Etanercept – review of efficacy and safety after five years of clinical use

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Etanercept (Enbrel®, Immunex corporation) was approved for use in rheumatoid arthritis 5 years ago for the treatment of patients with an incomplete response to methotrexate or disease-modifying antirheumatic drug failures and has since been approved for patients with early rheumatoid arthritis (including treatment-naïve patients), polyarticular course juvenile rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Etanercept has a dramatic effect on the clinical symptoms of disease and significantly retards x-ray progression in rheumatoid arthritis and in many patients, halts progression. The safety profile has been demonstrated to be relatively benign although there are specific safety issues which require continuing surveillance, including serious bacterial and opportunistic infections and the question as to whether there is an increased risk of lymphomas with continued use.

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Rheumatoid arthritis (RA) is an inflammatory disease with its primary manifestation in the synovium producing a chronic polyarthritis with systemic manifestations [1]. It has a worldwide prevalence of about 1%, with regional differences. The peak age of onset is between the fourth and sixth decades of life and women are twice as likely to be affected [2,3]. Mortality is increased [4,5] and mean life expectancy is shortened by 7 years in males and 3 in females [6]. Death most often results from infection, heart disease, respiratory or renal failure and gastrointestinal disease. Patients are prone to premature atherosclerosis [7]. Rates of work disability in the USA and Europe range from 22–85% and 31–80% respectively [8].

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

The definition of disease-modifying anti-rheumatic drugs (DMARDs) has changed significantly over the last decade. A DMARD not only needs to be active against the signs and symptoms of RA but must also significantly slow, if not halt, progression of the disease, as demonstrated by decreased x-ray progression and improved functional status [10].

Prior to the approval of etanercept (Enbrel®, Immunex Corporation), patients with RA were treated with a variety of DMARDs, either alone or in combination. Only methotrexate (MTX) and only when administered aggressively, has demonstrated to be of long-standing benefit to patients with RA, with respect to significantly decreased signs and symptoms and slowing of x-ray progression [11]. MTX and azulfidine have been shown to be of limited value in the treatment of psoriatic arthritis (PsA) [12–15] while no DMARD has been shown to be effective in the treatment of ankylosing spondylitis (AS) [16,17]. According to most national treatment guidelines, MTX has remained the treatment of choice for patients with RA, either alone or in combination, because it has been shown to be of at least some benefit to patients with RA and PsA, its safety profile is well understood and it is relatively inexpensive. Prior to the release of antitumor necrosis factor (TNF) agents, there was an unmet need for an efficacious medication with limited toxicity and the ability to significantly slow x-ray progression and improve patient function.

Overview of the market

Currently available traditional DMARDs do not maintain efficacy or are not well tolerated over time [11]. MTX, which has the best efficacy and tolerability profile of these medications, has significant toxicity, including bone marrow failure, hepatotoxicity and idiopathic lung reactions. Furthermore, as shown below, MTX is not as efficacious alone as monotherapy with etanercept or in combination with anti-TNF agents, such as etanercept, infliximab (Remicade®, Johnson & Johnson) and adalimumab (Humira™, Abbott Laboratories). Although etanercept has the longest experience of the anti-TNF agents in RA, PsA and AS, there are two other anti-TNF agents currently

available for the treatment of RA which includes infliximab and adalimumab. These agents are also currently being studied for the treatment of PsA and AS. In addition, there are a number of other agents currently in development for the treatment of RA including rituximab (MabThera®, Roche), CLTA4Ig, anti-interleukin (IL)-6 and -18, p55 inhibitors, anti-p38 map kinases and TNF-α-converting enzyme inhibitors, among others. Their efficacy and safety profiles will be defined when these studies are completed.

Introduction to the compound

Etanercept is a genetically engineered fusion protein which consists of two identical chains of recombinant human TNF-receptor p75 monomer fused with the Fc domain of human imunoglobulin (Ig)G1. Etanercept is a competitive inhibitor of the binding of TNF-α to the cell surface TNF receptors thus inhibiting the proinflammatory activity of TNF. For its production, recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system is utilized. It is injected subcutaneously (sc.) either as 25 mg twice a week or 50 mg weekly.

