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Safety and Efficacy of Disease-Modifying Anti-Rheumatic Agents

Focus on the Benefits and Risks of Etanercept

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Abstract

The traditional approach to the treatment of rheumatoid arthritis (RA) has been the use of nonsteroidal anti-inflammatory drugs usually in combination with a disease-modifying antirheumatic drug (DMARD) such as hydroxychloroquine, gold, sulfasalazine, methotrexate, leflunomide or cyclosporin. Each of these DMARDs has its own distinct toxicities but has also been shown to be effective in reducing signs and symptoms of disease and to some extent, reduce radiological progression.

Within the past 10 years, the combination of several traditional DMARDs has been shown to have increased efficacy over monotherapy without a significant increase in toxicity in a majority of studies.

Recently, the US Food and Drug Administration has approved infliximab, a chimeric monoclonal antibody to tumour necrosis factor (TNF)-α in combination with methotrexate, for the treatment of signs and symptoms of RA, delay of radiological progression of disease and improvement of physical function while anakinra, an interleukin-1 receptor antagonist, has been approved for the treatment of the signs and symptoms of RA either as monotherapy or in combination with methotrexate.

Etanercept is the first biological response modifier approved for use in RA in the US. Double-blind, randomised controlled studies have shown etanercept to be effective therapy in patients with RA who have had inadequate response to DMARDs, in combination with methotrexate, and as early monotherapy. Similar results were seen in juvenile and psoriatic arthritis in DMARD nonresponders. Open-label studies have shown efficacy in adult Still's disease, ankylosing spondylitis, progressive systemic sclerosis, Wegener's granulomatosis and chronic uveitis.

Safety issues are a concern because of the ubiquitous role of TNF. To date the only consistent adverse event seen with etanercept has been injection site reactions. Infections occur at the same rate and with the same frequency as the placebo population. There should be caution, however, with using etanercept in patients with a serious infection, or recurrent infections or patients with untreated or latent tuberculosis. As of yet there has not been seen an increase of malignancies. Rare neurological and haematological events have been noted.

Etanercept has been a significant addition to the armamentarium of medications for the treatment of RA, juvenile and psoriatic arthritis. Preliminary data show that it may be well tolerated and effective in other rheumatic diseases in which there is over production of TNFα.

1. Background

Rheumatoid arthritis (RA) is a systemic inflammatory disease with its primary manifestation in the synovium. The disease is characterised by a chronic, symmetric polyarthritis that typically affects the wrists, hands and feet as well as other synovial joints. It is a systemic disease characterised by fatigue, low-grade fever, anaemia, serositis and a systemic vasculitis.[1]

RA has been described worldwide with a prevalence of 1% in the adult population. The age distribution is unimodal with the peak age of onset between the fourth and sixth decades of life. Women are twice as likely to have the disease.[2,3]

Mortality is increased in patients with RA.[4,5] Mean life expectancy is shortened by 7 years in males and 3 years in female.[6] Death most often results from infection, heart disease, respiratory failure, renal failure and gastrointestinal disease. Patients with RA are prone to premature atherosclerosis.[7] Since it is a chronic disabling condition, one of the most important economic outcomes is work disability. Rates of work disability in the US and Europe range from 22 to 85% and 31 to 80%, respectively.[8]

The primary goals of management of RA include alleviation of pain, reduction of inflammation, preservation of muscle strength and joint function, prevention of joint damage and maintenance of as normal a lifestyle as possible.[9]

1.1 Efficacy and Safety of Traditional Disease-Modifying Anti-Rheumatic Drugs (DMARDs)

For many years the traditional approach to treatment of RA was to provide symptomatic relief with aspirin (acetylsalicylic acid) or nonsteroidal anti-inflammatory drugs (NSAIDs). As the disease progressed, usually by an average of 4 years, physicians would add disease-modifying anti-rheumatic drugs (DMARDs) and/or corticosteroids. The most commonly used compounds include gold (parenteral or oral), hydroxychloroquine, sulfasalazine, cyclosporin, methotrexate and, recently, leflunomide.

1.2 Hydroxychloroquine

Hydroxychloroquine has been used in early, mild disease primarily because it is relatively safe.[10] Many patients, however, have only a modest response. Hydroxychloroquine interferes with antigen processing, leading to reduced stimulation of CD4+ T cells resulting in down-regulation of autoimmune response.[11]

1.3 Gold

Parenteral organic gold compounds have been used since the 1920s for the treatment of RA.[10] Its clinical efficacy has been shown in double-blind studies[12] and radiographic efficacy has been demonstrated by decreased Sharp scores.[13] The comparison of weekly administration of parenteral gold 50mg with weekly administration of methotrexate 15mg showed a higher proportion of patients reaching remission with gold but also increased toxicity with gold.[14] Adverse reactions including mucocutaneous reactions, proteinuria and cytopenias have limited the use of gold.

1.4 Sulfasalazine

Early uncontrolled trials[15,16] in the late 1940s demonstrated efficacy of sulfasalazine, which was confirmed later in controlled trials.[17-26] Two of these trials[25,26] showed delay of radiographic progression when compared with placebo. In a meta-analysis,[27] sulfasalazine was comparable in efficacy to gold, penicillamine and methotrexate. Sulfasalazine has a wide range of adverse effects, which limits its clinical usefulness.[28] These include adverse gastrointestinal (GI) and hepatic effects (including transaminitis), rash, neutropenia, aplastic anaemia, agranulocytosis, haemolysis, yellowish skin discoloration of skin, urine and contact lenses as well as reversible infertility in men. Sulfasalazine, although not commonly used as first-line DMARD therapy in the US, remains very

popular with rheumatologists elsewhere in the world.

1.5 Methotrexate

Methotrexate, an analogue of folic acid, is an antimetabolite. Four double-blind, randomised, placebo-controlled trials with oral or intramuscular methotrexate showed superior efficacy to placebo.[29-32] A meta-analysis[33] showed that methotrexate-treated patients had significant improvement in swollen and tender joints, joint pain and morning stiffness. Multiple other studies have confirmed its efficacy.[34-40] It has become the 'gold' standard by which all new DMARD therapies for RA are judged.[41-44] A meta-analysis showed that methotrexate is superior to hydroxychloroquine and oral gold, and comparable with sulfasalazine, intramuscular gold, penicillamine and leflunomide in efficacy.[27] It is better tolerated than each of these other than leflunomide to which it is comparable.[27,45,46] Healing of erosions but not prevention of disease progression has been documented with methotrexate,[47-54] although it has recently been shown that it slows disease progression.[55] Prospective long-term studies have shown that methotrexate is better tolerated and more efficacious than older DMARDs and that a far higher percentage of patients remain on for a longer period of time when compared with these DMARDs.[56-58] Adverse effects include stomatitis, GI intolerance, and bone marrow suppression (all responsive to folic acid supplementation), idiosyncratic allergic-like lung injury and liver damage, the latter requiring frequent and careful monitoring of hepatic enzyme levels.[59,60] It is an abortifacient and causes birth defects. Conception should be avoided on this medication and both males and females should employ appropriate contraceptive measures.

