in joint destruction (Muller- lander., 1995; Firestein., 1996; Panayi et al.,1992; Feldman et al., 1996).

1.3.1 The normal joint

Rheumatoid Arthritis can affect many joints in the body, including the knee, ankle, elbow, and wrist. A normal joint is surrounded by a joint capsule that protects and supports it (Figure 1.3.1). Cartilage covers and cushions the ends of the two bones. The joint capsule is lined with a type of tissue called synovium, which secretes synovial fluid, that serves as a lubricant and carries nutrients for the joint.

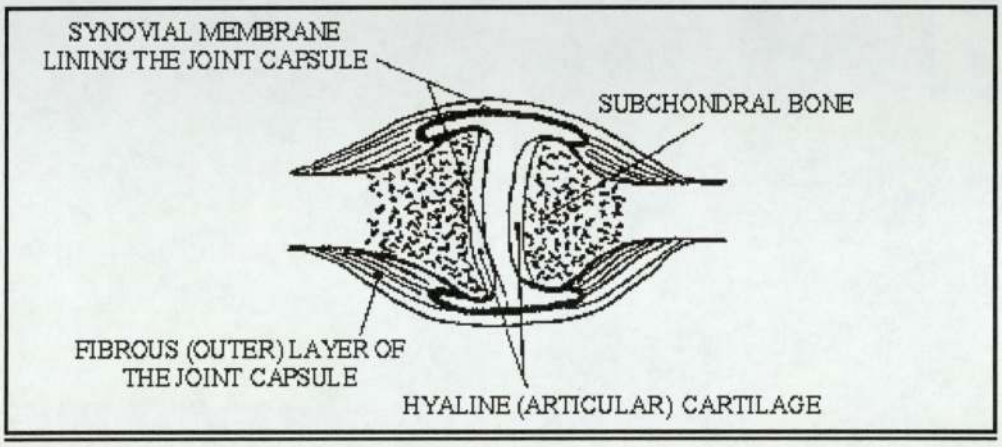


Figure 1.3.1. The normal joint *(adapted from http://www.mednets.com/Rheumatoid arthritis.htm)*

An inflamed synovium is central to the pathophysiology of RA. The synovium is divided into unevenly distributed functional compartments compromising of the lining region (synovial intima), the subintimal stroma, and the vasculature (Figure 1.3.2). The synovial lining, a specialised condensation of cells and extracellular matrix, is localised between the synovial cavity and stroma. Lining cells can be categorised as macrophage derived type A synoviocytes; fibroblast-derived type B synoviocytes; and transitional forms, sometimes refered to as type C cells (Ghadially and Roy., 1969). Type A synoviocytes can express most of the antigen characteristic of fully differentiated, mature macrophages. They are phagocytic, and like some macrophages they can interact with T-cells as antigen presenting cells (Edwards., 1994).

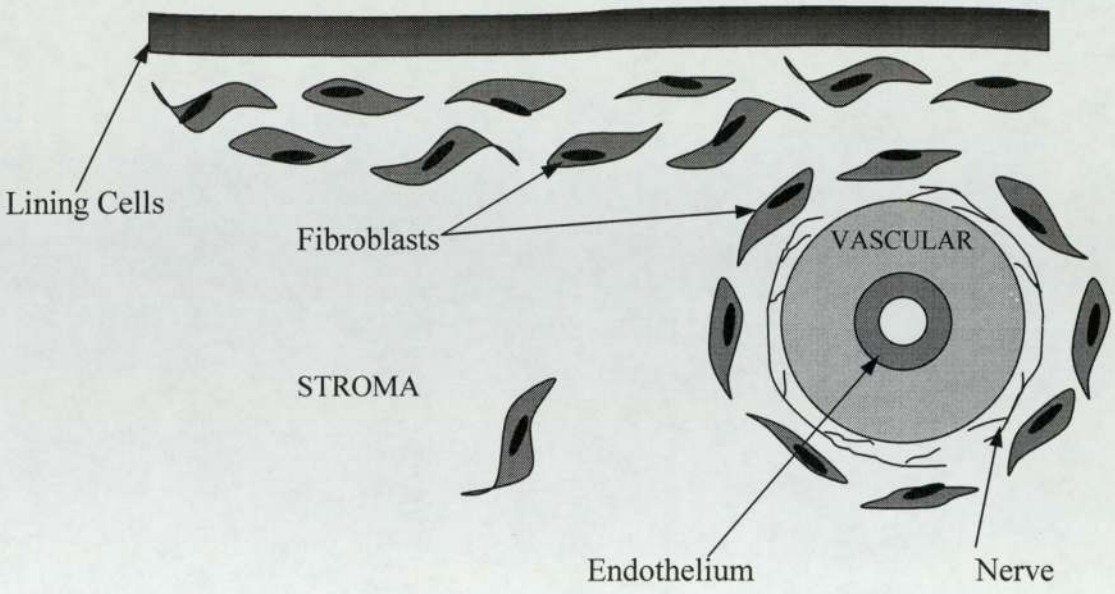


Figure 1.3.2. Schematic diagram showing functional compartmentalization of human synovium *(Adapted from Ruddy, S., Harris, E.D. & Sledge, C.B. Kelley's Textbook of Rheumatology., 2001)*

Normal synovial lining cells also express a rich array of adhesion molecules (Demazier and Athanasou., 1992; Johnson et al., 1993), which are potentially also involved in the recruitment of inflammatory cells during the advancement of RA.

Normal synovium is richly vascularised (Stevens et al., 1991), providing high blood flow required for solute and gas exchange. The synovial vasculature is essential in generating synovial fluid; it behaves like an endocrine organ generating factors that regulate synoviocyte function, and it is a selective gateway, recruiting inflammatory cells in times of need. The synovial stroma is well vascularised and cellular but becomes increasingly fibrous with increasing depth until it blends with the joint capsule. It acts as a host to inflammatory cell infiltrates, thus playing an important role in the response of synovium to RA.

The pathogenesis of RA is a complex phenomenon, which is not fully understood. Current pathogenic concepts of RA are based on the hypothesis that RA is driven by T-lymphocytes (T-cells) after an unknown initiating event. Possible cell-mediated immune responses have been explored in RA, which may play a vital role to establish and perpetuate rheumatoid synovitis.

1.3.2 T-cell activation

Whilst the T-cell travels around every tissue and organ in the body (except brain and other immunoprivileged sites) it awaits interaction with APCs carrying specific antigenic peptides. Subsequent to such interaction, there may be clonal expansion and initiation of events that lead to protective immunity. Tissue macrophages and dendritic-like cells present in the synovium are available to process and present an antigen (i.e. collagen, proteoglycan or viral antigens) to T-lymphocytes (Kurosaka and Ziff., 1983). Although the antigen remains undefined, this results in T-helper cell activation via the T-cell receptor. For maximal T-cell responsiveness, a second signal, in addition to antigen stimulation is usually required. Such important co-stimulatory molecules are present on T cells, including CD28 and CTLA-4 (Liu et al., 1996). Corresponding ligands (CD80 [or B7-1]and CD86 [or B7-2]), are also displayed on antigen presenting cells in the joint, thus promoting a good environment for T-cell activation. Ligation of another molecule CD 40 may be a vital step in induction of autoimmune disease. (Tellander et al., 2000). Interaction between CD40 (present on macrophages, B-cells, monocytes and endothelial cells) and the CD40 ligand exposed on T-cells is responsible for T-cell activation, cytokine production, upregulation of adhesion molecules, production of nitric oxide by macrophages, and immunoglobulin isotype switching by B-cells (Stout and Suttles., 1996).

B-cells are the effector cells of the humoral immune response, and in the pathogenesis of RA they act as a source of autoantibodies such as rheumatoid factor. Rheumatoid factors have been demonstrated in virtually all patients with RA. The majority have IgM antiglobulins, which react in the classical latex and sheep agglutination tests. Most RA patients and sero-negative patients who fail to react in these tests can be shown to have elevated levels of IgG rheumatoid factor. This 'isotype-switch' shows marked signs of affinity maturation of B-cells, indicating the T-cell dependency of the event (Randen, Brown et al., 1992; Randen et al., 1992). Although no data clearly implicates rheumatoid factor as a principal causative agent in RA, its role in the amplification and perpetuation of the process is certainly supported. Rheumatoid factor becomes involved in the pathogenesis when it forms immune complexes. These complexes can activate complements or be phagocytosed by macrophages or polymorphonuclear cells (PMNs), or both.

1.3.3 The role of cytokines in RA

Cytokines are hormone like proteins that enable immune cells to communicate. They can either interact with cells after being released in a soluble form or can be involved with direct cell to cell communication through membrane-bound factors. Beginning with activation of antigen-presenting cells and T-cells, cytokines are believed to play multiple roles in the pathogenesis of RA. Cytokines also maintain and perpetuate the immune response by interacting with nearby cells that bear the appropriate cell-surface receptors. Once activated, these cells produce their own cytokines and effector molecules; this sequential, expanded production of cytokines constitutes the "cytokine cascade." Accumulated PMNs, monocytes, macrophages, fibroblasts, and T-cells release numerous cytokines on stimulation. Although many cells respond to

cytokines, cytokine activated fibroblasts and macrophages are believed to be particularly important in the pathogenesis of RA (Feldman., 1996)

Cytokines such as interleukin-1 (IL-1), Tumour necrosis factor-alpha (TNFα) and interleukin-6 (IL-6) are major pro-inflammatory mediators. The expression of IL-1 and TNFα by synovial tissue is consistent with a number of consequences that are recognised clinically in patients with RA. Thus, they are likely to have primary roles in the pathogenesis of RA. Both cytokines permit the activation of mechanisms (summarised in fig 1.3.3) that result in synovial inflammation and cartillage and bone degradation (Bresnihan., 2002). They can stimulate mesenchymal cells, i.e., cells making up the connective tissue of organs and tissues, including fibroblasts found in all tissues, osteoclasts of bone, and chondrocytes of the cartilage of the joints (Shingu et al., 1993). Such cells are important in the production of the connective tissue matrices present in all tissues. Exposure of chondrocytes to IL-1 inhibits the synthesis of connective tissue components such as collagen and induces the synthesis of a family of enzymes, the matrix metalloproteinases (MMPs). MMPs are able to hydrolyse components of the extracellular matrix (such as collagen and proteoglycan) for remodelling of connective tissues, they are thought to be the main mediators of joint damage in RA.

Figure 1.3.3. Activities of TNFα and IL-1.

Effects on the vasculature
Upregulation of adhesion receptors (ICAM-1, VCAM-1, E Selectin) vi a activation of NF-κB
Stimulate angiogenesis
Alter endothelium toward procoagulant activities [TNF]
Effects on cells
Activate lymphocytes: increases antibody production [IL-1], modifies CD44 adhesion [TNF]
Dentritic cells; maturation and migration into secondary lymphoid organs [TNF]
Activate neutrophils (PMN) and platelets
Induce proliferation of fibroblasts/synoviocytes
Effects on mediators
Induce synthesis of proinflammatory cytokines, e.g. IL-6, GM-CSF, IL-1 [TNF]
Induce synthesis of proinflammatory chemokines (RANTES, IL-8, MIP-1α, MCP-1)
Induce other inflammatory mediators: PGE2, PAF, nitric oxide, reactive oxygen species
Induce synthesis of metalloproteinases that mediate bone and cartillage damage
Other effects
Mediate pain and fever; cachexia [TNF]
Mobilize calcium from bone
Modulate apoptosis [TNF]
Upregulate antiinflammatory factors (sTNF, IL-10, IL-1 receptor antagonist)

Abbreviations: ICAM-1, intercellular adheion molecule 1; VCAM-1, vascular cell adhesion molecule 1; NF-κB, nuclear factor κB; TNF, Tumour necrosis factor; IL-1, interleukin-1; GM-CSF, granulocyte-macrophage colony stimulating factor; MIP-1α, macrophage inflammatory protein 1α; monocyte chemotactic protein 1, PGE2, prostaglandin E2; PAF, platelet, activating factor; sTNFR, soluble TNF receptor; IL-1Ra *(Adapted from Kavanaugh, A. Combination cytokine therapy: The next generation of rheumatoid arthritis therapy? Arthritis Care Res 2002; 47:87-92)*

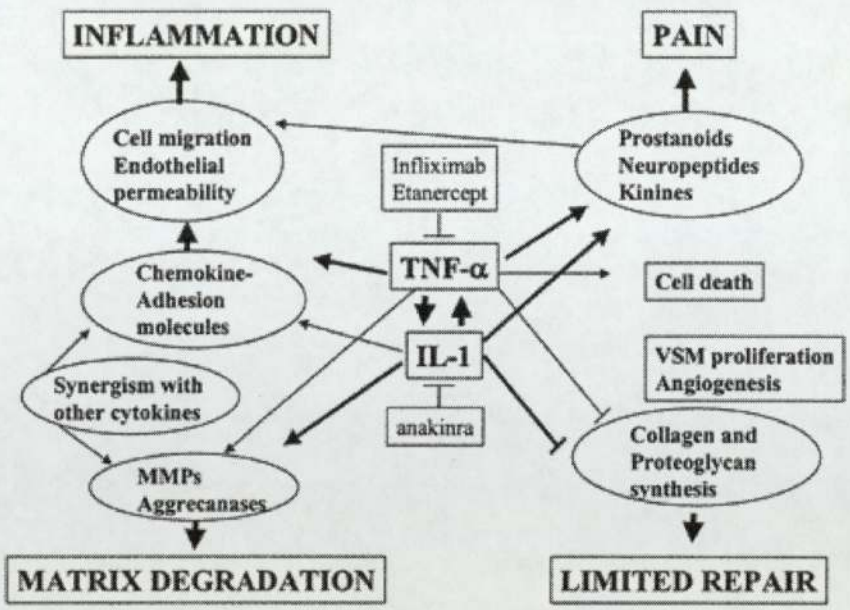
Many effects of IL-1 and TNFα on cells are associated with stimulation of prostaglandin production. Prostaglandins are derivatives of fatty acids and are produced in most tissues of the body. Prostaglandins, thromboxanes and leukotrienes are all classified as members of the prostaglandin or eicosanoid class. Prostaglandins are synthesised from the cyclooxygenase and lipoxygenase pathways, which complete with one another form prostaglandins and thromboxane or leukotrienes, respectively. Prostaglandins have diverse actions dependent on cell type and some of these actions are employed in the biology of RA.

Evidence supports the participation of prostaglandins in the development of the inflammatory response. However, they may be better at potentiating the effects of

other inflammatory mediators in RA rather than inducing inflammation directly (Ferreira., 1972). Prostaglandin compounds increase pain sensitivity to bradykinin and histamine and stimulate bone resorption. This enhances symptoms of pain and erosion of bone in RA patients (Raisz., 1990).

IL-1 and TNF-α also up-regulate the expression of cell adhesion molecules, and chemokines (a family of related chemoattractant peptides), which promote inflammatory cell migration and enhance endothelial permeability, leading to synovial inflammation. In some systems the effects of these two agents are synergistic (Figure 1.3.4) and these dual actions are thought to lead to progressive joint damage.

Figure 1.3.4. Central role of IL-1 and TNF-α in the pathogenesis of RA. *(Adapted from Bresnihan and Dayer. Targetting interleukin-1 in the treatment of rheumatoid arthritis. Arthritis Rheum 2002; 46:574-8)*



The accumulation of cytokines, such as interleukin-8, fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), TNFα and IL-1 can stimulate new blood

vessel growth from pre-existing vasculature, a process known as angiogenesis (Jackson et al., 1997). Inflammation may promote angiogenesis in a number of ways (Polverini., 1997; Walsh., 1994; McColley et al., 2000). Inflammatory tissue such as the RA synovium has a remarkably low synovial fluid oxygen tension. Hypoxia is a potent stimulus for angiogenesis and one of the mechanisms it achieves this is through the upregulation of factors such as VEGF (Schweiki D et al., 1992) or FGF, released by residence fibroblasts (Qu Z et al., 1995; Walsh et al., 1998).

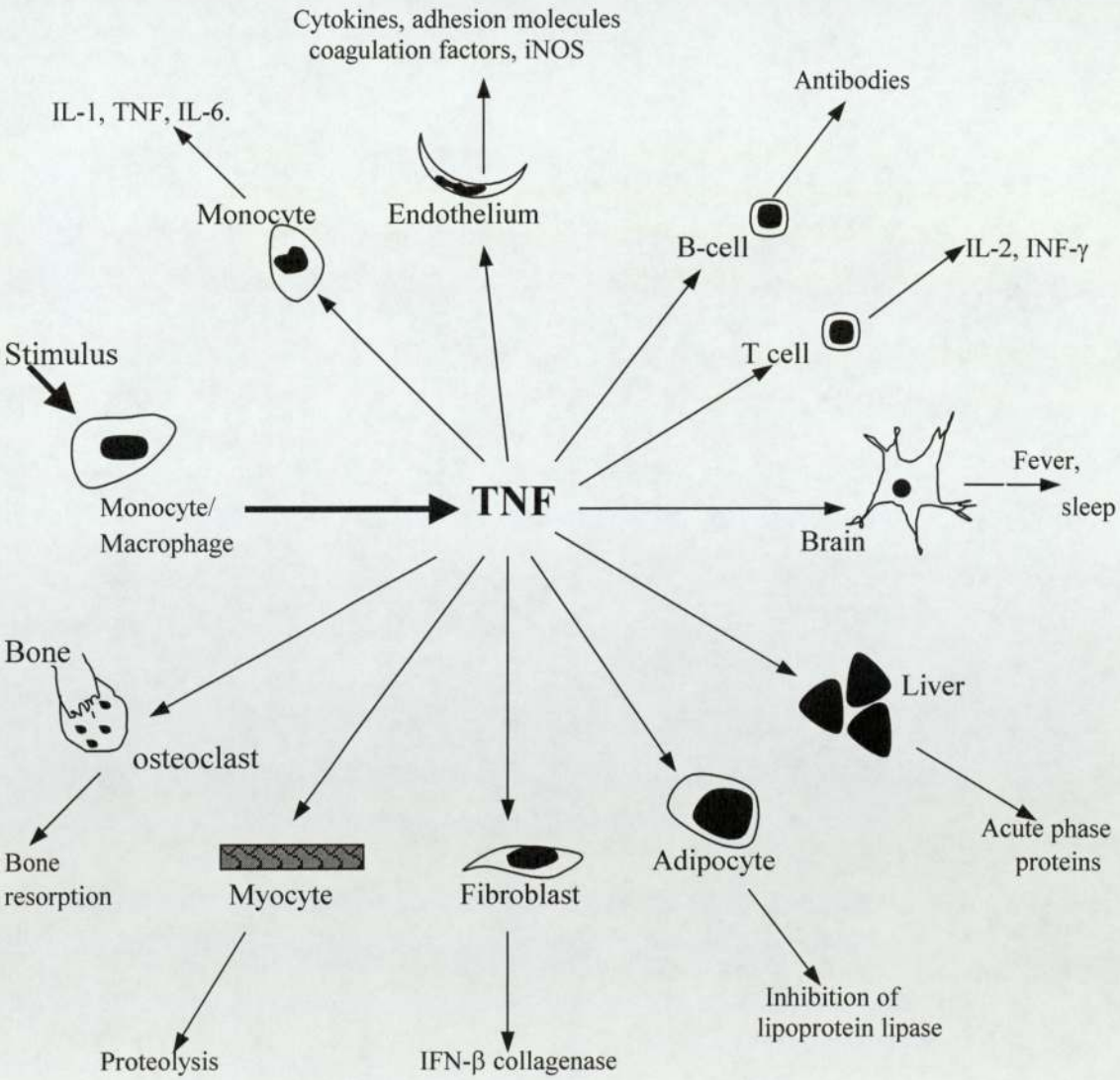
IL-6 is a pleiotropic inflammatory cytokine produced by T-cells, monocytes, macrophages, and synovial fibroblasts (Baumann and Kushner., 1998; Van Snick., 1990). Originally identified as a factor that induces the final maturation of B-cells into plasma cells, interleukin-6 is involved in diverse biologic processes. Such processes include the activation of T-cells, the regulation of the acute phase response proteins by the liver, the stimulation of the growth and differentiation of haematopoietic precursor cells, and the proliferation of synovial fibroblasts (Van Snick et al., 1989).

Not all cytokines promote inflammation. There are a number of anti-inflammatory mechanisms in the joint to modulate the immune response (Gerli et al., 2002). The two best-studied anti-inflammatory cytokines are IL-10 and IL-4. IL-10 is produced by monocytes, macrophages, B-cells, and T-cells. It inhibits the production of several cytokines, including IL-1 and TNF-α, and the proliferation of T-cells in vitro (Isomaki and Punnonen., 1997). IL-10 can also reverse the cartilage degradation mediated by antigen stimulated mononuclear cells from patients with RA.

1.3.4 Tumour necrosis factor

As discussed earlier, TNF-α is a potent cytokine that has been implicated as a key proinflammatory cytokine in RA, and it exerts diverse effects by stimulating a variety of cells (Figure 1.3.5). Newly synthesised TNF-α is inserted into the cell membrane and is subsequently released through the cleavage of its membrane-anchoring domain by a serine metalloproteinase (Black et al., 1997).

Figure 1.3.5. Biological activities of tumour necrosis factor (TNF). Abbreviations: IL, interleukin; IFN, interferon; iNOS, inducible nitric oxide synthase. *(Adapted from Eigler et al. Taming TNF: strategies to restrain this proinflammatory cytokine. Immunol Today 1997; 18:487-492)*



This enzyme may be considered as a therapeutic target, in that TNF-α secretion might be suppressed by inhibitors of this enzyme (McGeehan et al., 1994). TNF-α is an autocrine stimulator as well as a potent paracrine inducer of other inflammatory cytokines, including IL-1, IL-6 IL-8 and granulocyte monocyte colony-stimulating factor (GM-CSF) (Nawroth et al., 1986; Butler et al., 1995; Haworth et al., 1991). Other actions of TNF-α include stimulation of collagenase and prostaglandin production by human synovial cells and dermal fibroblasts (Dayer et al., 1985), induction of bone resorption, inhibition of bone formation in vitro, and stimulation of proteoglycan resorption (Saklatva., 1986). The biological activity of TNF-α is dependant upon binding to its cell surface receptors. Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms (Smith et al., 1994). Biological activity of TNF is dependant upon binding to either cell surface TNFR.

As an inflammatory cytokine TNF-α has important, perhaps, dominant roles in rheumatoid synovitis, since treatment with TNF-α antibodies or soluble TNF-receptor-Fc fusion protein to block TNF-α function have striking anti-inflammatory activity in RA (Elliot at al., 1994).

1.3.8 Joint destruction

The several biological mechanisms discussed earlier all contribute to progressive joint damage in RA. Early erosion of cartilage and bone is associated with the formation of a proliferating pannus. This synovial hyperplasia causes the synovial membrane to thicken, which is characterised by an extensive network of new blood vessels. T-cells

(CD4+) and B cells (some of which are plasma cells) infiltrate the synovial membrane, some of these cells are also found in the synovial fluid, along with a large number of leukocytes such as neutrophils. In the established lesion the synovial membrane becomes transformed into the pannus, an inflammatory tissue that consists of both type A and type B synoviocytes and plasma cells. Released IL-1 and TNF-α interact with synoviocytes and chondrocytes to stimulate matrix metalloproteinases that degrade cartillage and cause joint space narrowing through the breakdown of collagen and proteoglycans (Dayer et al., 1986; Dayer et al., 1985). In addition, together with a number of other factors they promote osteoclast differentiation and stimulate activation of mature osteoclasts which resorb bone, leading to joint erosions particularly at the marginal surfaces (Goldring and Gravallese., 2000; Lader and Flanagan., 1998) (Figure 1.3.6).

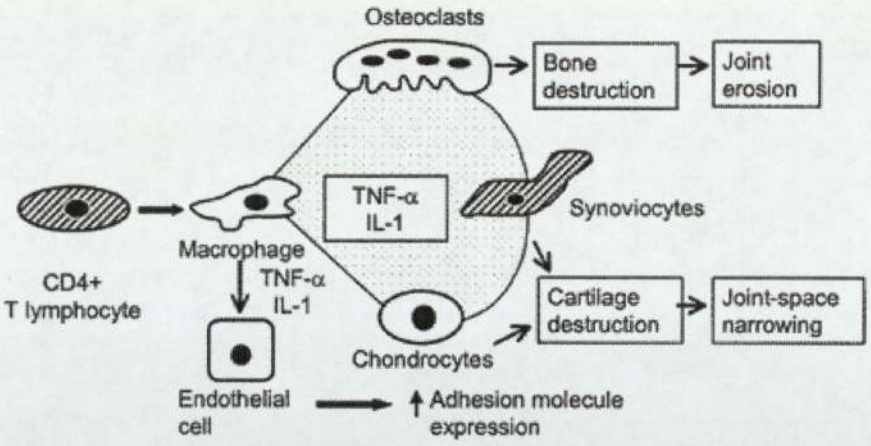


Figure 1.3.6. Mechanisms of structural damage in rheumatoid arthritis. *(Adapted from Arend, W.P. The mode of action of cytokine inhibitors. J Rheumatol 2002;29 Suppl 65:16-21)*

Studies indicate that effective early suppression of synovial inflammation will directly prevent the progression of cartilage and bone degradation and associated functional impairment (Wolfe and Sharp., 1998). To achieve this the management of the disease, such as the use of therapeutic commodities, is very important.

Inflammation is clinically perceived as disease activity, which can be quantified using laboratory techniques. Inflammatory components in RA are usually measured by acute phase reactants in the peripheral blood such as the erythrocyte sedimentation rate (ESR) (Wolfe., 1997; Hassel et al., 1993; Graudal et al., 2000), C-reactive protein (CRP), rheumatoid factor and others (Kushner and Ballou., 1994). In the joints, the damaged cartillage and bone resulting from the invading pannus can be detected using plain radiography of the affected joints (Larsen et al., 1977) using a variety of scoring methods (Sharp et al., 1971; van der Heidje et al., 1992; Genet., 1985). In RA dysfunctions and abnormalities start to appear when all the pathophysiological processes cross the clinical threshold (Escalante and Del Rincon., 2002). Such measures include clinical symptoms; pain, joint tenderness and joint swelling. As a result of these symptoms limitations in physical function follow. In RA actions that depend on an intact osteoarticular system, i.e. walking, climbing, gripping or handling are usually limited. Within a social and physical environment, functional impairments restrict the performance of certain activities. RA patients have most difficulty with physical activities such as dressing, bathing, carrying out household chores, shopping, writing or lifting and these may result in difficulty or inability to work (Baecke et al., 1982).

The symptoms and signs of RA may range from joint complications like pain, stiffness, swelling and functional impairment, to more constitutional problems like loss of general health. Because of this variety in disease expression, a huge number of disease activity or outcome variables are used to evaluate disease progression and intervention.

1.4. ASSESSMENT OF DISEASE ACTIVITY/OUTCOME MEASURES IN RA

Ideally the knowledge from clinical research results and experiences of other investigators helps to advance clinical management, mark out disease associations and mechanisms, or improve the quality or delivery of health care. Outcome is the result of the illness such as death, disability or quality of life (QoL) (Fries., 1983). For a given disease an important set of accepted criteria for measuring improvement or outcome are required. To evaluate the effects of a treatment on disease course or outcome, intermediate endpoints are often chosen for clinical trials, which through a proposed number of criteria (Bombardier and Tugwell 1982) are proven to correlate with the long-term or gold-standard outcome. In RA, endpoints may quantify objective physical signs such as the number of tender or swollen joints, symptoms such as the duration of morning stiffness or level of pain or functional status or overall health as perceived by the patient or the physician. To evaluate the definition of improvement, multiple outcomes are often assessed in clinical trials. Recommendations of a core set of outcomes to be used in clinical trials of RA have been prepared by the American College of Rheumatology (ACR) (Felson et al., 1993), the outcome measures in rheumatology (OMERACT) (Tugwell et al., 1993), and the European League Against Rheumatism (EULAR) (van Riel., 1992) (see Table 1.4.1).