Chemistry

Etanercept consists of 934 amino acids with an approximate molecular weight of 150 kDa. The Fc component of etanercept contains the CH_2 domain, the CH_3 domain and the hinge region [IMMUNEX CORPORATION: ENBREL® (ETANERCEPT) PACKAGE INSERT (2003)].

Pharmacodynamics

Etanercept binds soluble TNF-α, blocking it's ability to bind to cell-bound TNF receptors thus inhibiting signaling of the target cell and thereby preventing the biological affects of TNF production. Expression of adhesion molecules, such as E-selectin and intracellular adhesion molecule (ICAM)-1, IL-6 and neutral metalloproteases are also modulated by etanercept. The binding of etanercept to cells expressing transmembrane TNF-α does not cause cell lysis *in vitro* in the presence or absence of complement [IMMUNEX CORPORATION: ENBREL® (ETANERCEPT) PACKAGE INSERT (2003)].

Pharmacokinetics & metabolism

A study in 26 healthy volunteers who received a single dose of 25 mg etanercept sc. and had serial serum samples collected for 24 days, demonstrated that etanercept is slowly absorbed from the injection site [IMMUNEX CORPORATION: ENBREL® (ETANERCEPT) PACKAGE INSERT (2003)]. A peak concentration of 1.46 ± 0.72 mg/ml was reached in 51 ± 14 hours. The area under the curve (AUC) was 235 ± 98 mg/h/l. Apparent clearance and volumes of distribution were 132 ± 85 ml/h and 12 ± 6 l respectively. The half-life was 68 ± 19 h.

Clinical efficacy in rheumatoid arthritis

Etanercept in DMARD failures

Positive results from Phase I studies involving normal human volunteers [19] and a Phase I safety and dose-finding trial in 22 patients with refractory rheumatoid arthritis [20] led to a three month Phase II randomized, double-blind, placebo-controlled trial (RDBPCT) in patients with active RA who had failed at least one DMARD [21]. Patients were treated with placebo, 0.25 mg, 2 mg or 16 mg of etanercept per square meter of body surface (mg/m²). Etanercept was injected subcutaneously (sc.) twice weekly (b.i.w.). There was a significant dose response with the 16 mg/m² group having the highest American College of Rheumatology (ACR) response rates [22]; the ACR 20 was achieved in 75% and the ACR 50 in 58% of patients. Response was observed as early as week 2. By 8 weeks after cessation of therapy, all indicators of disease activity had returned to baseline values. The only side effects reported different from placebo were mild, transient injection site reactions (ISRs) and mild upper respiratory infections (URIs) that resolved on continued therapy with etanercept.

A Phase III, 6 month, RDBPCT of 234 patients with a mean of more than 10 years of disease and most of whom had failed MTX was conducted [23]. Patients received placebo, 10 mg or 25 mg (equivalent to 16 mg/m²) of etanercept sc. b.i.w. There was a significant response to 25 mg of etanercept b.i.w. with 62, 41 and 15% achieving an ACR 20, 50 and 70 respectively. Adverse events different from placebo were the development of mild-to-moderate transient ISR and an increase in URIs in the etanercept-treated groups. This study confirmed the efficacy of etanercept in DMARD failures and was the basis of approval of etanercept for this indication.

Etanercept in patients with incomplete response to MTX

To evaluate the safety of the combination of etanercept and MTX, a 24 week RDBPCT was conducted in 89 patients who had persistently active disease despite at least 6 months therapy with MTX at a stable dose of 15–25 mg per week (or as low as 10 mg per week if they

had toxicity to MTX) [24]. All patients had active disease defined by at least six tender and swollen joints at baseline. All patients received folic acid. Patients had long disease duration, failed numerous DMARDs, had active disease and continued their MTX for the duration of the study (mean 18 mg per week). Patients were also assessed for the development of autoantibodies and antibodies to etanercept. Randomization was in a 2:1 ratio to receive either etanercept 25 mg sc. b.i.w. or placebo. There was a significant benefit of the combination therapy with 71, 39 and 15% of the combination group achieving an ACR 20, 50 and 70, respectively, versus 27, 3 and 0%, respectively, in the MTX-only group. Although designed as a safety study, this result indicated that the addition of etanercept to MTX partial responders is efficacious and was the basis for the approval of etanercept for this indication. The only significant difference in side effects between the two groups was the development of transient, mild-to-moderate ISRs in the etanercept group.