1.6 Leflunomide

Leflunomide is an antiproliferative isoxazole compound. A placebo-controlled trial compared leflunomide, methotrexate and placebo for 52 weeks.[46] ACR 20[61] is defined as at least a 20% improvement in tender and swollen joint count as well as at least a 20% improvement in at least three of the following five parameters: (i) patient assessment of pain; (ii) patient global assessment of disease activity; (iii) physician global assessment of disease activity; (iv) acute phase reactants [erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)]; and (v) measurement of physical function [such as Health Assessment Questionnaire (HAQ)]. An ACR 50 would require at least a 50% improvement in these same parameters and an ACR 70 a 70% improvement. In this trial, ACR 20 response rates of 52, 48 and 26% and ACR 50 response of 34, 23 and 8% for leflunomide, methotrexate and placebo, respectively, were seen. The response with leflunomide and methotrexate were statistically equivalent and significantly greater than placebo. Several multinational trials have confirmed these results.[62,63] A 24-week double-blind, randomised, controlled trial comparing leflunomide, sulfasalazine and placebo showed ACR 20 response rates of 55, 56, and 29% and ACR 50 response of 33, 30, and 14% for leflunomide, sulfasalazine and placebo, respectively.[64] Leflunomide-treated patients had improved function as assessed by the HAQ when compared with sulfasalazine or methotrexate. Leflunomide, sulfasalazine, and methotrexate all significantly retarded x-ray progression compared with placebo, but the degree of disease progression was significantly less with leflunomide than with methotrexate or sulfasalazine.[55,65,66] Two trials explored the combination of leflunomide with methotrexate. Both showed a significant clinical improvement with the combination. A significant number of patients in both trials had elevated transaminase levels.[67,68] Common adverse effects of leflunomide are diarrhoea, dyspepsia, abdominal pain, elevation of liver transaminase levels, hypertension, rash, reversible alopecia and headaches. [46,55,62-68]

2. Combination Therapy

2.1 Triple Therapy

In a double-blind, controlled, randomised study, the combination of methotrexate 7.5 to 17.5 mg/week, sulfasalazine 500mg twice daily plus hydroxychloroquine 200mg twice daily was compared with methotrexate alone and the combination of sulfasalazine plus hydroxychloroquine.[69] After 24 months, 77% of patients receiving triple therapy, 40% of those receiving sulfasalazine plus hydroxychloroquine and 33% receiving methotrexate alone achieved a clinically significant response. The study has to be interpreted in the light of a slow escalation and low dose of methotrexate and use of low-dose sulfasalazine.

2.2 Cyclosporin Plus Methotrexate

In a 6-month randomised, double-blind trial, the combination of cyclosporin 2.5 to 5 mg/kg plus methotrexate ≤15 mg/week was compared with methotrexate plus placebo in patients with partial response to methotrexate.[70] 48% of patients treated with methotrexate plus cyclosporin achieved an ACR 20 compared with 16% of patients treated with methotrexate alone. However, serum creatinine levels increased significantly in patients treated with methotrexate plus cyclosporin.

2.3 Sulfasalazine Plus Methotrexate

In a double-blind, randomised, step-down design trial, the combination of sulfasalazine 500 mg/day (increased to 2000 mg/day over a period of 3 weeks), methotrexate 7.5 mg/week and a prednisolone taper (with an unusually high starting dosage of prednisolone) was compared with sulfasalazine alone in 155 patients with early RA.[71] After 40 weeks, patients were treated solely with sulfasalazine as prednisolone was discontinued after 28 weeks and methotrexate after 40 weeks. At 28 weeks 72% of patients in the combination therapy group achieved an ACR 20, as compared with 49% in the sulfasalazine only group. Radiological evaluation after 28 weeks of treatment showed that 31% of patients in the combination group had a stable Sharp's score with a slower rate of progression compared with only 13% in the sulfasalazine group.

3. Role of Tumour Necrosis Factor-α and Interleukin-1 in Rheumatoid Arthritis (RA)

Tumour necrosis factor (TNF)-α and interleukin (IL)-1 play pivotal roles in the inflammation and joint damage of RA. High levels of TNFα and IL-1 are found in the synovial fluid of patients with RA. Both of these cytokines have been shown to stimulate resorption of cartilage and inhibit synthesis of proteoglycan[72-75] and both are potent stimulators of synovial fibroblasts, osteoclasts and chondrocytes that release tissue destroying matrix metalloproteins and inhibit the production of tissue inhibitors of metalloproteins by synovial fibroblasts.[76] These actions are thought to lead to joint damage. TNFα may also stimulate the production of IL-11, which induces development of osteoclasts leading to bone degradation.[77] TNFα stimulates fibroblasts to express adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), which upon interacting with their respective ligands on the leucocyte surface results in increased transport of leucocytes into the joint.[78] IL-1 is produced by monocytes, macrophages, endothelial cells, B cells and activated T cells. Injection of IL-1 into the knee joints of rabbits results in the degradation of cartilage.[79] TNFα has a dominant role in RA, since it has been shown that in cultures of synovial cells from RA patients which were treated with TNFα antibodies, there was a significant reduction in IL-1, IL-6, IL-8 and granulocyte-monocyte colony stimulating factor.[80]

4. Anticytokine Therapy

4.1 Infliximab

Infliximab is a chimeric immunoglobulin (Ig) G1 monoclonal antibody that neutralises the biological activity of TNFα by binding with high affinity to soluble and transmembrane forms of TNFα and inhibiting binding of TNFα to its receptors.[81,82] It was the first antiTNFα agent to be used in patients with RA in whom previous DMARD therapy had failed.[83] A placebo-controlled trial confirmed efficacy of infliximab in RA with a 60 to 70% decrease in measures of disease activity.[84] A placebo-controlled trial of repeated treatment cycles of infliximab either as monotherapy or combined with methotrexate confirmed safety and the fact that methotrexate protects against the development of human antichimeric antibodies (HACAs).[85]

A 102-week placebo-controlled trial investigated the clinical response (at week 30), x-ray progression (at week 54) and change in patient function of infliximab (at week 102) in a population of RA patients with an incomplete response to methotrexate.[86,87] Patients received methotrexate plus placebo or one of four regimens of infliximab plus methotrexate: 3 mg/kg at 0, 2, and 6 weeks followed by additional infusions every 4 weeks or every 8 weeks, or 10 mg /kg of intravenous infliximab at 0, 2, and 6 weeks followed by additional infusions every 4 weeks or every 8 weeks. At 30 weeks, the ACR 20 response criteria was achieved in 53, 50, 58, and 52% of patients receiving 3 mg/kg every 4 or 8 weeks or 10 mg/kg every 4 or 8 weeks, respectively, compared with 20% of patients receiving methotrexate alone. At week 54, patients treated with infliximab and methotrexate (all doses) had marked decrease of radiographic progression when compared with methotrexate alone as assessed by the modified Sharp score and this had been maintained at the end of 2 years.[88] Repeated infusions occasionally were associated with flushing, headache or rash. No increased risk of serious infections or sepsis was observed. The development of tuberculosis, as well as other fungal infections, has been reported postmarketing with the use of infliximab, which has recently resulted in a change to the product label in the US.[89] Anti-double-stranded DNA, a marker of renal lupus has been reported in 7% of patients treated with infliximab but clinical lupus was rare.[90] 10% of patients developed human antichimeric antibodies.[90]

4.2 Anakinra (Interleukin-1 Receptor Antagonist)

The efficacy of anakinra (interleukin-1 receptor antagonist) has been evaluated as monotherapy and in combination with methotrexate. In a placebo-control study, patients received placebo or anakinra at 30, 75 or 150 mg/day.[91] In the 150 mg/day group, 43% of patients obtained an ACR 20 response, as compared with 27% of patients in the placebo group. Radiological evaluation measured by Larsen score showed a 41% slowing rate in joint damage and a 46% reduction in erosive joint count in the anakinra group. Modified Sharp score analysis showed a 58% slowing in the rate of progressive joint space narrowing and a 38% slowing in the rate of joint erosion. Injection site reaction was the most common adverse effect.[92,93]

The combination of methotrexate at a maintenance dose of 12.5 to 25mg weekly and anakinra at several doses (0.1, 0.4, 1.0 and 2.0 mg/kg/day) was compared with methotrexate plus placebo.[94] At 12 weeks of therapy, 46% ($p = 0.001$) of patients receiving anakinra 1 mg/kg/day and 38% ($p = 0.007$) of patients receiving anakinra 2 mg/kg/day dose obtained an ACR 20 response, as compared with only 19% of patients in the placebo group. No rationale for the higher ACR 20 response in the 1 mg/kg group versus the 2 mg/kg group was given. Injection site reaction was the most common cause of withdrawal. Infections occurred at the same rate in the anakinra groups as in the placebo group.

