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Biological Agents for Rheumatoid Arthritis

Targeting Both Physical Function and Structural Damage

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Abstract

Rheumatoid arthritis (RA) is a chronic progressive inflammatory disease of multifactorial aetiology. The pivotal role of proinflammatory cytokines in the pathogenesis and perpetuation of synovitis has been demonstrated in basic research since the late 1980s and in clinical research since the early 1990s. Biological agents are monoclonal antibodies or recombinant forms of natural inhibitory molecules which selectively interact with molecules or cell receptors affecting immune or inflammatory processes. In RA, etanercept, infliximab and adalimumab are currently available to target tumour necrosis factor (TNF) and an interleukin (IL)-1 receptor antagonist is available to target IL-1 activity. Trials have shown benefits as monotherapy, although the best results for disease control are seen when biological agents are coadministered with methotrexate.

The use of these agents in clinical trials and in practice has resulted in dramatic improvements in RA disease control, and delay and prevention of radiographic damage. The remarkable benefits to patients in well-being, quality of life and function, and the speed of onset of action are reminiscent of the early days of corticosteroid use. Ten years after the first clinical trials of anti-TNF therapies, the adverse effect profile is evolving and includes, for anti-TNF therapy, an increased risk of infections associated with immune suppression, injection and infusion reactions, and a risk of drug induced autoimmune syndromes such as systemic lupus erythematosus. Where these drugs are affordable, the prognosis of individuals for control of severe RA is better than ever before. This manuscript summarises the clinical trial results and post-marketing information regarding the biological agents currently in use for RA.

Rheumatoid arthritis (RA) is a chronic inflammatory disease with multifactorial aetiology. The pathophysiology of the disease is characterised by the infiltration of immunocompetent cells into the synovium, and stimulation and proliferation of synovial fibroblasts. Antigen-activated T-cells infiltrate the synovial membrane leading to a series of events, including vascular and synovial proliferation, and formation of pannus tissue, which invades and destroys articular cartilage and bone.[1] Joint erosions develop within the first year in 30%, and in 2 years in 70% of patients.[2] More than 40% of patients

with RA withdraw from the workforce within 4 years of diagnosis.[3] Not only is there loss of quality of life, but mortality is also increased in patients with RA.[4]

Conventional treatment with disease-modifying antirheumatic drugs (DMARDs) in RA is unsatisfactory. A minority of patients achieve long-term disease control or remission with a single DMARD and, in those with good control, the majority eventually discontinue therapy because of adverse effects or loss of effectiveness after months or years. Wolfe et al.[5] reported the median time to treatment discontinuation to be 2 years using monotherapy with hydroxychloroquine and gold, and under 5 years using methotrexate. The most common reason for treatment discontinuation was adverse effects. All long-term studies have reported similar disappointing results when looking at adherence. Remission is uncommon, regardless of treatment choice, and as long as there are no cures, lifelong treatment is needed. Evolution of conventional DMARD treatment has been in the direction of combination of DMARDs, coadministration with low-dose prednisone, and initiation of treatment with effective agents early in the disease process. These approaches have been evaluated in prospective controlled trials, and results in terms of disease control in appropriately screened patients are improved compared with traditional single-agent DMARD use.[6-11]

Regardless of such incremental improvements, conventional treatment of RA remained unsatisfactory until the advent of biological agents. Biological agents are monoclonal antibodies, or recombinant forms of natural inhibitory molecules, which selectively target molecules or cell receptors affecting immune or inflammatory processes. In RA, cytokines are the major targets of currently available biological agents. There are many biological processes that might yield to this approach to therapy, and numerous biological agents in every stage of development and investigation. This article focuses on those agents that are currently in use, their benefits, adverse effects, and the role and rationale for their use in RA. As of April 2004, etanercept, infliximab and adalimumab are available to target tumour necrosis factor (TNF) action, and an interleukin (IL)-1 receptor antagonist (IL-1RA) is available to target IL-1 activity.

1. Tumour Necrosis Factor (TNF)α and Interleukin (IL)-1

TNFα and IL-1 are major cytokines that are found in increased levels in synovial fluid of patients with active RA. Also found are increased levels of natural inhibitors of TNF and IL-1, including IL-1RA, soluble IL-1 receptors and soluble TNF receptors.[12-14]

TNFα was discovered in 1975. TNFα originates as a precursor molecule in a variety of cells; in RA the activated macrophage is the major cell of origin of TNFα. The precursor is cleaved by TNFα-converting enzyme to a soluble fragment, which then aggregates to trimolecular complexes of TNFα. These complexes bind to receptor sites on fibroblasts, endothelial cells or other inflammatory cells. The biological action of TNFα is initiated by cross-linking of two receptors on a target cell. TNFα induces the production of other inflammatory cytokines, stimulates endothelial cells to express adhesion molecules that attract leucocytes into affected joints, increases the rate of synthesis of metalloproteinases by synovial macrophages, fibroblasts, osteoclasts and chondrocytes, and inhibits the synthesis of proteoglycans in cartilage.[15] The biological effects of TNFα in human disease include fever, tissue inflammation, shock and an increase in acute phase proteins.

IL-1 refers to a family of three cytokines comprising two agonists (IL-1α and IL-1β) and one antagonist (IL-1RA). Activated monocytes and macrophages are the primary source of IL-1α and IL-1β. These cytokines compete for the binding sites on the IL-1 receptor, which is found on the outer membrane of rheumatoid synovial cells. These cells are activated by binding of IL-1 to its receptor, and this results in cell activation, synovial inflammation, and bone and cartilage resorption. IL-1 production is TNFα-dependent. Blocking TNFα with neutralising antisera in RA synovial cultures leads to

reduced IL-1 production within 3 days.[16] IL-1RA is a naturally occurring acute-phase anti-inflammatory protein. It acts by blocking the binding of IL-1 to its receptor on the outer surface of rheumatoid synovial cells and antagonises the effect of IL-1.[17] Greater than 95% of receptor occupancy is required to block IL-1 signalling.

2. Measurement of Treatment Effect, Function, Quality of Life and Damage

The American College of Rheumatology (ACR) and the World Health Organization have adopted a core set of criteria to distinguish improvement of arthritis activity in trials from placebo effects.[18] To meet the ACR definition of improvement, a patient must achieve a minimum of 20% improvement in tender and in swollen joint count, plus a 20% improvement in three of five of the following measures: patient global assessment, pain, physician global assessment, patient-assessed disability by the Health Assessment Questionnaire (HAQ),[19] and acute-phase reactants. Recent trials have adapted the ACR criteria to define greater percentages of improvement of 50% and 70%. The HAQ disability index is the arthritis-specific quality-of-life instrument most commonly used to measure functional status.[19] It is scored on a scale of three units, with higher numbers indicating increased disability. A 0.25 unit change in the HAQ is considered to be a clinically significant change in the level of disability.[20] Using the HAQ scores of 5012 RA patients, Wolfe and Michaud[21] have calculated that a 0.25 unit increase in the HAQ is associated with a 10% increase in work disability.[21]

In Europe, the measurement which is most commonly used to define improvement and worsening is the Disease Activity Score (DAS). The European League Against Rheumatism (EULAR) criteria defines improvement and disease control in terms of measurement of change and level attained in the DAS.[22] The DAS index is obtained using a formula combining the tender joint count, swollen joint count, patient global assessment and erythrocyte sedimentation rate (ESR) into a single number.[23]

The radiograph is regarded as the gold standard to measure damage in RA. The two methods used to score radiographic damage in most common use are the Larsen and the Sharp scores.[24-28] The latter was originally developed for the hands and was modified by van der Heijde et al.[29] to include the feet. Both methods provide a total score of damaged joints. The Larsen method assesses the amount of joint damage with a single score per joint before totalling over the joints and utilises standard radiographs for comparison to establish the score in individual joints. The Sharp score grades erosions and joint-space narrowing separately in each joint, and totals to a composite measure. Erosions are scored from 0 to 5, and joint-space narrowing from 0 to 4. The Genant/Sharp score is a modification of the Sharp scoring method that includes evaluation of 14 hand joints for erosions and 13 hand joints for narrowing. Each joint is evaluated qualitatively for erosions on a 0–3 scale and for narrowing on a 0–4 scale and there are allowances for half grades to improve the description. Paired films, blinded to sequence, are examined.[30]