Table 1.4.1 Outcome Measures in Rheumatoid Arthritis

Criteria	ACR (Felson 1993)	OMERACT (Tugwell 1993)	EULAR (van Riel 1992)
Swollen joints	+	+	+
Tender joints	+	+	+
Physicians global assessment	+	+	
Patient's global assessment	+	+	+
Pain	+	+	+
Functional status or physical disability	+	+	+
Acute phase reactant (CRP or WESR)	+	+	+
Radiographs	+*	+*	+

* For trial duration > 1 year and agent being tested as a "DMARD".
Abbreviations: ACR, American College of Rheumatology; OMERACT, the Outcome Measures in Rheumatoid Arthritis Clinical Trials; EULAR, European League Against Rheumatism; CRP, C-reactive protein; WESR, erythrocyte sedimentation rate

In 1991 the ACR in concert with the international rheumatology community developed a uniform core set of outcome measures for RA trials (Felson et al., 1993). The ACR and OMERACT criteria are generally accepted as the uniform outcome criteria for RA trials. Both organisations encompass the same efficacy endpoints, this core set was also approved by the World Health Organisation and International League Against Rheumatism in 1994 (Boers et al., 1994). Table 1.4.2 summarises the consensus proposed by the ACR regarding specific ways to measure each outcome.

Table 1.4.2. OMERACT recommendations for a core set of outcome measures and the specific methods of assessment. Abbreviations: ACR, American College of Rheumatology; AIMS, Arthritis Impact Measurement Scales; HAQ, Health Assessment Questionnaire; QWB, Quality (or Index) of Well Being; MHIQ, McMaster Health Index Questionnaire; MACTAR, McMaster Toronto Arthritis Patient Preference Disability questionnaire. *(Adapted from felson DT. Choosing a core set of disease activity measures for rheumatoid arthritis clinical trials. J Rheumatol 1993; 21:531-534.*

Outcome Measures	Method of assessment
Tender joint count	An assessment of 68 joints. The joint count should be done by scoring several aspects of tenderness, as assessed by pressure and joint manipulation on physical examination. The information on tenderness should then be collapsed into a single tender versus non-tender dichotomous variable
Swollen joint count	An assessment of 66 joints. Joints are classified as swollen or not swollen.
Patient's assessment of Pain	A horizontal visual analogue scale (VAS) (usually 100 mm) or Likert scale assessment of the patients current level of pain
Patient's global assessment of disease activity	The patient's global assessment of how the arthritis is progressing. One acceptable method for determining this is the question from the AIMS instrument: 'Considering all the ways your arthritis affects you, mark 'X' on the scale for how you are doing'. An anchored, horizontal VAS (usually 100 mm) should be provided.
Physician's global assessment of disease activity	A horizontal VAS (usually 100 mm) or Likert scale measure of the physician's assessment of the patient's current disease activity.
Patient's assessment of physical function	Any patient self-assessment instrument which has been validated, has reliability, has been proven in RA trials to be sensitive to change, and which measures physical function in RA patients is acceptable. Instruments which have been demonstrated to be sensitive in RA trials include the AIMS, the HAQ, the QWB, the MHIQ and the MACTAR.
Acute-phase reactant	A Westergren erythrocyte sedimentation rate or a C-reactive protein level.
For trial of duration ≥ 1 year and if agent being tested as a DMARD, also perform:	
Radiography or other imaging techniques.	

The outcome set helps define and standardise the outcomes to be measured in RA trials. This advance was later faced with the problem of how the information from

these multiple outcomes measures are to be combined when assessing therapeutic efficacy. If a treatment is superior to another in only some measures it becomes more difficult to interpret differences between therapies. However, when there are multiple outcomes, a composite index, such as a pooled index (Smythe et al., 1977) can be used. An index consists of a selection of outcome measures which when appropriately weighed yields a single score. A valid composite index can avoid the statistical and inferential difficulties associated with assessing multiple end points (Boers and Tugwell., 1993; Roberts., 1993). Unfortunately combining endpoints may be difficult, and the composite score is not readily interpretable by clinicians (Felson et al., 1990).

To evaluate more accurately the significance of a change and to enhance comparisons of improvements across trials the development of a single definition of improvement was encouraged. The most commonly used and most recent definition of improvement is that devised by the ACR: 20% improvement in tender and swollen joint counts and $\geq$ 20% improvement in three of the five remaining ACR core set measures: patient and physician global assessments, pain, disability, and an acute phase reactant (usually referred to as ACR 20) (Felson et al., 1995). This definition provides a single outcome measure that has been used in many RA trials and is usually given as a percentage, representing the number of patients fulfilling the criteria.

The extensive use of the ACR 20% definition as a primary outcome measure led to investigations of whether or not improvement of more than 20% in core set parameters should be required. The minimum threshold of 20% improvement is not high for comparing two treatments. The discriminant validity (i.e. the ability of a measure to distinguish clinically significant differences between treatments

[Bombardier and Tugwell., 1982]) is a key component of validity. High discriminant validity would give greater statistical power to distinguish between two treatments.

Evaluating the discriminant validity of four proposed definitions of improvement, Felson et al (1998) reanalysed data from six controlled clinical trials of RA treatment. In every reviewed trial they found that ACR 20 had higher statistical power than ACR 50 or ACR70. Adopting definitions of efficacy in RA trials with the higher 50% or 70% improvement thresholds were likely to compromise discriminant validity. Hence ACR 20 continues to be a primary measure of efficacy in RA trials, whereas improvements of more than 20% in core set parameters should be reported as secondary efficacy measures.

The ACR definition was not the first to be developed. Table 1.4.3 lists the definitions of improvement, devised by other investigators for RA. Firstly, the American Rheumatism Association (now the ACR) defined remission in RA (Pinals et al., 1981), but this outcome is so rare that it limits its usefulness for trials. Paulus and colleagues (1990) used data from multi-centre RA trials to devise a definition of improvement based on a set of measures that discriminated well between active second-line drug treatment and placebo and that limited placebo response to ~ 5%. Uniform definitions of improvement allow the percentage of improving patients to be compared across trials.

Table 1.4.3. Definitions of improvement in Rheumatoid Arthritis. Abbreviations: RA, rheumatoid arthritis; ESR, erythrocyte sedimentation rate; ACR, American college of Rheumatology.

Study/ Organisation	Criteria	Comments
Pinals., 1981. **The American Rheumatism Association.**	To define remission in RA, the presence of 5 or more of 6 criteria, for a period of 2 months: morning stiffness absent or not exceeding 15 minutes, no fatigue, no joint pain by history, no joint tenderness, no joint or tendon sheath swelling, and no elevation of erythrocyte sedimentation rate.	This has not been a useful outcome measure, since remission occurs so rare in RA patients undergoing a trial
Paulus., 1990. **Paulus criteria**	A response in at least 4 of 6 selected measures is required: 20% improvement in morning stiffness, ESR, joint tenderness score, and joint swelling score and improvement by at least two grades on a five-grade scale (or from grade two to grade one) for patient and physician global assessments of current disease severity.	The use of this definition in trials is clinically practical, however it has not consistently been employed, and relies on global severity scales (5-point adjectival scale) that are unique to a certain group of trials, thus are not widely used elsewhere. Elements included in this criteria do not correspond to the core set
Van der Heijde., 1990. **Disease Activity Score (DAS)**	DAS is used to assess improvement: 0.54 (Ritchie index of painful joints) + 0.065 (swollen joint count) + 0.331n (ESR) + 0.072 (patient global)	Takes into account several different outcome measures to assess disease activity, however it is not easy to compute.
Felson., 1995 **American College of Rheumatology (ACR) criteria**	A 20% improvement is defined as: 20% improvement in tender and swollen joint counts and $\geq$ 20% improvement in three of the five remaining ACR core set measures: patient and physician global assessments, pain, disability, and an acute phase reactant (ACR 20).	Definition of improvement uses elements from core set to provide a single outcome measure that can be used in all RA trials.

The use of a single measure to evaluate the response to therapy in RA may be overly simplistic, for example, some treatments may effect joint count more than acute phase reactant improvement.

1.4.1 Functional status

By using process measures such as ESR and the number of joints we can look at changes in disease activity or clinical outcome. Although these criteria may be relatively sensitive to change in a clinical trial, there is debate about their correlation with long-term patient outcomes such as quality of life and disability (Pincus., 1998).

Consequently self-reported patient-orientated outcome measures have been promoted. An important patient outcome, for example, would be the level of functional disability or the ability to work. Clinical trials in rheumatic diseases usually employ functional status questionnaires to capture the chronic and disabling nature of RA and to quantify its long term impact on the patients functioning and well being.

Clinical trials in rheumatic diseases usually include health status questionnaires to measure change in functional status and disability. Functional status is a subset of health status (or health-related QoL), while health status is itself a subset of QoL. However, due to the broad definition of QoL, measurements of QoL in RA are mainly restricted to health related QoL. Hochberg and colleagues (1992) developed a revised criterion for the classification of global functional status in RA (Figure 1.4.1) in conjunction with the many instruments used in the quantitative measurement of functional status.

Figure 1.4.1. ACR revised criteria for classification of global functional status in rheumatoid arthritis

Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
Class II	Able to perform usual self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV	Limited in ability to perform usual self-care, vocational, and avocational activities

Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific. *(Adapted from Hochberg M, Chang R, Dwosh I, Lindsey S, Pincus T. & Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum 1992; 35: 498-502)*

Table 1.4.4 lists a number of health status measures, available for functional status or disability assessment for patients with RA, some of which are disease specific (more sensitive to change) and some generic. The ACR and European groups strongly recommend that functional assessment by self-report questionnaire should form part of the 'core' of outcome measures. Since its development, the Stanford health assessment questionnaire (HAQ) is the most commonly used measure of functional status (Fries et al., 1980; Fries et al., 1982). In research carried out on RA patients, such as randomised controlled trials (RCT) and observational studies, the HAQ has virtually become a compulsory outcome measure.

Table 1.4.4. A summary of some of the QoL instruments that have been used in RA studies. *(Adapted from Bell MJ, Bombardier C, Tugwell P. Measurement of functional status, quality of life and utility in rheumatoid arthritis. Arthritis Rheum 1990; 35:591-601 and Bendtsen P, Akerlind I, Hrnquist JO. Assesment of quality of life in rheumatoid arthritis-methods and implications. Pharmacoeconomics 1990; 5:286-298).*

Instruments	Type	Change or Status item	Capacity or performance Oriented	Mode of administration	Quoted administration time (mins)
HAQ	specific	status	performance	interviewer/ self-report	3-5
MHAQ	specific	status/ change	performance	interviewer/ self-report	5-8
AIMS	specific	status	capacity/ performance	self-report	20
AIMS2	specific	status	capacity/ performance	self-report	23
MACTAR	specific	status/ change	capacity/ performance	interviewer	10-20
MHIQ	generic	status	performance	interviewer	20-40
QWB	utility	status	performance	interviewer/ self-report	10-15
SIP	generic	status	performance	interviewer/ self-report	20-30
NHP	generic	status	performance	self-report	5

Abbreviations: HAQ, Health Assessment Questionnaire; MHAQ, modified Health Assessment Questionnaire; AIMS, Arthritis Impact Measurement Scales; AIMS2, Arthritis Impact Measurement Scales 2; MACTAR, McMaster-Toronto Arthritis Questionnaire; MHIQ, McMaster Health Index Questionnaire; QWB, Quality (or index) of Well Being; SIP, Sickness Impact Profile; NHP, Nottingham Health Profile

It was originally devised in 1978 by James F. Fries MD and colleagues at Stanford University, and has become a dominant instrument in many disease states. The HAQ is often referred to the disability index and pain scale (Appendix 6). However the additional domains are included in the full HAQ. As a comprehensive outcome measure the full dimension HAQ constitutes four domains: (1) disability, (2) discomfort and pain, (3) drug side effects (toxicity) and (4) dollar costs, which assess patient outcomes usually as a long-term outcome assessment. While death is not a self-reported outcome, however, it does form a vital part in the theoretical model of patient outcome.

As well as measuring physical disability other instruments address more emotional and social aspects of a condition; such measures include the Arthritis Impact Measurement Scale (AIMS) (Meenan et al., 1980) and the subsequent AIMS 2 (Meenan et al., 1992), the Nottingham Health Profile (NHP) (Hunt et al., 1981) and the Sickness Impact Profile (Bergner et al., 1981). However, uncertainty about their adequate reliability and their consistent unresponsiveness (Fitzpatrick et al., 1993; Kazis et al., 1990) are clear problematic issues. The SIP and NHP generic instruments, for example, were designed to assess health status covering a spectrum of conditions in populations, consequently RA-specific issues are more-likely to be omitted, thus limiting their ability to detect change in the RA patients (McKenna., 1995; Guyatt et al., 1993). A more recent generic health related quality of life instrument is the Short Form-36 health survey (SF-36) (Ware and Sherbourne., 1992). Although it focuses on function and incorporates some aspects of wellbeing, it has limited reliability and responsiveness for use in clinical studies (Brazier et al., 1992; Dixon et al., 1994; Tennant et al., 1995).

1.5 THE CLASSIFICATION & DIAGNOSIS OF RA

Rheumatoid arthritis can be difficult to diagnose in its early stages. There is no specific feature or single test for the disease. Symptoms and severities differ from person to person, they can be similar to those of other types of arthritis and joint conditions, thus taking some time for other conditions to be ruled out as possible diagnoses. The full range of symptoms develops over time, and only a few symptoms may be present in the early stages. Growing evidence suggests that therapeutic strategies result in better long-term outcome, when applied early in the disease course (Emery., 1994; Kim and Weisman., 2000). Furthermore, given potential toxicity of the variety of anti-rheumatic drugs the importance of developing accurate diagnostic criteria for RA is self-evident. As a result, one of the major goals for rheumatologists is to determine which RA patients will have persistent disease.

The proposed classification criteria for rheumatoid arthritis (RA) was initially developed in 1958 by the committee of the American Rheumatism Association (ARA), in an attempt to improve specificity and simplicity (Ropes et al 1958). In 1987, data from 262 RA patients and 262 control patients with other diseases led the American college of Rheumatology (ACR) (formerly, the ARA) to publish a new list of classification criteria. This has been presented in the form of a traditional list format (see appendix 4) and a classification tree (Figure 1.5.1).

By achieving improved simplicity, sensitivity and specificity, the revised criteria were found to be better than the earlier criteria (MacGregor., 1995) and has been regularly adopted as a diagnostic criteria for early RA (Kaarela et al., 1995; Hulsemann and Zeidler., 1999),. However, the criteria perform less well in distinguishing those

patients primarily showing inflammatory arthritis who will have a persistent, disabling or erosive course from those who will not. There is much debate as to whether the ACR 1987 criteria should be used for initial classification purposes or as a diagnostic tool, since its effectiveness in both areas has not been established (Saraux et al., 1996; Saraux et al., 2001).

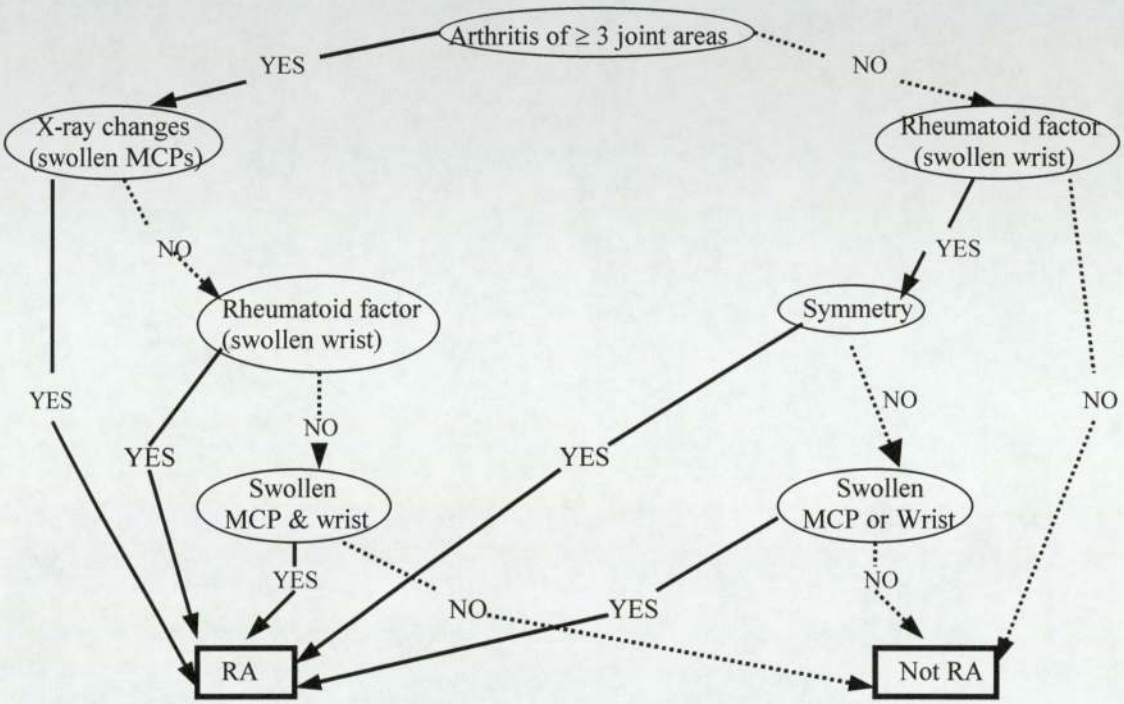


Figure 1.5.1. 1987 ACR decision tree algorithm for RA classification (variables in parentheses can be used when data on the first listed variable is not available). Abbreviations: MCP, metacarpophalangeal *(Adapted from Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.)*

Clinical assessments or lab tests employed in diagnosis lack sensitivity and specificity (Schellekens 2000), in addition they are operator dependant and therefore subject to bias. Alternative strategies for the diagnosis of RA have been suggested over the past decade, and the introduction of early arthritis clinics have resulted in the effective diagnosis of RA (van der Horst-Bruinsma et al 1998). More recently a prediction

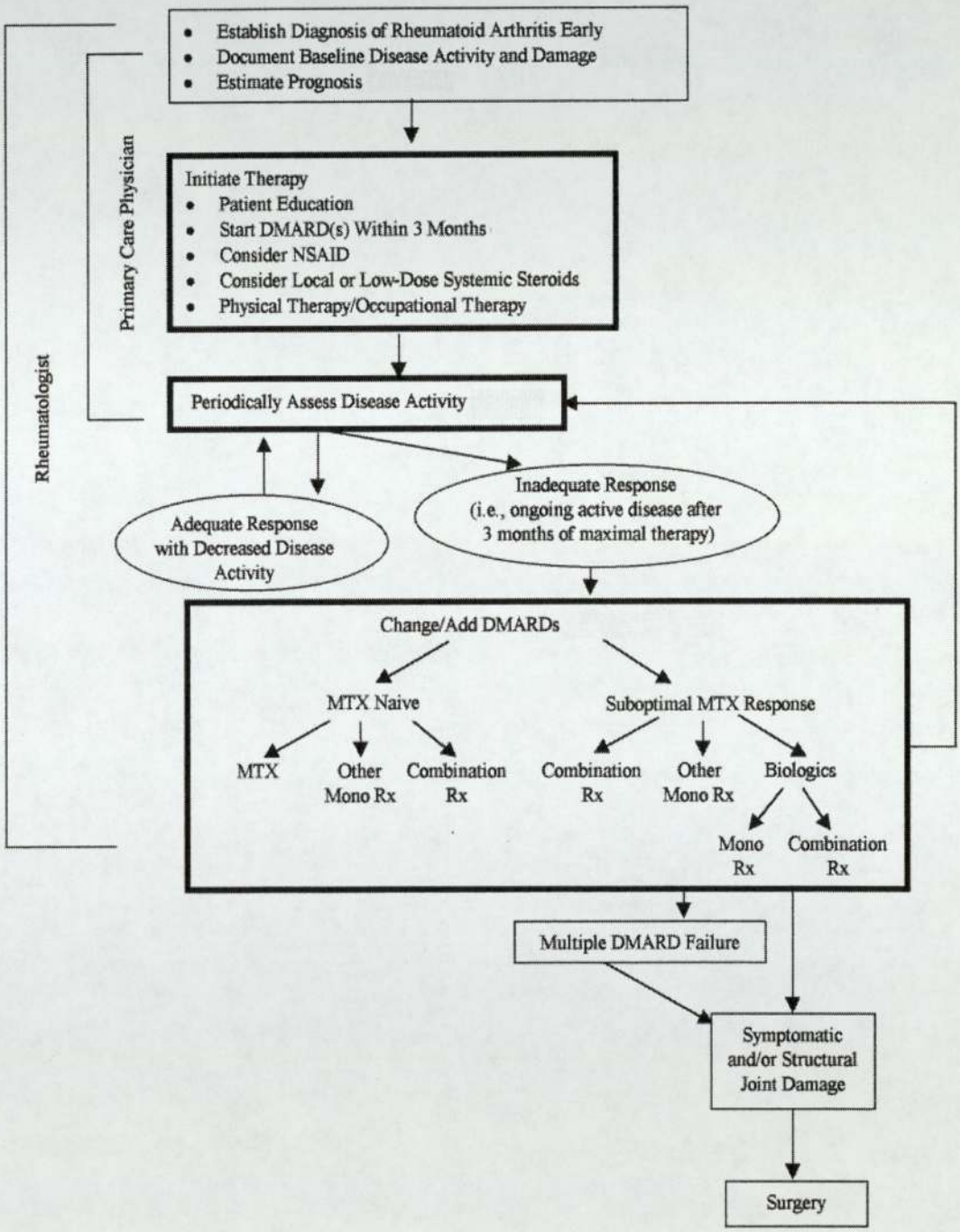
model for RA diagnosis has been devised by Visser and collegues (Visser et al., 2002).

1.6 THE MANAGEMENT OF RA

Disease activity over time leads to structural damage, functional loss, work disability, radiographic abnormality, joint replacement, premature mortality and increased costs (Wolfe., 1997; Yelin and Wanke., 1999; van Zeben et al., 1993; Coste et al., 1997; Kuper et al.,1997). The aims of RA management are to prevent or control joint damage, prevent loss of function, and decrease pain. Guidelines for the management of RA and monitoring of drug therapy were initially developed in 1996 by the American College of Rheumatology (ACR) subcommittee on RA guidelines (American College of Rheumatology Ad Hoc Committee on Clinical Guidelines., 1996). More recently these guidelines have been reworked with an evidence-based approach and introducing newer classes of drugs (ACR subcommittee on RA guidelines., 2002), Figure 1.6.1 outlines the revised ACR guidelines.

Successful treatment to limit joint damage and function is determined by early diagnosis and timely initiation of disease-modifying agents. To achieve remission (disease arrest) non-pharmacologic, pharmacologic and if necessary surgical interventions are usually required. Systemic and regular evaluation of disease activity, patient education, use of anti-rheumatic drugs, assessment of the adequacy of the treatment programme and general health maintenance form essential components of the management of RA.

Figure 1.6.1. The management of rheumatoid arthritis: an outline. Boxes with heavy borders represent major decision points in management. A sub-optimal response to methotrexate (MTX) is defined as intolerance, lack of satisfactory efficacy with a dosage of up to 25mg/week, or a contraindication to the drug. Abbreviations: DMARD, disease-modifying antirheumatic drug; NSAID, nonsteroidal anti-inflammatory drug; mono Rx, monotherapy; combination RX, combination therapy. *(Adapted from American College of Rheumatology Subcommittee on RA guidelines. Guidelines for the management of RA. Arthritis Rheum, 2002; 46(2): 328-346)*



1.6.1 Pharmacologic treatment of RA

The pharmacological agents used in the therapy of RA have been traditionally subdivided into non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying/ slow acting anti-rheumatic drugs (DMARDs / SAARDs), and corticosteroids. All these drugs are clinically effective and according to a recent classification they can be denominated as symptom modifying antirheumatic drugs (SMARDs). The term disease controlling anti-rheumatic therapy (DC-ART) applies to those SAARDS that are capable of modifying not only clinical symptoms, but also radiological and functional outcome (Edmonds et al., 1993).

Table 1.6.1. Proposed classification of anti-rheumatic drugs (*Adapted from Edmonds JP, Scott DL, Furst DE, Brooks P, Paulus HE. Antirheumatic drugs: a proposed new classification. Arthritis Rheum 1993; 36:336-339.)*

1. Symptom-modyfying antirheumatic drugs (SM-ARDs)
   These improve the symptoms and clinical features of inflammatory synovitis.
   a. Non steroidal anti-inflammatory drugs (NSAIDs)
   b. Corticosteroids
   c. Slower acting drugs e.g., antimalarials, gold penecillamine, sulphasalazine, cytotoxic agents (category III SM-ARD)

2. Disease controlling antirheumatic therapy (DC-ART)
   These change the course of RA i.e.,
   I. Improve and sustain function in relation with decreased inflammatory synovitis.
   II. Prevent or significantly decrease the rate of progression of structural joint damage.
   These changes must be sustained for a minimum period of 1 year; the classification must include reference to the time period for which criteria has been satisfied e.g., 2-year DC-ART etc.

The majority of DMARDs have entered rheumatology only because of clinical intuition, and their mechanisms of action are unclear.

1.6.2 Non steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are among the most commonly used medications in the world. They are capable of controlling the symptoms in RA, however, they do not alter the course of the disease or prevent joint destruction, and a major factor limiting their use is gastrointestinal toxicity (Wolfe., 1999). Thus, they should not be used as the sole treatment for RA. The analgesic, antipyretic and anti-inflammatory effects of NSAIDs have led to their widespread application in the symptomatic management of aches and pains of all types. Their effects are achieved through the inhibition of cyclooxygenase (COX) (Vane., 1971; Dubois et al., 1998), to reduce joint pain and swelling and improve joint function. The existence of two isoforms of COX is well established (Vane., 1971; Dubois et al., 1998). COX 1 is constitutively expressed and synthesised at a constant rate by many tissues including blood platelets, cells of the gastric and intestinal mucosa and endothelial cells. It plays an important role in the stomach by producing protective prostaglandins. COX 2 is an enzyme produced by tissue insult that then sets off the pro-inflammatory cascade.

NSAIDs as a group tend to cause gastric irritation and to exacerbate peptic ulcers. This is probably because of their ability to suppress prostaglandin synthesis, all traditional prostaglandin inhibitors, until the release of celecoxib, suppressed both forms of COX. Celecoxib, the selective COX-2 inhibitor approved for the treatment of RA appears to be as effective as moderate doses of standard NSAIDs, e.g. naproxen (van Ryn and Pairet., 1997). Although selective COX-2 inhibitors have a significant lower risk of serious adverse GI effects than do non-selective NSAIDs (Bombardier et al., 2000; Silverstein et al., 2000) they are no more effective and may cost as much as fifteen to twenty times more than generic NSAIDs. COX-2 is constitutively expressed

in human kidneys, the inhibitor appears to convey no particular advantage over traditional non-selective NSAIDs with regard to kidney function. Indeed there is some concern about their adverse renal effects, and more recently their cardiovascular risk (Stichtenoth and Frölich., 2000; Fitzgerald and Patrono., 2001).