5. Efficacy and Tolerability of Etanercept in Adult and Juvenile RA

Etanercept is a TNFα inhibitor. It is a recombinant protein consisting of human p75 tumour necrosis factor receptor (TNFR) fused to the Fc fragment of human immunoglobulin G1. It is a dimer, formed by combining two identical TNFR moieties with the Fc moiety (TNFR: Fc). Compared with the naturally occurring monomeric sTNFR, the etanercept molecule has increased TNF binding affinity, a longer half-life (4 days) and more potent TNF inhibitory activity both *in vitro* and *in vivo*.

Etanercept has been studied in randomised, double-blind, comparator studies in adult patients with RA who did not respond to treatment with DMARDs, as sole treatment and in combination with methotrexate, and in early RA as well as in juvenile arthritis and in psoriasis and psoriatic arthritis. There have also been several small studies reported in other rheumatic diseases including adult Still's disease, Wegener's granulomatosis, scleroderma, polymyositis/dermatomyositis, ankylosing spondylitis, and uveitis in children.

5.1 Etanercept in Patients with RA not Responding to DMARDs

Based on positive results in a phase I study in normal human volunteers[95] and a phase I safety and dose-finding trial in 22 patients with refractory RA,[96] a phase II randomised, double-blind, placebo-controlled trial of etanercept in patients with active, refractory RA was conducted.[97]

This 3-month trial included patients who met the American Rheumatism Association criteria for RA[98] and had experienced a lack of efficacy with between one and four specified DMARDs (including methotrexate). These DMARDs had to be discontinued a minimum of four weeks prior to administration of etanercept. Patients were allowed to continue NSAIDs and corticosteroids (<10 mg/day of prednisone or equivalent) if the dose had been stable for at least 4 weeks. Patients were required to have active disease defined by at least 10 swollen joints (SJC), 12 tender joints (TJC) and either demonstration of inflammation by an ESR >28 or CRP >2.0 mg/dl or morning stiffness of at least 45 minutes.

Patients were evaluated at baseline and then every 2 weeks for the next 3 months. Assessments included joint counts, duration of morning stiffness, HAQ, physician and patient's global assessment of disease activity, patient's assessment of pain, ESR and CRP. Patients were randomly assigned to one of four treatment groups: placebo or etanercept 0.25, 2 or 16 mg/m^2. Study drug was administered twice weekly by subcutaneous injection. The demographics of the 180 patients enrolled are listed in table I. Clearly all of these patients had very active disease that had not responded to treatment with numerous DMARDs (table II).

The results of the study (table III) showed a significant dose response relationship. As shown in table IV, most of the patients treated with the highest dose of etanercept completed the study and they also had the highest ACR response rates (table V). Response was seen as early as the first assessment at week 2. By 8 weeks after cessation of therapy, all indicators of disease activity were almost back to baseline values. The only adverse effects reported (table VI) were mild, transient injection site reactions and mild upper respiratory infections that resolved on continued therapy with etanercept. Thus, this trial showed that etanercept, particularly in the 16mg group was very efficacious in patients with refractory RA and had a relatively benign safety profile.

Based on these results, a phase III 6-month controlled trial was conducted.[99] The inclusion criteria were similar to the phase II trial. Stable NSAID and prednisone ≤10 mg/day if stable 4 weeks prior to baseline was maintained during the study. Patients were randomly assigned to placebo, 10 or 25mg (equivalent to 16 mg/m^2) of subcutaneous etanercept twice weekly. The demographics of the 234 patients in this trial (table I) were also

Table I. Demographics of patients enrolled in trials of etanercept

Study	Treatment	No. of patients	Mean age (y)	% Female	Disease duration (y)	% White	% RF+	% Prior MTX	Duration of MTX (y)	Mean dose MTX (mg/wk)	Prior DMARD	No. of DMARD nonresponders	% CS	Mean dose CS	% NSAIDs
Phase II[97]	PLA	44	55	82	>5y 71%	91	NR	34[a]	NR	0	100	NR	66	NR	73
	SC ETA 0.25 mg/m^2 twice/wk	46	54	70	>5y 76%	96	NR	41[a]	NR	0	100	NR	59	NR	70
	SC ETA 2 mg/m^2 twice/wk	46	52	61	>5y 80%	100	NR	30[a]	NR	0	100	NR	65	NR	80
	SC ETA 16 mg/m^2 twice/wk	44	52	82	>5y 89%	93	NR	27[a]	NR	0	100	NR	77	NR	75
Phase III[99]	PLA	80	51	76	12	89	79	90	NR	0	100	3	58	6.8	84
	SC ETA 10mg twice/wk	76	53	84	13	96	82	92	NR	0	100	3.4	66	7.5	67
	SC ETA 25mg twice/wk	78	53	74	11	94	79	87	NR	0	100	3.3	81	7.3	67
MTX + ETA[100]	MTX only	30	53	73	13	83	90	100	2.9	18	100	2.8	70	NR	80
	MTX + SC ETA 25mg twice/wk	59	48	90	13	76	84	100	4.9	19	100	2.7	53	NR	75
Early RA[101-104]	MTX only	217	49	75	1	88	89	0	NA	18.2	46	0.6	41	7	80
	SC ETA 10mg twice/wk	208	50	75	0.91	84	88	0	NA	0	39	0.5	42	7	76
	SC ETA 25mg twice/wk	207	51	74	1	86	87	0	NA	0	40	0.5	39	9	86
JRA Part I[105]	SC ETA 0.4 mg/m^2 twice/wk	69	10.5	62	5.9	75	22	100	NR	0	100	NR	36	5.6	96
JRA Part II[105]	PLA	26	12.2	58	6.4	88	31	100	NR	0	100	NR	50	5.5	92
	SC ETA 0.4 mg/m^2 twice/wk	25	8.9	76	5.3	56	16	100	NR	0	100	NR	24	6.5	100
Psoriasis[106]	PLA	30	43.5	40	9.5	83	NA	47[b]	NR	NR	82	2	40	NR	77
	SC ETA 25mg twice/wk	30	46	47	9	90	NA	47[b]	NR	NR	82	2	20	NR	67

a In the year prior to study.

b During study.

CS = corticosteroid; **ETA** = etanercept; **DMARD** = disease-modifying anti-rheumatic drugs; **JRA** = juvenile rheumatoid arthritis; **MTX** = methotrexate; **NA** = not applicable; **NR** = not reported; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **PLA** = placebo; **RA** = rheumatoid arthritis; **RF+** = rheumatoid factor positive; **SC** = subcutaneous.

similar to the phase II trail as was their baseline clinical activity (table II).

There was a dramatic response to etanercept 25mg twice weekly (table III). Again completer status (26 from the placebo group; 52 from the etanercept 10mg and 59 from the etanercept 25mg twice weekly groups) [table IV] and ACR response (table V) indicated a dose response relationship favouring higher doses of etanercept.

No significant adverse effects were noted (table VI) other than the development of mild to moderate, transient injection site reactions (ISR) and some increase in upper respiratory infections in the etanercept-treated groups. The incidence of infections, including upper respiratory tract infections, was similar between the etanercept and placebo groups when the time of therapy was taken into consideration.

Table II

5.2 Etanercept in Combination with Methotrexate

A 24-week randomised study was conducted in 89 patients who had persistently active disease despite at least 6 months' therapy with methotrexate at a stable dose of 15 to 25 mg/week (or as low as 10 mg/week if they were unable to tolerate a higher dose).[100] Demographics of these patients are shown in table I and baseline clinical activity is shown in table II. All patients fulfilled the revised criteria for RA and had active disease defined by at least six tender and swollen joints at baseline. All patients received folic or folinic acid. All DMARDs, other than methotrexate, were discontinued a minimum of 2 to 4 weeks prior to the baseline visit depending on the DMARD.