3. Biological Agents Targeting TNFα

3.1 Etanercept

There are two cell surface TNF receptors, p55 (55 kDa) and p75 (75 kDa), that mediate the activity of TNF on effector cells. Soluble TNF receptors consist of the extracellular portions of the receptor, which serve as physiological regulators of the inflammatory response by inhibiting TNF activity. Etanercept, a human TNF receptor p75 fusion protein, was developed to neutralise TNF activity in RA. DNA encoding the soluble portion of human TNF receptor p75 was linked to DNA encoding the Fc portion of a human IgG1 molecule, and the combined DNA was then expressed in a mammalian cell line.[31] The first reports of dose-finding studies were published in 1996[32] and the first placebo-controlled trial was published in 1997.[31]

Patients eligible for this trial had failed between one and four DMARDs, had a 1-month DMARD-free washout, and had a minimum of ten swollen

joints. Etanercept produced significant improvement in all measures of disease activity. By 3 months, there was a 58% reduction in swollen joint count at the 16 mg/m^2 twice weekly dosage, compared with a 24% reduction in patients assigned to placebo (figure 1) The tender joint count was also reduced to a greater extent by etanercept 16 mg/m^2 twice weekly than by placebo (figure 2). Fifty-nine percent of patients achieved ACR20 by 1 month and 57% achieved ACR50 by 3 months, compared with 20% and 7%, respectively, for placebo. Cessation of therapy caused an increase in disease activity, confirming that continued administration of etanercept is necessary to sustain the therapeutic effect.

In a 6-month trial comparing twice weekly subcutaneous injections of etanercept 10mg, etanercept 25mg and placebo, the primary endpoints were ACR20 and ACR50 improvements at 3 and 6 months.[33] Inclusion criteria included failure of between one and four DMARDS, a minimum of ten swollen joints and either 45 minutes of morning stiffness or elevated C-reactive protein (CRP) or ESR. Patients enrolled had a mean of 25 swollen joints at baseline and 80% were rheumatoid factor (RF) positive. Ninety percent had previously received methotrexate. Mean ESR was 40mm. Improvement was rapid. By 2 weeks, 32% of the etanercept 25mg group had achieved ACR20 compared with 1% of the placebo patients. By 3 months, the mean number of swollen joints had fallen by 47% in the etanercept 25mg group compared with 1% of placebo-treated patients. By 3 months, 62% of the etanercept 25mg group had achieved ACR20, 41% had achieved ACR50 and 15% had achieved ACR70; these responses were maintained at the 6-month assessment. In etanercept-treated patients, ESR fell from a mean of 35mm at baseline to 15mm at 6 months, compared with an increase from 39mm at baseline to 53mm at 6 months in placebo-treated patients. Fifty-three percent of placebo-treated patients withdrew prematurely because of lack of effect compared with 15% of those who received etanercept 25mg ($p < 0.001$). The impressive results in terms of quality of life are illustrated in figure 3. There were statistically significant and clinically important improvements in general health status, arthritis-specific health status, vitality and disability indexes, each of the subscales of the HAQ, and in the mental health domain.

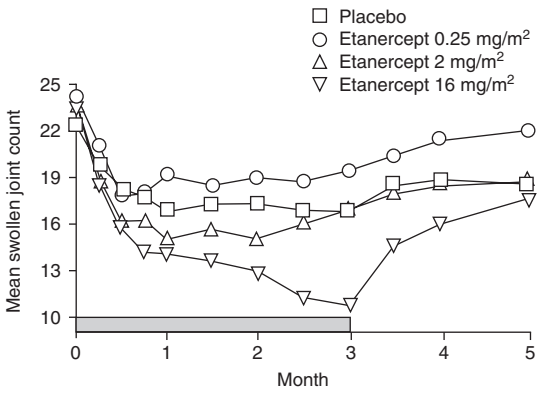

Fig. 1. Mean swollen joint count with etanercept versus placebo treatment. The shaded bar represents the treatment period. For each patient, missing values were replaced by the last available value (reproduced from Moreland et al.,[31] with permission from the Massachusetts Medical Society).

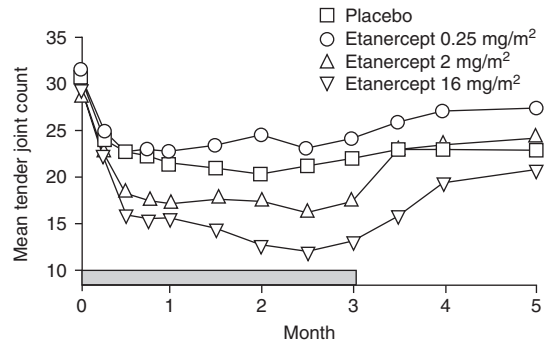

Fig. 2. Mean tender joint count with etanercept versus placebo treatment. The shaded bar represents the treatment period. For each patient, missing values were replaced by the last available value (reproduced from Moreland et al.,[31] with permission from the Massachusetts Medical Society).

In the Etanercept in Early Rheumatoid Arthritis trial (ERA), etanercept was compared with methotrexate in a double-blind, randomised controlled trial which enrolled patients with RA for <3 years.[34] This study was designed to evaluate radiographic progression as well as clinical outcomes. Consequently, inclusion criteria were developed so that patients at high risk of disease progression would be enrolled and the duration of the trial was

12 months. Eligible patients were required to have a positive RF, or at least three erosions on hand and feet radiographs and an elevated ESR or CRP or 45 minutes of morning stiffness. The rate of progression of erosions estimated based on the degree of radiographic damage and the duration of RA at baseline and assuming no treatment for a year, was 4–5 points per year. This is equivalent to five new erosions per year, or the erosion of 80–100% of one joint per year, or complete loss of the joint space in a single joint per year. No patient had received prior methotrexate, and there was a 4-week washout for other DMARDs. Methotrexate dosage was escalated to 15mg per week by 4 weeks and 20mg per week by 8 weeks, with adjustment permitted for toxicity such that ultimately the mean methotrexate dosage was 19mg per week orally, given with placebo injections. The etanercept patients received either 10 or 25mg twice per week subcutaneously. Baseline disease characteristics of enrolled patients included: positive RF in 88%; average disease duration of 12 months; mean of 24 swollen joints; 86% had erosions; and 40% were taking prednisone at a mean daily dose of 7mg for the methotrexate-treated patients and 9mg for those randomised to etanercept

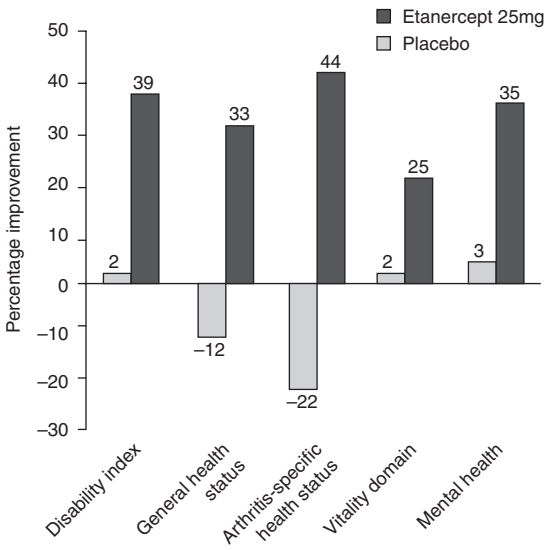

Fig. 3. Percentage improvement in quality-of-life measures over 6 months; etanercept 25mg compared with placebo.[33]

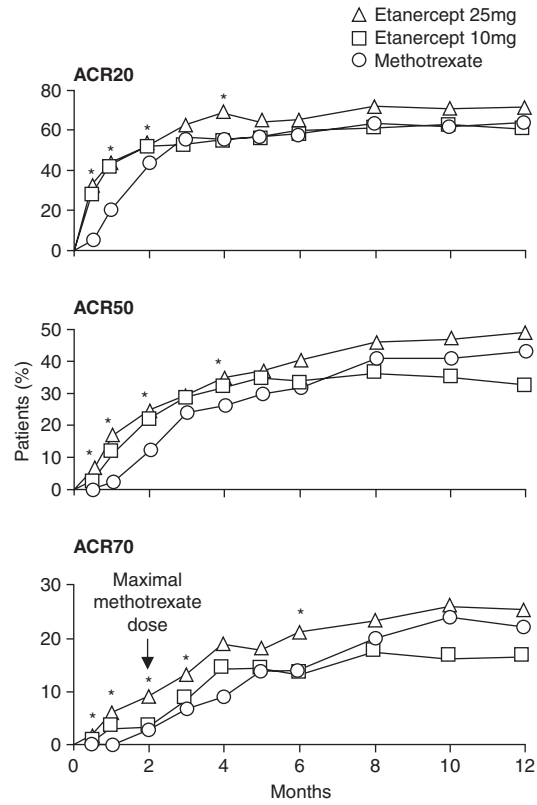

Fig. 4. Percentages of patients with rheumatoid arthritis who had an improvement, according to the criteria of the American College of Rheumatology (ACR), of 20% (ACR20), 50% (ACR50) and 70% (ACR70) during treatment with etanercept 25mg, etanercept 10mg or methotrexate (reproduced from Bathon et al.,[34] with permission from the Massachusetts Medical Society). * indicates significant differences ($p < 0.05$) between the methotrexate group and the group assigned to receive etanercept 25mg.