1.6.3 Disease-modifying antirheumatic drugs (DMARDs)

According to the older stratagem of the 'treatment pyramid' approach, treatment of newly diagnosed RA was to be started with a NSAID alone, and if this drug failed to alleviate symptoms, more and more portent DMARDs were to be tried. According to definition, a DMARD, is able to induce a decrease in general inflammatory activity. Certain DMARDs can improve long-term outcome in RA by reducing or preventing joint damage, preserving its function and ultimately reducing total health care costs (Scott et al., 1987). Recent advances in the pathophysiological understanding of RA have led the treatment pyramid to become the subject of much criticism. Rheumatologists have emphasised that it is important to suppress rheumatoid inflammation early. Thus the RA patient would be treated with a potent DMARD as soon as the diagnosis has been made. As they were conventionally employed, only after other treatments such as NSAIDs, the DMARDs are referred to as second-line agents. Although patients eventually seem clinically improved with DMARD therapy, benefits may be delayed for weeks or months, hence the origin of another term applied to these agents, slow-acting antirheumatic drugs (Table 1.6.1). DMARDs include drugs from many classes (Table 1.6.2), which improve inflammatory symptoms or lower progression of joint erosions for a subset of patients, often through incompletely understood mechanisms. Many studies have demonstrated the benefit of DMARD therapy, including improved signs and symptoms (i.e. ACR20 score), improved

functional status (i.e. Health Assessment Questionnaire) and disease progression (i.e. radiographic evidence for erosions). The ACR subcommittee on RA guidelines has sited many studies evaluating the efficacy of the many DMARDs available for RA treatment (ACR subcommittee on RA guidelines., 2002).

Table 1.6.2. Available second-line drugs and their therapeutic indication. The therapeutic indications for these drugs are as recommended in the British National Formulary (BNF), Number 42 (September 2001).

DRUG	THERAPEUTIC INDICATION	
Antimalarials	Mild or early active RA- moderate	
Chloroquine	inflammatory activity	
Hydroxychloroquine		
Sulphasalazine	Active RA	
Gold compounds		
Sodium Aurothomalate	Active progressive RA	
Auranofin	Active progressive RA	
Methotrexate	Moderate to severe RA	
Penicillamine	Severe, active RA	
Leflunomide	Severe, active RA,	considered
Azathioprine	Severe, active RA	more toxic, and
Cyclosporin	Severe, active RA	are used when
Cyclophospahmide	For RA with severe,	other DMARDs
	systemic manifestations	have failed.

Many considerations such as tolerance, safety, efficacy and cost reflect the choice of DMARD. Factors unique to the rheumatoid process also play an important role, i.e. how quickly and effectively does the drug control inflammation. Table 1.6.3 lists commonly used DMARDs in RA and their duration to benefit. Also listed are their dosages and costs. Gold and penicillamine can take over 3 months to work, during which time joint destruction can progress substantially. Given the importance of early pharmacologic intervention and the prolonged course of treatment usually required, safety and adverse events are another pressing concern. DMARDs are often associated with considerable toxicity requiring frequent monitoring of blood and

physical examination, ultimately this limits their usefulness (Boyce., 1992). In long-term therapy they are often only partly effective and poorly tolerated. In meta-analysis of dropout rates from clinical trials, 20-40% of patients discontinued use of DMARDs assessed as mono-therapy, and in clinical practice, the median duration of DMARD mono-therapy was less than 2 years for non-methotrexate agents (Felson at al., 1990; Morand et al., 1992; Pincus et al., 1992). Major reasons for lack of long-term adherence to treatment, included poor efficacy, delayed onset of action and toxic effects (Felson et al., 1992). Results from clinical trials do show that DMARD therapy decreases markers of inflammation such as erythrocyte sedimentation rate and swollen joint counts, and that symptoms improved in subsets of patients. However, most patients continue to show progression of irreversible joint destruction on radiography (Mulherin et al., 1996).

Table 1.6.3. Dosages, costs and approximate time to benefit of disease modifying anti-rheumatic drugs used in the treatment of rheumatoid arthritis

Drug	Time to benefit (Approx.)	Usual maintenance dose	Annual drug cost (generics), dollars*
Hydroxychloroquine	2-6 months	200 mg twice a day	1,056(559)
Sulfasalazine	1-3 months	1,000 mg 2-3 times a day	509-763 (205-308)
Methotrexate	1-2 months	Oral 7.5-20 mg/week; injectable 7.5-20 mg/week	697-1,859 (259-691); 419-806 (42-81)
Leflunomide	4-12 weeks (skewed earlier)	20 mg/day in a single dose, if tolerated; otherwise, 10 mg/dayψ	2,938
Etanercept	A few days to 12 weeks	25 mg subcutaneously twice a week	15,436
Infliximab plus oral and subcutaneous methotrexate	A few days to 4 months	3-10 mg IV every 8 weeks or 3-5mg IV every 4 weeks	13,940-30,287 or 28,040-36,694§
Azathioprine	2-3 months	50-150 mg/day	579-1,737(471-1,414)
D-penicillamine	3-6 months	250-750 mg/day	865-2,595(398-1,194)
Gold, oral	4-6 months	3 mg twice a day	1,622
Gold, intramuscular	3-6 months	25-50 mg intramuscularly every 2-4 weeks¶	198# (142)
Minocycline	1-3 months	100 mg twice a day	2,592 (582)
Cyclosporine	2-4 months	2.5-4 mg/kg/day**	4,432-8,859 (3,512-7,022)
Staphylococcal protein A immunoadsorption	3 months	Weekly for 12 weeks	20,433

* Annual drug costs are provided for comparison purposes only. Values are based on costs from the 2001 Red Book (except where indicated otherwise) and on the usual maintenance dose or range of maintenance doses for a 70-kg individual. Values in parentheses represent lower-cost generics. These values do not include either physicians' office visit fees or laboratory costs associated with monitoring. ψThe recommended loading dose for leflunomide is 100 mg/day for 3 days. Start infusions at the first visit (week 0), followed by infusions at weeks 2 and 6, and then every 8 weeks thereafter. Can consider increasing the frequency of infusions from every 8 weeks to every 4-6 weeks if there is an incomplete response. IV = intravenous. § Costs for infliximab are based on costs from the 2001 Red Book and on the Medicare reimbursement rates for outpatient procedures. They include the costs associated with the infusion, but not the cost of the weekly methotrexate that is recommended. ¶ Start with a 10-mg intramuscular test dose, followed by a loading dose of 50 mg intramuscularly every week until a cumulative dose of 1,000 mg is reached. # Does not include the cost of administering the intramuscular injections. ** Start at 2.5 mg/kg/day in 2 divided doses taken 12 hours apart, and increase the dosage by 0.5 mg/kg/day every 2-4 weeks until a clinical repsonse is noted or a maximum dosage of 5 mg/kg/day is reached. Costs for the staphylococcal protein A immunoadsorption treatments are based on Medicare reimbursement rates for outpatient procedures. *(Adapted from American College of Rheumatology Subcommittee on RA guidelines. Guidelines for the management of RA. Arthritis Rheum, 2002; 46(2): 328-346)*

For patients with early diagnosis of mild RA, hydroxychloroquine and sulfasalazine are usually prescribed (Table 1.6.2). Both agents produce the symptomatic benefit in mild RA (Van der Heijde et al., 1989; Tsakomas et al., 2000; Ebringer et al 1992; Skosey., 1998; Davis et al., 1991). In addition they have considerable advantage over other DMARDs in relation to safety, convenience, and cost. Other commonly used DMARDS include methotrexate, and the more recently introduced leflunomide, etanercept and infliximab. These are usually used to control active RA. Azathioprine, D-penicilammine, gold salts, minocyline and cyclosprine are used less frequently.

Among the DMARDs the most successful is methotrexate, this cytotoxic agent is immunosuppressive and anti-inflammatory. The introduction of low-dose weekly methotrexate as monotherapy for RA has provided a huge improvement in tolerability and efficacy for many patients. The efficacy of methotrexate is well established, particularly in patients with more severe disease. Results of clinical trials of methotrexate showed a consistent 50-80% clinical response relative to baseline with long-term stabilization of functional status (Weinblatt et al., 1998; Kremer., 1997; Tugwell et al., 2000). In these studies and additional studies, patients showed long-term adherence to low-dose weekly methotrexate monotherapy (Weinblatt et al., 1994; Sany et al., 1991). Furthermore, in longitudinal observational studies, methotrexate slowed the rate of joint destruction as measured by radiography and improved quality of life (Tugwell et al., 2000, Weinblatt et al., 1993; Sharp et al., 2000). Thus, for these reasons low-dose weekly methotrexate has become the most widely prescribed DMARD. Its extensive use has helped to well define its safety and efficacy. In clinical practice methotrexate doses of more than 10mg/week are generally needed, and many patients require dose escalation to 15-25mg/week to achieve maximum

response. Onset of action takes 4-8 weeks. Good tolerability, low cost, favourable efficacy and an established track record have allowed methotrexate to become a benchmark agent with which other agents are compared in clinical trials. However, liver toxicity, a major drawback associated with methotrexate therapy still remains. Liver function must be monitored to identify elevation of liver enzymes (Kremer et al., 1994). Patients receiving methotrexate therapy are more likely to discontinue treatment because of adverse reactions such a alopecia, stomatitis, nausea than because of lack of efficacy (Suarez-Almazor et al., 2001)

1.6.4 Corticosteroids

Corticosteroids exert both anti-inflammatory and immunosuppressive effects. They have been reported to decrease circulating monocyes, reduce macrophage phagocytosis and IL-1 secretion, inhibit collagenase and lysosomal enzyme release, and inhibit prostaglandin and leukotriene synthesis (Boyce., 1992). These many actions contribute to low doses of the drug's effect in slowing the rate of joint damage (Kirwan., 1995). The symptoms of RA are effectively lowered by low-dose oral corticosteroids, and local injections of corticosteroids. In active RA, rapid and improved functional status may be prevalent within a couple of days following initiation of low-dose corticosteroids. However, once discontinued, disabling or joint damaging synovitis may reoccur (Hickling et al., 1998). Thus many patients with RA become functionally dependent on corticosteroids and continue them long-term. Depending on the route of administration (i.e. oral, systemic or topical), the dose of corticosteroid differs for each preparation. Prednisolone is a well-established corticosteroid used in RA treatment. This drug is well absorbed and has a plasma half-life of 2-3.5 hours. It is metabolised in the liver and excreted mainly via the

kidneys. Corticosteroids are closely associated with adverse effects (Schuna., 1998), such as osteoporosis, hypertension, hyperglycaemia, cataracts, weight gain, fluid retention, central nervous system effects, and progression of atherosclerosis. Due to their multiple adverse effects, small oral doses (e.g. 7.5-10mg prednisone daily) are recommended, and large daily doses are generally given reserved for short-term use (Lipsky., 1998). Corticosteroids may be given chronically when combination therapy with NSAIDs plus DMARDs fails.

1.6.5 Treatment approach: Combination therapy

Major transformation in approach and choice of drugs for the treatment of rheumatoid has been seen in the past decade. The treatment pyramid had traditionally begun with mild strategies/drugs with aggressive therapies used only as a last resort. The aim was to control inflammation and joint damage, and to minimise drug toxicity. In this approach DMARDs were invariably prescribed after joint damage was established. Radiographic evidence of early joint damage, within the first two years of developing RA, has led to support for earlier, more aggressive treatment models (Fuchs et al., 1989; Iannuzzi et al., 1983).

The step down bridge approach begins treatment with a fast acting steroid plus methotrexate to control inflammation (Wilske and Healy., 1990). The steroid and methotrexate are discontinued and replaced with slower acting drug, such as hydroxychloroquine once inflammation is reduced (Figure 1.6.2). The step-down bridge course of therapy has the objective to keep treatment effective, simple and inexpensive. Inflammation is controlled before extensive joint damage occurs and duration of treatment with toxic drugs is shortened. A successful example of the step-

down approach was the COBRA trial (Boers et al., 1997), which evaluated efficacy in patients with RA for up to two years. However this scheme has never been validated by randomised controlled trials.

Fig. 1.6.2. The "Step-down bridge" approach. *(Adapted from Wilske KR, Healey LA. Challenging strategies for rheumatoid arthritis. J Rheumatol 1990; 17(suppl 25):4-7.*

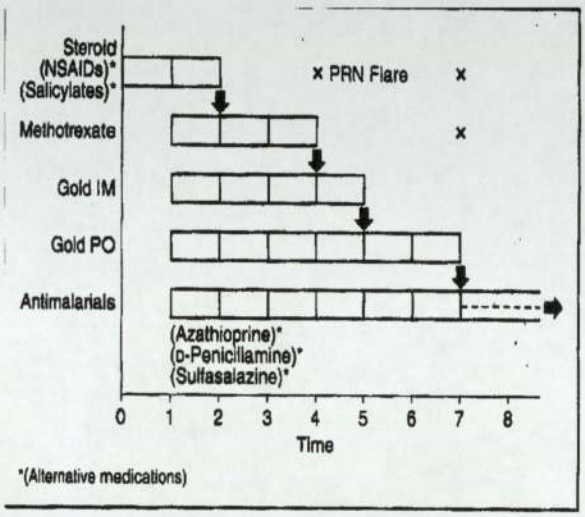
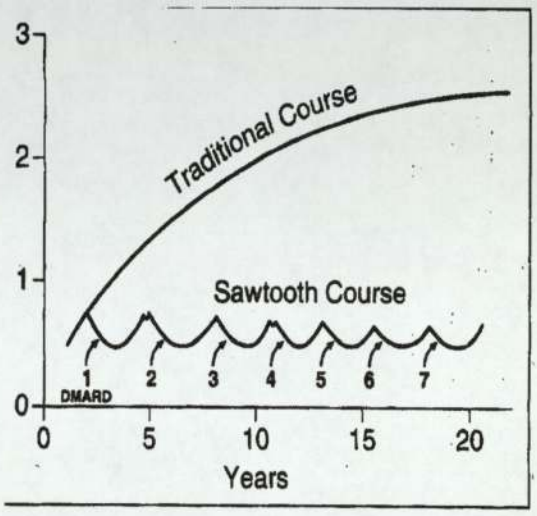


Fig. 1.6.3. The 'Sawtooth' strategy. *(Adapted from Fries JF. Reevaluating the therapeutic approach to rheumatoid arthritis: the 'sawtooth' strategy. J Rheumatol 1990; 17(suppl 22):12-15.*



The sawtooth strategy has also been evaluated in early RA. Here, a DMARD is initiated early and replaced with other, similar agents as each loses efficacy. Patients are not placed on maintenance therapy. Instead, they see-saw over the course of many years, from the high levels of efficacy achieved with each new drug to diminished therapeutic effect and then back up to improved relief (Figure 1.6.3). The principle behind this approach requires monitoring the clinical variables at diagnosis and subsequently at regular intervals. The application of this strategy has been suggested improved outcome (Mottonen et al., 1996). An alternative approach is the graduated step-up approach, which involves initial staging of RA into mild, moderate and severe. Patients with mild disease might receive an NSAID in combination with a DMARD such as hydroxychloroquine or sulfasalazine. Patients with moderate RA might receive gradually escalating doses of MTX and, sequentially, combinations of

hydroxychloroquine, sulfasalazine, or both. Patients with more severe RA are now likely to receive up to 25 to 30mg MTX per week followed, in some countries, by targeted biologic agents that inhibit either TNF or IL-1 (Bresnihan., 2002).

1.6.6 The cost of RA

Cost is an implicit part of every medical decision making. In RA, economic costs not only refer to money but also to costs associated with reduced productivity and the effects of pain and suffering (see Table 1.6.4).

Table 1.6.4. Economic impact of RA

Direct costs	Indirect costs	Intangible costs
Medical	Productivity loss by patients	Mortality (value of premature loss of life)
Hospital	Productivity loss by carers	
Nursing home	Reduced family income	Morbidity (pain and suffering)
Ambulance		Quality of life
Aids and devices		
Pharmaceuticals (administration, monitoring &toxicity)		

(Adapted from March, L. and Lapsley, H. What are the costs to society and the potential benefits from the effective management of early rheumatoid arthritis? Best Prac & Res Clin Rheumatol 2001;15(1):171-185)

In the US, RA sufferers have three times the direct medical cost, twice the hospitalisation rate, and ten times the work disability rate of an age and sex-matched population (Felts and Yelin., 1989). Moreover annual medical costs for an RA sufferer has been estimated to be $8,500 (Yelin and Wanke., 1995). Indirect costs are usually two to three times higher than direct costs (Yelin and Callahan., 1995; March and Bachmeier., 1997). However, other pieces of evidence also suggest that direct costs are catching up (Clarke et al., 1997; Lanes et al., 1997).

Drug costs make up 6-17% of the annual direct cost of treating RA (March and Lapsley., 2001). The novel DMARDs are costly (see Table 1.6.3). Therefore whether their use is justified is dependant on whether they slow radiographic damage, improve patient functional status, and increase patient ability to work.

1.7 NEWER DMARDS

1.7.1 Anti-TNF Alpha Therapy

Important progress in the understanding of the pathogenesis of RA has led to the mapping of a number of molecular targets for immunotherapeutic intervention. Among these, TNF-α and IL-1 have been identified as good targets for treatment. Drugs that block the effects of TNF-α are novel and to date, two biological agents that target TNF-α have been licensed for clinical use in Europe and USA. These newer DMARDS are infliximab (Remicade®) and etanercept (Enbrel®). Etanercept is a soluble, dimeric, recombinant molecule consisting of two copies of the extracellular ligand-binding portion of human TNF-α receptor (p75), linked to the constant region of human IgG_1 (class 1). In comparison infliximab is a chimeric (Figure 1.7.1) monoclonal anti-TNF-α antibody preparation that consists of a human $IgG_1\kappa$ antibody with a mouse Fc of high affinity and neutralising capacity (Knight et al., 1993). Both agents competitively inhibit the binding of TNF-α to its receptor (Mohler et al., 1993).

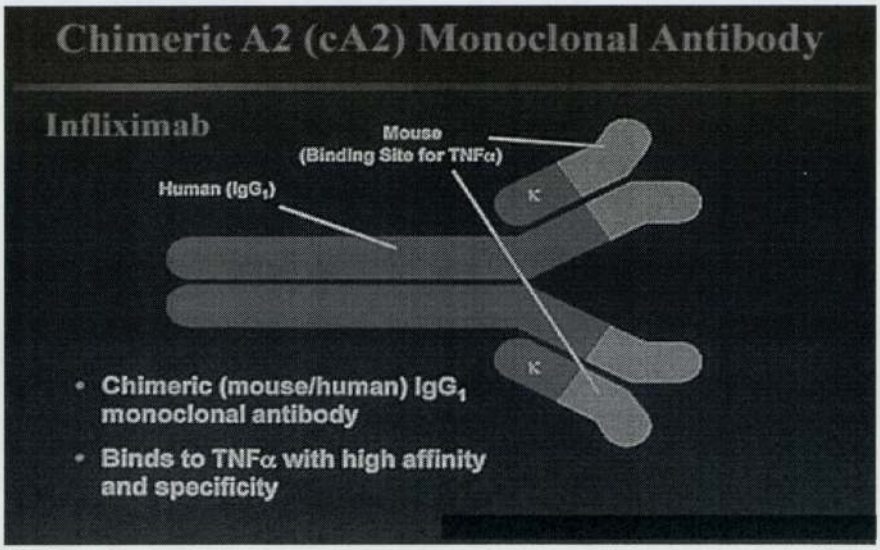


Figure 1.7.1. Schematic diagram of infliximab *(Adapted from Knight et al. 1993. Construction and initial characterisation of a mouse-human chimeric anti-TNF antibody. Mol Immunol; 30(16): 1443-1453)*

1.7.2 *Etanercept*

The Centre for Biologics Evaluation and Research of the United States Food and Drug Administration (FDA) granted marketing authorisation of Enbrel™ in November 1998. It was approved for reduction of the signs and symptoms of moderate to severe active RA. It is also indicated for juvenile idiopathic or chronic arthritis, patients with polyarticular disease who have had an inadequate response to one or more DMARDs. Etanercept exhibits a median half-life of 4.8 days (range, 4.1-12.5 days), and is administered subcutaneously at a dose of 25mg twice a week. The drug has been assessed in patients with early RA and in patients with RA who showed an inadequate response to prior DMARD therapy (Maini et al., 1997; Maini et al 1999; Bathon et al., 2000). Clinical improvement in these trials was assessed according to ACR criteria.

1.7.3 *Infliximab*

Infliximab was initially cleared for marketing in the US in 1998, for short-term use in patients with Crohn's disease, a serious gastrointestinal disorder. It is licensed for concomitant use with methotrexate for inhibiting the progression of structural damage in patients with moderate to severe active RA who have had an inadequate response to DMARDs, including methotrexate. The drug is given by intravenous infusion (under medical supervision) over 2 hours at doses of 3mg/kg at 0, 2 and 6 weeks, and every 8 weeks thereafter. The terminal half-life of infliximab is 8-9.5 days. The approval of infliximab was based on 54-week data from the 2-year ATTRACT trial (Anti-TNF trial in RA with concomitant therapy), one of the largest controlled RA clinical trials which included 428 patients at 34 centres in north America and Europe (Lipsky et al., 1999; Lipsky et al., 2000; Maini et al., 1999).

1.7.4 *Leflunomide*

Like the antagonists to TNF-alpha, leflunomide was one of the first DMARD approved in the past couple of years for RA after a lapse of 10 years. Leflunomide is an immunomodulator with anti-inflammatory, analgesic, and antipyretic activity (Hermann et al., 2000), mediated primarily via inhibition of dihydroorotate dehydrogenase, an enzyme required for the de novo production of pyrimidine. This property permits selective inhibition of the proliferation of activated T-cells (Fox., 1998). Although its specific mechanism of action in RA is not known, leflunomide affects lymphocyte function in vivo and in vitro (Elder et al., 1997; Cherwinski et al., 1995). Leflunomide is taken orally. After ingestion it is rapidly converted to its active metabolite A771726. Drug elimination occurs slowly via fecal and renal routes

with a mean half-life of 14 days. A loading dose of 100mg daily is given over 3 days, because of the length of time required to achieve steady state. Thereafter leflunomide is dosed orally at 10-20mg daily.

Table 1.7.1. Efficacy of leflunomide in randomised controlled trials. *(Adapted from Breedveld FC. Is there a place for leflunomide in the treatment of rheumatoid arthritis? Lancet 2001; 358:1198-1200 (commentary))*

			Joint count†			
Reference/ Responders duration	No. of patients	Treatment*	Pain	Swelling	C-reactive protein (mg/L)	(%)▸
Mladenovic 1995/6 months	402	Leflunomide 5mg/day	-10.5	-7.6	+2.4	30
		Leflunomide 10mg/day	-13.6	-10.4	-14.9	52
		Leflunomide 25mg/day	-16.5	-11.7	-9.5	60
		Placebo	-9.7	-6.5	+5.3	31
Strand 1999/ 12 months	482	Leflunomide 20mg/day	-7.7	-5.7	-0.6	52
		Methotrexate 7.5mg/week	-6.6	-5.4	-0.5	46
		Placebo	-3	-2.9	+0.5	26
Smolen 1999/ 6 months	358	Leflunomide 20mg/day	-9.7	-7.2	-2.3	55
		Sulfasalazine 2g/day	-8.1	-6.2	-1.1	56
		Placobo	-4.3	-3.4	-0.2	29
Emery 2000/ 12 months	999	Leflunomide 20mg/day	-10.2	-8.6	-2.2	51
		Methotrexate 7.5mg/week	-11.0	-10.0	-2.9	65

* Loading dose of 100 mg Leflunomide during the first 3 days of treatment. Methotrexate dose was increased to 15 mg when response was inadequate.
† Based on 28 joint count
▸ Proportion of patients with 20% response rate, by American College of Rheumatology criteria, at endpoint.

The efficacy of leflunomide has been shown in several double-blind placebo controlled trials. Table 1.7.1 presents an overview of pivotal randomised, double blind phase III clinical trials of leflunomide. Leflunomide is viewed as a useful alternative compared to other established anti-rheumatic agents such as methotrexate and sulfasalazine, which can be ineffective or intolerable in some patients. The safety and efficacy of leflunomide used in combination therapy with low-dose weekly

methotrexate has been assessed in a small open-labelled trial (Weinblatt et al., 1999) and in a multicentre randomised controlled trial (Kremer et al., 2000). These studies found that leflunomide plus methotrexate was more effective than methotrexate plus placebo (proportion with 20% improvement in ACR of 52% vs 23%). Possibly the effects of leflunomide could complement those of methotrexate by affecting separate metabolic pathways. However, this well tolerated combination is potential hepatotoxic.

1.7.5. Perspective of regulatory agencies

Before patients can use any medical product it needs to be proven to be acceptably safe and effective. In the United States the Food and Drug Administration (FDA) undertakes the regulation of food, drugs, medical devices, biologics and veterinary medicines. For official approval of a drug, manufacturers submit evidence on its efficacy and safety to the FDA. For RA treatment, the FDA issues specific guidance (***http://www.fda.gov.htm***). This guidance sets out criteria, which new therapies must meet. FDA approved indications for etanercept, infliximab and leflunomide are shown in Table 1.7.2.

Table 1.7.2. FDA approved indications for RA

Leflunomide (Arava)	1. Reduction of signs and symptoms of active RA in adults 2. Retard structural damage as evident by x-ray erosions and narrowing of the join spaces
Etanercept (Enbrel)	1. Reduction of signs and symptoms of active RA in adults. 2. Delaying structural damage in patients with moderate-severe active RA, including those who have not previously failed therapy with other DMARDs
Infliximab (Remicade)	1. For combination use with MTX to: reduce signs and symptoms of RA, and improve physical function in patients with inadequate response to MTX. 2. For combination use with MTX to inhibit progression of structural damage in moderate-severe RA.

For all three treatments the pre-clinical documentation and experience in clinical trials is extensive.

1.8 EVIDENCE BASED MEDICINE

It is professionally desirable that initial decision-making is informed by the best available evidence. Evidence based medicine (EBM) acknowledges that intuition, unsystematic clinical experience and patho-physiological rationale are insufficient grounds for clinical decision making. Thus it stresses the examination of evidence from clinical research (Haynes at al., 1996). Sackett et al (1998) define EBM as clinical expertise informed by the best available evidence obtained from systematic research. It is generally accepted that there is a hierarchy of evidence (Table 1.8.1) (Sackett at al., 1998) with randomised controlled trials (RCTs) at the top.

Table 1.8.1. A Hierarchy of strength of evidence for treatment decisions

- N of 1 randomised controlled trial
- Systematic reviews of randomised trials
- Single randomised trial
- Systematic review of observational studies addressing patient-important outcomes
- Single observational study addressing patient-important outcomes
- Physiologic studies (studies of blood pressure, cardiac output, exercise capacity, etc..)
- Unsystematic clinical observations

(Adapted from Guyatt G, Rennie D, Hayward R. Users' Guides to the Medical Literature. A manual for evidence-based clinical practise. JAMA and archives, 2002.)

RCTs are devised to answer a therapeutic question, for example, the efficacy of leflunomide in RA. A process equivalent to flipping a coin (randomisation) determines whether a participant will receive an experimental treatment or a control/standard treatment. Once participants are allocated to a treatment group they

are followed for an outcome of interest, such as swollen joint count or pain in RA. The quality of RCTs is best assessed by attention to randomisation and blinding of all participants, and by making sure that all these entered in the study are involved in the analysis of data (intention to treat [ITT]).

Some interventions, which reliable research shows to have significant benefits can largely be ignored. Through a systematic way results of trials can be combined together. Appraising the quality of results with relevance to the question and synthesizing results in an explicit and accessible way can increase the awareness of evidence by researchers, policy makers, practitioners and the public. The varying qualities, running of optional methods and contradictory findings are apparent across single studies. Research findings can be hard to interpret, there may be several aspects, several duplicates and several missing information. A systematic review provides EBM with a tool that is capable of pulling together the existing evidence in a format used by practitioners. Explicit and rigorous methods are used for the identification, inclusion and critical appraisal of relevant studies to produce secondary data.