Patients were assessed weekly for the first 2 weeks, at week 4 and then every 4 weeks until week 24 or termination. The same assessments were done as in the phase II and III studies. All patients continued their methotrexate in a stable manner for the duration of the study (mean 18 mg/week). Patients were assessed as well for the development of autoantibodies and antibodies to etanercept. Randomisation was in a 2 : 1 ratio to

Table II. Clinical activity at baseline in patients enrolled in trials of etanercept

Study	Treatment	No. tender joints	No. swollen joints	Morning stiffness (h)	HAQ (0-3)	ESR (mm/h)	CRP (mg/dl)	Pain (VAS) [0-10]	MD assess (0-10)	PT assess (0-10)
Phase II[97]	PLA	29	22	4.9	146[a]	40	3.9	6.4	7	6.7
	SC ETA 0.25 mg/m^2 twice/wk	32	24	4.3	153[a]	44	4.1	6.9	7.4	7.1
	SC ETA 2 mg/m^2 twice/wk	32	24	5.2	138[a]	36	3.6	6.7	7.2	6.9
	SC ETA 16 mg/m^2 twice/wk	30	24	4.9	135	35	3.6	6.3	6.5	6.5
Phase III[99]	PLA	35	25	4.8	1.7	39	4.1	6.5	6.9	6.9
	SC ETA 10mg twice/wk	34	25	4.4	1.7	44	5.3	6.6	6.9	6.9
	SC ETA 25mg twice/wk	33	25	5	1.6	35	4.7	6.7	6.9	7
MTX + ETA[100]	MTX only	28	17	2	1.5	36	2.6	5.6	6.5	6
	MTX + SC ETA 25mg twice/wk	28	20	1.5	1.5	25	2.2	5	6	6
Early RA[101-104]	MTX only	30	24	3.7	1.4	NR	3.7	5.6	6	6.1
	SC ETA 10mg twice/wk	31	24	3.7	1.4	NR	4.4	5.6	6.3	6.1
	SC ETA 25mg twice/wk	31	24	3.8	1.5	NR	3.3	5.9	6.2	6.1
JRA Part I[105]	SC ETA 0.4 mg/m^2 twice/wk	28	25	0.75	1.4	35	3.5	3.6	7	5
JRA Part II[105]	PLA	7.5	6	0.08	0.4	12	0.3	0.3	1	1
	SC ETA 0.4 mg/m^2 twice/wk	13	12	0.25	0.9	15	0.2	1.3	2	2
Psoriasis[106]	PLA	19	14.7	NR	1.2	16	1.2	6.2	6.8	5.8
	SC ETA 25mg twice/wk	22	14	NR	1.3	22	1.4	6	6.6	6.6

a HAQ scale = 45-245.

CRP = C-reactive protein**; ESR** = erythrocyte sedimentation rate; **ETA** = etanercept; **HAQ** = Health Assessment Questionnaire; **JRA** = juvenile rheumatoid arthritis; **MD assess** = doctor's assessment; **MTX** = methotrexate**; NR** = not reported; **PLA** = placebo; **PT assess** = patient assessment; **RA** = rheumatoid arthritis; **SC** = subcutaneous; **VAS** = visual analogue scale.

Table III

receive either subcutaneous etanercept 25mg twice weekly or placebo injections.

Response to therapy is shown in tables III, IV and V. As in the previous trials in patients with refractory RA, the combination of etanercept and methotrexate was far superior to methotrexate treatment alone.

Adverse events are shown in table VI. The only significant difference in adverse effects between the two groups was again the development of transient, mild to moderate ISR in the etanercept group. Non-neutralising antibodies to etanercept were detected in only one patient at the week 24 visit. Several of the patients had antibodies to double-stranded DNA prior to the study. One patient in the placebo group and 4 patients in the etanercept group did develop antibodies to double-stranded DNA during the study. Half of these patients did not have a positive ANA (anti-nuclear antibody). A small number of patients shifted from negative to positive and positive to negative with regard to ANA and anticardiolipin antibodies. No patients had new connective-tissue disorders, thrombotic events or thrombocytopenia.

Radiographs of the hands and feet were not performed. For this reason, it is still not proven that the combination of etanercept and methotrexate is superior to methotrexate alone with respect to radiographic progression.

5.3 Etanercept in Early Disease

Etanercept has been studied in patients with RA of less than 3 years' duration who were naïve to methotrexate therapy. This was a 24-month study with efficacy the primary endpoint at 6 months and x-rays the primary endpoint at 1 year with a 12-month extension.[101-104] This study compared methotrexate (mean dose of 19 mg/week), subcutaneous etanercept 10mg twice weekly and subcutaneous etanercept 25mg twice weekly. Patients had to have disease duration of less than 3 years and no prior treatment with weekly. In addition, patients had to have active disease as defined by >12 tender and >10 swollen joints as well as an

Table III. Response (% improvement versus baseline) in patients enrolled in trials of etanercept

Study	Treatment	No. tender joints	No. swollen joints	Morning stiffness (h)	HAQ (0-3)	ESR (mm/h)	CRP (mg/dl)	Pain (VAS) [0-10]	MD assess (0-10)	PT assess (0-10)
Phase II[97]	PLA	28	24	16	4	0	33	5	16	7
	SC ETA 0.25 mg/m^2 twice/wk	25	16	0	10	11	41	19	24	18
	SC ETA 2 mg/m^2 twice/wk	46	32	50	11	25	44	31	40	33
	SC ETA 16 mg/m^2 twice/wk	64*	58*	78**	16*	40*	75*	51*	58*	51*
Phase III[99]	PLA	6	−7	−23	2	−18	−207	−22	2	−3
	SC ETA 10mg twice/wk	44	45	34	34	10	−18	39	33	31
	SC ETA 25mg twice/wk	56*	47*	13*	39***	18*	31*	53*	44*	46*
MTX + ETA[100]	MTX only	39	35	37	27	16	38	22	38	33
	MTX + SC ETA 25mg twice/wk	75*	70*	89*	47*	40*	77*	64*	67*	67*
Early RA[101-104]	MTX only	NR	NR	NR	NR	NR	NR	NR	NR	NR
	SC ETA 10mg twice/wk	NR	NR	NR	NR	NR	NR	NR	NR	NR
	SC ETA 25mg twice/wk	NR	NR	NR	NR	NR	NR	NR	NR	NR
JRA Part I[105]	SC ETA 0.4 mg/m^2 twice/wk	56	58	75	37	50	60	63	60	50
JRA Part II[105]	PLA	−73	−83	−760	−300	−250	−1000	−1200	−500	−500
	SC ETA 0.4 mg/m^2 twice/wk	39	67	66	11	−20	−100	−15	0	−50
Psoriasis[106]	PLA	19	14.7	NR	1.2	16	1.2	6.2	6.8	5.8
	SC ETA 25mg twice/wk	22	14	NR	1.3	22	1.4	6	6.6	6.6

CRP = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **ETA** = etanercept; **HAQ** = Health Assessment Questionnaire; **JRA** = juvenile rheumatoid arthritis; **MD assess** = doctor's assessment; **MTX** = methotrexate**; NR** = not reported; **PLA** = placebo; **PT assess** = patient assessment; **RA** = rheumatoid arthritis; **SC** = subcutaneous; **VAS** = visual analogue scale; * $p < 0.001$; ** $p = 0.004$; *** $p < 0.05$.

Table IV

ESR >28, a CRP >2.0 mg/dl or morning stiffness of at least 45 minutes. The population was more likely to have x-ray progression by requiring that they had to be rheumatoid factor positive or have at least three bone erosions evident on x-rays of the wrists, hands or feet at baseline. Stable NSAIDs and corticosteroids were allowed at doses similar to those used in the phase II and III trials. Patients in the methotrexate group were started at 7.5 mg/week (plus folic acid 1 mg/day). At week 4 if the patient had any tender or swollen joints, it was mandatory that the methotrexate dose be increased to 15 mg/week for an additional 4 weeks. At week 8, if the patient had any tender or swollen joints, methotrexate was increased to 20 mg/week. A reduction of the methotrexate dose by 5mg was allowed once if their serum aminotransferase concentrations were >2.5 times the upper limit of normal. Patients were assessed clinically at screening, baseline, 2 weeks, 1, 6, 8, 10 and 12 months and for x-ray at baseline, 6 and 12 months. Assessments were similar to the previous trials. In addition, a determination of the total Sharp score, erosions and joint space narrowing on x-ray was determined at the intervals noted above.[107,108] Baseline demographics of these patients are in table I, baseline clinical activity in table II, the clinical response in table III, completer analysis in table IV and the ACR response in table V.