25mg. The percentages of patients improved and the time course to improvement according to ACR20, ACR50 and ACR70 criteria are illustrated in figure 4. At 2 months, the differences between etanercept and methotrexate for ACR20, ACR50 and ACR70 responses were statistically significant. At 6 and 12 months, however, the benefit of methotrexate was evident and there was no longer a statistically significant difference in ACR20 or ACR50; ACR70 remained superior in the etanercept group. At 12 months, 72% of patients in the etanercept 25mg group had achieved ACR20 compared with 65% in the methotrexate group, and 44% of the etanercept

group had achieved ACR50 compared with 40% of the methotrexate group (not significant). Although results for etanercept were superior in a number of measures, and although the benefits of etanercept were evident earlier, the ERA trial has been interpreted by many to highlight the effectiveness of methotrexate therapy using rapid dose escalation in early RA.

Evaluation of radiographic progression showed that there was a difference in the rate of erosion development comparing methotrexate and etanercept 25mg, which was evident by 6 months of therapy. Over the initial 6 months, mean increase in erosion score was 0.3 in etanercept 25mg recipients and 0.68 in the methotrexate-treated group. In the methotrexate group, the rate of change in erosion slowed during the second 6 months compared with the first 6 months. Mean changes from baseline in erosion scores and total damage scores are illustrated in figure 5. During the second 6 months of therapy, the rate of change in erosions was similar in the groups assigned to methotrexate and etanercept. At 6 months, the mean total score on the Sharp scale had increased by 0.57 in the etanercept 25mg group and by 1.06 in the methotrexate group ($p = 0.001$), and the respective increases were 1 and 1.59 at 12 months. Comparing methotrexate with etanercept 25mg, the rate of erosion development represents one new erosion each year on methotrexate and one every 2 years on etanercept, with the differences most evident during the first 6 months of therapy. Of interest, the majority of patients did not develop new or worsening erosions. Over 1 year of treatment, 72% of patients receiving etanercept and 60% of patients receiving methotrexate did not have any erosion progression ($p = 0.007$). Changes in joint-space-narrowing scores were no different comparing the two groups at 6 and 12 months.

In the ERA trial involving 632 RA patients, there were two deaths: one in the etanercept 10mg group from metastatic lung cancer after 2 months and one in the etanercept 25mg group from ruptured aortic aneurysm.[34] There were three cases (1%) of methotrexate pneumonitis, and nausea occurred in 29% of patients receiving methotrexate and 17% of etanercept recipients ($p < 0.05$). Alopecia occurred in 12% of methotrexate and 6% of etanercept recipients. Injection site reactions occurred in 37% of patients receiving etanercept 25mg. Upper respiratory tract infections occurred in 39% of methotrexate recipients compared with 35% of etanercept 25mg recipients. Infections requiring hospitalisation or intravenous antibacterials were similar, occurring in <3% of patients in each group.

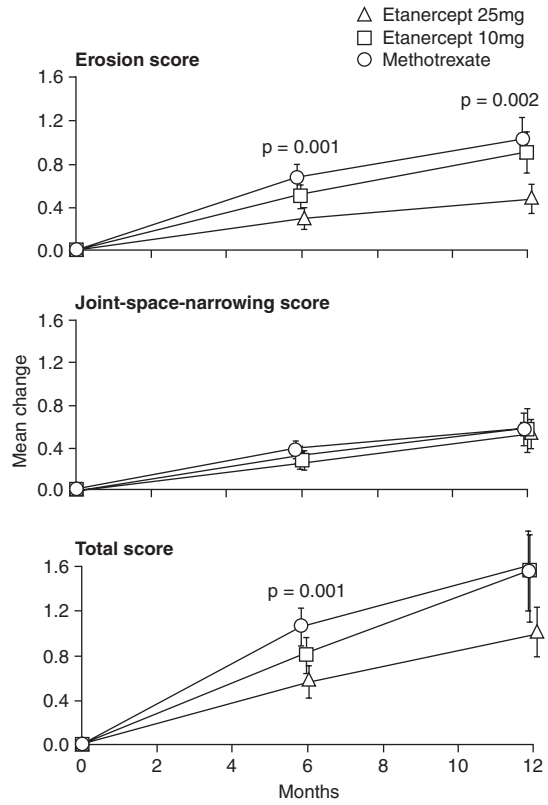

Fig. 5. Mean (± SE) changes from baseline in erosion scores, joint-space-narrowing scores and total scores on the Sharp Scale at 6 and 12 months in patients with rheumatoid arthritis who received etanercept 25mg, etanercept 10mg or methotrexate. p-Values indicate significant differences between the methotrexate group and the group assigned to receive etanercept 25mg (reproduced from Bathon et al.,[34] with permission from the Massachusetts Medical Society).

A 24-week, randomised, double-blind trial evaluated the benefit of etanercept 25mg twice weekly versus placebo, added to baseline methotrexate in 89 patients with active RA despite methotrexate at dos-

ages between 15 and 25mg (mean 19mg) per week.[35] Baseline and outcome measures are included in table I and table II. These tables also include similar data from recent trials of biological agents added to methotrexate and from one trial of a conventional DMARD, ciclosporin (cyclosporin), added to methotrexate in severe RA. The latter is included as an example of trials of DMARD combination with methotrexate in the prebiological era. Because of differences in patient population, trial design and duration, outcome measures and statistical analysis, it is inappropriate to use these studies to compare effectiveness of therapy. Table I illustrates these important differences between trial populations in terms of disease duration and activity as well as methotrexate dose at baseline.

Etanercept added to methotrexate resulted in improvement in all ACR response criteria at 24 weeks.[35] At 6 months, ACR20 was achieved by 71% of patients in the etanercept plus methotrexate group compared with 27% in the placebo plus methotrexate group. ACR50 and ACR70 were achieved by 39% and 15%, respectively, in the etanercept/methotrexate group versus 3% and 0% in the methotrexate/placebo groups. Median number of swollen joints fell from 20 to 7 in those taking etanercept/methotrexate, compared with a change from 17 to 11 in patients taking methotrexate/placebo (figure 6). The benefit of adding etanercept to methotrexate partial responders or nonresponders was rapid. At every evaluation, beginning at week 1, a significantly greater proportion of patients receiving the combination achieved ACR20. By 4 weeks, the benefit in terms of ACR50 was statistically significant; at 3 months the difference in ACR70 responses was significantly different comparing the combination with methotrexate/placebo. The time course and extent of improvements are illustrated in figure 6. The median disability index score from the HAQ improved over 24 weeks from 1.5 to 0.8, an improvement of 47%, in patients receiving etanercept/methotrexate, compared with 27% in the methotrexate/placebo group. Injection site reactions were reported by 42% of patients receiving etanercept/methotrexate compared with 7% of those re-

Table I. Demographics and disease characteristics from recent trials of biological agents added to methotrexate and from a trial of ciclosporin added to methotrexate. All trials were double-blind and randomised with placebo/methotrexate comparators

Drug and dosage	Duration of trial (wks)	No. of patients (active/placebo)	RA duration (y)	Concomitant corticosteroids (%)	RF+ (%)	Methotrexate dose (mg/week)	Reference
Etanercept 25mg twice weekly	24	59/30	13	53	88	19	35
Infliximab 3mg/kg q8w	30	86/88	8.4	63	84	15	36
Adalimumab 40mg q2w	24	67/62	12	46	81	16	37
Anakinra	24						38
1 mg/kg/day		59/74	6.5	63	73	17	
2 mg/kg/day		72/74	8	65	83	17	
Ciclosporin 2.97 mg/kg/day (mean dose)	24	75/73	10	NR	NR	<15	6

NR = not reported; **qxw** = every *x* weeks; **RA** = rheumatoid arthritis; **RF+** = rheumatoid factor-positive.