1.8.1 Meta-analysis

In the process of evidence based decision-making the systematic review supplies the research evidence input. A meta-analysis is the analytical or statistical part of a systematic review. Here statistical methods are used to combine results of primary studies quantitatively (Der Simonian and Laird., 1986) enabling the exploration of heterogeneity across study results, the estimation of overall measure of association or effect and the assessment of the sensitivity of the results to possible threats to validity

such as publication bias and study quality (Thompson., 1994). More patients are included in a meta-analysis than any single consistent study, and so this may reduce the random errors in the assessment of treatment (Collins et al., 1997). In addition combining studies carried out in different places or with different entry criteria may also produce more generaliseable results, taking into account the range of settings and contexts.

For meta-analysis the data that is being analysed is usually categorised into one of three groups. These include binary or dichotomous data, such as whether patients are alive or dead, diseased or non-diseased; continuous data (e.g. blood pressure) and categorical (ordinal) data, for example from a disease severity scale. Depending on the type of data the outcomes or study effects can be expressed in different ways. For example, dichotomous data can be expressed as a relative risk or risk ratio (RR), an absolute risk reduction (ARR) or risk difference (RD), an odds ratio (OR) or number needed to treat (NNT), all of which convey a variety of different information.

1.8.2 Dichotomous data

Dichotomous outcomes are associated with risks and odds measures. Risk is the chance, or probability of having a specific event; it can be applied to both a good and a bad event. The risk is the number of people with the outcome divided by the total number of people. The odds is an alternative measure, and indicates how likely an event will happen. The odds of an event is the ratio of the probability of events to the probability of non-events. The odds ratio represents the ratio of two odds, usually that with the test treatment and that with the control treatment. The calculation of OR, RR,

RD and NNT can be explained by a 2 × 2 table (Mantel and Haenzel., 1958) (Table 1.8.2).

Table 1.8.2. The 2 × 2 table.

		outcome	
		Yes	No
exposure	Yes	a	b
	No	c	d

Relative Risk $= \dfrac{a/(a+b)}{c/(c+d)}$

Risk Difference $= \dfrac{c}{c+d} - \dfrac{a}{a+b}$

Number Needed to Treat $= \dfrac{1}{RD}$

Odds Ratio $= \dfrac{a/b}{c/d} = \dfrac{ad}{cb}$

1.8.3 Fixed-effects and Random-effects model

In a meta-analysis the method used to pool the primary study results can be adopted as a fixed effects or a random effect model (Fleiss., 1993). It can be assumed that all studies included in a meta-analysis the same estimate of effect. The fixed effect model is based on such an assumption. If all studies were infinitely large every study would give the same identical or common treatment effect. Here, the observed estimates of effect differ from each other only because of random error (Lau et al., 1998). Thus, the model ignores the variation or heterogeneity between studies. In contrast, the random effects model assumes variation of the true treatment effect does

exist in individual studies. The underlying true effect is different for each study estimate and the distribution of these effects is assumed normal around a mean value (Lau et al., 1998). Unlike the fixed effect model that is too simplistic, the random effects model tries to explain this variation.

Evidence of treatment effectiveness does not automatically imply that treatment should be administered. A judgement about the trade-off between risks and benefits should be incorporated in the management decision. In fields like rheumatology, definitions of clinical expertise and best evidence would usually pose a problem (Ellard., 1998). Important issues including the contributions of paramedics (i.e. occupational therapists), as well as other professionals involved in patient care and overall costs associated with alternative management strategies should be incorporated in decision-making. Varying values and preferences among patients and clinicians will also reflect the best course of action.

OBJECTIVES OF THE STUDY

This study was undertaken to:

- Systematically review the effectiveness of the newer agents, etanercept, infliximab and leflunomide compared to placebo or any other disease modifying anti-rheumatic drug (DMARD) in the treatment of rheumatoid arthritis (RA).
- Conduct a meta-analysis of the efficacy of leflunomide, etanercept and infliximab in RA treatment.

CHAPTER 2

METHODS

2.1 SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Published randomised controlled clinical trials (RCTs) of leflunomide, etanercept and infliximab were identified through systematically searching the following electronic databases: Cochrane Library, Medline, Science Direct, Food and Drug Administration (FDA) website and Web of Science. In addition websites of Health Technology Assessment (HTA) organisations, (Canadian Co-ordinating Office for Health Technology Assessment [CCOHTA] and UK National Co-ordinating Centre for Health Technology Assessment Programme [NCCHTA]) and the National institute of clinical Excellence (NICE) were also thoroughly searched.

Relevant studies were identified through the use of the following medical subject headings:

1) Etanercept/ Infliximab/ Leflunomide
2) Randomised controlled trials/ Double-blind trials/ Single blind trials/ Open label trials and 'Arthritis, Rheumatism'
3) 'Disease modifying anti-rheumatic agents'
4) Drug therapy/ Combination therapy
5) 'Arava', 'Remicade', 'Enbrel'

In order to confirm that electronic databases had offered all possible literature the bibliographies of retrieved randomised controlled trials, systematic reviews and

selected review articles were hand searched. In addition the websites of the manufacturers of the three drugs were contacted for unpublished trials.

All databases were searched from 1994 to March 2002. A further search of the databases was performed in September 2002 to retrieve any recent publications. Possible unpublished trials were requested by writing to the manufacturers of the drugs.

2.2 INCLUSION AND EXCLUSION CRITERIA FOR RCT SELECTION

Study participants were patients diagnosed with adult RA as defined by the American College of Rheumatology (Arnett at al., 1988). The experimental intervention was Etanercept, Infliximab, or Leflunomide, using any dose regimen. Only randomised controlled studies evaluating etanercept infliximab or leflunomide versus placebo or any other DMARD, either singly or in combination were eligible. The search was not restricted to year of publication or language. For pooling, studies that did not measure the response rate using the ACR response criteria (i.e. ACR20, 50 or 70) were excluded. Publications cited as abstracts were only included if no corresponding full publications were available.

2.3 QUALITY OF TRIALS

Quality assessment was undertaken on the basis of randomisation and inclusion of an appropriate control for determining suitability for inclusion only. An all or nothing approach rather than a scoring approach was adopted. Blinding was assessed to allow appropriate sensitivity analyses if necessary. Scores were not calculated, as they are likely to mislead due to potential discordance between the quality of the conduct of the trial and the quality of reporting of the trial (Huwiler-Muntener et al., 2002).

2.4 DATA EXTRACTION

Quantitative data was extracted by myself and checked by my supervisor. Statistical analyses of radiographs related to the effects of treatment on disease progression were also extracted. Safety data related to the frequency and type of adverse events were assessed for the identified trials. Other important material, such as the patient characteristics in each trial and descriptive methodologies, were also extracted.

2.5 OUTCOMES

The primary efficacy outcome of the treatment was evaluated using the ACR20 index of the American College of Rheumatology criteria. The ACR criteria categorises response as a treatment success if the patient shows a 20% improvement (ACR20) in tender and swollen joint counts and a 20% improvement in 3 of the 5 remaining ACR core set measures: patient and physician global assessments, pain, disability, and an acute phase reactant (Felson et al., 1995). ACR50 and ACR70 responses are similarly defined with the numbered suffixes indicating the extent of improvement required. Published trials are usually powered on the basis of ACR20 as this is regarded as the minimum effect that is clinically meaningful to patients. The ACR50 and ACR70 measures require substantially larger sample sizes and most published trials are not sufficiently powered to detect effects of those magnitudes (Felson et al., 1998). However, meta-analyses may provide the necessary power to detect differences in those more demanding responses (chapter 4).

2.6 OUTCOMES CONVERSIONS AND STATISTICAL ANALYSIS

Differences in the number of ACR 20 responders in patients receiving leflunomide relative to placebo or control drug were estimated through estimates of the risk difference. Homogeneity of effect were tested using Cochran's Q statistic (Cochran.,

1954) at a significance level of 0.1. A fixed effect model (Mantel and Haenszel., 1959) was used unless trials demonstrated heterogeneity, whereby DerSimonian and Laird's random effects (DerSimonian and Laird., 1986) method was used.

CHAPTER 3

THE EFFICACY OF ETANERCEPT, INFLIXIMAB & LEFLUNOMIDE IN THE TREATMENT OF ACTIVE RHEMATOID ARTHRITIS

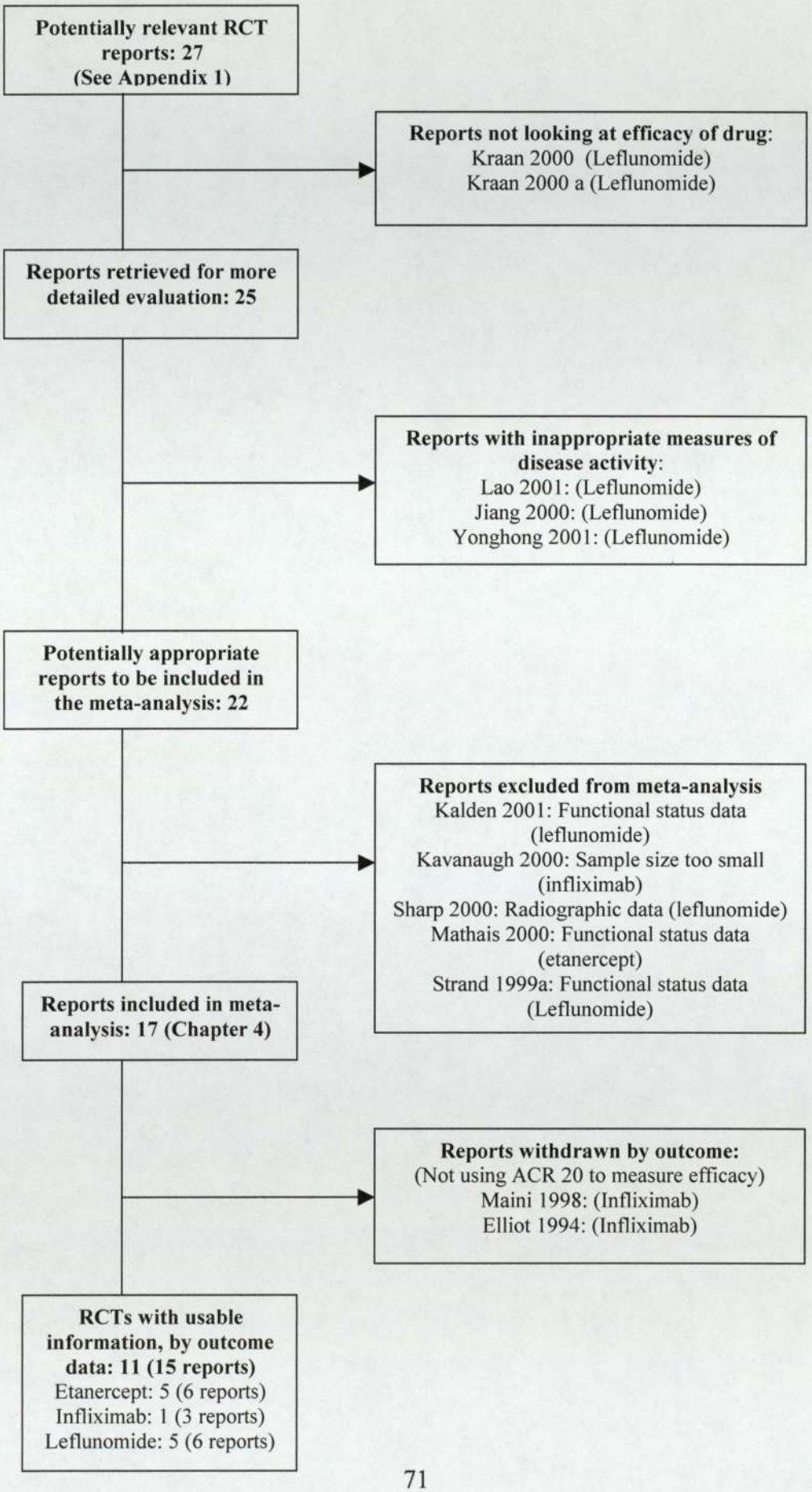
3.1 INTRODUCTION & OBJECTIVES

Medical therapy of RA aims to reduce joint pain and swelling, slow radiological progression of joint damage, and prevent functional impairment. In the last decade several new drugs have been introduced for the treatment of rheumatoid arthritis, including three biological agents, infliximab, etanercept and leflunomide. In addition to the randomised controlled trials (RCTs) required by drug licensing authorities to support applications for marketing authorisation, a number of other RCTs of those drugs have also been published. The objective of this section is to systematically review the evidence for the efficacy and safety of those three novel drugs for RA.

3.2 CHARACTERISTICS OF RCTS

At completion of the systematic search, many relevant reports were cited. The reports were screened according to certain inclusion and exclusion criteria. Excluded reports included case reports, review articles, and observational studies. A list of all potentially relevant RCTs are listed in Appendix 1, briefly stating why they were excluded or included. Among the potentially relevant randomised controlled trials (RCTs), reports that were used for the systematic review and meta-analysis are shown in Figure 3.2.1.

Figure 3.2.1. The process by which the trials were selected for meta-analysis. See Appendix 1 for reasons for exclusion of reports.



The key study characteristics of these trials are summarised in Tables 3.2.1, 3.2.2 and 3.2.3. More details of the patient's characteristics for each trial are summarised in Appendix 2.

3.2.1 Etanercept

From the search, 7 RCTs relevant to etanercept were identified, Figure 3.2.2 presents all these trials, indicating how some of them are associated with each other to form follow-on studies, or are reports of the same trial but with different data, or extension data.

Figure 3.2.2. Randomised controlled trials of etanercept and trial inter-linkage.

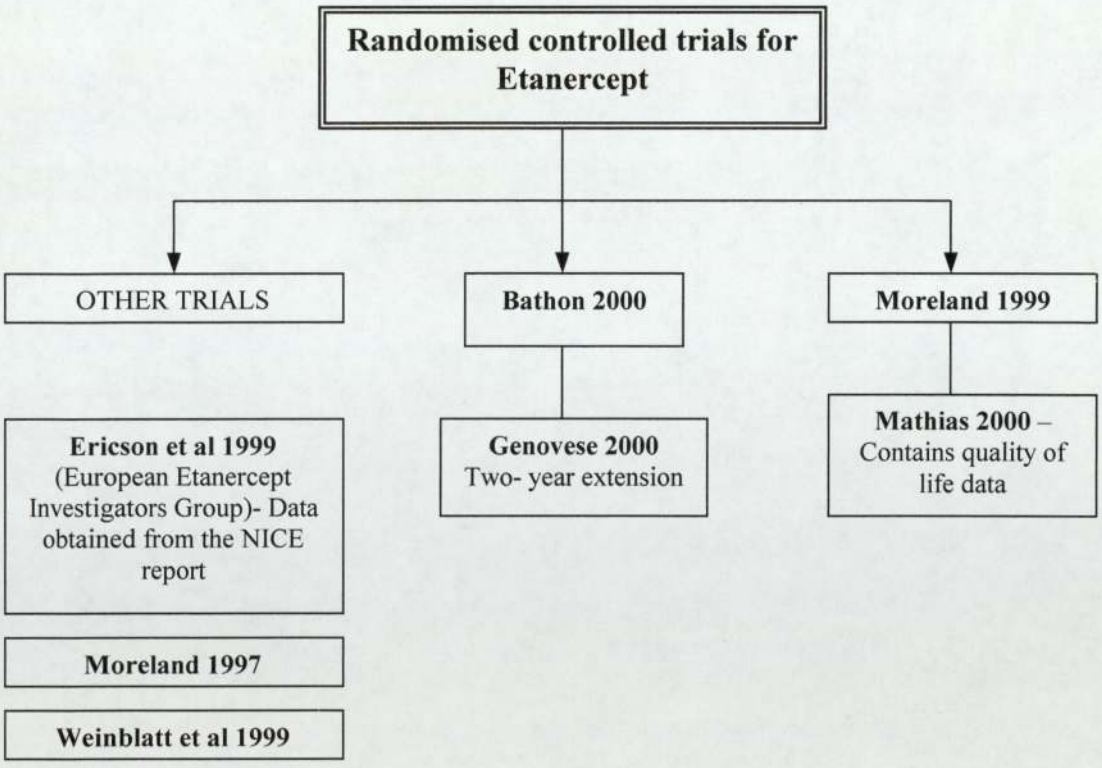


Table 3.2.1. Characteristics of randomised controlled trials of etanercept. Abbreviations: DB, double blind; SB, single blind; OL, open label; IMAB, infliximab; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; DMARD, disease modifying anti-rheumatic drugs; ET, etanercept.

Study	Type of Study	Duration	Drug	Dose of specified drug	No. of patients	Mean Age (Yrs)	Female (%)	Mean duration RA (Yrs)	Mean no. of previous DMARD	Concomitant use (%)	
										NSAIDS	Steroids
Moreland et al., 1997	DB, Phase II	12 weeks	ET	0.25 mg/m² twice a wk	46	54	70	76% > 5 yrs	-	70	59
				2 mg/m² twice a wk	46	52	61	80% > 5 yrs	-	80	65
				16 mg/m² twice a wk	44	52	82	80% > 5 yrs	-	75	77
			Placebo	Twice a wk	44	55	82	71% > 5 yrs	-	73	66
Moreland et al., 1999	DB, Phase III	26 weeks	ET	10 mg twice a wk	76	53	84	13	3.4	67	66
				25 mg twice a wk	78	53	74	11	3.3	67	81
			Placebo	Twice a wk	80	51	76	12	3.0	84	58
Weinblatt et al., 1999	DB, Phase III	24 weeks	ET + MTX	25mg/wk + 12.5 - 25 mg/wk	59	48	90	13	2.7	75	53
			Placebo + MTX	MTX 12.5-25 mg/wk	30	53	73	13	2.8	80	70
The European Etanercept Investigators Group. (Data obtained from Nice report., 2002)	DB, Phase II	12 weeks	ET+ Placebo	10mg/wk	122	53	-	7	3.2	-	79
				10mg twice a wk	110	54	-	7	3.0	-	72
				25mg/wk	111	54	-	7	3.3	-	70
				25 mg twice a wk	111	53	-	8	3.6	-	69
			Placebo	Twice a wk	105	53	-	7	3.5	-	72
Etanercept ERA trial (Bathon et al., 2000; Genovese et al., 2002)	RCT, DB for 1 year, OL in year 2, Phase III	2 years	ET+ Placebo	10 mg twice a wk	208	50	75	11 months	0.5	76	42
				25 mg twice a wk	207	51	74	1	0.5	86	39
			Placebo + MTX	MTX 7.5 - 20 mg/wk	217	49	75	1	0.6	80	41

The trial reported by Ericson and Wajdula (2000) was only in abstract form. The efficacy data for this trial was obtained form the NICE report (Jobanputra et al., 2002). Mathias (2000) reported quality of life data from the same trial described by Moreland (1999). Key characteristics for each trial are described in Table 3.2.1.

3.2.2 Infliximab

Of the six infliximab reports, one is a one-year extension (Lipsky et al., 2000), a second is a two-year extension (Lipsky et al., 2000 [abstract]) of the ATTRACT (Anti-Tumour Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy) trial. Table 3.2.2 summarises the appropriate patient characteristics.

Table 3.2.2. Characteristics of randomised controlled trials for infliximab. Abbreviations: DB, double blind; SB, single blind; OL, open label; IMAB, infliximab; MTX, methotrexate; N SAIDs, non-steroidal anti-inflammatory drugs; DMARD, disease modifying anti-rheumatic drugs; F, female; N, number of patients. * Values are median for Maini 1998. Inflixmab and placebo infusions were given at: *0, 2, 6, 10 and 14 weeks; ϕ 0, 2 & 6 weeks.

Study	Type of Study	Duration	Intervention and dose	N	Mean Age (Yrs)	F (%)	Mean duration RA (Yrs)	No. of previous DMARD (mean)*	Concomitant use (%)	
									NSAIDS	Steroids
Elliot 1994	DB, Phase II	4 weeks	IMAB 10 mg/kg (single infusion)	25	56	80	7.5	2.8	-	-
			IMAB 10mg/kg (single infusion)	24	51	83	-	3.1	-	-
			Placebo (Single infusion)	24	48	71	-	3.7	-	-
Maini 1998*	DB, Phase II	14 weeks	IMAB 1 mg/kg	15	49	73	7.6	3	-	67
			IMAB 1 mg/kg + MTX 7.5 mg/wk	14	54	71	14.3	2	-	43
			IMAB 3 mg/kg	14	47	86	7.8	2.5	-	50
			IMAB 3 mg/kg + MTX 7.5 mg/wk	15	59	67	12.1	2	-	60
			IMAB 10 mg/kg	15	56	67	9.7	2	-	60
			IMAB 10 mg/kg + MTX 7.5 mg/wk	14	50	79	11.1	2	-	29
			Placebo + MTX 7.5 mg/wk	14	49	71	7.6	2	-	50
ATTRACT Study ϕ (Maini 1999; Lipsky 2000; Lipsky 2000 [abstract])	DB, Phase III	6-24 months	IMAB 3mg/kg every 8 weeks + MTX 15 mg/wk	86	56	81	10	2.8	79	63
			IMAB 3mg/kg every 4 weeks + MTX 15 mg/wk	86	51	77	9	2.6	76	53
			IMAB 10mg/kg every 8 weeks + MTX 15 mg/wk	87	55	77	11	2.5	77	57
			IMAB 10mg/kg every 4 weeks + MTX 15 mg/wk	81	52	73	12	2.5	68	65
			Placebo + MTX 15 mg/ wk	88	51	80	11	2.5	72	64
Kavanaugh 2000	SB-OL	12 wks (SB) – 40 wks (OL)	IMAB 5mg/kg (single infusion) + MTX 10 mg/wk	7	47	71	7.4	-	7 patients	5 patients
			IMAB 10mg/kg (single infusion) + MTX 10 mg/wk	7	53	86	7.5	-	6	5
			IMAB 20mg/kg (single infusion) + MTX 10 mg/wk	7	37	100	4.9	-	5	6
			Placebo (single infusion) + MTX 10 mg/wk	7	44.6	86	4.9	-	4	2

3.2.3 Leflunomide

The combined search strategies identified nine publications that met the inclusion criteria. The publications; Strand (1999), Smolen (1999), Emery (2000), Mladnovic (1995) and Kremer (2002) are independent trials. The other four publications were reports of one of these trials (Figure 3.2.3). Strand 1999 (a), was a subgroup analysis of quality of life measures of Strand (1999). Cohen (2000) and Scott (2001) are 24-month extensions of Strand (1999) and Smolen (1999), respectively. Sharp (2000), included radiographic outcome data, some of which was not reported in Strand (1999), Smolen (1999) or Emery (2000). A summary of the patients' characteristics of all trials is shown in Table 3.2.3.

Figure 3.2.3. Randomised controlled trials of leflunomide and trial inter-linkage.

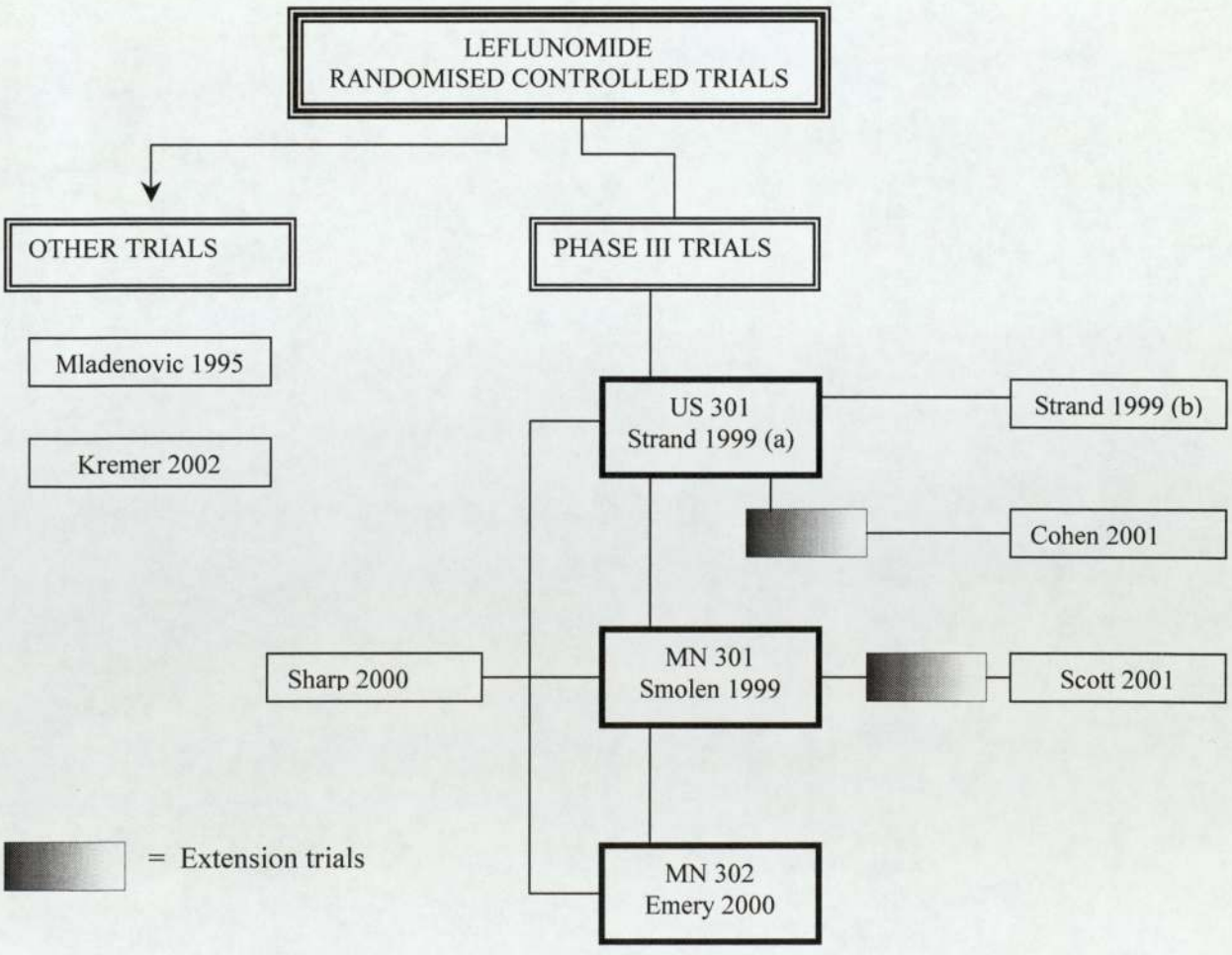


Table 3.2.3. Characteristics of randomised controlled trials for leflunomide. Abbreviations: LEF, Leflunomide; PL, placebo; SSZ, Sulfasalazine; PL-SSZ, placebo group switch to sulphasalazine; DB, double-blind; n, number of patients in each treatment group; RA, rheumatoid arthritis; DMARD, disease-modifying anti-rheumatic drug; NSAIDs, non- steroidal anti-inflammatory drugs; DE, dose escalation. *100mg/d for the first three days, **100mg/d for the first 2 days. ϕ See also Appendix 2.