Etanercept 25mg twice daily was clinically effective very early with response seen as early as 2 weeks. In the first 4 months of the trial, etanercept 25mg was statistically superior to methotrexate with respect to the percentage of patients who reached an ACR 20, 50 and 70. By 12 months, however, there was no statistically significant difference between the two groups. By 24 months there was a statistically significant difference between the two groups as those patients on etanercept maintained their efficacy while there were some patients on methotrexate had lost efficacy.

With respect to x-ray changes at 12 months, there was a significant reduction in the total Sharp

Table IV. Number of patients enrolled in trials of etanercept who completed or discontinued treatment

Study	Treatment	No. entered	No. patients completed	No. of patients discontinued drug	No. of patients discontinued due to AE	No. of patients discontinued due to lack of efficacy	No. of patients discontinued for other reason
Phase II[97]	PLA	44	23	21	2	19	0
	SC ETA 0.25 mg/m^2 twice/wk	46	28	18	2	16	0
	SC ETA 2 mg/m^2 twice/wk	46	36	10	2	8	0
	SC ETA 16 mg/m^2 twice/wk	44	41	3	1	2	0
Phase III[99]	PLA	80	26	54	3	42	9
	SC ETA 10mg twice/wk	76	52	24	5	16	3
	SC ETA 25mg twice/wk	78	59	19	2	12	5
MTX + ETA[100]	MTX only	30	24	6	2	4	0
	MTX + SC ETA 25mg twice/wk	59	57	2	2	0	0
Early RA[101-104]	MTX only	217	172	45	24*	8	13
	SC ETA 10mg twice/wk	208	166	42	12	15	15
	SC ETA 25mg twice/wk	207	176	31	11	10	10
JRA Part I[105]	SC ETA 0.4 mg/m^2 twice/wk	69	64	5	1	2	2
JRA Part II[105]	PLA	26	7	19	0	18	1
	SC ETA 0.4 mg/m^2 twice/wk	25	19	6	0	6	0
Psoriasis[106]	PLA	30	26	4	NR	NR	NR
	SC ETA 25mg twice/wk	30	30	0	0	0	0

AE = adverse event; **ETA** = etanercept; **JRA** = juvenile rheumatoid arthritis; **MTX** = methotrexate; **NR** = not reported; **PLA** = placebo; **RA** = rheumatoid arthritis; **SC** = subcutaneous;
* $p < 0.03$ MTX versus etanercept.

Table V. ACR[a] improvement in patients enrolled in trials of etanercept (% of patients)

Trial	Treatment	Time of improvement (mo)	ACR 20	ACR 50	ACR 70	ACR N
Phase II[97]	PLA	3	14	7	NR	NA
	SC ETA 0.25 mg/m^2 twice weekly	3	33	9	NR	NA
	SC ETA 2 mg/m^2 twice weekly	3	46	22	NR	NA
	SC ETA 16 mg/m^2 twice/wk	3	75*	57*	NR	NA
Phase III[99]	PLA	6	11	5	1	NA
	SC ETA 10mg twice/wk	6	51*	24*	9	NA
	SC ETA 25mg twice/wk	6	59*	40*	15*	NA
MTX + ETA[100]	MTX only	6	27	3	0	NA
	MTX + SC ETA 25mg twice/wk	6	71*	39*	15***	NA
Early RA[101-104]	MTX only	12	65	≈40	≈20	≈38
	SC ETA 10mg twice/wk	12	≈60	≈30	≈15	≈32
	SC ETA 25mg twice/wk	12	72	≈50	≈25	45**
JRA Part I[105]	SC ETA 0.4 mg/m^2 twice/wk	3	74[b]	64	36	NA
JRA Part II[105]	PLA		NA	NA	NA	NA
	SC ETA 0.4 mg/m^2 twice/wk		NA	NA	NA	NA
Psoriasis[106]	PLA	3	13	3	0	NA
	SC ETA 25mg twice/wk	3	73*	50*	13	NA

a See section 1.6 for definition of ACR.

b 30% improvement.

ETA = etanercept; **JRA** = juvenile rheumatoid arthritis; **MTX** = methotrexate; **NA** = not applicable; **NR** = not reported; **PLA** = placebo; **RA** = rheumatoid arthritis; **SC** = subcutaneous; * $p < 0.001$; ** $p < 0.05$; *** $p = 0.03$.

score, erosions and joint space narrowing in all the treatment groups compared with their predicted change over time with an intent to treat analysis. There was a statistically significant difference favouring etanercept 25mg twice weekly over methotrexate and etanercept 10mg twice weekly with respect to erosions and a trend with respect to total Sharp score. By 2 years however, there was a statistically significant change favouring etanercept 25mg twice weekly versus methotrexate for both total Sharp score and erosions with very little progression in the etanercept 25mg group for both of these measures.

With respect to the x-ray changes there were several other important points noted at 1 year. No progression was seen in 75 and 57% of patients receiving etanercept 25mg twice weekly and patients receiving methotrexate, respectively. At 2 years, 63% of the patients receiving etanercept 25mg twice weekly had no progression in total Sharp score versus 51% of patients receiving methotrexate. 70% of patients receiving etanercept did not progress with respect to erosions versus 58% receiving methotrexate while 78% did not progress with respect to joint space narrowing versus 62% of methotrexate recipients. Very few patients who had no erosions at baseline, whether treated with etanercept or methotrexate, had erosions at 1 year. This would suggest that early aggressive therapy in patients with no erosions could, at least in the short term, prevent the development of erosions. Also it was noted that patients receiving methotrexate 20 mg/week were more likely not to progress radiographically than those receiving less than 20 mg/week (59 *vs* 45%, respectively). Etanercept 25mg twice weekly, however, was more effective in this regard (75% of patients did not progress).

This trial showed that in early aggressive RA, both methotrexate in high dose and etanercept 25mg twice weekly are effective in reducing the signs and symptoms of RA, improving patient function and slowing disease progression as mea-

Table VI. Adverse events recorded in patients enrolled in trials of etanercept (% of patients)

Study	Treatment	Injection site reactions	Rash	Skin infection	Infection	Flu-like illness	URI	Rhinitis	Sinusitis	Pharyngitis	Cough	Others
Phase II[97]	PLA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NS
	SC ETA 0.25 mg/m^2 twice/wk	[a]	NR	NR	NR	NR	[a]	[a]	[a]	[a]	[a]	NS
	SC ETA 2 mg/m^2 twice/wk	[a]	NR	NR	NR	NR	[a]	[a]	[a]	[a]	[a]	NS
	SC ETA 16 mg/m^2 twice/wk	[a]	NR	NR	NR	NR	[a]	[a]	[a]	[a]	[a]	NS
Phase III[99]	PLA	13	NR	NR	NR	NR	0.93[b]	11	11	NR	NR	NS
	SC ETA 10mg twice/wk	43	NR	NR	NR	NR	0.85[b]	12	11	NR	NR	NS
	SC ETA 25mg twice/wk	49*	NR	NR	NR	NR	1.11[b]	10	12	NR	NR	NS
MTX + ETA[100]	MTX only	7	NR	NR	63	NR	NR	3	NR	7	10	NS
	MTX + SC ETA 25mg twice/wk	42**	NR	NR	51	NR	NR	14	NR	2	3	NS
Early RA[101-104]	MTX only	7	23	10	NR	12	39	14	17	NR	NR	NS
	SC ETA 10mg twice/wk	30*	16	11	NR	10	27*	17	13	NR	NR	NS
	SC ETA 25mg twice/wk	37*	12*	14	NR	13	33	13	10	NR	NR	NS
JRA Part I[105]	SC ETA 0.4mg/m^2 twice/wk	39	10	NR	NR	NR	35	16	NR	14	NR	NS
JRA Part II[105]	PLA	4	≈Pt I	NR	NR	NR	≈Pt I	≈Pt I	NR	≈Pt I	NR	NS
	SC ETA 0.4mg/m^2 twice/wk	4	≈Pt I	NR	NR	NR	≈Pt I	≈Pt I	NR	≈Pt I	NR	NS
Psoriasis[106]	PLA	3	NR	NR	NR	20	12	13	17	10	NR	NS
	SC ETA 25mg twice/wk	20	NR	NR	NR	0*	27	17	10	17	NR	NS

a Occurred in the trial but no numbers given.

b Events/patient-year.