Table II. Data from recent ≥24-week trials of biological agents added to methotrexate and from one trial of ciclosporin added to methotrexate. All trials were double-blind and randomised with placebo/methotrexate comparators[a][6,35-38]

Drug	Swollen joints (no.)			HAQ (units)			C-reactive protein (mg/L)			ACR response (active/placebo [%])			Reference
	baseline	final	% change active/ placebo	baseline	final	% change active/ placebo	baseline	final	% change active/ placebo	20	50	70	
Etanercept*	20	7	65/35	1.5	0.8	47/27	2.2	0.5	77/31	71/27	39/3	15/0	35
Infliximab*													
3 mg/kg q8wk	19	9	52/20	1.8	1.5	17/3	3.1	0.8	74/9	50/20	27/5	8/0	36
Adalimumab	17.3	6.9	60/18	1.55	0.93	40/17	2.1	0.5	71/21	45/9	55/5	26.9/4.8	37
Anakinra													38
1 mg/kg/day	17.6	11.2	36/23	1.3	0.93	28/11	1.55	0.78	50/10	42/23	24/4	10/0	
2 mg/kg/day	17.4	9.8	44/23	1.3	0.79	39/11	2	1.23	39/10	35/23	17/4	2/0	
Ciclosporin	15.2	9.5	38/11	1.4	1.15	18/2	NR	NR	NR	48/16	NR	NR	6

a Results in mean values except where * indicates medians.

ACR = American College of Rheumatology; **HAQ** = Health Assessment Questionnaire; **NR** = not reported; **q8wk** = every 8 weeks.

ceiving placebo/methotrexate. There were no deaths. Infections were reported by 63% of methotrexate/placebo and 51% of etanercept/methotrexate recipients.

In October 2002, Kremer et al.[39] reported the results of median 4-year follow-up in 79 of 89 patients who had been enrolled in the earlier trial of etanercept added to methotrexate.[35] At the time of reporting, 64 of 79 patients remained on therapy; the authors noted reduction or discontinuation of methotrexate treatment in 55%, and of corticosteroids in 82% of patients. In 42 patients who had completed 4 years of treatment, 12% had achieved ACR70, 28% had no tender joints and 20% had no swollen joints.[39] Withdrawals during the median 4-year follow-up were because of lack of efficacy in three patients, adverse effects in four, patient's decision in five, and miscellaneous in three patients.

Patients who entered the ERA trial,[33] 161 randomised initially to etanercept and 143 randomised initially to methotrexate, were followed up at 4 years. After 4 years of continuous etanercept therapy, radiographic progression was 0.9 Sharp units in the first year, 0.57 Sharp units in the second year and 0.37 Sharp units in the third year.[40]

3.2 Infliximab

Infliximab is a chimeric human/mouse monoclonal anti-TNFα antibody consisting of the constant region of human IgG1 coupled to the Fv region of a high-affinity neutralising anti-human TNFα antibody. Infliximab binds to both soluble and transmembrane forms of TNFα. Binding to soluble TNFα results in loss of bioactivity; binding to membrane-bound TNFα leads to cell death by complement- and/or antibody-dependent cell-mediated mechanisms.[41] Pharmacodynamic effects and effects on inflammatory cytokines, lymphocyte migration and neovascularisation have been previously reviewed.[42]

The first studies of use of infliximab in RA were published in 1993.[43] Twenty patients with active RA were treated in an open-label, phase I/II trial with infliximab 20 mg/kg as a single dose; impressive benefits were measured at 6 weeks. A placebo-

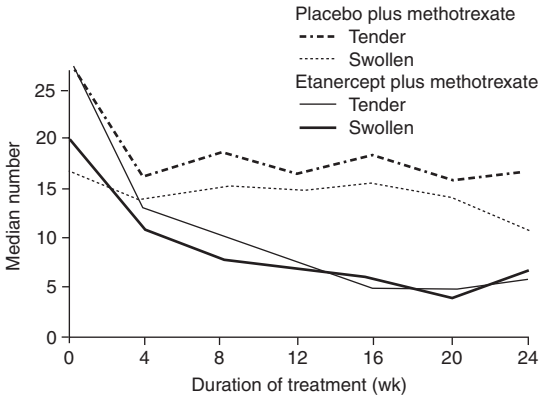

Fig. 6. Median number of tender and swollen joints in patients receiving etanercept plus methotrexate compared with placebo plus methotrexate during the study by Weinblatt et al., 1999[35] (reproduced from Weinblatt et al.,[35] with permission from the Massachusetts Medical Society).

controlled trial comparing single doses of infliximab 10 mg/kg with 1 mg/kg and with placebo in 93 patients confirmed these early results.[44] A subsequent controlled trial aimed to establish the optimum dose and the benefits and adverse effects of repeated infusions of infliximab with and without methotrexate versus placebo added to methotrexate.[45]

One hundred and one patients entered this multicentre, 26-week, double-blind, placebo-controlled trial, which compared infliximab at doses of 1, 3 or 10 mg/kg with or without methotrexate, with placebo plus methotrexate.[45] Infusions of infliximab/placebo were administered at 0, 2, 6, 10 and 14 weeks, and final assessment was done at 26 weeks. Enrolled patients had been receiving methotrexate for a minimum of 6 months at a dosage of 7.5–15mg per week. Median swollen joint count at baseline ranged between 16 and 20 for the seven treatment groups, and median ESR ranged from 44 to 60mm. The best outcomes were seen in patients randomised to infliximab 3 or 10 mg/kg together with weekly methotrexate. Clinical response, measured by Paulus 20% improvement and 50% improvement, respectively, were 40% and 40% for the 3 mg/kg dose, and 38% and 42% for the 10 mg/kg dose. Discontinuations in the infliximab plus methotrexate groups were for lack of effect in one patient at the 10 mg/kg dose, and adverse effects in one patient at the 10 mg/kg dose. There were three remissions in 28 patients assigned to infliximab 3 or 10 mg/kg. Median swollen joint counts fell from 15 to 4 on the 3 mg/kg dose, and from 18 to 6 on the 10 mg/kg dose, both doses given with methotrexate. Seven patients withdrew, five of these because of infusion reactions. Twenty-eight of 87 patients (32.2%), who received infliximab in any dose, developed infections that required treatment with antibacterials, compared with 3 of 14 infections in patients receiving placebo plus methotrexate (21.4%). Two infections were serious: one bacterial endophthalmitis after cataract surgery 9 weeks after the fifth dose of infliximab 3 mg/kg; and one death from staphylococcal septicaemia and septic shock, 15 weeks after the third infusion of infliximab 10 mg/kg. Anti-DNA antibodies developed in 8% of patients, without symptoms of lupus. Human antichimeric antibodies (HACA) occurred in 21% of infliximab 3 mg/kg recipients and 7% of infliximab 10 mg/kg recipients who did not receive methotrexate, and in 7% and 0%, respectively, who did receive methotrexate. The apparent synergy of the action of infliximab plus methotrexate was suggested to be partly based on decreased immunogenicity of infliximab as manifested by reduced HACA in those taking concomitant methotrexate.