Study	Type of Study	Months	Drug	Dose of Specified drug ϕ	No. of patients	Mean Age (Y)	Female (%)	Mean duration RA (Y)	No prior DMARD (%)	Concomitant use (%)	
										NSAIDS	Steroids
Mladenovic 1995	DB	6	LEF	5, 10, 25 mg/d	402	51.0	83.1	8.3	-	95	35
			PL	-	102	52.8	75.4	8.3	-	95	37
Smolen 1999	DB	6	LEF	20 mg/d*	133	58.3	76	7.6	40	85	29
			PL	-	92	58.8	75	5.7	53	83	25
			SSZ	0.5 – 2.0 g/d	133	58.9	69	7.4	51	82	28
Strand 1999	DB	12	LEF	20 mg/day*	182	54.1	72.5	7	44.5	75.2	53.8
			PL	-	118	54.6	70.3	6.9	39.8	65.2	55.1
			MTX	7.5 – 15 mg/wk	182	53.3	75.3	6.5	44	69.7	52.7
Emery 2000	DB	12	LEF	20 mg/day*	501	58.3	70.7	3.7	-	80	36.3
			MTX	7.5 – 15 mg/wk	498	57.8	71.3	3.8	-	84.7	33.5
		24	LEF	20 mg/day*	292	57.7	71.2	3.5	-	37.3	14
			MTX	7.5 – 15 mg/wk	320	57	71.3	3.8	-	42.3	11.3
Cohen 2001	DB	12	LEF	20 mg/day*	190	54	73	6.9	44	-	-
			MTX	7.5 – 20 mg/wk	190	53	74	6.5	44	-	-
		24	LEF	20 mg/day*	98	55	69	5.9	45	-	-
			MTX	7.5 – 20 mg/wk	101	53	68	6.7	46	-	-
Scott 2001	DB	6	LEF	20 mg/day*	133	58	76	8	40	84	34
			PL	-	92	59	75	6	53	85	33
			SSZ	0.5, 2 g/d	133	59	69	7	51	74	32
		12	LEF	20 mg/day*	80	58	75	6	39	83	44
			PL-SSZ	2 g/d (DE)	41	59	76	6	51	81	46
			SSZ	0.5 – 2.0 g/d	76	59	66	7	51	72	47
		24	LEF	20 mg/day*	60	58	82	7	40	80	50
			PL-SSZ	2 g/d (DE)	26	59	73	5	50	85	52
			SSZ	0.5 – 2.0 g/d	60	59	68	6	53	78	46
Kremer 2002	DB	6	LEF + MTX	10-20mg/d**+ 10-20mg/wk	130	55.6	76.2	10.5	-	65.4	59.2
			PL + MTX	10 – 20mg/wk	133	56.6	80.5	12.7	-	72.9	64.7

3.3 THE EFFICACY OF ETANERCEPT, INFLIXIMAB & LEFLUNOMIDE IN THE TREATMENT OF RA

The focal end point in all trials was the proportion of patients responding as defined by the ACR 20 criteria; ACR 50 and 70 responses have also been tabulated. Radiographic data, HAQ scores, adverse events and study withdrawals are also shown (see Appendix 5 for other outcomes studied in each trial).

3.3.1 Etanercept versus placebo

Moreland and colleagues (1997), first evaluated etanercept as a single agent in a 3 month, double-blind, randomised, placebo-controlled trial involving 180 patients with DMARD failure and active RA. Twice-weekly etanercept produced dose-related falls in ACR 20 and 50 responses at 3 months (Table 3.3.1). The 16 mg/m² (per square meter of body surface) (equivalent to 25 mg) dose resulted in 75% of patients achieving an ACR20 response compared with 14% of the placebo group. The continued benefit of etanercept with longer-duration therapy was confirmed in the phase III trial in which Moreland conducted a six-month trial on 234 patients with active RA (Moreland et al., 1999). In this study, participants receiving 25 mg etanercept twice-weekly had achieved higher ACR20 (59%) and ACR50 (40%) responses by 3 months than with etanercept 10mg (51% and 24%) or placebo (23% and 8%), again indicating a dose response relationship. Most patients obtained clinical benefits as early as the first month of therapy. By the end of therapy disease activity had fallen almost to baseline values. In both monotherapy studies, the extent of improvement in HAQ was significantly better in the etanercept groups.

Table 3.3.1. Proportion of patients showing different ACR responses and numbers withdrawn due to adverse events or lack of efficacy when treated with etanercept. Abbreviations: ADR, adverse drug reaction; LOE, lack of efficacy; ITT, intention to treat.

Duration	Study	Intervention/dose	ITT	ACR response (% patients)			Patients withdrawn (n)	
				ACR 20	ACR 50	ACR 70	ADR	LOE
3 months	Moreland 1997	Etanercept (all doses)	136	-	-	-	1	27
		Etanercept 0.25 mg/m2	46	33	9	-		17
		Etanercept 2 mg/m2	46	46	22	-		8
		Etanercept 16 mg/m2	44	75	57	-		2
		Placebo twice weekly	44	14	7	-		19
	The European Etanercept Investigators Group (Data obtained from Nice report 2002)	Etanercept 10 mg/wk	122	47	22	4	-	-
		Etanercept 10 mg twice weekly	110	63	28	9	-	-
		Etanercept 25 mg/ wk	111	59	26	10	-	-
		Etanercept 25 mg twice weekly	111	70	34	13	-	-
		Placebo twice a week	105	12	5	1	-	-
6 months	Moreland 1999	Etanercept 10 mg twice weekly	76	51	24	9	5	16
		Etanercept 25 mg twice weekly	78	59	40	15	2	12
		Placebo twice weekly	80	11	5	1	3	42
	Weinblatt 1999	Etanercept 25 mg twice weekly +MTX	59	71	39	15	0	0
		Placebo + MTX	30	27	3	0	0	4
12 months	Etanercept ERA Trial (Bathon 2000)	Etanercept 10 mg twice weekly	208	62	32	16	9	15
		Etanercept 25mg twice weekly	207	72	49	25	10	10
		MTX	217	65	43	22	22	8
24 months	Etanercept ERA Trial (Genovese 2002)	Etanercept 10 mg twice weekly	166	61	35	19	2	18
		Etanercept 20 mg twice weekly	177	72	49	30	5	6
		MTX	169	59	42	24	5	15

In Moreland (1997) HAQ scores were reduced by 23 to 49 % in patients receiving etanercept (16 mg/m² or 25 mg twice weekly) and by 2 to 26 % in patients receiving placebo.

3.3.2 Etanercept in combination with methotrexate versus methotrexate

Evaluated in combination with methotrexate (Weinblatt et al., 1999), fifty-nine adults with active RA and receiving methotrexate (mean dose of 18mg/week) were randomised to 25mg of etanercept twice weekly. At 6 months, 71% of patients receiving etanercept compared with 27% receiving placebo, achieved an ACR20 response, and 39% of etanercept-treated patients achieved an ACR50 response (Table 3.3.1). No patient in the etanercept group withdrew because of lack of efficacy or an adverse drug reaction while four patients withdrew due to lack of efficacy in the placebo group. The study indicates that the use of etanercept in patients with active RA receiving methotrexate provides additional benefit.

3.3.3 Etanercept in early disease and radiological efficacy.

Etanercept produced a more rapid improvement in both disease activity and a slowing of joint damage than methotrexate in patients with early active RA at 12 months (Bathon et al., 2000) (Table 3.3.2). The benefit of etanercept was also sustained in the non-blind extension study (Genovese et al., 2002). Patients had RA less than three years and were methotrexate naïve. The ACR response was more rapid with 25 mg etanercept than with methotrexate at several time points up to 4 months. At 12 months, 72% patients assigned to 25mg etanercept had an ACR 20 response. This response was also achieved in 61% patients in the 10mg etanercept group and 65% of patients in the methotrexate group, indicating that at the lower 10 mg etanercept dose,

any difference in efficacy relative to methotrexate was less pronounced. Patients on etanercept showed continued response for up to 24 months, while this was lost in some patients treated with methotrexate (Genovese et al., 2002).

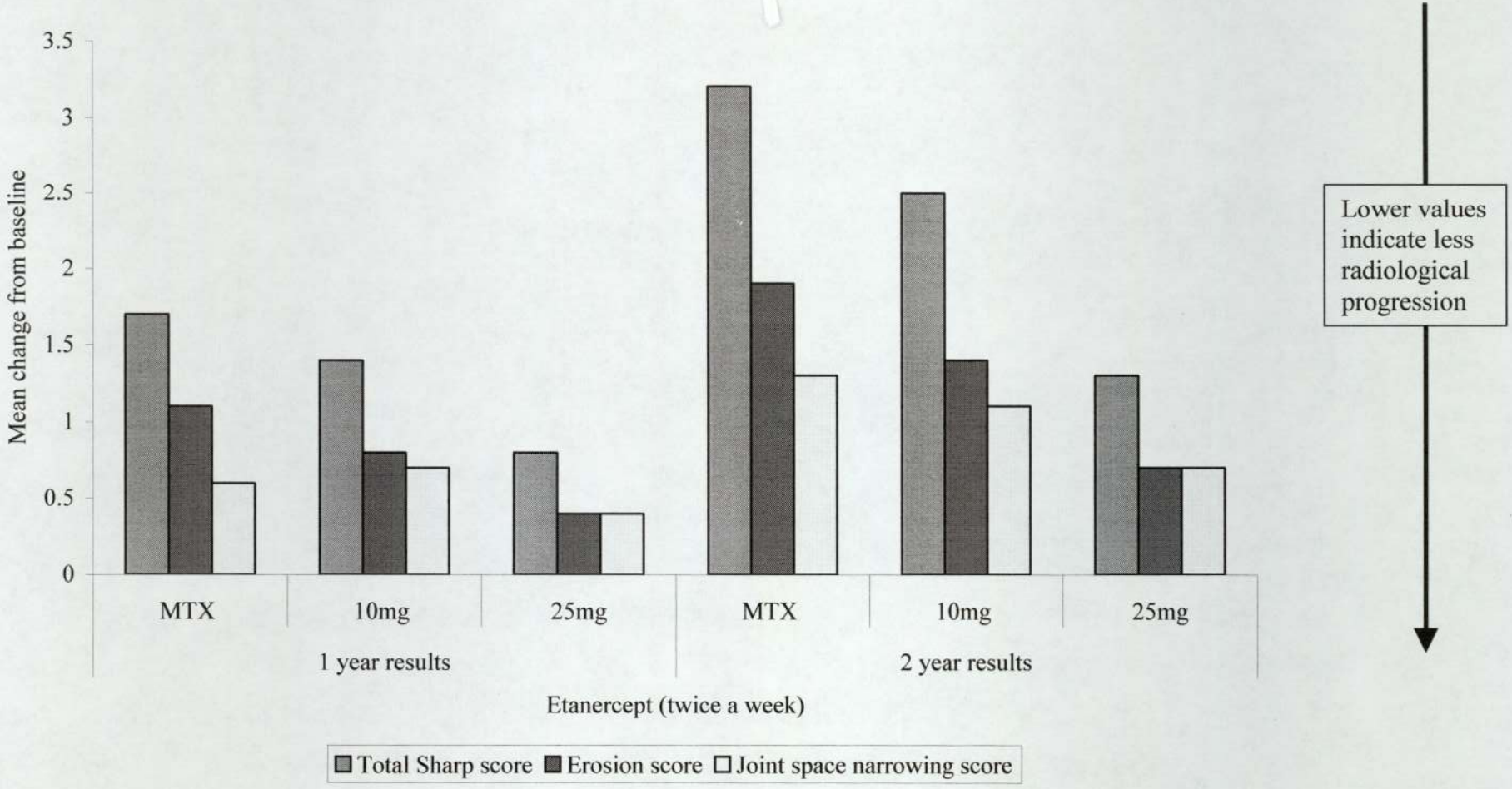
Evidence of radiographic progression, on the basis of Sharp scores was generally less prevalent among the group assigned to 25mg etanercept than in the methotrexate group (Figure 3.3.1 and Table 3.3.2). At 12 months no increase in erosion score was seen in 72% of patients receiving 25mg etanercept, compared with 60% of patients in the methotrexate group. Differences in joint space narrowing scores and total Sharp scores at 12 months were not major. However at 2 years total Sharp score changes were more significant, and mean changes from baseline were 1.3 units in the 25-mg group versus 3.2 units in the MTX group. Mean changes in erosion scores were 0.7 and 1.9 units for the 25-mg etanercept and methotrexate groups, respectively. The changes in joint space narrowing were less significant, with 78% patients on 25-mg etanercept experiencing no increase in joint space narrowing, compared to 69% in the methotrexate group.

Table 3.3.2. Radiological outcomes in patients receiving etanercept. Abbreviations: ET, etanercept; MTX, Methotrexate.

Study	Duration	Drug/ (no. of patients that followed up radiographs)	Total score		Erosion		Joint space narrowing		Improvement * (% patients)	No Progression # (% patients)
			Baseline	Mean change from Baseline	Baseline	Mean change from Baseline	Baseline	Mean change from Baseline		
Bathon 2000, Etanercept ERA trial	1 year	ET 10mg/ twice weekly (208)	11.2	1.4	6.1	0.8	5.0	0.7	21	62
		ET 25mg/twice weekly (207)	12.4	0.8	6.4	0.4	6.0	0.4	21	62
		MTX (217)	12.9	1.7	7.5	1.1	5.4	0.6	18	56
Genovese 2002, Etanercept ERA Trial	2 year	ET 10mg/ twice weekly (208)	11.2	2.5	6.1	1.4	5.0	1.1	21	53
		ET 25mg/twice weekly (207)	12.4	1.3	6.4	0.7	6.0	0.7	21	63
		MTX (217)	12.9	3.2	7.5	1.9	5.4	1.3	18	51

The Etanercept ERA trial used the modified Sharp method (Sharp et al., 1985) (see Appendix 4).
* Improvement in total radiological scores.
# These are figures for the sharp score: No progression is defined as a change of < 0.5 units.

Fig 3.3.1. Radiological outcomes in patients receiving etanercept in the ERA trial for 1 and 2 years. (Bathon et al., 2000; Genovese et a[illegible], 2002)



3.3.4 Infliximab versus placebo

Elliot and colleagues (1994) randomly allocated 73 active RA sufferers to a single infusion of placebo, 1 mg/kg or 10 mg/kg of infliximab. After 4 weeks 89% of patients in the 10 mg/kg group showed at least 20% improvement, measured by the Paulus criteria (Appendix 3). However along with this sustained response, some patients also developed serum antibodies to infliximab (see section 3.4)

3.3.5 Infliximab in combination with methotrexate

Multiple infliximab administration was investigated in subsequent phase II and III clinical trials. In the phase II trial patients were taking methotrexate (7.5-15 mg per week) for at least 6 months prior to study entry. Serial infusions of infliximab (1, 3 or 10 mg/kg at weeks 0, 2, 6, 10 and 14) with or without concomitant low dose methotrexate or intravenous placebo (plus methotrexate) were randomly assigned to 101 patients. Compared to placebo, patients receiving infliximab showed significantly better improvement as measured by the Paulus 20 response (60% Vs 15%). Adding methotrexate produced a higher rate and duration of treatment response than without any methotrexate. This study indicated that the 3 mg/kg and 10 mg/kg were potentially effective doses, and that infliximab treatment would be more effective if coadministered with methotrexate. Based on this finding the ATTRACT trial was conducted, with the aim of investigating the efficacy of these two doses (given after 4 or 8 week intervals) and their potential in slowing down radiographically measurable erosion in patients not responding sufficiently to methotrexate (Table 3.3.3, Table 3.3.4 and Figure 3.3.2). The addition of methotrexate to infliximab was also supported by another 12-week phase II trial that only evaluated 24 patients (Kavanaugh et al., 2000). Here patients were given a single infusion of infliximab (5,

10, or 20 mg/kg) or placebo in addition to weekly methotrexate. Again, clinical improvement was evident in the infliximab treated patients (Table 3.3.3).

In ATTRACT the primary endpoint, ACR 20 (Table 3.3.3), reached 50%-60% (vs. 20% of placebo treated patients) by the 30-week endpoint. Significantly better ACR50 responses (26-31% vs. 5%) and ACR70 responses (8-18% vs. 0%) were obtained in infliximab-treated than placebo-treated patients. ACR responses were generally sustained for one year. However, at week 54, ACR 50 response rate for the 3 mg/kg every eight-week group was only 21%. While this proportion is greater than that seen in the placebo group (8%), this lower dose showed smaller effects compared to the higher infliximab doses, 3mg/kg every 4 weeks, 10mgkg given every 8 and 4 weeks (ACR50 response rates at 34%, 39% and 38%, respectively).

Table 3.3.3. Proportion of patients showing different ACR responses and numbers withdrawn due to adverse events or lack of efficacy when treated with infliximab. Abbreviations: ADR, adverse drug reaction; LOE, lack of efficacy; ITT, intention to treat.

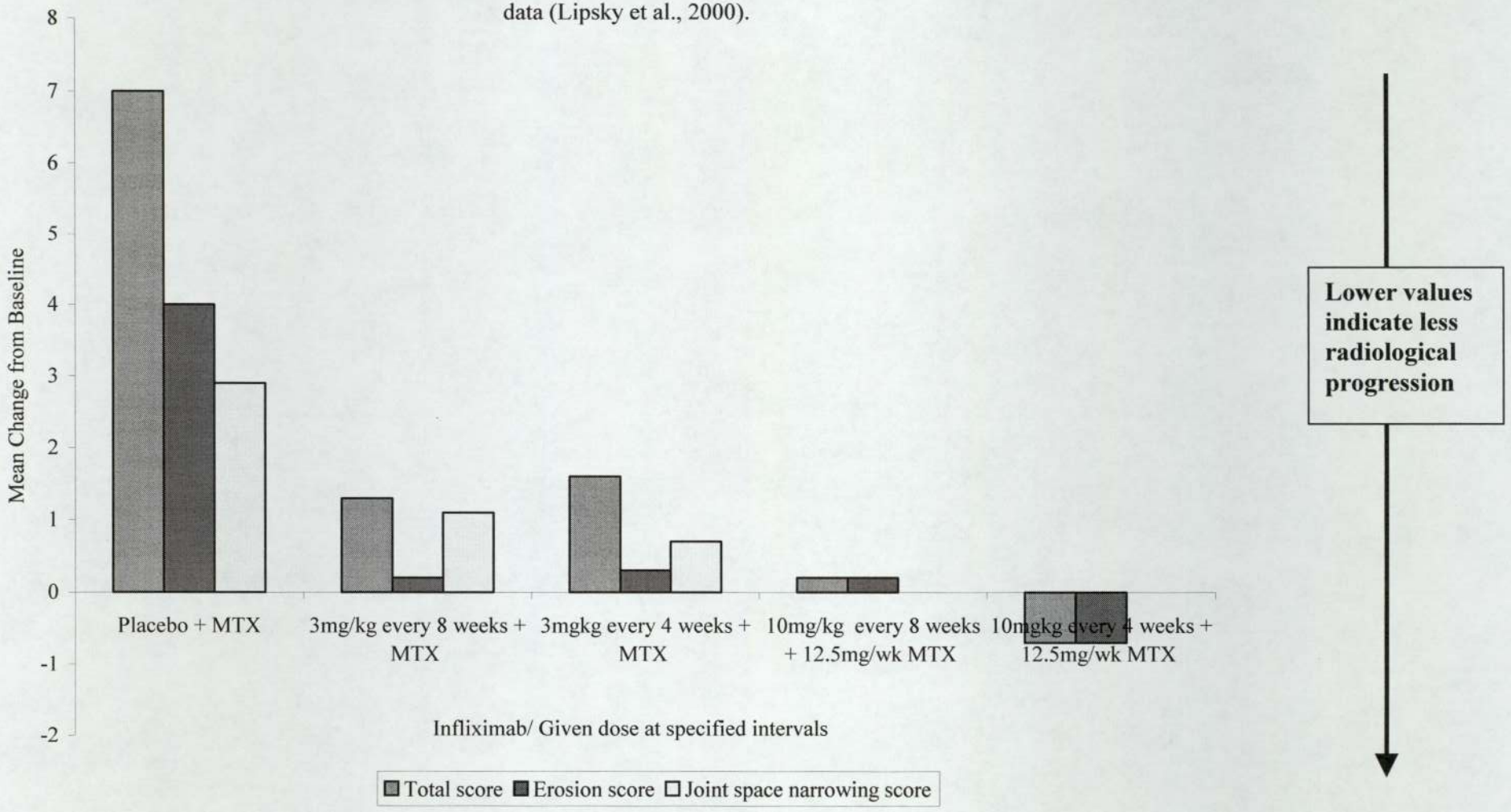
Duration	Study	Intervention	ITT	ACR respondents (% patients)			Patients withdrawn (%)	
				ACR 20	ACR 50	ACR 70	LOF	ADR
12 weeks	Kavanaugh 2000	Infliximab 5mg/kg + MTX 10 mg/wk	7	43	29	-	-	-
		Infliximab 10mg/kg + MTX 10 mg/wk	7	57	14	-	-	-
		Infliximab 20mg/kg + MTX 10 mg/wk	7	57	43	-	-	-
		Inflixmab + MTX all doses	21	52	29	-	-	-
		Placebo + MTX 10 mg/wk	7	14	14	-	-	-
30 weeks data	ATTRACT (Maini 1999)	IMAB 3mg/kg every 8 weeks + MTX 15mg/wk	86	51	27	8	-	-
		IMAB 3mg/kg every 4 weeks + MTX 15 mg/wk	86	53	29	11	-	-
		IMAB 10mg/kg every 8 weeks + MTX 15mg/wk	87	52	31	18	-	-
		IMAB 10mg/kg every 4 weeks + MTX 15mg/wk	81	58	26	11	-	-
		Placebo + MTX 15 mg/ wk	88	20	5	0	-	-
1 year data	ATTRACT (Lipsky 2000)	IMAB 3mg/kg every 8 weeks + MTX 15mg/wk	86	42	21	10	20	6
		IMAB 3mg/kg every 4 weeks + MTX 15mg/wk	86	48	34	17	12	10
		IMAB 10mg/kg every 8 weeks + MTX 15mg/wk	87	59	39	25	7	5
		IMAB 10mg/kg every 4 weeks + MTX 15mg/wk	81	59	38	19	9	10
		Placebo + MTX 15mg/wk	88	17	8	2	36	8

Table 3.3.4. Radiological outcomes in patients treated with Infliximab. Abbreviations: ET, etanercept; MTX, Methotrexate.

Study	Duration	Drug/ (no. of patients that followed up radiographs)	Total score		Mean change from Baseline		Improve-ment * (% patients)	Major progression (%)**
			Base-line	Mean change from Baseline	Erosion	Joint space narrowing		
Lipsky 2000, ATTRACT Study	1 year	IMAB 3mg/kg every 8 weeks + MTX (71)	79	1.3	0.2	1.1	44	8
		IMAB 3mg/kg every 4 weeks + MTX (71)	71	1.6	0.3	0.7	48	13
		IMAB 10mg/kg every 8 weeks + MTX (77)	67	0.2	0.2	0	39	1
		IMAB 10mg/kg every 4 weeks + MTX (66)	76	-0.7	-0.7	0	55	0
		Placebo + MTX (64)	82	7	4	2.9	14	31

The ATTRACT trial used the van der Heijde modification of the Sharp scoring system (van der Heijde et al., 1992) (see Appendix 4)
* improvement in total radiological scores
** Major progression was defined as patients with changes from baseline that exceed the 95% confidence intervals of the mean of the scores of the two readers (Lassere et al., 1999)

Fig. 3.3.2. Radiological outcomes in patients treated with infliximab in the ATTRACT trial, 54 week data (Lipsky et al., 2000).



The ATTRACT was extended from 54 to 102 weeks (Lipsky et al., 2000 [abstract]). However, some patients had several months gap in experimental treatment, and not all patients completed the study under blinding. At week 102 ACR responses (not tabulated) were slightly lowered (40.7% and 39.5% for infliximab 3 mg/kg given at weeks 8 and 4, respectively; 48.3% and 42% for infliximab 10 mg/kg given at weeks 8 and 4, respectively and 15.9% for placebo). By week 54, 15-27% of patients treated with infliximab had discontinued therapy, lack of efficacy accounted for most of these discontinuations. In the placebo group, 36 patients discontinued treatment due to lack of efficacy.

The combination of infliximab had a greater effect on functional disability, as assessed by the HAQ, than did treatment with methotrexate alone (Table 3.3.5).

Table 3.3.5. Improvement in HAQ scores over two years in ATTRACT. Score ranged from 0 (no difficulty) to 3 (unable to perform the activity) (See Appendix 5). Abbreviations; IMAB, infliximab; MTX, methotrexate.

Treatment group	HAQ score (% mean improvement)			
	Baseline	**30 weeks**	**1 year**	**2 years**
IMAB 3mg/kg every 8 weeks + 15mg/wk + MTX	1.8	0.2 (12)	0.3 (17)	0.4 (17)
IMAB 3mg/kg every 4 weeks + 15 mg/wk + MTX	1.7	0.5 (29)	0.4 (28)	0.5 (29)
IMAB 10mg/kg every 8 weeks + 15mg/wk + MTX	1.7	0.4 (28)	0.5 (33)	0.5 (29)
IMAB 10mg/kg every 4 weeks + 15mg/wk + MTX	1.7	0.5 (31)	0.5 (32)	0.4 (24)
Placebo + 15 mg/ wk + MTX	1.7	0.2 (10)	0.2 (11)	0.2 (12)

Out of the total 428 patients, 346 completed 30 weeks and 313 patients completed the 54 weeks. Table 3.3.6 shows the number of patients in each treatment group completing the trial.

Table 3.3.6. The number of patients completing 30 and 54 weeks of treatment in ATTRACT

Treatment group	Patients undergone randomisation	Patients completing 30 weeks of treatment	Patients competing 54 weeks of treatment
IMAB 3mg/kg every 8 weeks + 15mg/wk + MTX	86	70	63
IMAB 3mg/kg every 4 weeks + 15 mg/wk + MTX	86	75	66
IMAB 10mg/kg every 8 weeks + 15mg/wk + MTX	87	79	75
IMAB 10mg/kg every 4 weeks + 15mg/wk + MTX	81	69	65
Placebo + 15 mg/ wk + MTX	88	53	44

3.3.6 Infliximab: radiological efficacy

Joint damage was determined by the van der Heijde modification of the Sharp score (Appendix 4). Bone erosions and joint space narrowing were analysed in 44 and 40 joints, respectively. Total scores range from 0-440, with higher score denoting greater damage. At baseline the scores across treatment groups were 67-82 (Table 3.3.4), and indicated moderately severe joint damage. The mean changes from baseline (Figure 3.3.2) show significant improvements for the erosion and joint space narrowing components of the score. More patients in the infliximab groups showed improvement in radiologic retardation than in the placebo group. In a subgroup

analysis, infliximab treatment arms seemed to decrease radiologically visible progression of joint damage for both ACR20 responders and non-responders.

3.3.7 Leflunomide: dose-response

The safety and effectiveness of leflunomide compared to placebo was assessed in 402 patients with active RA (Mladenovich et al., 1995). Patients were allocated to four treatment groups (Table 3.3.7). Only participants in the 10 mg to 25 mg groups had a significant improvement in ACR20 response compared to placebo. Patients in the 5 mg group responded similarly to placebo-treated patients.

3.3.8 Leflunomide versus methotrexate

Two Phase III trials that compared leflunomide with methotrexate were US301 (Strand et al., 1999; Strand et al., 1999a; Cohen et al., 1999) and MN302 (Emery et al., 2000). Leflunomide has also been used in combination with methotrexate compared to methotrexate alone in a more recent trial by Kremer and colleagues (2002) (Table 3.3.7).

In the US 301 trial Strand and colleagues also compared leflunomide with placebo (Table 3.3.7). In comparison with placebo more patients in the leflunomide and methotrexate groups showed ACR20 responses at week 52 (26 vs. 52 and 46, respectively). Onset of effect occurred at a mean of 8.6 weeks for patients receiving leflunomide and 9.5 weeks for those in the methotrexate group. Due to poor treatment response in more than half of the methotrexate users, doses of methotrexate increased from 7.5 mg/week to 15mg (109 patients).

Table 3.3.7. Proportion of patients showing different ACR responses and numbers withdrawn due to adverse events or lack of efficacy when treated with leflunomide. Abbreviations, ACR, American college of Rheumatology; LEF, leflunomide; MTX, methotrexate; ITT, intention to treat; ADR, adverse drug reaction; LOE, lack of efficacy.