ETA = etanercept; **JRA** = juvenile rheumatoid arthritis; **MTX** = methotrexate; **NR** = no information reported; **NS** = not significantly different from placebo; **PLA** = placebo; ≈**Pt I** = approximately the same as Part I; **RA** = rheumatoid arthritis; **SC** = subcutaneous; **URI** = upper respiratory infection; * $p < 0.05$; ** $p < 0.001$.

sured by x-ray changes. By 2 years, however, significantly more patients had a response to etanercept than methotrexate in each of these categories, although many patients on methotrexate did do very well.

5.4 Long-Term Open Studies in Adult RA with Etanercept

Patients who completed phase I, II, and III studies with etanercept as monotherapy and whose disease did not respond to at least one DMARD were allowed to enter an open-label safety study.

In the initial reports,[109,110] 105 patients who had previously been treated with etanercept in clinical trials for up to 3 months and then stopped etanercept for a median of 17 months (while waiting for this open-label safety trial to begin) were restarted on subcutaneous etanercept at 25mg twice weekly. Patients were allowed to continue NSAIDs, corticosteroids (≤10 mg/day) and analgesics. Patients had an immediate response to retreatment with etanercept, which was sustained. By 3 months of therapy, >50% improvement was seen in 68% of patients for TJC and 57% for SJC. By 18 months the improvement was 75 and 74%, respectively.

Long-term safety has been reported in 782 patients.[111] By 33 months, patients continued to have a sustained response with 16% having no active joints. More importantly no significant differences in rate or type of adverse events were seen when compared with placebo or etanercept-treated patients in the controlled trials. The most common adverse event was ISR (43%) which were mild with < 0.5% of patients withdrawing for this reason. Clinically, it is important to advise patients of the possibility of the development if these reactions.

Safety and efficacy data has recently been reported on 628 patients from the original group followed up to 4.3 years (mean 2.4 years).[112,113] 479 patients have received etanercept for over 1 year, 420 for over 2 years, 164 for over 3 years and 12 for over 4 years. 69% achieved an ACR 20, 50% an ACR 50 and 25% an ACR 70. Some patients had no tender or swollen joints and some achieved a zero HAQ. 59% of patients receiving corticosteroids decreased their dose by a mean of 71%, 29% discontinued corticosteroids and only 5% increased their dose. Etanercept continued to be well tolerated. No significant or unusual adverse events were seen compared with normal populations and the controlled trials. Serious infections occurred at a rate of 0.05 per patient-year in the long-term trial versus 0.04 in etanercept-treated patients and 0.05 in placebo-treated patients in the controlled trials. Nine malignancies were seen versus 12.7 expected from the National Cancer Institute database, which is a national database in the US of malignancies seen in the general population.

Several abstracts [114-116] have described the long-term safety and efficacy of 79 patients who continued in an open-label trial of subcutaneous etanercept 25mg twice weekly and methotrexate. In the extension, reduction of methotrexate and corticosteroids was allowed after a minimum of 3 months' treatment. In the most recent report,[116] patients had received treatment for a median of 32 months (maximum 37). These patients were doing well clinically at follow-up and had not developed increased or unusual adverse effects. It should be noted that one patient in the initial study developed a malignancy (non-Hodgkin's lymphoma) while two in the extension study have done so (carcinoma of the breast and larynx). Both patients recovered and resumed therapy with etanercept. At baseline, 100% of patients were taking methotrexate at a mean dose of 18 mg/week. 68% have reduced their dose by a mean of 63%, and 28% discontinued methotrexate. In the 45 patients originally receiving corticosteroids, the mean dose was 6.3mg. 67% have reduced their dose by a mean of 78%, and 42% have discontinued corticosteroids. Even with these reductions, response to treatment has been sustained with 69% of patients achieving an ACR 20, 51% an ACR 50 and 27% an ACR 70. 19 of 70 patients had no tender joints, 10 of 70 no swollen

joints and 12 of 70 had a zero HAQ at this time point.

5.5 Etanercept in Juvenile RA

The Juvenile Rheumatoid Arthritis (JRA) study group[105] studied etanercept in children with polyarticular course JRA of any onset type. The study had a unique design for RA trials. 69 children were entered into an open-label study for 3 months (Part I) with all patients receiving subcutaneous etanercept at a dose of 0.4 mg/m^2 twice weekly (equivalent to 25mg twice weekly in the adult population). Inclusion criteria for the Part I study was age between 4 and 17, refractory or intolerant to methotrexate (>10 mg/m^2/week), and have at least five active joints and at least three joints with loss of motion (LOM) with pain and tenderness. Patients had to discontinue methotrexate for at least 2 weeks prior to baseline and other DMARDs for at least 4 weeks. Stable NSAIDs and low-dose corticosteroids were allowed. To be eligible for Part II, which was the randomised, double-blind placebo-controlled study, patients had to respond to etanercept in Part I with a >30% improvement in at least three of the six JRA core set criteria[117,118] and have >30% worsening in no more than one of the six criteria. The endpoint of Part II was the number of patients who flared when either continued on etanercept or placed on placebo. Flare was defined as >30% worsening in at least three of the six JRA core set criteria and >30% improvement in not more than of the criteria with at least two active joints or two unit increase of global assessments. In Part I, patients were assessed at screening, baseline, day 15, 30, 60 and 90 and in Part II each 30 days until flare. Also assessed at screening, month 3 and 7 was serum for autoantibodies and for antibodies to etanercept. The baseline demographics are presented in table I, clinical activity in table II, clinical response in table III, completer analysis in table IV and ACR response in table V.

Of the 69 patients entered into the 3-month open-label study, 64 (93%) completed the study and 51 (74%) met the requirements to enter Part II as a responder. As in adults, response was very rapid with response seen as early as 2 weeks. By 3 months, 100% of the patients (by definition) had at least a 30% improvement. Approximately 90% improved by 50%, and 50% improved by 70%. In Part II patients continued to receive etanercept by and large continued to maintain their significant clinical improvement (table III) while the placebo group began to deteriorate towards their Part I baseline values within 2 months. No patient had persistent elevations in autoantibodies or had signs or symptoms of an autoimmune disease. Two patients developed non-neutralising antibody to etanercept.

This trial showed that etanercept at 0.4 mg/m^2 is as efficacious in children for the signs and symptoms of RA as well as function measured by the CHAQ (Childhood HAQ) as in adults. Etanercept was rapidly effective and needed to be maintained for continued efficacy as flare occurred as early as 1 to 2 weeks after discontinuation. The 74% of children who responded are similar to the percentage of adults with RA who respond to etanercept in clinical trials. Joint x-rays were not done in this trial. For this reason it is not yet proven that the excellent clinical response will correspond to decreased joint damage over time which is even more important in this group than in adults.

6. Etanercept in Other Diseases

6.1 Psoriasis

The largest study reported with etanercept in diseases other than RA is in psoriasis.[106] This study was a 3-month placebo-controlled trial with patients treated either with subcutaneous etanercept 25mg twice daily or placebo. To be included in this trial, patients had to have active psoriatic arthritis defined as >3 swollen and tender or painful joints with an inadequate response to NSAIDs and requiring immunomodulatory therapy. Methotrexate ≤25 mg/week was allowed if stable for at least 4 weeks prior to the study and stable through-

out the study. All other DMARDs were discontinued at least 2 weeks prior to baseline. Prednisone ≤10 mg/day was also allowed if stable ≥4 weeks prior to baseline and throughout the study. The endpoints of this study were the psoriatic arthritis response criterion.[119] Patients were assessed at screening, baseline and at 12 weeks both for their arthritis and psoriasis. The baseline demographics are in table I, clinical activity in table II, clinical response in table III, completer analysis in table IV and ACR response in table V. The results of this study were similar to those seen in the RA trials. In addition, a majority of the patients had significant improvement in their psoriatic skin lesions as well.