Following this successful short-term trial, infliximab was evaluated in a 54-week, multicentre study involving 428 patients with active RA despite at least 12.5mg of methotrexate per week. The first analysis of clinical outcomes was done at 30 weeks and reported in December 1999.[36] Outcomes at 54 weeks, which included evaluation of radiographic damage, were reported in 2000.[46] In this trial, commonly named ATTRACT (Anti-Tumour necrosis factor Trial in Rheumatoid Arthritis with Concomitant Therapy), patients were randomised to one of four doses of infliximab or to placebo. Mean duration of disease ranged from 9 to 12 years in the various treatment groups. Baseline disability and radiographic scores of patients in ATTRACT indicate that patients had very severe RA with fairly extensive joint damage at baseline. Of all the recent

trials reporting radiographic outcomes, ATTRACT enrolled a group which is distinguished by the extent of radiographic destruction at baseline. Approximately 80% were positive for RF and mean ESR was 50mm. At baseline, mean methotrexate dosage was 15mg weekly. All dosages of infliximab were effective in terms of ACR20, ACR50 and ACR70 at 30 weeks. All dosages of infliximab resulted in improvement in HAQ scores. Baseline and 30-week outcome measures for the 3 mg/kg every-8-week dosage are included in table I and table II. ACR 20% improvement was seen in 50% of patients who received 3 mg/kg every 8 weeks and in 50% of those receiving 10mg/kg every 8 weeks. ACR 50% improvement was seen in 27% and 31% of those who received 3 or 10 mg/kg every 8 weeks, respectively. There appeared to be a dose-response effect in terms of improvement in clinical and laboratory outcomes. ACR50 response rates were significantly higher in the groups receiving infliximab 3 mg/kg every 4 weeks (34.1%), 10mg/kg every 8 weeks (40%) and 10 mg/kg every 4 weeks (37.5%) than in the group receiving 3mg/kg every 8 weeks (21.5%). At a dosage of 10 mg/kg every 4 weeks there was a 63% reduction in swollen joints and a 65% reduction in tender joints, compared with 50% and 55% for 3 mg/kg every 4 weeks, and 37% and 49% for 3 mg/kg every 8 weeks. At the 3 mg/kg dose every 8 weeks, 73% of patients completed the 54 weeks compared with 86% at the 10 mg/kg dose every 8 weeks. A more recent analysis of data from ATTRACT explored further the issue of optimal dosage.[47] St Clair et al.[47] hypothesised that inadequate responses at the 3 mg/kg every 8 weeks dosage is likely to result from incomplete suppression of TNFα. In analysing serum samples from ATTRACT patients receiving infliximab 3 mg/kg every 8 weeks, 22–30% of serum samples had undetectable trough concentrations of infliximab prior to infusions at weeks 22–54. Furthermore, the authors reported that joint damage prevention was superior in patients with higher serum infliximab trough concentrations.

At 54 weeks, radiographic score had increased by 10% in methotrexate-treated patients compared with zero mean change in radiographic score for all infliximab-treated patients. Thirty-one percent of patients assigned to methotrexate alone had radiographic evidence of major progression compared with 0–13% in the groups assigned to infliximab plus methotrexate. Improvement in radiographic scores occurred in 39–55% of infliximab-treated patients versus 14% of methotrexate-treated patients. The results in terms of radiographic outcomes are illustrated for methotrexate/placebo and methotrexate/infliximab in figure 7.

Infections requiring antibacterial therapy developed in 35% of patients receiving methotrexate and in 44% of those receiving infliximab plus methotrexate. Thirty-four percent of patients receiving infliximab/methotrexate developed upper respiratory infections versus 22% of those receiving placebo/methotrexate. Seventeen percent of infliximab/methotrexate recipients developed sinusitis compared with 6% of those receiving placebo/methotrexate. Neither deaths nor cancer incidence were increased in the infliximab/methotrexate-treated patients compared with placebo/methotrexate-treated patients over the 54-week course. Autoantibodies

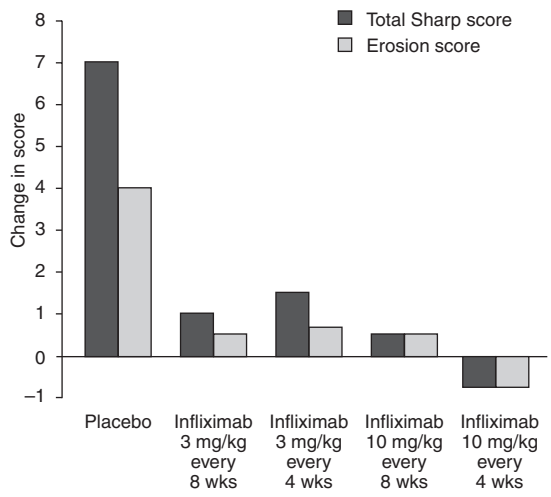

Fig. 7. Change in total radiographic score and erosion score after 54 weeks of treatment: placebo or infliximab at varying dosages added to methotrexate (mean dosage 16mg per week in the Anti-Tumour necrosis factor Trial in Rheumatoid Arthritis with Concomitant Therapy [ATTRACT].[46]

were present in 8% of 60 post-treatment discontinuation samples.

3.3 Adalimumab

Adalimumab is the first fully human (100% human peptide sequences) anti-TNFα monoclonal antibody to be investigated for the treatment of RA. Early trials enrolled patients with long-standing disease refractory to several conventional DMARDS and active RA manifested by a DAS >3.2. The first clinical trial randomised 120 European patients to a single intravenous dose of adalimumab varying from 0.5 to 10 mg/kg; these patients were evaluated weekly for 1 month.[48] Benefit was noted between 1 and 7 days after treatment and peaked between 1 and 2 weeks. Within the month, 28% of patients who received either 5 or 10 mg/kg achieved an ACR50 response at one or more weekly assessments. In 61% of patients the benefit from a single intravenous injection lasted 29 days or longer. This was followed by an open-label phase of treatment during which injections were administered at intervals that were adjusted according to the DAS. Patients received injections when the DAS rose above 2.4. Following this regimen, the mean adalimumab dose interval was 2.5 weeks. Response, defined as a reduction of 1.2 in the DAS, was achieved by 80% of patients. Swollen joint count and tender joint count were reduced by 60%. Ten percent of patients discontinued adalimumab because of lack of effect in six, adverse effects in five and patient request in one patient. In a subset of 66 patients with a 12-year history of RA, radiographs showed no change in Sharp score over 12 months.[49,50] In 36 patients with radiographs at baseline and after 2 years of treatment, 42% receiving adalimumab monotherapy showed no increase in joint damage.[51]

DE007 was a randomised, double-blind, placebo-controlled trial involving 283 European patients designed to evaluate varying dosages of adalimumab monotherapy (20, 40 and 80mg subcutaneously every 2 weeks) compared with placebo over 12 weeks.[49] Adalimumab resulted in an ACR20 response in 49% of patients receiving the 20mg dose, 57% of those receiving the 40mg dose and 56% of those receiving the 80mg dose, compared with 10% of placebo/methotrexate recipients. The 40mg and the 80mg dose were equally effective and the 20mg dose less effective.

The 24-week North American DE009 Anti-TNF Research Study Program of the Monoclonal Antibody Adalimumab (ARMADA) phase II/III trial involved 271 patients with a mean disease duration of 12 years, 81% of whom were RF-positive. It compared adalimumab in varying doses with placebo, both added to methotrexate (mean dosage 16.8 mg/week).[37] Baseline and outcome measures are included for the 40mg every 2 weeks dosage in table I and table II. Mean baseline swollen joint count was 17.3 in these patients who had received a mean of three previous DMARDs and were partial responders to methotrexate. By 1 week after initiation of treatment, 17% of patients receiving the adalimumab 40mg dose had achieved an ACR20, compared with 4% of placebo-treated patients. By week 24, mean swollen joint count in patients receiving adalimumab 40mg every 2 weeks with methotrexate was seven. CRP fell from mean of 2.1 to a mean of 0.5 mg/L. At week 24, ACR20 response was achieved by 65.7% of patients receiving the 40mg dose and 65.8% of those receiving the 80mg dose with methotrexate, compared with 14.5% for placebo/methotrexate recipients. ACR50 responses were achieved by 53.7% at the 40mg dose compared with 8.1% in the placebo/methotrexate group. ACR70 responses were seen in 26.9% of patients taking adalimumab 40mg with methotrexate, and in 4.8% of placebo/methotrexate recipients. Injection site reactions were reported by 1.5% of adalimumab-treated patients compared with 3.2% of placebo-treated patients. Infections occurred at a rate of 1.38 per patient per year in placebo/methotrexate-treated patients, and 1.55 per patient per year in adalimumab/methotrexate-treated patients. Pneumonia occurred in two adalimumab/methotrexate recipients who remained in the trial. Discontinuation because of adverse effects occurred in five patients receiving adalimumab/methotrexate (injection site plus other cutaneous reactions in four, cough and asthenia in one) and two receiving placebo/methotrexate. Of

patients treated with adalimumab/methotrexate, 3.9% became positive for ANA (anti-double stranded DNA antibodies), whereas none of those receiving placebo/methotrexate did.