Duration	Study	Intervention / dose	ITT	ACR response (% patients)			Patients Withdrawn (%)	
				ACR 20	ACR 50	ACR 70	ADR	LOE
6 months	Kremer 2002	LEF 10 or 20mg/d + MTX 10 - 20mg/wk	130	46	26	10	12	7
		Placebo + MTX 10 – 20mg/wk	133	20	6	2.3	7	11
	Mladenovic 1995	Leflunomide 5 mg/d	95	32	-	-	3	3
		Leflunomide 10 mg/d	101	51	-	-	7	2
		Leflunomide 25 mg/d	104	58	-	-	11	2
		Placebo	102	30	-	-	2	10
	Smolen 1999 MN301	Leflunomide 20mg/d	133	55	24	-	14	8
		Placebo	92	29	-	-	5	31
		Sulfasalazine 0.5 - 2.0 g/d	133	56	24	-	19	11
12 months	Emery 2000 MN302	Leflunomide 20 mg/d	501	51	-	-	19	7
		Methotrexate 7.5, 10 or15 mg/wk	498	65	-	-	15	3
	Scott 2001 MN301	Leflunomide 20mg/d	80	67	42	17	3	5
		Placebo switch to sulfasalazine 2.0 g/d	41	-	-	-	7	5
		Sulfasalazine 2.0 g/d	76	69	39	19	22	3
	Strand 1999 US301	Leflunomide 20mg/d	182	52	34	20	22	17
		Placebo	118	26	8	4	9	53
		Methotrexate 7.5 mg/wk	182	46	23	9	10	24
24 months	Cohen 2001 US 301	Leflunomide 20mg/d	190	53	34	17	27	-
		Placebo	128	26	-	-	9	-
		Methotrexate 7.5 mg/wk	190	48	28	12	17	-
	Scott 2001 MN301	Leflunomide 20 mg/d	60	82	52	25	10	2
		Placebo switch to sulfasalazine 2.0 g/d	26	-	-	-	4	12
		Sulfasalazine 2.0 g/d	60	60	25	17	15	5

ACR success rates were not significantly different for patients receiving 15 mg/week compared to those receiving 7.5 mg/week (34% vs 37%). ACR 20 responses were maintained in the 24-month extension (Cohen et al., 2001), where 53% achieved it in the leflunomide group and 48% in the methotrexate group. Withdrawals caused by lack of efficacy occurred much more frequently in the placebo group. In contrast, the response with methotrexate (65%) in MN302 was statistically higher than with leflunomide (51%) during the first year of treatment. This distinction was less apparent at 2 years (see Table 3.3.7). In both trials leflunomide produced significant improvement in the HAQ score, and the drug was superior to both placebo and methotrexate in US 301 (Table 3.3.8).

The results of radiographic assessments for both studies, carried out by Sharp and colleagues (2000), are shown in Table 3.3.9 and Figure 3.3.3. Radiographs for the MN 302 trial were also evaluated using the Larsen method, however results of this method have not been presented. Strand and colleagues obtained radiographs for 352 (of 482) patients for the first year. From total Sharp scores the estimated yearly progression was 3.30, 3.68 and 3.50 for leflunomide, placebo and methotrexate respectively. The mean changes indicate a higher degree of disease progression in the placebo treated patients. Although patients receiving methotrexate showed significantly less disease progression, patients on leflunomide reported better results. Twenty-four month radiographs were analysed for only 137 patients. While both leflunomide and methotrexate continued to produce retardation of disease progression, the effect of methotrexate seemed higher.

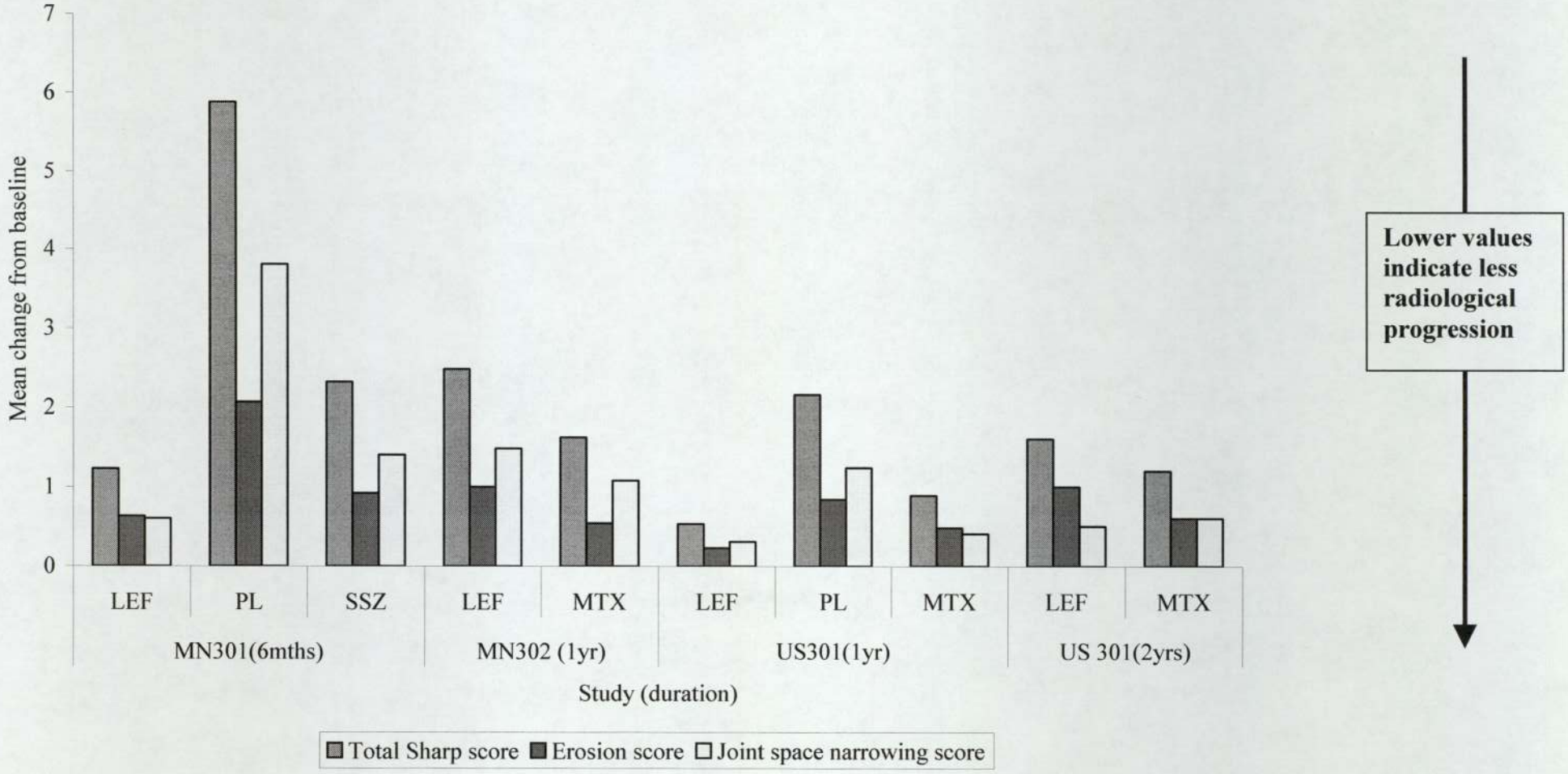
Table 3.3.8. HAQ scores for leflunomide treated patients.

Study	Duration	Drug/Dose	ITT	HAQ Score	
				Baseline	Change from baseline
Mladenovich 1995	6 months	Leflunomide 5mg/d	95	-	-5.8
		Leflunomide 10mg/d	100	-	-14.5
		Leflunomide 25mg/d	101	-	-13.6
		Placebo	102	-	-8.1
Smolen 1999 (MN301)	6 months	Leflunomide 20 mg/d	130	1.1	-0.5
		Sulfasalazine (0.5 - 2.0 g/d)	132	1	-0.29
		Placebo	91	1.1	-0.04
Kremer 2002	6 months	Leflunomide (10 or 20 mg/d) + Methotrexate (10 - 20 mg/wk)	130	1.6	-0.4
		Placebo + Methotrexate (10 - 20 mg/wk)	133	1.5	-0.1
Strand 1999 (US 301)	12 months	Leflunomide 20 mg/d	182	1.3	-0.45
		Methotrexate (7.5 - 15 mg/wk)	182	1.3	-0.26
		Placebo	118	1.3	0
Emery 2000 (MN 302)	12 months	Leflunomide 20 mg/d	501	-	-0.38
		Methotrexate (7.5-15 mg/wk)	498	-	-0.48
*Scott 2001 (MN 301)	12 months	Leflunomide 20 mg/d	130	1.1	-0.58
		Sulfasalazine (2.0 g/d)	132	1	-0.41
		Placebo switch to Sulfasalazine (2.0 g/d)	91	1	-0.29
Cohen 2001 (US 301)	24 months	Leflunomide 20 mg/d	190	1.2	-0.6
		Methotrexate (7.5 - 20 mg/wk)	190	1.2	0.37
*Scott 2001 (MN 301)	24 months	Leflunomide 20 mg/d	130	1.1	-0.65
		Sulfasalazine (2.0 g/d)	132	1	-0.36
		Placebo switch to Sulfasalazine (2.0 g/d)	91	0.8	-0.2

Table 3.3.9. Radiological outcomes in patients treated with leflunomide.

Study/ code	Duration	Drug (no. of patients that followed up radiographs)	Mean disease duration	Total sharp score		Erosion score		Joint space narrowing	
				Baseline	Mean change	Baseline	Mean change	Baseline	Mean change
Smolen 1999-MN301	6 months	Leflunomide (87)	7.6	46.26	1.23	-	0.63	-	0.60
		Placebo (59)	5.7	46.18	5.88	-	2.07	-	3.81
		Sulfasalazine (84)	7.4	46.18	2.32	-	0.92	-	1.40
Emery 2000-MN302	12 months	Leflunomide (302)	3.7	24.94	2.48	-	1.00	-	1.48
		Methotrexate (324)	3.8	24.60	1.62	-	0.54	-	1.08
Strand 1999-US301	12 months	Leflunomide (131)	7	23.11	0.53	-	0.23	-	0.31
		Placebo (82)	6.9	25.37	2.16	-	0.84	-	1.24
		Methotrexate (136)	6.5	22.76	0.89	-	0.48	-	0.41
Cohen., 2001-US301	24 months	Leflunomide (71)	6.9	23.8	1.6	10.3	1.0	13.5	0.5
		Methotrexate (66)	6.5	25.1	1.2	10.6	0.6	14.5	0.6

Figure 3.3.3. Radiological outcomes in patients treated with leflunomide in three phase III trials



The ability of methotrexate, compared to leflunomide, to diminish disease progression was also slightly higher in the MN302 trial. In general, both drugs produced the slowing of progression in radiographic scores.

Kremer and colleagues demonstrated that the addition of leflunomide to methotrexate produced a considerable improvement compared to placebo and methotrexate. In the leflunomide and placebo groups, 46% and 20% of patients met the ACR20 criteria at 6 months. Clinical improvement with this combination was also indicative from the HAQ score, where a 0.4 decrease was seen with leflunomide and methotrexate and a 0.1 decrease with methotrexate alone (Table 3.3.8).

3.3.9 Leflunomide versus Sulfasalazine

The efficacy and safety of leflunomide relative to sulfasalazine was assessed in 6 (Smolen et al., 1999), 12 and 24 (Scott et al., 2001) month cohorts (MN301). There was no significant difference between the two treatments, both of which showed improvement over placebo (Table 3.3.7). Onset of action with leflunomide was faster than with sulfasalazine based on most outcome measures. Improvements in ACR response continued up to 12 months. At 24 months ACR 20 responses for leflunomide were significantly greater than sulfasalazine (82 vs. 60%). Differences were even more significant with respect to ACR 50 responses (52% vs 25%). Furthermore, changes from baseline in HAQ scores were significantly greater at 6, 12 and 24 months with leflunomide. Radiographic progression was significantly less in patients treated over 24 weeks with either leflunomide or sulfasalazine than in patients on placebo. Total radiographic scores for both drugs were 1.23 and 2.32, respectively.

3.4 ADVERSE EVENTS

Common adverse events for all three drugs are shown in Tables 3.4.1, 3.4.2 and 3.4.2.

3.4.1 Etanercept

The adverse event most evident with etanercept is injection site reaction. Such reactions, i.e. erythma, itching, pain or swelling, tend to occur early in treatment and resolve with time. In most of the trials response to infection is very high, however the rate is similar to patients treated with placebo or methotrexate. Upper respiratory tract infection in the etanercept treated patients occurred more frequent in the Moreland 1997 (data not reported) and 1999 trials. Autoantibodies were detected in more patients receiving etanercept. During treatment ten patients (1 in the placebo and 9 in the etanercept groups) were positive for anti-double stranded DNA antibodies by radioimmunoassay in Moreland 1999. Similar patterns were also seen in the European trial (Ericson et al., 1999) and against methotrexate (Weinblatt 1999).

3.4.2 Infliximab

The most common adverse event experienced with infliximab was infection (particularly upper respiratory infection), some of which were serious and some requiring antibiotic treatment (see Table 3.4.2). In the ATTRACT trial 14-16 patients receiving infliximab, compared with nine treated with placebo developed an infusion reaction (defined as any adverse experience occurring during, or up to 1 hour after completion of, the infusion) at 30 weeks. Most infusion reactions were mild, the most common being nausea and headache. As a result of infusion reactions four patients (1.2%) developed urticaria, eight (2.3%) developed hypotension and two (0.6%)

developed dysponea at week 54. In the one year there were 3 deaths in the methotrexate (and placebo) treated patients and 5 in the groups given infliximab and methotrexate. During this trial, a significantly higher proportion of patients receiving the infliximab treatments developed antinuclear antibodies (65%) and antibodies against double stranded DNA (ds DNA) (10%). Antibodies to Ds DNA were also detected among patients in the infliximab groups (8%) in the earlier infliximab trial (Maini et al., 1998).

3.4.3 Leflunomide

The frequency of patients withdrawn during leflunomide treatment was slightly higher than patients on methotrexate (US301: Strand et al., 1999; Cohen et al., 2001) and notably higher for patients on placebo. In comparison to sulfasalazine, study withdrawals were slightly lower for leflunomide (Smolen et al., 1999; Scott et al., 2001). Diarrhoea, alopecia, nausea, allergy, headache and elevated plasma liver enzyme were commonly experienced leflunomide-related adverse reactions. Leflunomide-related hypertension has also been noted, but the incident is fairly low. Clinically significant elevation of plasma liver enzymes in all trials are classified as >2 times the upper limit of normal (ULN) of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (Table 3.4.4). Compared to methotrexate abnormal liver enzymes were more prevalent with leflunomide in US 301, in contrast, the incidence of elevations was significantly high in methotrexate treated patients in the MN 302 trial (Emery et al., 2000) (16% at 2 years).

Table 3.4.1. A summary of the common adverse events in randomised controlled trials of etanercept. * Rates were calculated per patient-year as many recipients discontinued treatment before 6 months. **Infections graded as severe, or requiring hospitalisation or antibiotics.

Adverse event		Study (duration)/ treatment groups / % patients							
		Moreland 1999 * (6 months)		Weinblatt 1999 (24 week trial)		European Etanercept Investigators group (3 month trial)		ERA trial 12 month data	
		Placebo (n=80)	Etanercept (n=154)	Placebo + MTX (n=30)	Etanercept + MTX (n=59)	Placebo (n=105)	Etanercept (n=454)	MTX (n=217)	Etanercept (n=415)
Injection site reaction		13	46	7	42	1	23	7	34
Infection	Any	-	-	63	51	34	30	72	64
	Medically Important**	-	-	-	-	2	1	3	1
Upper respiratory tract infection		6	31	-	-	27	23	39	31
Sinusitis		11	12	-	-	-	-	17	12
Diarrhoea		6	8	20	12	-	-	12	13
Nausea		-	-	23	10	-	-	29	15
Hypertension		-	-	0	7	3	4	-	-
Headache		-	-	17	20	-	-	27	24
Antinuclear antibodies		-	-	-	-	55	56	19	24
Antibodies to double stranded DNA		1	6	3	7	1	4	-	-
Malignancy		0	0	-	-	1	0.4	1	1

Table 3.4.2. A summary of the adverse events in the ATTRACT trial. Serious infections included *bacterial, bronchitis, cellulites, fungal infection, herpes zoster infection, peritonitis, pnemonia, pyelonephritis and urinary tract infection, sepsis and tuberculosis; ☆endophthalmitis, septicaemia . ** Patients who had a serum titre of at least 1:320 at any time during the trial were positive. *** Patients tested positive had both a positive immunofluorescence assay and a positive Farr assay at any time during the trial.

Adverse event	Trial/ Treatment groups (n)/ % patients					
	Maini 1998		ATTRACT trial: 30 weeks data/		ATTRACT trial: 54 weeks data	
	Infliximab groups (87)	Placebo + MTX group (14)	Infliximab groups (340)	Placebo + MTX (88)	Infliximab groups (340)	Placebo (88)
Upper respiratory infection	5		25	16	34	22
Infection needing antibiotic	32	21	32	21	44	35
Serious infection *	5☆	0☆	4	6	6*	8*
Headache	13	-	22	10	26	16
Sinusitis	-	-	9	15	17	6
Nausea	-	-	16	19	-	-
Diarrhoea	9	-	10	12	-	-
Hypertension	-	-	6	3	-	-
Rash	7	-	11	5	-	-
Malignancy	-	-	-	-	1.5 (5 patients)	0
Antinuclear antibodies**	-	-	-	-	65	26
Antibodies against double stranded DNA***	8	-	-	-	10	0

Table 3.4.3. A summary of the common adverse events in randomised controlled trials for leflunomide. * Enzymes including alanine aminotransferase and aspartate aminotransferase. ⅄ During second year of treatment. ♦ Recorded in > 10 patients per 100 patient years. ϕ In these trials elevated enzymes levels was not reported as an adverse event (see Table 3.4.4).

Adverse event	Study (duration)/ treatment groups (n)/ % patients																
	Mladenovic 1995 (6 months)		US 301						MN301					MN302 Emery 2000 (12 months)		Kremer 2002 (6 months)	
			Strand 1999 (12 months			Cohen 2001 24 months			Smolen 1999 (6 months)			Scott 2001 (12-24 months)					
	LEF (402)	PL (102)	LEF (182)	PL (118)	MTX (182)	LEF (190)	PL (128)	MTX (190)	LEF (133)	PL (92)	SSZ (133)	LEF (60)	SSZ (60)	LEF (501)	MTX (498)	LEF (130)	PL (133)
Total gastrointestinal symptoms	9	3	60	42	52	-	-	-	-	-	-	-	-	-	-	-	-
Diarrhoea	-	-	34	17	20	37	20	32	17	5	9	2	8	18	7	25	14
Infections	13	18	57	48	60	8	9	5	-	-	-	-	-	-	-	41	52
Respiratory infections	-	-	-	-	-	37	25	38	14	20	15	-	-	5	5	22	24
Nausea	-	-	21	19	19	18	19	21	10	7	17	0	7	11	16	16	11
Rash/Allergy	4	5	24	14	17	5	1	4	10	4	9	-	-	7	5	8	8
Alopecia	1	2	10	1	6	11	1	6	8	2	5	5	0	16	9	6	4
Headache	-	-	-	-	-	20	17	23	7	5	11	2	0	6	5	10	8
Hypertension	-	-	11	5	3	18	9	5	6	3	4	5	3	7⅄	3⅄	-	-
Elevated plasma liver enzyme levels*	8	6	15	3	12	13♦	4♦	10♦	ϕ	ϕ	ϕ	ϕ	ϕ	5⅄	16⅄	ϕ	ϕ

Table 3.4.4. Incidence of plasma liver enzyme elevations. Abbreviations; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; LEF, leflunomide; MTX, methotrexate; SSZ, sulfasalazine.

Enzyme	Trial							
	US301			MN301			Kremer 2002	
	LEF	PL	MTX	LEF	PL	SSZ	LEF+ MTX	PL + MTX
ALT level								
> 2 times ULN	11.0	2.5	9.3	2.3	1.1	6.0	-	-
>2 to ≤ 3 times ULN	6.6	0	6.6	-	-	-	6.2	1.5
> 3 times ULN	4.4	2.5	2.7	1.5	1.1	1.5	3.8	0.8
AST level								
> 2 times ULN	8.2	3.4	6.6	2.3	1.1	3.8	-	-
>2 to ≤ 3 times ULN	6.0	1.7	6.0	-	-	-	3.1	0
> 3 times ULN	2.2	1.7	0.5	1.5	0	3.8	1.5	0.8

3.5 CONCLUSION

Data from clinical trials involving TNFα inhibitors provide compelling evidence to support the pivotal role of TNFα in RA. As mono-therapy or in combination with methotrexate, both agents demonstrate a sustained improvement in the signs and symptoms of disease, as well as patients' quality of life. The overall safety of anti-TNF therapies is at least as good as that of any other anti-rheumatic drugs, their sole target is to remove excess TNFα and so hardly show any toxicity. Infection was largely associated with infliximab, whereas injection site reactions were mainly experienced with etanercept.

In terms of efficacy, radiological progression and quality of life leflunomide treatment was superior to placebo and comparable to methotrexate and sulfasalazine (Strand et al., 1999; Smolen et al., 1999; Emery et al., 2000; Scott et al., 2001; Cohen et al., 2001). The most common adverse events experienced with leflunomide include gastrointestinal problems, allergic reactions, alopecia, and elevated liver enzymes. The addition of leflunomide to methotrexate compared to methotrexate alone also showed significant improvements in efficacy, however, with this combination there is more concern about potential hepatotoxicity, since both drugs promote the elevation of liver enzymes.

CHAPTER 4

META-ANALYSIS

4.1 INTRODUCTION & OBJECTIVES

There is a reasonable need to compare ACR performances across different trials, the most appropriate technique that allows this is the systematic review, with or without pooling of data of different trials. The results in chapter 3 showed that clinical benefit for RA was apparent in all trials evaluating leflunomide, infliximab, and etanercept. This chapter has as objective to analyse the clinical response as measured by the ACR 20 criteria. To obtain a more precise estimate of treatment effect, pooling of the data was considered. Pooling was only justified if the original studies used the same study design as well as showing statistical homogeneity. The included studies were only homogenous with respect to the disease (RA), the drug (including a distinction between monotherapy or combination therapy), the outcome (ACR 20), and the duration of treatment. All analyses adopted an intention to treat approach.

Recently, both the Health Technology Assessment (HTA) programme (National Health Service, Research and Development) and the Cochrane Collaboration have carried out meta-analyses of the newer anti-rheumatic agents. The HTA report looks at the effectiveness of infliximab and etanercept in the treatment of RA (Jobanputra et al., 2002). Those investigators assumed homogeneity if disease (RA) and drug used (irrespective of whether the drug is given as mono-therapy or given in combination) were the same. The Cochrane reviewers undertook two separate meta-analyses on leflunomide and infliximab, and included assessments of both efficacy and safety

(Osiri et al., 2003; Blumenauer et al., 2003). Analyses in these two reports were not performed on the ITT populations.

4.2 RESULTS & DISCUSSION

4.2.1 Leflunomide

Table 4.2.1 and Figure 4.2.1 give the estimates of effect from the two eligible trials of leflunomide versus placebo. The data indicates that at six months, leflunomide at a dose of 20 mg/day was significantly better than placebo based on the ACR20 response rate. The estimate of effect suggests that the proportion of patients obtaining an ACR20 response with leflunomide is much higher than that with placebo. The data from Strand shows that the effect is maintained at the 12 months assessment point (Risk difference of 0.26 95%CI 0.15, 0.36). The time effect of this trial is shown in Table 4.2.2. This data was obtained from a 24-month extension trial, US301 (Cohen et al., 2001). It is of note that the RD at 6 and 12 months are slightly different to those given by Strand 1999, although both estimates were from the same trial. The discrepancy occurred due to a difference in what was defined as the ITT population in both studies (Strand et al. had 182 patients on leflunomide in their analysis whereas Cohen et al. had 190). Table 4.2.3 suggests a dose-effect response with increasing dose of leflunomide. At six months, doses of 5, 10 and 25 mg/day produced responses greater than placebo (Mladenovic et al. 1995).

Table 4.2.1. Leflunomide (20 mg/d) versus placebo 6 months ACR20

Study	Stratum (for Fig. 4.2.1)	RD	95% CI (Miettinen)	M-H weight
Smolen 1999	1	0.26	0.13, 0.38	243.29
Strand 1999	2	0.28	0.17, 0.38	329.47
Pooled estimate (Greenland-Robins)		0.27	0.19, 0.35	
Chi-square (for pooled risk difference) statistic = 42.35 (df = 1) P < 0.0001				
Q ("non-combinability" for risk difference) statistic = 0.03 (df = 1) P = 0.8618				

Figure 4.2.1. Leflunomide (20 mg/d) versus placebo at 6 months

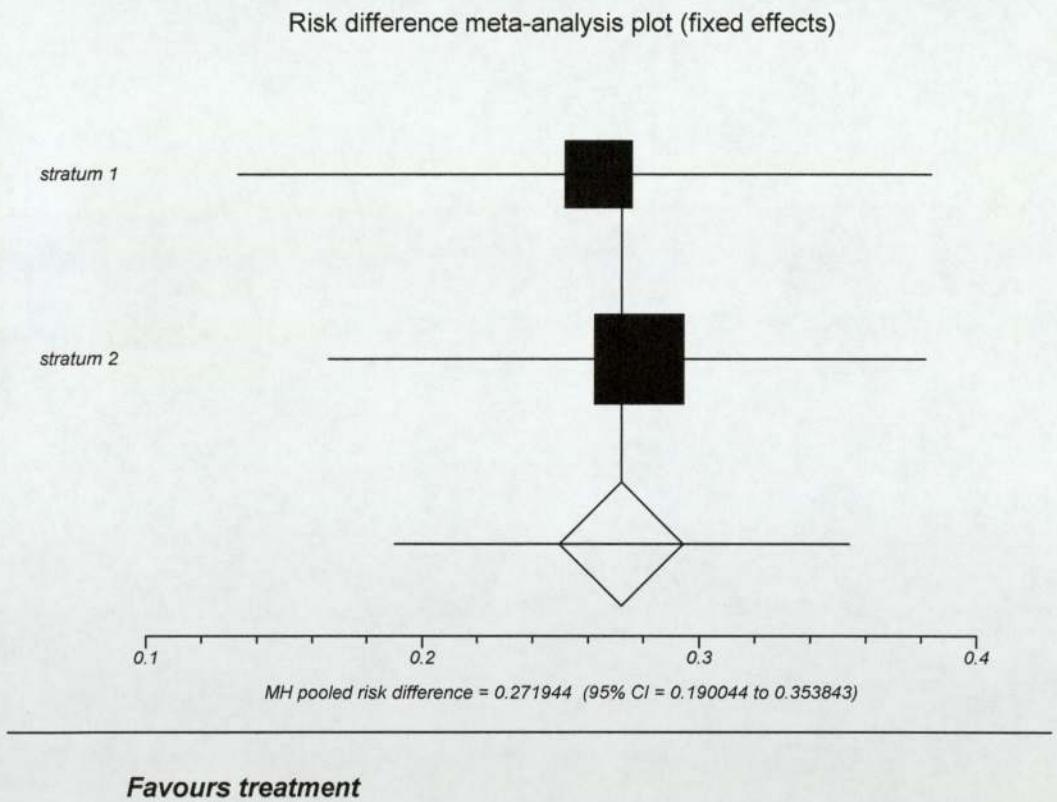


Table 4.2.2. Time effect data of leflunomide (20 mg/ day) versus placebo (US 301 extension study, Cohen 2001).