6.2 Still's Disease in Adults

A 6-month, open-label study was conducted in 12 adults with Still's disease who met the criteria for systemic onset JRA and who had active arthritis. They were treated with subcutaneous etanercept 25mg twice weekly for 2 months.[120] If no response was seen by that time, etanercept was increased to 25mg three times weekly (four patients). Demographics included a mean age 36 years, 10 of 12 were female, mean disease duration of 10.7 years and patients had taken a mean of 3.6 prior DMARDs. Four of 12 had onset of their disease prior to age 16 years. The patients had active disease with multiple tender and swollen joints, elevated ESR and three patients had fever and rash as disease manifestations. Ten patients completed the study while two discontinued because of disease flare. Patients who completed the study (10 of 12) had a significant response with marked decrease of TJC (54%), decreased SJC (63%) and decreased ESR (27%). At the end of 6 months 67% achieved an ACR 20, 42% an ACR 50 and 17% an ACR 70. Only one of the three patients with fever and rash had decrease of the fever or resolution of the rash. No unusual adverse events were seen in these patients.

6.3 Ankylosing Spondylitis

Ten patients with spondyloarthropathy with inflammatory back pain and peripheral arthritis resistant to DMARDs were studied in a 6-month open-label trial with subcutaneous etanercept 25mg twice weekly.[121] Patients were assessed every 4 weeks for day and night pain on a 100mm visual analogue scale (VAS) as well as for the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI). Magnetic resonance imaging (MRI) of the axial skeleton and sacro-iliac joints was performed at baseline and month 6. At the time of the report, six patients completed 6 months of therapy of which four had AS and two spondyloarthropathy. There was a significant improvement in both the day and night VAS as well as in the BASFI and the BASDAI. In 5 of 6 patients bone oedema improved and in 3 of 6 patients there was resolution of the entheseal associated bursal soft tissue oedema. In a second study,[122] 16 patients with AS were treated for 4 months in a placebo-controlled study followed by a 6-month open-label extension. Their mean disease duration was 12 years, 50% were taking two or more medications for their AS, 25% were taking prednisone, methotrexate or sulfasalazine and 63% had not responded to at least one DMARD. Patients were treated with etanercept 25mg twice daily or placebo and were allowed to continue ≤10 mg/day of prednisone and various DMARDs as long as their dose was stable throughout the study. The patients were assessed for duration of morning stiffness, spinal night pain by VAS, BASFI, patient global assessment and SJC. A positive response was defined by at least a 20% improvement in three of these five criteria, which had to include morning stiffness and spinal night pain without worsening of any of the criteria. Eleven patients had completed the 4-month double-blind portion and were in the open-label extension. There was improvement in morning stiffness of 92%, spinal night pain

of 68%, BASFI of 56%, patient global of 48% and SJC of 59%.

These two studies indicate that there might be a significant role for etanercept in AS.

6.4 Progressive Systemic Sclerosis

A 6-month open-label study of ten patients with diffuse progressive systemic sclerosis (PSS) was performed.[123] All patients were treated with subcutaneous etanercept 25mg twice daily. The Rodnan skin score was the primary outcome measurement. Secondary outcome measurements were pulmonary function tests, physician and patient global assessments, oral aperture opening, hand extension and a modified HAQ. Four of nine patients had significant decrease in Rodman skin scores (mean 44%). Three of the four patients who started the study with digital ulcers improved. Pulmonary function tests and diffusion capacity of carbon monoxide remained unchanged. There was slight improvement in physician and patient global assessment as well as in HAQ. Oral aperture and hand extension was unchanged. Thus some patients seemed to improve in dermatological but not in pulmonary manifestations. A larger, double-blind study in early patients as defined by disease manifestations would be useful to see if there is a role for etanercept in PSS.

6.5 Wegener's Granulomatosis

Twenty patients with Wegener's granulomatosis were evaluated in a 6-month open-label study in which etanercept was added to conventional therapy.[124] All patients met the ACR criteria for Wegener's[125] and had active disease as defined by the Birmingham Vasculitis Activity Scale for Wegener's granulomatosis (BVAS/WG)[126] within 1 month of their baseline visit. All patients were treated with subcutaneous etanercept 25mg twice daily. Sixteen of 20 had limited disease and 4 of 20 had severe disease at baseline. Six of the 20 received a new immunosuppressive at baseline while the other 14 continued on their pre-existing immunosuppressives. One patient who had retro-orbital disease withdrew at 4 months. Because of the heterogeneity of the patient population and the differences in treatment regimens, this study was designed to evaluate safety rather than efficacy. The most frequent adverse event was ISRs, two infections (pneumococcal tracheobronchitis and localised Herpes zoster) in one patient, elevated liver transaminase levels in one patient, and neutropenia in five patients (related to concomitant cyclophosphamide or methotrexate). There seemed to be efficacy in that the mean BVAS/WG decreased from 3.6 to 0.6, the mean daily dose of prednisone was reduced from 19mg to 7.4 mg, five patients were in remission at 6 months and two patients discontinued corticosteroids. These results would suggest that a larger, double-blind study should be conducted, as there did not appear to be safety concerns and there may have been efficacy secondary to etanercept.

6.6 Uveitis

Reiff et al.,[127] studied ten children with treatment-resistant, chronically active uveitis in a 6-month open-label study. Seven of the ten had uveitis associated with pauciarticular JRA while three had idiopathic uveitis. Five had anterior uveitis, four had pan uveitis and one had pars plantis. All patients had failed to respond to treatment with topical corticosteroids, methotrexate and/or cyclosporin. The patients were treated with 0.4 mg/kg subcutaneously twice weekly for 3 months. If no improvement was noted, then the children were treated with 25mg subcutaneously twice weekly for the next 3 months. Seven of ten required such a dose increase. At baseline 18 eyes in the ten children were involved. Ten of the 18 eyes examined for anterior chamber density improved or remitted by 3 months. Intraocular pressure and visual acuity were unchanged. Increase of the dosage of etanercept to 25mg twice weekly led to no further improvement. A uveitis flare occurred in 5 of 18 eyes while on etanercept while 3 of 18 went into remission. The only adverse event noted was ISR. These

results would indicate a limited role for etanercept in treatment-resistant chronic uveitis in children.

7. Other issues with Etanercept

7.1 Institution of Therapy

These reports clearly show that etanercept is effective and has a fairly benign safety profile. It is, however, an expensive medication. There is, therefore, much discussion as to when etanercept should be employed in the treatment of patients with RA considering that the older DMARDs may be effective with less cost. Etanercept is effective in early RA, in combination with methotrexate and in patients who have not responded to DMARD treatment. If employed early, there is, in addition to its excellent anti-inflammatory effect, a marked inhibition of x-ray progression that may lead to decreased disability in the long term. Two patient populations were compared (those with early RA *vs* DMARD failures)[128] to address whether patients treated early in disease will have improved HAQ score versus those treated late. It was found that, although they had similar clinical activity prior to therapy including their HAQ scores (1.5 *vs* 1.6), by 24 months of therapy all of the disease activity measures were similarly dramatically reduced with the exception of the HAQ score. Those patients with late disease reduced the HAQ score to 1.0 while those with early disease were able to reduce their score to 0.6. The difference between a HAQ of 0.6 and 1.0 represents a significant difference in patient function. This would strongly suggest that early therapy is important with respect to maintaining patient function.