3.4 Long-Term Safety of Anti-TNF Therapy

The evaluation of long-term safety requires observation of patients followed according to normal practice for a minimum of 5 years. Such data are not yet available. Typically, industry-sponsored clinical trials select for patients with high disease activity but exclude those with potentially serious co-morbid conditions and serious rheumatoid extra-articular involvement. Therefore, safety results from trials may not translate into safety in practice. There is a sparse literature on safety of anti-TNF therapy as it is used in the community. Selected safety data from trials and published observational cohort studies are summarised here. Information from the US FDA March 2003 update on the safety of new drugs for RA[52] is included for completeness.

Four-year safety data for 64 patients from the ERA trial were recently reported.[40] This population of patients with disease duration averaging 12 months does not compare with those who were enrolled in ATTRACT[36,46] or with other observational cohorts with more severe long-standing disease and co-morbidity. Infection requiring intravenous antibacterial therapy or hospitalisation occurred at a rate of 0.05 per patient in year 1, and 0.02 per patient in year 4. No cases of tuberculosis (TB) or opportunistic infections developed during 4 years of follow-up of ERA trial patients who continued on etanercept. Safety results of all patients who had participated in etanercept trials in North America and Europe have been reported in abstract form.[53] The report included data on 1442 patients in North America and 612 in Europe, encompassing 5547 patient-years. The incidence of infection requiring intravenous antibacterials or hospitalisation was 0.04 per patient-year.

Phillips et al.[54] performed a retrospective review of 180 patients who were started on etanercept between December 1998 and April 2000. 144 of 180 patients had RA and 56% were receiving corticosteroids; 26% discontinued etanercept – 2.9% because of serious adverse events, most commonly infections; there were two deaths resulting from infection. Phillips et al.[54] considered that anti-TNF therapy might have contributed to infectious complications, including two cases of septic arthritis and a case of psoas abscess caused by *Mycobacterium avium intracellulare* complex.

Upper respiratory infections and sinusitis were increased in trial patients receiving infliximab in ATTRACT.[36,46] Although the incidence of serious infections in ATTRACT was not significantly increased, infections were more common in the 10 mg/kg dose groups. In the second 6 months of the trial, two deaths occurred: one from disseminated TB and one from coccidioidomycosis. Among 1897 patients followed in infliximab trials, 4% developed one or more serious infections compared with 7% reported in placebo-treated patients.[55]

An observational cohort included 529 Belgian patients who had received infliximab 3 mg/kg every 8 weeks for 1 year up until January 2002. Serious infections developed in 7.1% of patients.[56] These included two cases of TB; there were three deaths from pneumonia, endocarditis and multifocal leukoencephalopathy. Fitzcharles et al.[57] reported the results of 9 months of experience in 41 patients who had received a total of 300 infliximab infusions between June 2000 and January 2002. Seventy-three percent of this population had RA, 68% were taking concomitant corticosteroids and 54% were receiving methotrexate with infliximab. Three patients experienced anaphylactic reactions occurring between the second and eighth infusions and two developed cutaneous leukocytoclastic vasculitis. One-third of patients developed minor allergic-type reactions, including rash and itching. Twenty-nine percent experienced an infection requiring antibacterial therapy, and one developed histoplasmosis.

Post-marketing surveillance by the US FDA identified an increased risk of TB and of infections normally associated with immunosuppression in patients receiving all TNF-blocking agents.[52,58,59] As of March 2003, there were 38 reports of TB in 230 000 patient-years (150 000 patients) with etan-

ercept, 172 cases in 230 000 patient-years (200 000 patients) with infliximab, and 13 cases in 4900 patient-years (2500 patients) with adalimumab.[52] The majority of cases have developed in European patients prior to recommendations for TB screening, and the majority are a result of reactivation of latent infections. However, it is evident that the increased risk of TB is a class effect, and that screening is not identifying all individuals at risk. Extrapulmonary involvement including dissemination has been reported in between 40% and 50% of TB cases (compared with 18% in the general population with TB) and also appears to be a class effect of anti-TNF therapy. TNF plays an important role in containment of tubercle bacilli, probably by enhancing macrophage function and granuloma formation. Thus, inhibition of TNF may facilitate reactivation of TB. The reason for an excess of TB cases in infliximab-treated patients is partly because of the fact that the earlier trials and greater experience with infliximab has been in Europe, where the prevalence of latent TB is also greater. Furthermore, it is possible that the effect of the monoclonal antibody causing lysis of cells critical to granuloma formation confers added risks for reactivation.

Screening for latent TB infection with Purified Protein Derivative of *Mycobacterium tuberculosis* (PPD) should be recommended for all patients considered for anti-TNF therapy. In patients with documented previous infection or positive skin testing, TB prophylaxis is recommended. Continuous vigilance for TB with atypical presentation is required.

Other opportunistic infections occurring in patients receiving either infliximab or etanercept have included infection with *Pneumocystis jiroveci* (previously *P. carnii*), *Aspergillus* spp., cryptococci, *Coccidioides immitis* and atypical mycobacterium. Experience with adalimumab suggests a similar profile of infectious complications.

Placebo-controlled trials of etanercept and infliximab aimed at improving outcomes of congestive heart failure have been prematurely discontinued because of a trend towards worsening of heart failure, including hospitalisation and mortality.[52] This has not been observed in RA clinical trials.

Concerns have been raised by post-marketing surveillance regarding other potential risks of anti-TNF therapy, including cases of demyelinating disease possibly triggered by anti-TNF therapy and rare reports of drug-induced lupus. While there is no doubt that the latter does occur rarely, all the reported cases have reversed with discontinuation of anti-TNF therapy and serious sequelae have not been seen. Regarding demyelinating disease, there remains uncertainty whether the incidence in RA patients receiving anti-TNF drugs is higher than the incidence in a matched population without drug exposure; furthermore, there has been no reassurance that cases that develop while patients are receiving anti-TNF drugs are reversible. In January 2003, the US FDA published reports of 26 cases of lymphoma: 18 in patients taking etanercept and eight in patients taking infliximab at a median of 6 weeks after initiation of treatment.[60] Subsequent to submission of this report and prior to its publication in January of 2003, there were 75 further reports of lymphomas possibly related to anti-TNF therapy.[60] Two individuals with previously treated lymphoma in remission at the time of initiation of anti-TNF therapy quickly developed recurrence of lymphoma and died. On the basis of these two cases, the US FDA report suggests that RA patients with a history of lymphoma should be ineligible for anti-TNF therapy. To date, the relationship of lymphoma development with Epstein-Barr virus has not been adequately explored. Furthermore, the US FDA cannot draw firm conclusions regarding a relationship to drug exposure because there is an increased incidence of lymphoma in patients with RA.