Time	Risk difference	95% CI (Miettinen)
6 months	0.28	0.17, 0.38
12 months	0.27	0.16, 0.37
24 months	0.27	0.17, 0.37

Table 4.2.3. Dose effect of leflunomide versus placebo at 6 months (Mladenovic 1995)

Dose	Risk difference	95% CI (Miettinen)
5 mg/day	0.01	-0.12, 0.14
10 mg/day	0.21	0.08,0.34
25 mg/day	0.27	0.14, 0.40

Table 4.2.4. Leflunomide (20 mg/d) versus methotrexate at 12 months

Study	Stratum (for graph, Fig 4.2.2)	RD	95% CI (Miettinen)	M-H weight
Emery 2000	1	-0.14	-0.20, -0.08	1037.81
Strand 1999	2	0.06	-0.04, 0.16	365.434
Pooled estimate (DerSimonian-Laird chi-square)		-0.04	-0.24, 0.15	
DerSimonian-Laird Chi-square (for pooled risk difference) statistic = 0.189 (df = 1) P = 0.0015				
Q ("non-combinability" for risk difference) statistic = 10.60 (df = 1) P = 0.0011				

Table 4.2.5. Leflunomide (20 mg/d) versus methotrexate at 24 months

Study	Stratum (for Fig 4.2.3)	RD	95% CI (Miettinen)	M-H weight
Cohen 2001	1	0.05	-0.05, 0.15	381.10
Emery 2000	2	-0.12	-0.19, -0.05	726.69
Pooled estimate (DerSimonian-Laird chi-square)		-0.04	-0.21, 0.13	
DerSimonian-Laird Chi-square (for pooled risk difference) statistic = 0.18 (df = 1) P = 0.6676				
Q ("non-combinability" for risk difference) statistic = 7.46 (df = 1) P = 0.0063				

Figure 4.2.2. Leflunomide (20 mg/d) versus methotrexate at 12 months

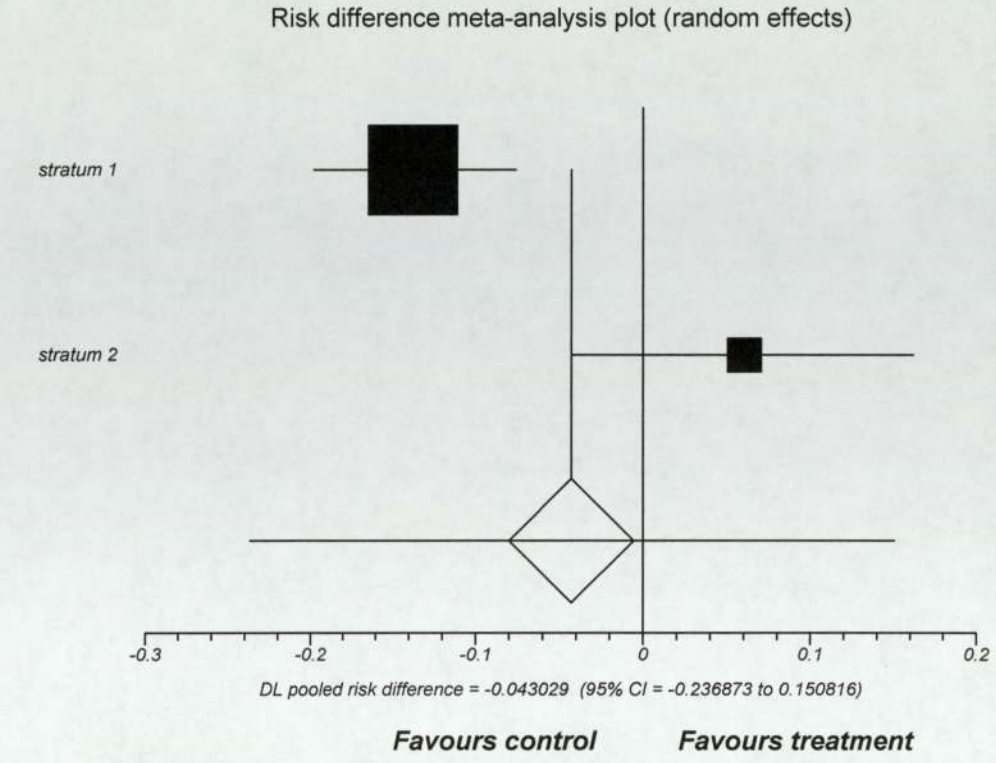
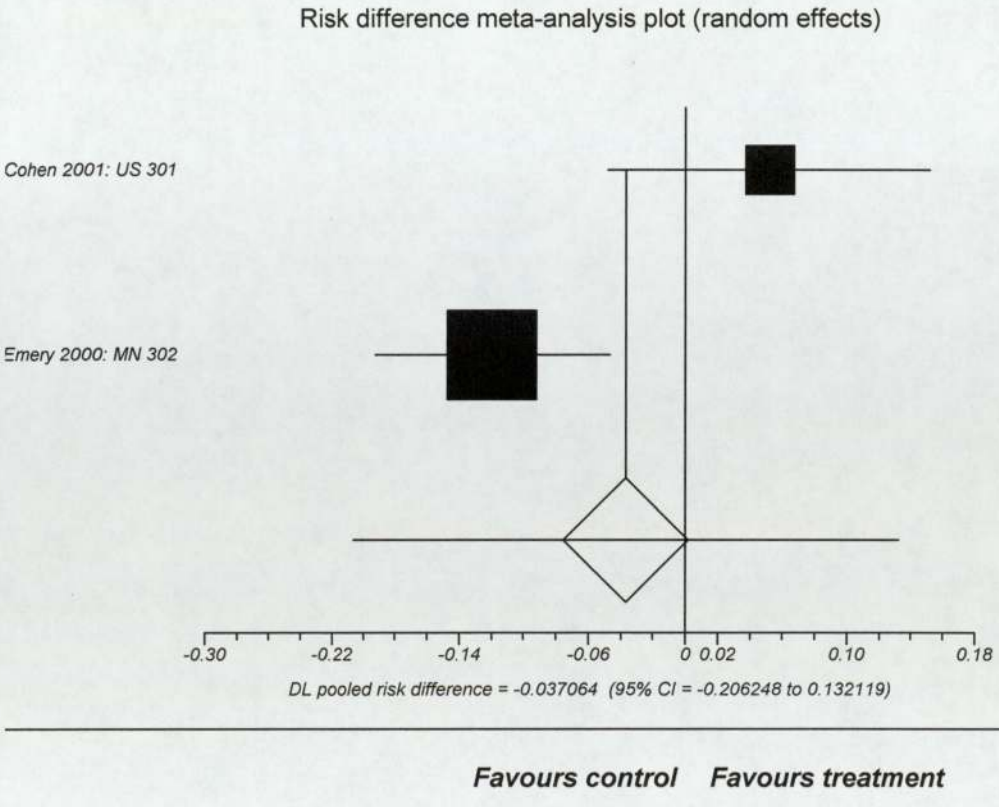


Figure 4.2.3. Leflunomide (20 mg/d) versus methotrexate at 24 months



The homogeneity chi-squared test suggested significant heterogeneity in effects from the Emery (1999) and the US (Strand 1999; Cohen 2000) studies. Therefore for comparing the ACR 20 responses the more appropriate random effects model was used. Against methotrexate, leflunomide monotherapy displayed a slightly lower response rate, giving a pooled RD estimate of -0.04 at 12 months (95% CI -0.24, 0.15) (DerSimonian Laird Random effect Model) (Table 4.2.4 and Figure 4.2.2). Similar estimates were obtained at 24 months (-0.04: 95% CI -0.21, 0.13) (Table 4.2.5 and Figure 4.2.3). However when the two drugs are given in combination the estimate of effect (RD = 0.27 at 6 months 95% CI 0.15, 0.37) showed that it was significantly better than treatment with methotrexate alone (control) (Table 4.2.6). In this study leflunomide doses ranged from 10-20g/d rather than the single 20 mg/d given in trials US 301 (Strand et al., 1999) and MN 302 (Emery et al., 2000).

Table 4.2.6. The combination of leflunomide (10-20g/d) and methotrexate versus methotrexate alone at 3 months and 6 months

Time	Dose leflunomide	Risk difference	95% CI (Miettinen)
3 months	10 or 20 mg/d	0.23	0.12, 0.33
6 months	10 or 20 mg/d	0.27	0.15, 0.37

Table 4.2.7. Leflunomide (20g/d) versus sulfasalazine (Smolen 1999; Scott 2001): dose-effect

Time	Risk difference	95% CI (Miettinen)
6 months	-0.01	-0.13, 0.11
12 months	-0.02	-0.17, 0.13
24 months	0.25	0.09, 0.40

There was no major difference between leflunomide and sulfasalazine at 6 and 12 months (Table 4.2.7). However, at 24 months a significantly better ACR 20 response

rate was achieved with leflunomide compared to sulfasalazine (RD 0.25 CI 0.09, 0.40).

4.2.2 Infliximab

For infliximab only one study was available, which was investigated over three reports (Maini et al., 1999; Lipsky 2000; Lipsky 2000 [abstract]). As early as 2 weeks, after starting treatment, the combination of infliximab and methotrexate produced a higher ACR 20 response than with methotrexate alone (Table 4.2.8). This response was even better at 30 weeks, with all infliximab doses studied.

Table 4.2.8. Time effect & dose effect: Infliximab and methotrexate versus methotrexate alone.

Time	Dose (infliximab)	RD	95% confidence interval
2 weeks	3 mg/kg every 8 weeks	0.23	0.12, 0.35
	3 mg/kg every 4 weeks	0.20	0.09, 0.31
	10 mg/kg every 8 weeks	0.24	0.13, 0.36
	10 mg/kg every 4 weeks	0.20	0.09, 0.32
30 weeks	3 mg/kg every 8 weeks	0.30	0.17, 0.44
	3 mg/kg every 4 weeks	0.33	0.19, 0.46
	10 mg/kg every 8 weeks	0.31	0.17, 0.44
	10 mg/kg every 4 weeks	0.38	0.23, 0.50
1 year	3 mg/kg every 8 weeks	0.25	0.11, 0.38
	3 mg/kg every 4 weeks	0.31	0.17, 0.43
	10 mg/kg every 8 weeks	0.42	0.28, 0.54
	10 mg/kg every 4 weeks	0.42	0.28, 0.55
2 years	3 mg/kg every 8 weeks	0.25	0.12, 0.37
	3 mg/kg every 4 weeks	0.23	0.11, 0.36
	10 mg/kg every 8 weeks	0.32	0.19, 0.45
	10 mg/kg every 4 weeks	0.32	0.13, 0.39

Responses were generally sustained at one and two years. Doses of 10 mg/kg given every 4 and 8 weeks (at 1 year RD reached 0.42 CI 0.28, 0.55 and 0.42 CI 0.28, 0.54,

respectively) showed a slightly higher response than with 3 mg/kg given every 4 or 8 weeks (1 year results: RD 0.31 CI 0.17, 0.43 and RD 0.25 CI 0.11, 0.38, respectively).

4.2.3 Etanercept

Analysis for etanercept was based on six trials. Compared to placebo 25 mg (twice weekly), etanercept produced a considerably higher ACR 20 response at 3 months (pooled estimate RD 0.52; CI 0.45, 0.60) (Table 4.2.9, Figure 4.2.4). The response was sustained at six months (RD of 0.48; CI 0.34, 0.60) (Moreland et al., 1999).

Table 4.2.9. Etanercept 25 mg (twice weekly) versus placebo at 3 months

Study	Stratum (see Fig. 4.2.4)	RD	95% CI (Miettinen)	M-H weight
Moreland 1997	1	0.61	0.43, 0.75	1.44.14
Ericson 1999	2	0.58	0.46, 0.68	343.03
Moreland 1999	3	0.39	0.24, 0.52	191.79
Pooled estimate (Greenland-Robins)		0.52	0.45, 0.60	
Chi-square (for pooled risk difference) statistic = 181.12 (df = 1) P < 0.0001				
Q ("non-combinability" for risk difference) statistic = 5.66 (df = 2) P = 0.0591				

Table 4.2.10. Etanercept 10 mg (twice weekly) versus placebo at 3 months

Study	Stratum (see Fig. 4.2.5)	RD	95% CI (Miettinen)	M-H weight
Ericson 1999	1	0.50	0.39, 0.61	316.59
Moreland 1999	2	0.22	0.07, 0.36	184.07
Pooled estimate (DerSimonian-Laird)		0.37	0.09, 0.64	
DerSimonian-Laird chi-square = 6.74 (df = 1) statistic P < 0.0094				
Q ("non-combinability" for risk difference) statistic = 9.31 (df = 1) P = 0.0023				

Fig 4.2.4. Etanercept 25 mg (twice weekly) versus placebo at 3 months

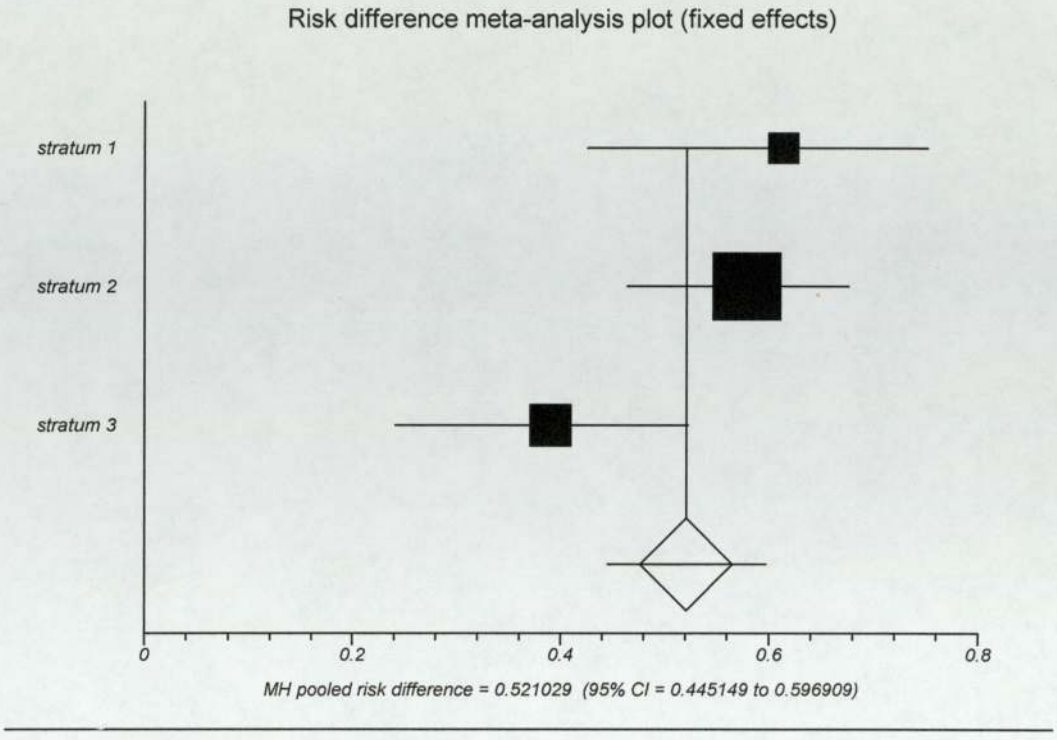
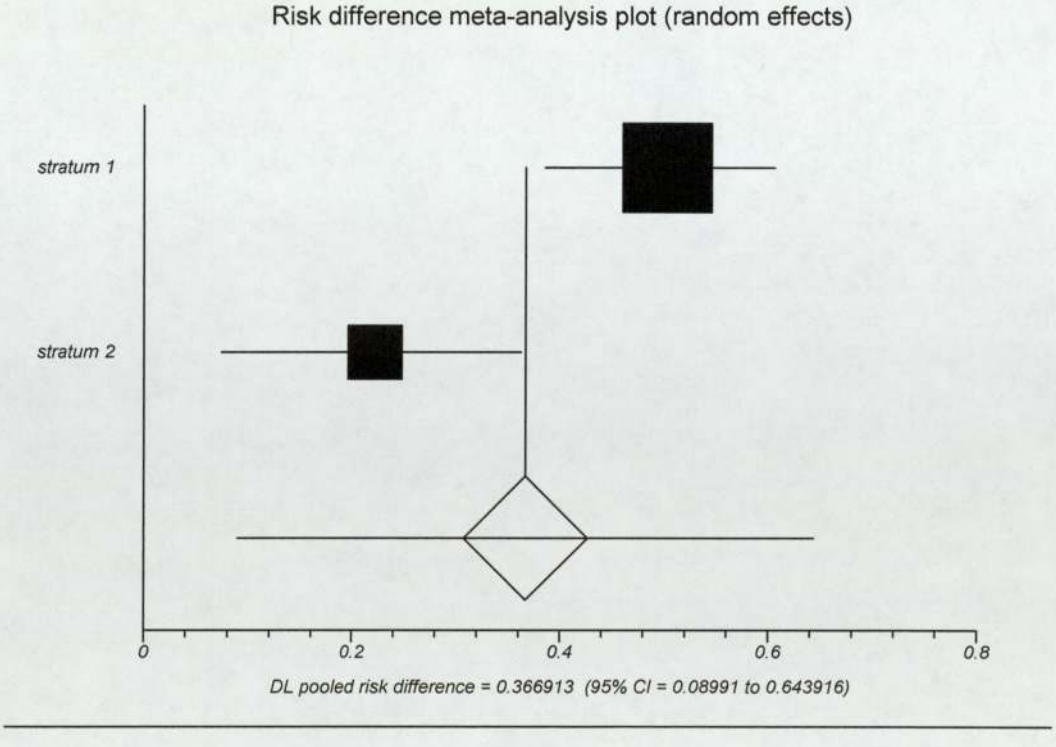


Figure 4.2.5. Etanercept 10mg (twice weekly) versus placebo at 3 months



Etanercept 10mg responses when compared were heterogeneous in the Moreland 1999 and Ericson 1999 trials. Therefore, a random effects model was used. With this model ACR 20 responses with 10 mg (twice weekly) were also significantly better than placebo but not as marked as with etanercept 25 mg (Table 4.2.10, Figure 4.2.5).

Compared to methotrexate ACR 20 response with etanercept was not significantly higher, this was demonstrated in patients with early disease (Table 4.2.11) (Bathon et al., 2000; Genovese 2002). Only at 24 months was the response with 25 mg etanercept better than with methotrexate (RD 0.13; CI 0.04, 0.22). However the combination resulted in a much higher response rate than with methotrexate monotherapy, in active RA. At 6 months the RD value was 0.45 (CI 0.23, 0.62) (Weinblatt et al., 1999) (Table 4.2.12)

Table 4.2.11 Time-effect and dose-effect: etanercept versus methotrexate in early RA

Time	Etanercept dose	RD	95% CI (Miettinen)
6 months	10 mg	0.03	-0.06, 0.12
	25 mg	0.05	-0.05, 0.14
12 months	10 mg	-0.03	-0.12, 0.06
	25 mg	0.07	-0.02, 0.16
24 months	10 mg	0.02	-0.07, 0.11
	25 mg	0.13	0.04, 0.22

Table 4.2.12 Time-effect: etanercept (25mg twice weekly) in combination with methotrexate versus methotrexate alone

Time	Risk difference	95% CI (Miettinen)
3 months	0.33	0.11, 0.51
6 months	0.45	0.23, 0.62

4.3 CONCLUSION

In relation to placebo all three agents are much more likely to produce an ACR20 response in patients with active RA. The highest response rates were obtained with the two anti-TNF agents, etanercept in particular, as monotherapy or in combination with methotrexate. Etanercept was slightly better than methotrexate this was especially evident at 24 months, in patients who had early disease. Infliximab was only used in combination with methotrexate, and ACR 20 responses were considerable and were sustained over a two-year period with all regimens studied. The pooled estimate suggested that methotrexate was slightly more effective than leflunomide. However, in combination the two drugs were better than methotrexate alone. Follow-up studies suggest that leflunomide is still efficacious at 2 years.

CHAPTER 5

DISCUSSION

Although a cure for RA is unavailable, advances in molecular technology have allowed the identification of novel therapeutic targets, including cell-subsets and cytokines, which contribute to the inflammatory and destructive components of the disease. TNF-α, a principal cytokine in RA is targeted by two commercially available therapeutic agents, a chimeric monoclonal antibody (infliximab) and a recombinant human soluble TNF receptor (etanercept). Auto-reactive T-cells are more sensitive to the depletion of pyrimidine than other types of lymphocyte in the body (Fox et al., 1998). Leflunomide, another novel DMARD inhibits de novo pyrimidine synthesis, and thus removes the infiltrating auto-reactive T-cells. This study reviewed the evidence from RCTs of these novel DMARDs. Outcomes that were focused on included ACR 20 response, which when possible was pooled, functional status data, as measured by the HAQ and radiographic data. Because these drugs are relatively new only a small number of trials were obtained. Despite this, the evidence for efficacy was strong.

Direct comparisons of leflunomide with methotrexate and sulfasalazine indicate that leflunomide is roughly equivalent to the two drugs. It is worth mentioning that leflunomide appears slightly better, with regard to effect on quality of life, than sulfasalazine. On the other hand, methotrexate may be slightly more effective than leflunomide in slowing disease progression. Thus, according to the efficacy data leflunomide can be used as a first-line alternative to methotrexate or sulfasalazine. It

can be employed in patients who cannot tolerate or have found treatment with methotrexate to be ineffective.

Leflunomide and methotrexate have a similar frequency of side effects. However, the types of side effects are somewhat different. The common side effects experienced with leflunomide are gastrointestinal symptoms, such as diarrhoea and nausea, alopecia, rashes and allergic reactions, transient elevations of liver enzymes and hypertension. None of the trials recorded any life-threatening side effects. However several cases of fatal liver toxicity have been reported (Weinblatt et al, 2000). Many more studies based on post-marketing surveillance are needed to judge how significant leflunomides' potential for other types of toxicity may be.

The difference in the efficacy of leflunomide versus methotrexate in the US 301 and MN 302 trials may have been due to the absence of folate supplementation in the US 301 trial. Folate supplementation is used to reduce the toxic side effects of methotrexate without affecting the efficacy of the drug for the treatment of RA (Morgan et al., 1994; Morgan et al., 1998; Ortiz et al., 1998). However, a more recent trial suggests that to achieve the same degree of methotrexate efficacy, higher doses of methotrexate were required if folate supplementation is used. For example, folic acid and folinic acid did not affect response to methotrexate although higher doses were required. Doses of 18, 16.4 and 14.5 mg/week were required for the folic acid, folinic and placebo groups, respectively (Van Ede et al., 1999). Thus, folic acid may have lowered both the efficacy and toxicity of methotrexate. Another difference between the two trials was the stage of the disease. RA disease duration ranged between 6.5-7 years in US 301 and 3.7-3.8 years in the MN302.

The three phase III trials (US 301, MN 301 and MN302) trials demonstrated that methotrexate and sulfasalazine were as effective as leflunomide in the retardation of radiographic progression. However, in the ERA trial (Bathon et al., 2000; Genovese et al., 2002) etanercept demonstrated superiority over methotrexate in slowing radiographic progression. X- ray changes showed that in early RA, both high dose methotrexate and etanercept (25 mg) are effective in reducing disease progression.

Etanercept monotherapy produced clear and rapid improvement in disease activity, as measured by the ACR20 response, in two multi-centre placebo controlled trials, in which patients were treated for three (Moreland et al., 1997) or six months (Moreland et al., 1999). The addition of 25mg etanercept twice-weekly to a stable dose of methotrexate produced incremental benefit (Weinblatt et al., 1999). (Bathon et al., 2000; Genovese et al., 2002).

The other anti-TNF agent, infliximab was proven successful when used alone (Eliott et al., 1994). However concern about the development of antibodies against the hybrid molecule led to the idea of using infliximab and methotrexate in combination (Maini et al., 1998). This combination is now the current standard treatment with infliximab. For patients with active disease with a mean duration of 9-12 years, the combination was better than methotrexate alone in producing clinical (ACR 20) response and in improving quality of life (HAQ) (Maini et al., 1999; Lipsky et al., 2000). Despite methotrexate treatment for at least 6 months and high base-line radiographic scores, the addition of infliximab at all doses and regimens studied, led to statistically significant retardations of radiographic progression (major progression:

31% on placebo vs. 0-13% in infliximab groups [Table 3.3.4]). The rapid onset of action of the drug may make it an ideal starting therapy for severe active RA.

Most side effects of anti-TNF therapy are not serious, and both agents are generally well tolerated during and immediately after administration. However, wider clinical use of these agents in patients with RA has led to reports of occasional severe infections. The most common is tuberculosis, which is more frequently reported with infliximab (Keane et al., 2001). Although the incidence of infection was high for both agents in the clinical trials, the difference between placebo and treatment groups were not statistically significant, and in the case of infliximab, were not life threatening (6% for placebo vs 1% for 3mg/kg every 8 weeks and 6% for 10mg/kg every 4 weeks). Post-marketing surveillance has revealed an association of anti-TNF therapy with infection, but no increase in the rate of serious infections (Krosen et al., 2003). Reactivation of tuberculosis, though infrequent, was reported. It is thus vital to carefully screen patients for active infection (acute or chronic), including both active and inactive tuberculosis before initiating anti-TNF therapy. Developing antibodies against dsDNA, as usually seen in systemic lupus erythematosus were also associated with the biologicals, but are rare, reported cases were diminished after anti-TNF treatment was stopped (Maini et al., 1999; Charles et al., 2000; Shakoor et al., 2002) were.

At present the anti-TNF biologicals are only prescribed if the RA sufferer has failed or is intolerant to DMARD therapies including methotrexate. The substantial cost of this therapy was one main basis for this consensus (Smolen et al., 2000). Kvien et al found that these guidelines permitted the use of these agents in only 15% of the total

RA population of Oslo (Kvien et al., 2001). Whether these agents should or should not be initiated in early disease depends on how cost-effective they are. Leflunomide, in comparison, not only has lower up-front costs compared to anti-TNF therapy but also the convenience of daily oral intake. However, cost effective analysis may well show that infliximab and etanercept are worthwhile in very early RA, because of a reduction in joint damage and in reducing other primary or secondary costs. A few investigators have carried out such analyses for infliximab and etanercept and claim them to be cost effective (Wong et al., 2002; Malone., 2001). However, full access to the data is not available and the validity of those claims remains to be confirmed.

The anti-TNF agents appear to perform slightly better than leflunomide in ACR 20 responses. A Swedish study of clinical experience with the three agents over a period of 20 months suggests that the TNF agents were superior, that 79% and 75% of patients continued on etanercept and infliximab compared with only 22% of those on leflunomide (Geboreck et al., 2002). This study demonstrated that in the 'real-world' those agents were also effective. RCTs do not usually recruit patients who are fully representative of those in clinical practise, because of strict inclusion criteria (van der Linden et al., 1994). A longitudinal observational study is another study design, which can also give important information about effectiveness of RA therapies in clinical practice (Hawley and Wolfe., 1991). RCTs and observational studies provide complementary information (Kvien et al., 2003).

One of the most difficult biases to overcome is publication bias. This occurs when the publication of research depends on the direction of the study results and whether they are statistically significant (Easterbrook et al., 1991; Misakian and Bero., 1998). All

of the studies included in this review had positive results, such positive studies may be as much as three times more likely to be published than negative studies (Egger and Smith., 1998). Even if negative studies are chosen for publication they can face an increased delay (Misakian and Bero., 1998; Stern and Simes., 1997) or be published to a less visible source (Frank., 1994). Negative publications produced by non-English authors may be submitted to a local non-English language journal that is less likely to be indexed by well-known databases such as Medline (Gregoire et al., 1995). As a consequence, reviews may produce the same exaggerated estimates of treatment effect. To reduce such bias the search strategy adopted in this research included search of a variety of databases, with no language restriction. Hand searching of journals and systematic reviewing of the reference lists were also undertaken.

Reviewers may assess to what extent publication bias is influencing their results. Useful diagnostic plots, such as the funnel plot (Egger et al., 1997), and statistical testing (Begg et al., 1988) can help detect, and to some extent adjust for publication bias. However, these strategies do not fully overcome the problem.