7.2 Administration

It has been shown that there is a dose response with increasing dose of etanercept.[97,99,103,129] While subcutaneous etanercept 10mg twice weekly[104] is more effective than placebo with respect to clinical improvement and x-ray progression, it is not quite as effective as methotrexate and less effective than etanercept 25mg twice weekly. A 6-month, double-blind, trial[130] was conducted comparing etanercept 25mg twice weekly to 50mg twice weekly in 77 patients. Although the patients in the 50mg twice weekly group had a faster response, by 6 months the response was similar. At 6 months the ACR 20, 50 and 70 were 65, 38 and 15% in the 25mg twice weekly group compared with 63, 37 and 16% in the 50mg group. Four patients in the 50mg group discontinued treatment because of adverse events compared with none in the 25mg group. Eight percent of the patients in the 25mg group and 6% in the 50mg group discontinued for lack of efficacy. Adverse events were similar in the two groups.

7.3 Effects in Special Populations

The phase III study was analysed for differences in clinical response between those patients 65 years of age or older and those who were younger.[131] 42 of the 234 patients in the phase III trial who were aged >65 were treated with either 10 or 25mg of etanercept for 6 months. 63% of the elderly patients in the 25mg group reached an ACR 20 and 44% an ACR 50 versus 58 and 39% in the <65 age group. Similar changes were seen with respect to decreased tender and swollen joint counts. Although both groups had an improvement in their HAQ score, the percentage improvement favoured the younger patients (43 *vs* 24%).

7.4 Effects on Immune Function

In the large phase III study of patients who had not responded to DMARD therapy, serum samples were collected pre- and post-study from 49 patients in order to detect the effect of etanercept on immunocompetence.[132] Delayed type hypersensitivity skin testing, determination of serum immunoglobulin levels and enumeration of immune effector cell populations by flow cytometry analysis were preformed at baseline, 3 and 6 months. Lymphoproliferation was also assessed. No differences between placebo and etanercept was seen other than an increase in the immunoglobulin (Ig) M levels in

etanercept treated patients. In this same patient population serum was collected pre and post treatment for the detection of autoantibodies and antibody development to etanercept. It was found that 5% of patients had autoantibodies to DNA prior to the study. Five percent developed anti-DNA antibodies during the study but 67% of these had a negative ANA. No patients developed other autoantibodies or clinical systemic lupus.

8. Safety

8.1 Injection Site Reactions

As seen in table VI the only adverse effect that clearly occurs with etanercept is ISR. ISRs occur in approximately one-third of patients and are generally mild to moderate and self-limiting. The reactions tend to occur early in treatment and resolve with time.

8.2 Infection

When introduced into clinical practice, there was concern about the development and response to infection. During the double-blind and open clinical trials, the incidence of infections, when adjusted for length of therapy was similar to those patients treated with placebo. In addition the type of infection and response to therapy was similar. In post-marketing surveillance there have been infrequent reports of serious infections some of which have had a fatal outcome. The associated risk factors seem to be diabetes mellitus and recurrent infections. For this reason there was an update to the label in the US, which states that if a patient develops a new infection while on etanercept, that they should be monitored closely. Etanercept should be discontinued if the patient develops a serious infection or sepsis. It is also suggested that etanercept should not be initiated in patients with active infections including chronic or localised infections.[133]

8.3 Development of Malignancy

The second area of concern is malignancy. In the double-blind and open-label studies there have been patients who have developed malignancies. The rate of development and types of malignancies, however, is no different than that expected from the National Cancer Institute database.[112] This question will not be able to be answered until etanercept has been used clinically for many more years.

8.4 Neurological Effects

Four cases of patients who developed confusion and difficulty walking while on etanercept have been reported[134] out of the approximately 90 000 patients who have been treated with etanercept. The events were temporally related and resolved or diminished on discontinuation of therapy. One patient had a positive rechallenge. Such events have been reported with other inhibitors of TNF and thus this may be a class effect. It is therefore suggested that etanercept not be instituted in patients with demyelinating diseases and that if a patient develops neurological symptoms while on etanercept, therapy should be discontinued.

8.5 Haematological Effects

During regulatory revue in Europe, several cases of pancytopenia and aplastic anaemia were seen. Most of the patients were receiving concomitant therapy associated with these adverse events. No causal relationship was established between these events and the use of etanercept. As of yet, there has been no change in the recommendation for laboratory testing although the clinician may elect to follow complete blood counts on a regular basis.

8.6 Pregnancy and Lactation

There are no published data on pregnancy as pregnant patients were excluded from all the trials and patients had to be on adequate birth control. With respect to nursing mothers, it is recom-

mended that patients discontinue nursing or etanercept.

8.7 Use in Malignancy and Hepatitis C

There are also no published data on the use of etanercept in patients with malignancy or with hepatitis C other than in the open-label safety trial as noted above.

8.8 Rare Events

The only other unusual adverse effects reported have been single case reports of atrial fibrillation,[135] leukocytoclastic vasculitis,[136] and type I diabetes mellitus.[137]

8.9 Autoantibodies

Non-neutralising antibodies to etanercept have been detected rarely in patients treated with etanercept. In trials, a small number of patients had antibodies to double-stranded DNA prior to the study and rare patients in both the placebo group and etanercept group did develop antibodies to double-stranded DNA during the study. Half of these patients did not have a positive ANA. A small number of patients shifted from negative to positive and positive to negative with regard to ANA and anticardiolipin antibodies. No patients had new connective-tissue disorders, thrombotic events or thrombocytopenia. It has been reported that some patients treated with etanercept for RA, however, do develop autoimmune skin rashes but there have been no cases reported of active systemic lupus erythematosus.[138] In addition, it has been reported that some patients treated with etanercept will develop antibodies that can interfere with some laboratory assays.[139]

9. Conclusions

Unfortunately, one cannot compare the clinical trials conducted with methotrexate, leflunomide, infliximab, etanercept or anakinra. The reasons for this is that the trials were all conducted in different patient populations who had significantly different disease characteristics such as length of illness and background therapy. In addition, there were significant differences in study design. The only way to compare the therapies would be to conduct a double-blind comparator study that compares one to another. These studies have not as yet been done.

Etanercept, the first biological response modifier (BRM) approved for use in RA in the US, is a very effective medication for the treatment of RA and is effective in patients with early disease, in combination with methotrexate, in patients who have not responded to DMARD treatment and in juvenile arthritis. It also appears to be effective in psoriatic arthritis. Its efficacy in Wegener's, PSS, Still's, chronic uveitis in children and AS can not be fully known until double-blind studies have been performed. Its safety profile to date has been excellent although the development of malignancies, serious infections and demyelinating diseases will have to be monitored in the future. Etanercept, as well as the other BRMs released to date, have had an impact on patients and their lives that has not been seen previously. The dramatic clinical responses and apparent safety have allowed many patients with RA (as well as other rheumatic diseases) resume a normal or near normal life. No other medications introduced for RA have had as dramatic effect than the introduction of corticosteroids.

Practically, a patient with early RA or psoriasis which is active despite NSAID therapy for several weeks (while diagnosis is being established) should be treated, in my opinion, first with methotrexate as a first-line DMARD therapy as long as there are no contraindications to methotrexate. If there are contraindications, then the use of sulfasalazine or leflunomide would be acceptable. Corticosteroid use as 'bridge therapy' is also helpful. methotrexate should be aggressively administered so that by around 3 months it should be clear whether the patient will have a sufficient response (or to leflunomide or sulfasalazine). If the patient has had a response, but still has active disease, then the addition of etanercept would be reasonable at

this timepoint. Other reasonable uses for etanercept are certainly in addition to methotrexate when there is only a partial response to methotrexate (or to other DMARDs) or in patients who have not responded to DMARDs. Similarly, etanercept should be considered in addition to methotrexate in juvenile arthritis or psoriatic arthritis when there is continued disease activity. In theses two diseases, similar to RA, it can be used in DMARD failures. In certain patients in whom methotrexate and other DMARDs are contraindicated for one reason or another, etanercept can be used as first-line therapy.

There are still questions as to the long-term adverse events that may occur with any new medication, including etanercept. For patients with RA, it would be hoped that the efficacy and safety of etanercept seen in the short term, will continue for many years.

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