4. Biological Agents Targeting IL-1

4.1 Anakinra

The objective of IL-1RA-based therapy is to occupy enough IL-1 receptors to block IL-1 cell signalling.[61] Anakinra is a recombinant form of the human IL-1RA. It is a 17.3 kDa protein of 153 amino acids produced through recombinant DNA technology using an *Escherichia coli* bacterial expression system.[14] Its spectrum of biological ef-

fects is identical to that of the human IL-1RA. It acts as a competitive receptor antagonist, inhibiting binding of IL-1α and IL-1β to the IL-1 receptor. Tissue effects of anakinra include reduction of synovial T-lymphocyte and macrophage numbers, and levels of vascular endothelial cell adhesion molecules. Pharmacokinetic studies in RA patients demonstrate a mean elimination half-life of 7 ± 2.3 hours.[14]

The effectiveness of anakinra administered as a daily subcutaneous injection has been studied as monotherapy and in combination with methotrexate. A 24-week, randomised controlled trial in 472 patients evaluated varying dosages of anakinra; results demonstrated efficacy in terms of ACR20 in 43% of RA patients receiving anakinra 150mg daily versus 27% of placebo recipients ($p = 0.014$), and improvement in each individual ACR core outcome.[61] Response occurred early: the rate of decrease in clinical endpoints was greatest during the first 6 weeks and the greatest fall in CRP was observed in the first week of therapy. Dosages under 30 mg/day were ineffective. Statistically significant improvement in the HAQ disability index was seen by 4 weeks. Over the course of 24 weeks, the HAQ disability index improved from 1.3 to 0.93 in the 75 mg/day dosage group and from 1.3 to 0.79 in the 150 mg/day dosage group (fixed doses). The trial continued into extension for a further 24 weeks in 229 patients randomised to anakinra 30, 75 or 150 mg/day.[62] Forty-six percent of patients who continued anakinra, at all dosages, demonstrated a sustained ACR20 response at 48 weeks. At 48 weeks, an ACR50 response was seen in 18% and an ACR70 in 3% of completers.[62] After 48 weeks, the benefit of anakinra (all dose groups combined) included a 45% reduction in erosion count measured by the Larsen method, but the change in the total Larsen score was not statistically significant.[63] In patients initially randomised to placebo for 24 weeks, the introduction of anakinra was associated with a statistically significant 50% slowing of damage progression when the Genant method was used, but this benefit was not shown using the Larsen score. Productivity over a 12-month period was evaluated using a self-administered questionnaire. After 6 months of treatment with anakinra 150 mg/day, patients had gained more productive days (mean 15.66) compared with placebo (3.55) [$p < 0.05$], but this benefit was not seen at the 30 or 75 mg/day dose.[64]

The effectiveness of anakinra added to baseline methotrexate (mean weekly dose 15–25mg) was studied in 419 patients randomised to varying dosages of anakinra or placebo.[38] Patient characteristics, baseline and 24-week outcome measures are included in table I and table II for the 1 and 2 mg/kg/day dosage of anakinra. ACR20 response at week 12 for anakinra/methotrexate combination therapy was higher than for placebo/methotrexate for all dosages of anakinra: 46% for 1 mg/kg/day versus 19% for placebo/methotrexate ($p = 0.001$). ACR50 responses at 24 weeks were 24% for the 1 mg/kg/day dosage and 17% for the 2 mg/kg/day dosage compared with 4% in the placebo group. For the individual ACR endpoints, the 2 mg/kg/day dosage showed greater benefit at 24 weeks compared with the lower dosages. The improvement in swollen joint count was not statistically significant at either the 1 or 2 mg/kg/day dosage compared with placebo or baseline. The 1 mg/kg/day dosage of anakinra added to methotrexate showed statistically significant improvement in terms of all other measures except morning stiffness, number of tender joints, pain and CRP. The 2 mg/kg/day dosage showed statistically significant benefit in all measures except swollen joints, tender joints, morning stiffness and CRP.

Lack of effect was the stated reason for withdrawal prior to 24 weeks in 4% of the patients receiving the 1 and 2 mg/kg/day dosage and in 5% of placebo-treated patients. Injection site reactions occurred in 56% of patients receiving the 1 mg/kg/day dosage and 64% of patients receiving 2 mg/kg/day, resulting in withdrawal in 7% and 10%, respectively, compared with 3% in the placebo group. There was no increase in the rate of infection and no serious infections. Five anakinra-treated patients developed leukopenia that normalised when anakinra was discontinued and was not associated with infection.

4.2 Safety of IL-1 Receptor Antagonists

During a 6-month, placebo-controlled, double-blind trial of IL-1RA,[61] and its 48-week extension,[62] the most common adverse effect was injection site reaction resulting in withdrawal of approximately 15% of patients during the first 24 weeks. The most common symptoms were erythema, pruritus and rash.[61] Use of IL-1RA as monotherapy or in combination with methotrexate has not been associated with an increased risk of infection or with opportunistic infections. In contrast, combined treatment with anakinra and etanercept in 58 patients was associated with a 7% incidence of serious infections requiring hospitalisation and a 48% incidence of infection.[65]

5. Conclusion

There is ongoing debate as to the optimal role of biological agents in the treatment of RA. Should these agents be used early to prevent damage or should they be used in patients who have failed methotrexate or multiple DMARDs, which is the population that has received the most study to date? The greatest cost of RA is in work loss and the greatest financial and societal benefit will be in prevention of work loss. In a Swedish study, patients who remained in the workforce and were in part-time employment at the start of infliximab or etanercept therapy achieved an increase in weekly hours of work.[66] The number of hours per week worked was 8.55 prior to treatment and this increased to 20 hours by the end of 2 years. The authors calculated an annual indirect economic benefit based on this gain in work hours amounting to $US10 600 (2002 value). Complete cost-effectiveness studies based on differing treatment strategies will be needed.

The recent availability of these biological agents to treat RA has raised our expectations and the expectations of patients for control of RA.[28] Benefits, in terms of quality of life and functional improvement, are of a measure and speed which has not been seen since the discovery of cortisone. Studies extending to 2 years have demonstrated the ability of these products to prevent joint damage in severe RA. These improvements are so great, in trials and in practice, that the ACR is having to revisit its measurements in RA, and the US FDA is rewriting definitions of RA medications in terms of symptom control, disease control and damage prevention. Radiographic measurements in RA must be reassessed to determine that they are able to measure healing as well as harm. Undoubtedly, the benefits of biological agents have translated into clinical practice and, where these drugs are affordable, the outlook for people with this disease is changed. Experience has shown that with anti-TNF therapies, vigilance for common bacterial and opportunistic infection is mandatory.

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References

1. Kaldin JR. How do the biologics fit into the current DMARD armamentarium? J Rheumatol 2001 Jun 28; S62: 27-35
2. van der Heijde DM. Joint erosions and the patient with early rheumatoid arthritis. Br J Rheumatol 1995; 34 Suppl. 2: 74-8
3. Dougados D, Suurmeiher T, Krol B, et al. Work disability in early rheumatoid arthritis. Ann Rheum Dis 1995; 54: 445-60
4. Mitchell DM, Spitz PW, Young DY, et al. Survival, prognosis and causes of death in rheumatoid arthritis. Arthritis Rheum 1986; 29: 706-14
5. Wolfe F, Hawley DJ, Cathey MA. Termination of slow acting antirheumatic therapy in rheumatoid arthritis: a 14-year prospective evaluation of 1017 consecutive starts. J Rheumatol 1990; 17: 994-1002
6. Tugwell P, Pincus T, Yocum D, et al. Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. N Engl J Med 1995 Jul 20; 333 (3): 137-41
7. O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 1996; 334 C20: 1287-91
8. Boers M, Verhoeven AC, Markusse HM, et al. Randomized comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997; 350: 309-18
9. Verhoeven AS, Boers M, Tugwell P. Combination therapy in rheumatoid arthritis: updated systematic review. Br J Rheumatol 1998; 37 (6): 612-9
10. The HERA Study Group. A randomized trial of hydroxychloroquine in early rheumatoid arthritis: the HERA Study. Am J Med 1995; 98: 156-68
11. Kirwan J. The effect of glucocorticoids on joint destruction. N Engl J Med 1995; 333 (3): 142-6
12. Hughes LB, Moreland LW. New therapeutic approaches to the management of rheumatoid arthritis. Biodrugs 2001; 15 (6): 379-93