In Rheumatology, the availability of funding and interests within pharmaceutical companies make it more likely that a drug study will be funded than a trial of a physical intervention (Dippe., 1998). Thus the industrially supported drug studies included in this research may not have addressed the most important clinical question. It has also been demonstrated that negative studies funded by pharmaceutical companies are less likely to get published than negative studies funded by non-profit organizations or government agencies (Easterbrook et al., 1991; Dickersin et al., 1995;

Friedberg et al., 1999). Possible unpublished trials were requested from drug manufacturers, but no response was obtained.

All included trials were conducted in the US, Europe and South Africa, as a result nearly all patients were Caucasian. Trials investigating the efficacy of these drugs in other races should also be conducted, as the response of these drugs towards other races may vary.

CONCLUSION

The potential benefit and harm of etanercept, infliximab and leflunomide have been summarised in this review. The efficacy of leflunomide and the TNF blocking agents has been shown in international trials as well as daily practice (Geborek et al., 2002). This study has reviewed the evidence to date, and suggests that these agents are very effective in reducing the signs and symptoms of RA, as well as improving patient quality of life. Compared to standard DMARDs, the use of these therapies increases the chance of lowering disease activity in any given RA patient. Although the effectiveness of leflunomide, etanercept and infliximab was recognized in single RCTs, through this study it has been made more clear to us what pieces of research have been carried out and what investigations needs to be carried out. The identification of new themes and proposals are vital for the development and optimisation of RA drug therapy.

Pooling of results was only limited to the ACR20 response. Because of lack of homogeneity a summary treatment of effect was not obtained for radiographic scores,

HAQ scores, and ACR50 and 70 scores, which are useful in capturing major improvement. Individual study results of these scores were included in the narrative summary (Chapter 3).

Trials investigating leflunomide, infliximab and etanercept in combination with other DMARDs other than methotrexate would be of great interest. Among the trials investigating infliximab and etanercept, none evaluated mono-therapy against methotrexate in active RA. Direct comparison between anti-TNF mono-therapy and a standard DMARD such as methotrexate and sulfasalazine needs to be investigated in future trials. A major concern in the use of the newer agents is the long-term toxicity. Further studies aimed at finding optimum strategies for preventing such toxicity are necessary. After establishing the effectiveness profiles of the newer agents in this study, risk-benefit and cost effective analyses of these drugs can indeed be a next step. As newer trials are being produced systematic reviews will need to be updated to include more recent evidence on leflunomide and anti-TNF therapy.

The newer DMARDS have certainly increased the therapeutic repertoire for RA patients. Guidelines for DMARD therapy have been developed to help ensure appropriate choices of treatment, as the newer agents are not useful for every patient. Development of even more effective and safer agents is certainly required. An improvement in disease control does not mean a cure for RA. More emphasis should also be placed on finding cures for RA.

APPENDIX 1

Excluded and included trials from potentially relevant randomized controlled trials.

Reference	Inclusion/ exclusion	Reason for inclusion/exclusion
Bathon et al., 2000	✓	RCT on etanercept.
Cohen et al., 2001	✓	RCT on leflunomide, extension report (Strand et al., 1999)
Elliot et al., 1994	✓	RCT on infliximab
Emery et al., 2000	✓	RCT on leflunomide
Erickson et al., 1999 (abstract)	✓	RCT on etanercept- Data obtained from the NICE report
Genovese et al., 2002	✓	RCT on etanercept, extension report (Bathon et al., 2000)
Jiang et al., 2000	×	RCT on leflunomide - does not use the ACR criteria to measure efficacy
Kalden et al., 2001	✓	Contains quality of life data for Smolen et al., 1999
Kavanaugh et al., 2000	✓	RCT on infliximab
Kraan et al., 2000	×	RCT on leflunomide- preliminary data on neutrophil migration
Kraan et al., 2000 (a)	×	RCT on leflunomide- data based on modulation of inflammation and metalloproteinase expression in synovial tissue.
Kremer et al., 2002	✓	RCT on leflunomide
Lao et al., 2001	×	RCT on leflunomide- does not use the ACR criteria to measure efficacy.
Lipsky et al., 2000	✓	RCT on infliximab, one year extension of ATTRACT trial (Maini et al., 1999)
Lipsky et al., 2000	✓	Abstract- two year extension report for ATTRACT trial (Maini et al., 1999)
Maini et al., 1998	✓	RCT on infliximab
Maini et al., 1999	✓	ATTRCT trial, a RCT on infliximab
Mathias et al., 2000	✓	RCT on etanercept- includes measure of health assessment questionnaire
Mladenovic et al., 1995	✓	RCT on leflunomide
Moreland et al., 1997	✓	RCT on etanercept
Moreland et al., 1999	✓	RCT on etanercept
Sharp et al., 2000	✓	Radiographic results from three RCTs on leflunomide
Smolen et al., 1999	✓	RCT on leflunomide
Strand et al., 1999	✓	RCT on leflunomide
Strand et al., 1999 (a)	✓	Contains quality of life data for Strand et al., 1999
Weinblatt et al., 1999	✓	RCT on etanercept
Yonghong 2001	×	RCT on leflunomide- does not use the ACR criteria to measure efficacy.

APPENDIX 2

Characterization of included randomized controlled trials: Participant information

RCTs: ETANERCEPT

Moreland and colleagues (1997)

- Patients were 18 years of age or older who met the ACR criteria for RA and were in functional class I, II, or III
- Eligible patients were unsuccessfully treated who had failed between one and four of the following DMARDs: hydroxycholoroquine, gold, methotrexate azathioprine, penicillamine, and sulfasalazine.
- Patients had at least 4 weeks of the washout period and remained so throughout the study and follow up period.
- Active RA (eligibility criteria for entry) defined as:
  - 10 or more swollen joints
  - 12 or more tender joints

  and one of the following three criteria
  - Westergren ESR of at least 28 mm/h
  - CRP level: more than 2.0 mg/decilitre
  - morning stiffness lasting at least 45 minutes
- Subjects receiving NSAIDs or corticosteroids (<10mg per day) were eligible if the dose had been stable 4 weeks prior to study entry and throughout the study. The total 180 patients were randomly assigned to one of four treatment groups. All regimens were given subcutaneously, twice weekly.

Moreland and colleagues (1999)

- In total 234 patients, who had mean disease duration of 12 years, were randomly assigned to participate at 13 North American study centers.
- Patients were 18 years of age or older who met the ACR criteria for RA and were in functional class I, II, or III.

- Eligible patients were unsuccessfully treated who had failed between one and four of the following DMARDs: hydroxycholoroquine, gold, methotrexate azathioprine, penicillamine, and sulfasalazine.
- Active RA (eligibility criteria for entry) defined as:
    - 10 or more swollen joints
    - 12 or more tender joints

  and one of the following three criteria
    - Westergren ESR of at least 28 mm/h
    - CRP level: more than 20 mg/L
    - morning stiffness lasting at least 45 minutes
- Patients receiving DMARDs completed a washout period of 4 weeks. The mean daily corticosteroid dose was between 6.8 and 7.5 mg.
- Rheumatoid factor positive patients made up 79 percent of the placebo group, 82% of the etanercept 10mg group and 79% of the etanercept 25mg group.
- Among the 234 patients 80 received placebo, 76 received 10mg etanercept and 78 received 25mg etanercept. Both doses were given twice weekly, subcutaneously.

Weinblatt and colleagues (1999)

- In seven study centers, 89 patients participated in this 24-week double-blind trial.
- Patients were 18 years of age or older who met the ACR criteria for RA and were in functional class I, II, or III.
- Active RA (eligibility criteria for entry) manifested by at least:
    - 6 or more swollen joints
    - 6 or more tender joints
- Initially all patients had been taking methotrexate for at least six months, at a stable dose of 15 to 25 mg per week (doses of 10mg were used if higher doses were intolerable). To lessen the toxic effects of methotrexate folic or folinic acid was taken by all participants.
- Other than methotrexate, DMARD therapy was discontinued at least four weeks before, except sulfasalazine and hydroxychloroquine, which were discontinued at least two weeks before starting the trial.
- Study interventions were given subcutaneously, twice weekly and included:

methotrexate plus placebo (30 patients) and methotrexate plus etanercept 25mg (59 patients).

- Patients receiving NSAIDs and corticosteroids (prednisone at 10mg daily or less) were eligible if doses had been stable for at least four weeks before the study period, and continued to be stable during the study period.
- Patients that dropped out before study completion were classified as non-responders.

Etanercept early RA (ERA) Trial: Bathon and colleagues 2000; Genovese and colleagues 2002

- The ERA phase III trial was initially carried out to investigate the effectiveness of etanercept and methotrexate in preventing radiographic joint damage.
- Patients were double blinded for the first twelve months; in the second year of the study an open label strategy was adopted.
- Patients had RA no more than three years and had not been treated with methotrexate.
- Eligible patients were positive for rheumatoid factor or had at least 3 bone erosions evident on radiographs of the hands wrists, or feet and had at least 10 swollen joints and at least 12 tender of painful joints.
- A wash out period of 4 weeks was permitted for patients on DMARDs. Stable doses of prednisone ($\leq$10 mg daily) and NSAID were allowed.
- At baseline 632 patients were randomly assigned to one of three treatment groups (given twice weekly): 10 mg etanercept and placebo tablets (207 patients); 25 mg etanercept and placebo tablets (208 patients); and methotrexate that had reached 20mg by week 8 (217 patient) and placebo injections.
- Of the 632 patients, 80 percent of them were rheumatoid factor positive.

RCTs: INFLIXIMAB

Elliot and colleagues 1994

- Patients aged between 18-75 met the ACR criteria for RA
- Active RA (eligibility criteria for entry) defined as:
  - 6 or more swollen joints
  - 6 or more tender joints

  and one of the following three criteria
  - Westergren ESR of at least 28 mm/h
  - CRP level: more than 20 mg/L
  - morning stiffness lasting at least 45 minutes
- Patients had a history of failed treatment with at least one DMARD and had radiographic evidence of hand and feet erosion.
- DMARD treatment was discontinued 4 weeks prior study entry. Patients on corticosteroids (≤ 12.5 mg/day) and NSAIDs continued to receive stable doses.

Maini and colleagues 1998

- Patients met the ACR criteria for RA and received methotrexate 7.5-15mg/week for a minimum of six months.
- Active RA (eligibility criteria for entry) defined as:
  - 6 or more swollen joints
  - 6 or more tender joints

  and one of the following three criteria
  - Westergren ESR of at least 28 mm/h
  - CRP level: more than 20 mg/L
  - morning stiffness lasting at least 45 minutes
- During the study and 4 weeks prior study entry patients received stable doses of 7.5 mg/week methotrexate.
- DMARDs (except methotrexate) were withdrawn at least 4 weeks before screening. Corticosteroid users were on a stable dose of 7.5 mg/day (4 weeks prior screening).
- Infliximab or placebo infusions were given at 2, 6, 10 and 14 weeks.

Kavanaugh and colleagues 2000

- Patients were between 18 to 75 years of age and had established diagnosis of RA according to the ACR classification criteria. Patients were in functional class II, III or IV and had a disease duration of less than 15 years.
- Active RA (eligibility criteria for entry) defined as:
  - 6 or more swollen joints
  - 8 or more tender joints

  and one of the following three criteria
  - Westergren ESR of at least 28 mm/h
  - CRP level: more than 20 mg/L
  - morning stiffness lasting at least 45 minutes
- Eligible participants were previously treated with methotrexate for a minimum of 3 months. Participants were required to have taken a stable dose of methotrexate (10 mg /week) and folic acid (1 mg/day) 4 weeks prior study entry.
- Stable doses of corticosteroids (≤ 7.5 mg prednisone) and NSAIDs were permitted if they were stable for at least 4 weeks before study entry.
- Patients were randomised to a single intravenous infusion of infliximab or placebo. Patients completing the blinded phase of the study were eligible to enter the open label multi-dose extension, where patients received three additional infusions of infliximab (10 mg/kg) at weeks 12, 20 and 28.

The ATTRACT trial: Maini and colleagues 1999; Lipsky and colleagues 2000; Lipsky 2000 (Abstract)

- All three publications investigate the efficacy of infliximab after 30 weeks, its effects on radiographic joint damage at week 54 and physical function at weeks 102.
- Patients met the ACR criteria for RA and were in functional class I, II, or III.
- Active RA (eligibility criteria for entry) defined as:
  - 6 or more swollen joints
  - 6 or more tender joints

and one of the following three criteria

- Westergren ESR of at least 28 mm/h
- CRP level: more than 20 mg/L
- morning stiffness lasting at least 45 minutes

- Eligible patients had been receiving methotrexate for at least three months. Stable doses of 12.5 mg/week (or more) methotrexate and folic acid were required for at least 4 weeks before screening.
- Corticosteroid (10 mg/kg or less equivalent) and NSAID doses were stable for at least 4 weeks before screening.
- The 482 patients that met the entry criteria, were randomised to five treatment groups in a double blind manner:
- Intravenous infusions were initially given at weeks 0, 2 and 6 in all patients.
- Methotrexate was kept constant during the trial unless it had to be reduced for possible methotrexate toxicity.
- The study population had advanced disease, with a mean disease duration ranging from 9-12 years across the five treatment groups.
- More than 54% of patients in each group were taking oral corticosteroids.

RCTs:LEFLUNOMIDE

Mladenovic and colleagues 1995: Phase II trial

- Patients were enrolled in 6 study centres in Yugoslavia, Croatia and Slovenia.
- Patients were diagnosed according to the ACR criteria and had active RA (eligibility criteria for entry) defined as: 3 of the following 4 crteria
  - 8 or more swollen joints
  - 8 or more tender joints
  - Westergren ESR of at least 28 mm/h
  - morning stiffness lasting at least 45 minutes
- Doses of NSAIDs and Corticosteroids (≤10 mg daily prednisone) remained stable during the trial, and at least 4 weeks and 8 weeks, respectively, before enrolment.
- Patients on DMARDs went through a washout period of at least 3 months prior to study entry.

- Based on a phase I study (unpublished data) patients were split into four treatment groups.
- Between these treatments base-line characteristics were not significantly different.

Kremer and colleagues 2002

- In 20 centers, in the US and Canada, 263 patients with active RA were randomly assigned to 2 treatment groups in a double-blind manner.
- Patients were between 18 to 75 years of age and had established diagnosis of RA according to the ACR classification criteria.
- Active RA (eligibility criteria for entry) defined as, 3 of the following:
    - 6 or more swollen joints
    - 9 or more tender joints
    - Westergren ESR of at least 28 mm/h
    - morning stiffness lasting at least 45 minutes
- Despite receiving at least 6 months of methotrexate therapy, patients were receiving stable doses of methotrexate (15-20mg/wk or 10-15 mg/wk) for 8 weeks.
- Patients on corticosteroids were taking a stable daily dose of 10mg or less throughout the study, which were taken at least 30 days before the trial.
- The two treatment groups consisted of:
    - 100 mg/day Leflunomide for 2 days, followed by 10mg/d (130 patients). This dose was reduced to 10 mg every other day if patients showed intolerance. If active diseases was still present at week 8 or thereafter the dose was increased to 20 mg/day. However if patients developed substantial adverse effects the dose was reduced back to 10 mg/day.
    - Placebo (133 patients).
- Folate supplementation was authorized at 1 mg/d by the protocol.
- Patients were categorised as non-responders for ACR 20 if they had dropped out prior to study completion.

MN302: Emery and colleagues 2000

- This study was performed in 117 centers across Europe and South Africa. Patients were double-blinded and randomized to receive treatment for 54 weeks or 104 weeks.
- Subjects, 18 years or older were diagnosed according to the ACR criteria and had active disease defined by the following criteria at enrollment:
  - 6 or more swollen joints
  - 6 or more tender joints
  - physician and patient global assessment as fair, poor or very poor
  - Westergren ESR of at least 28 mm/h
  - CRP level: more than 20 mg/L
- DMARD users had discontinued the DMARD therapy for at least 28 days before trial enrolment.
- NSAIDs and steroids ($\leq$ 10 mg/day prednisone) were allowed, provided the subject had been receiving a stable dose for at least 28 days prior to study entry.
- Patients were assigned to two treatment groups:
  - Leflunomide (501 patients): A starting dose of 100 mg/day, followed by a daily dose of 20mg for the remainder of the study (dosages could be reduced to 10mg/day if un-tolerated)
  - Methotrexate (498 patients): subjects were assigned to 7.5 mg, 10mg and 10 or 15 mg in week 1-4, 5-12 and 13-52 respectively (folate supplementation
- Folate supplementation for subjects on methotrexate was not mandated by protocol. All patients in both groups also received placebo.
- Patients completing 52 weeks volunteered to continue a further 52 weeks of treatment, continuing the same dosage (292 patients receiving leflunomide and 320 receiving MTX).

US301: Strand and Colleagues 1999; Cohen and colleagues 2001

- Patients, 18 years or older were included if they met the ACR classification criteria for having RA for 6 months or longer.

- Active RA (eligibility criteria for entry) defined as 3 of the following:
  - 6 or more swollen joints
  - 9 or more tender joints
  - Westergren ESR of at least 28 mm/h
  - morning stiffness lasting at least 45 minutes
- Patients were assigned to 1 of 3 treatment groups:
  - Leflunomide 20m mg/day (three days loading dose of 100 mg/day) (182/190* patients)
  - Methotrexate, 7.5 mg/week (182/190* patients). Doses could also increase to 15 mg over weeks 7 and 9 and continued thereafter. In the two year cohort (Cohen et al., 2001) doses could increase to 17.5 mg and 20 mg.
  - Placebo (118 patients)

* Figures from the 24-month extension, Cohen (2001).

- All patients received 1 mg of folate once or twice daily.
- Previous DMARD treatment was discontinued 30 days before enrolment.
- NSAIDs and Prednisone (≤ 10 mg/day) treatment remained stable during the study and was only allowed if initiated at least 30 days prior to study entry.

MN301: Smolen and Colleagues 1999; Scott and Colleagues 2001.

- In 36 centers across Europe, South Africa and Australia 358 patients took part in a randomized, double-blind placebo controlled trial.
- Eligible participants had a diagnosis of active RA based on the ACR criteria Active disease was defined as:
  - 6 or more swollen joints
  - 6 or more tender joints
  - physician and patient global assessment as fair, poor or very poor
  - Westergren ESR of at least 28 mm/h or CRP level: more than 20 mg/L
- Eligible participants had not been taking sulfasalazine for at least a year before enrolment.
- Most patients (93%) were of ACR functional class II or III.
- DMARD treatment was discontinued 28 days before trial entry.
- NSAIDs and corticosteroids (≤ 10 mg prednisone) had been constant at least

30 days before the study.

- Patients were assigned to three treatment groups:
  - Leflunomide 20 mg/ day (Loading dose of 100 mg daily for three days) (133 patients)
  - Placebo (92 patients)
  - Sulfasalazine 0.5 g, 1.0 g, and 1.5 g given once or twice daily during weeks 1, 2 and 3 respectively, and 2.0 g daily during weeks 4-24 (133 patients).
- After six months completing patients volunteered to continue treatment for up to 12 or 24 months.
- Patients in the leflunomide and sulfasalazine continued to receive the same dose, those in the placebo group switched to sulfasalazine in a blinded manner. The Placebo-sulfasalazine arm patients received forced-dose escalation to 2.0 g.

APPENDIX 3

Definitions of improvement in RA

ACR 20 RESPONSE:

20 percent improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR core set measures: patient and physician global assessments, pain, disability, and acute phase reactant.

ACR 50 AND 70 RESPONSE

50 or 70 percent improvement in tender and swollen joint counts and 50 or 70 percent improvement in 3 of the 5 remaining ACR core set measures: patient and physician global assessments, pain, disability, and acute phase reactant.

PAULUS 20 RESPONSE

A response in at least 4 of 6 selected measures is required: 20% improvement in morning stiffness, ESR, joint tenderness score, and joint swelling score and improvement by at least two grades on a five-grade scale (or from grade two to grade one) for patient and physician global assessments of current disease severity.

APPENDIX 4

Radiological scores

Radiographs of the hands, wrists and feet are scored; the following methods are used for subsequent scoring:

Modified Sharp method (Sharp et al., 1985)

A total sharp score compromises the scores for joint space narrowing and erosions. In all 46 joints are scored for erosions, these are scored on a 6 point scale, where each point increase signifies an occurrence of a new erosion or 20% worsening of an existing erosion. A score of 0 indicates no new erosion and no worsening of existing erosion. For joint space narrowing 42 joints are scored on a 5-point scale. A score of 0 indicates no narrowing, 1: minimal narrowing, 2: loss of 50% of the joint space, 3: loss of 75% of the joint space and 4: complete loss of the joint space.

Van der Heijde modification of Sharp method (van der Heijde et al., 1992)

The maximum erosion score for hands is 160 and for feet 120. Here, 44 joints are scored for erosions, 32 in the hands and wrists, and 12 in the feet, each of which is scored on a 5 point scale according to the surface area involved, 0 indicates no erosion, 5: extensive loss of bone from more than one-half of the articulating bone. Each foot joint is scored a maximum of 10. For joint space narrowing a maximum score of 120 for hands and 48 for feet is allocated. Joint space narrowing is scored on a 4-point scoring system in 30 hand and wrist joints, and 10 joints in the feet. A score of 0 indicates no narrowing, 1: focal or doubtful narrowing, 2: general narrowing of < 50%, 3: general narrowing of > 50% of the original joint space and 4: bony ankylosis or complete luxation.

A summary of the original sharp method is described below, this method is used by studies US 301 (Strand et al., 1999; Cohen et al., 2001), MN301 (Smolen et al., 1999; Scott et al., 2001) and MN302 (Emery et al., 2000)

Differences in composite (Sharp) scoring method in the trials that reported radiographic assessments. Abbreviations: JSN, joint space narrowing.

Variable	US 301, MN 301, MN302 (Sharp et al., 1971; Sharp et al., 1985)	ATTRACT (Lipsky et al., 2000)	ERA (Bathon 2000; Genovese 2002)
Hands			
Erosions, no. of joints	34	34	34
Scoring range	0-5	0-5	0-5
JSN, no. of joints	36	30	30
Scoring range	0-4	0-4	0-4
Feet			
Erosions, no. of joints	12	10	12
Scoring range	0-5	0-10	0-5
JSN, no of joints	12	10	12
Scroing range	0-4	0-4	0-4
Maximum total score	422	440	398

APPENDIX 5

Classification criteria

1987 revised 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 for 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 juxtaarticular regions, observed by a physician
6. Serum rheumatoid arthritis	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 or these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is *not* to be made. Abbreviations; PIP(s), proximal interphalangeal joint(s); MCPs, metacarpophalangeal joint(s); MTP (s), metatarsophalangeal joint(s) ***(Arnett et al., 1988)***

ACR revised criteria for classification of global functional status in rheumatoid arthritis

Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
Class II	Able to perform usual self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV	Limited in ability to perform usual self-care, vocational, and avocational activities

Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific. ***(Hochberg et al., 1992)***

APPENDIX 6

Health Assessment Questionnaire (Fries et al., 1980)

Date: **Patient Name:**

Please tick the one response which best describes your usual abilities over the past week

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
1. DRESSING and GROOMING				
Are you able to:				
a. Dress yourself, including tying shoelaces and doing buttons?				
b. Shampoo your hair?				
2. RISING				
Are you able to:				
a. Stand up from an armless straight chair?				
b. Get in and out of bed?				
3. EATING				
Are you able to:				
a. Cut your meat?				
b. Lift a full cup or glass to your mouth?				
c. Open a new carton of milk (or soap powder)?				
4. WALKING				
Are you able to:				
a. Walk outdoors on flat ground?				
b. Climb up five steps?				

PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES:

Cane (W)
Walking frame(W)
Built-up or special utensils (E)
Crutches (W)
Wheelchair (W)
Special or built-up chair (A)
Devices used for dressing (button hooks, zipper pull, shoe horn)
Other (specify).....

PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON:

Dressing and Grooming
Eating
Rising
Walking

Please tick the one response which best describes your usual abilities over the past week

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
5. HYGIENE				
Are you able to:				
a. Wash and dry your entire body?				
b. Take a bath?				
c. Get on and off the toilet?				
6. REACH				
Are you able to:				
a. Reach and get down a 5 lb object (e.g. a bag of potatoes) from just above your head?				
b. Bend down to pick up clothing off the floor?				
7. GRIP				
Are you able to:				
a. Open car doors?				
b. Open jars which have been previously opened?				
c. Turn taps on and off?				
8. ACTIVITIES				
Are you able to:				
a. Run errands and shop?				
b. Get in and out of a car?				
c. Do chores such as vacuuming, housework or light gardening?				

PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES:

Raised toilet seat (H)
Bath seat (H)
Bath rail (H)
Long handled appliances for reach (R)
Jar opener (for jars previously opened) (G)
Other (specify)

PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON:

Hygiene
Gripping and opening things
Reach
Errands and housework

Scoring of HAQ:

The scores for the 8 categories* are added together and divided by the number of categories answered (must be a minimum of 6 categories). This yields a single disability index from 0-3 that indicates the extent of the respondent's functional limitations.

*A category score is determined from the highest score of the sub-categories in that category, except when aids or devices are taken into account (see below). For example, if there are three sub-category items (e.g., in the category ARISING), and the patient responds 1, 2, and 0, respectively, to the three sub-category items, the score for the ARISING category will be a 2.

APPENDIX 7

Primary and secondary efficacy (outcome) measures used in all included reports

Abbreviations: HAQ, health assessment questionnaire; MHAQ, modified health assessment quetionnaire; SF-36, PET, problem elicitation technique; ESR. Erythrocyte sedimentation rate; RF, rheumatoid factor; ACR, American College of Rheumatology.

TRIAL	OUTCOME MEASURES																CRITERIA				
	Health Status questionnaires				Symptoms		Global Assessment		Laboratory Measures				Radiography		Physical Signs		ACR			Paulus	
	HAQ	MHAQ	SF-36	PET	Pain	Morning Stiffness	Patient	Physician	Acute phase proteins	ESR	RF	Heam-atology	Sharp score	Larsen score	Tender joints	Swollen joints	20	50	70	20	50
Leflunomide																					
Mladenovic 1995	•				•	•	•	•	•	•	•				•	•	•			•	
Strand 1999	•	•					•	•	•				•		•	•	•	•	•		
Strand 1999 (a)	•	•	•	•	•		•	•	•						•	•	•				
Smolen 1999	•						•	•	•	•				•	•	•	•	•		•	
Emery 2000	•						•	•	•	•	•	•		•	•	•	•				
Sharp 2000	•								•	•			•				•				
Cohen 2001	•	•	•	•	•	•	•	•	•	•			•		•	•	•	•	•		
Kalden 2001	•				•	•	•	•	•	•	•				•	•	•				
Scott 2001	•				•		•	•	•	•	•			•	•	•	•	•	•		
Kremer 2002	•				•		•	•	•						•	•	•	•	•		
Etanercept																					
Moreland 1997	•				•	•	•	•	•	•		•			•	•					
Ericson 1999	•				•	•	•	•	•	•					•	•	•	•	•		
Weinblatt 1999	•				•		•	•	•	•	•	•			•	•	•	•	•		
Moreland 1999	•		•				•	•	•	•	•	•			•	•	•	•	•	•	•
Bathon 2000					•		•	•	•		•		•		•	•	•	•	•		
Genovese 2002	•												•				•	•	•		
Infliximab																					
Elliot 1994					•	•	•	•	•	•	•	•			•	•				•	•
Maini 1998	•				•	•	•	•	•	•	•				•	•	•			•	•
Maini 1999	•					•			•	•	•	•			•	•	•	•	•		
Kavanaugh 2000	•				•		•	•	•	•	•				•	•	•	•			
Lipsky 2000	•		•		•		•	•	•	•			•		•	•	•	•	•		

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