13. Arend WP, Malyak M, Guthridge CJ, et al. Interleukin-1 receptor antagonist: role in biology. Annu Rev Immunol 1998; 16: 27-55
14. Cvetkovic RS, Keating G. Anakinra. Biodrugs 2002; 16 (4): 303-11
15. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med 2001; 344: 907-16
16. Brennan FM, Chantry D, Jackson A, et al. Inhibitory effect of TNFα antibodies on synovial cell IL1 production in rheumatoid arthritis. Lancet 1989; II: 244-7
17. Arend WP, Dayer J-M. Inhibition of the production and effects of interleukin-1 and tumor necrosis factor α in rheumatoid arthritis. Arthritis Rheum 1995 Feb; 38 (2): 151-60
18. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995; 38: 727-35
19. Fries JF, Spitz PW, Young DY, et al. The dimensions of health outcomes: the Health Assessment Questionnaire, Disability and Pain scales. J Rheumatol 1982; 9: 789-93
20. Wells GA, Tugwell P, Kraag G, et al. Minimum important differences between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol 1993; 20: 557-60
21. Wolfe F, Michaud K. Work disability in a national sample of RA patients [abstract]. Arthritis Rheum 2002 Sep; 46 (9): S90
22. van Gestel AM, Prevoo M, Van't Hof MA, et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis: comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum 1996; 39: 34-40
23. Boers M, Tugwell P, Brooks PM. Progress towards optimal trial endpoints in rheumatoid arthritis. Biodrugs 1997 Jan; 7 (1): 40-50
24. Boers M. Validity of radiography as outcome measure in rheumatoid arthritis. J Rheumatol 1995; 22: 1783-6
25. Boers M, van der Heijde DMFM. Prevention or retardation of damage in rheumatoid arthritis: issues of definition, evaluation and interpretation of plain radiographs. Drugs 2002; 62 (12): 1717-24
26. Sharp TJ, Lidsky MD, Collins LC, et al. Methods of scoring the progression of radiologic changes in rheumatoid arthritis: correlation of radiologic, clinical and laboratory abnormalities. Arthritis Rheum 1971; 14: 706-20
27. Larsen A, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. Acta Radiol Diagn (Stockh) 1977; 18: 481-91
28. Strand V, Sharp JT. Radiographic data from recent randomized controlled trials in rheumatoid arthritis: what have we learned? Arthritis Rheum 2003 Jan; 48 (1): 21-34
29. van der Heijde DM, van Leeuwen MA, van Riel PL, et al. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum 1992 Jan; 35 (1): 26-34
30. Genant HK, Jiang Y, Peterfy C, et al. Assessment of rheumatoid arthritis using a modified scoring method on digitized and original radiographs. Arthritis Rheum 1998; 41: 1583-90
31. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p 75)-Fc fusion protein. N Engl J Med 1997 Jul 17; 337: 141-7
32. Moreland LW, Margolies G, Heck LW Jr, et al. Recombinant soluble tumor necrosis factor receptor (p80) fusion protein: toxicity and dose finding trial in refractory rheumatoid arthritis. J Rheumatol 1996 Nov; 23 (11): 1849-55
33. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis: a randomized controlled trial. Ann Intern Med 1999 Mar 16; 130 (6): 478-86
34. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000 Nov 30; 343 (22): 1586-93
35. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999 Jan 28; 340 (4): 253-9
36. Maini R, St Clair EW, Breedveld F. Infliximab (chimeric anti-tumour necrosis factor a monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomized phase 111 trial. Lancet 1999; 354: 1932-9
37. Weinblatt ME, Keystone EC, Furst DE. Adalimumab, a fully human anti-tumor necrosis factor-a monoclonal antibody for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 2003 Jan; 48 (1): 35-45
38. Cohen S, Hurd E, Cush J, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of twenty-four week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002 Mar; 46 (3): 614-24
39. Kremer JM, Weinblatt ME, Fleischmann RM, et al. Etanercept added to background methotrexate in rheumatoid arthritis: continued observations [abstract]. Arthritis Rheum 2002 Oct; 46 (9S): S531
40. Genovese MC, Martin RW, Fleischmann RM, et al. Etanercept in early erosive rheumatoid arthritis (ERA trial): observations at 4 years [abstract]. Arthritis Rheum 2002 Oct; 46 (9S): S530
41. Feldmann M, Elliott MJ, Woody NJ, et al. Anti-tumor necrosis factor-a therapy of rheumatoid arthritis. Adv Immunol 1997; 64: 283-350
42. Markham A, Lamb HM. Infliximab: a review of its use in the management of rheumatoid arthritis. Drugs 2000 Jun; 59: 1341-59
43. Elliott MJ, Maini RN, Feldmann M, et al. Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor-a. Arthritis Rheum 1993 Dec; 36: 1681-90
44. Elliott MJ, Maini RN, Feldmann M, et al. Randomized double blind comparison of chimeric monoclonal antibody to tumour necrosis factor-a (cA2) versus placebo in rheumatoid arthritis. Lancet 1994 Oct 22; 344: 1105-10
45. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor a monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998 Sep; 41 (9): 1552-63
46. Lipsky PE, van der Heijde DMFM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000 Nov 30; 343: 1594-602
47. St Clair EW, Wagner CL, Fasanmade AA, et al. The relationship between infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002 Jun; 46 (6): 1451-9
48. den Broeder A, van de Putte KBA, Rau R, et al. A single dose, placebo controlled study of the fully human anti-tumor necro-

sis factor-a antibody, Adalimumab, (D2E7) in patients with rheumatoid arthritis. J Rheumatol 2002 Nov; 29 (11): 2288-98

49. Rau R. Adalimumab (a fully human anti-tumour necrosis factor alpha monoclonal antibody) in the treatment of active rheumatoid arthritis: the initial results of five trials. Ann Rheum Dis 2002 Nov; 61 Suppl. 2: ii70-3
50. Rau R, Herborn G, Sander O, et al. Long term treatment with the fully human anti-TNF antibody D2E7 slows radiographic disease progression in rheumatoid arthritis [abstract]. Arthritis Rheum 1999; 42: S400
51. den Broeder AA, Joosten CA, Saxne T, et al. Long term anti-tumour necrosis factor alpha monotherapy in rheumatoid arthritis: effect on radiologic course and prognostic value of markers of cartilage turnover and endothelial activation. Ann Rheum Dis 2002 Apr; 61 (4): 311-8
52. FDA briefing document – March 4, 2003 meeting of Arthritis Advisory Committee. Safety update on TNFα blocking agents [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/03/briefing/3930B1_01_B-TNF.Briefing.pdf [Accessed 2004 Mar 15]
53. Moreland LW, Cohen SB, Klareskog L, et al. Global safety and efficacy of more than five years of etanercept therapy in rheumatoid arthritis [abstract]. Arthritis Rheum 2002 Oct; 46 (9S): S532
54. Phillips K, Husni ME, Karlson EW, et al. Experience with etanercept in an academic medical center: are the infection rates increased? Arthritis Care Res 2002 Jan; 47 (1): 17-21
55. Kavanaugh A, Keenan S, De Woody K, et al. Long term follow up of patients with Remicade (infliximab) in clinical trials [abstract]. Arthritis Rheum 2001; 44S: S108
56. Durez P, Van den Bosch F, Corluy L, et al. Safety of combination methotrexate and infliximab in a large Belgian observational cohort with refractory rheumatoid arthritis [abstract]. Arthritis Rheum 2002 Oct; 46 (9S): 536
57. Fitzcharles M-A, Clayton D, Menard HA. The use of infliximab in academic rheumatology practice: an audit of early clinical experience. J Rheumatol 2002 Dec; 29 (12): 2525-30
58. The Food and Drug Administration Centre for Biologics Evaluation and Research. Safety update on TNFα antagonists: infliximab and etanercept. Rockville (MD): The Food and Drug Administration Centre for Biologics Evaluation and Research, 2001 Aug 17
59. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001 Oct 11; 345 (15): 1098-104
60. Brown SL, Green MH, Gershon SK, et al. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. Arthritis Rheum 2002; 46 (12): 3151-8
61. Bresnihan B, Alvaro-Gracia JM, Cobby M, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 1998 Dec; 41 (12): 2196-204
62. Nuki G, Bresnihan B, Bear MB. Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized double-blind, placebo-controlled trial. Arthritis Rheum 2002 Nov; 46 (11): 2838-46
63. Jiang Y, Genant HK, Watt I, et al. A multicenter, double-blind, dose ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. Arthritis Rheum 2000 May; 43 (5): 1001-9
64. Bresnihan B, Chan WW, Woolley JM. Productivity improvement in patients with rheumatoid arthritis receiving anakinra (IL-1ra) treatment [abstract no. 0074]. Annual European Congress of Rheumatology EULAR; 2002 Jun 12-15; Stockholm
65. Schiff M, Bulpit K, Weaver AA, et al. Safety of combination therapy with anakinra and etanercept in patients with rheumatoid arthritis. Arthritis Rheum 2001; 44S: S79
66. van Vollenhoven, Brannemark S, Lindblad S, et al. Treatment with TNFα antagonists results in significant gradual increases in workforce participation: data from the STURE registry [abstract]. Arthritis Rheum 2002; 46: S535

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