Of the original 89 patients, 79 were enrolled in an extension study [25]. Patients who were receiving MTX and etanercept continued to receive the same treatment. Patients given MTX only received etanercept and MTX in the extension study. After 3 months of combination therapy, investigators were allowed to lower the corticosteroid and MTX dose if clinically indicated. Of the patients, 96, 80 and 72% were evaluable for 1-, 2- and 3-year efficacy. At 3 years, 57 patients continued in the study and 77% achieved an ACR 20, 47% an ACR 50 and 23% an ACR 70. Of the patients, 83% were able to decrease or discontinue corticosteroids. MTX dose was decreased or discontinued in 62% of the patients.

As part of the safety profile, there was an assessment of antibodies and autoantibodies [26]. Non-neutralizing antibodies to etanercept were detected in 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 four patients in the etanercept group developed antibodies to double-stranded DNA during the study. Of these patients, two did not have a positive antinuclear antibody (ANA). A small number of patients shifted from negative to positive and positive to negative with regard to ANA and anticardiolipin antibodies. None of the patients developed systemic lupus erythematosus, new connective-tissue disorders, thrombotic events or thrombocytopenia.

Etanercept versus MTX in early RA & MTX-naïve patients

The efficacy of etanercept in early RA has been studied in patients with less than 3 years of disease who were naïve to MTX in a 24-month study with efficacy the primary end point at 6 months and x-rays the primary end point at 1 year with a 12-month extension [27,28]. This RDBPCT compared aggressively dosed MTX (mean dose of 19 mg/week), etanercept 10 mg sc. b.i.w. and etanercept 25 mg sc. b.i.w. Patients had no prior treatment with MTX and active disease. The population was enriched for x-ray progression by requiring that patients have a positive rheumatoid factor or at least three bone erosions in x-rays of the wrists, hands or feet. Patients in the MTX group were commenced at 7.5 mg per week (plus folic acid at 1 mg per day). At week 4, if the patient had any tender or swollen joints, it was mandatory that the MTX dose be increased to 15 mg per week for an additional 4 weeks. At week 8, if the patient had any tender or swollen joints, MTX was increased to 20 mg per week. Patients were assessed clinically throughout the study and for x-ray at baseline, 6 and 12 months. A determination of the total Sharp score (TSS) [29], erosions and joint space narrowing (JSN) was determined for each x-ray. The patients had mean disease duration of 11 months.

Etanercept 25 mg b.i.w. was effective as early as 2 weeks. In the first 4 months of the trial, etanercept 25 mg was statistically superior to MTX with respect to the percent of patients who reached an ACR 20, 50 and 70. However, by 12 months there was no statistically significant difference between the two groups with respect to ACR 20, 50 and 70 with both groups doing well. By 24 months there was a statistically significant difference between the two groups as those patients on etanercept maintained their efficacy whilst some patients on MTX lost efficacy.

Radiographically at 12 months, there was a significant reduction in the TSS, erosions and JSN in all the treatment groups compared with their predicted change over time. There was a statistically significant difference favoring etanercept 25 mg b.i.w. over MTX and etanercept 10 mg b.i.w. with respect to erosions only (the clinical significance of which is not clear) but not with respect to TSS or JSN. However, by 2 years there was a statistically significant change favoring etanercept 25 mg b.i.w. versus MTX for both TSS and erosions with very little progression in the etanercept 25 mg group for both of these

measures. Of the patients on 25 mg etanercept, 75% did not progress at all while 57% of the patients on MTX had no progression. Very few patients who had no erosions at baseline, whether treated with etanercept or MTX, had erosions at 1 year. This would suggest that early aggressive therapy in patients with no erosions could prevent the development of erosions. No x-ray progression was seen in 75% of etanercept 25 mg b.i.w., 59% of patients on MTX 20 mg per week and 45% of patients on less than 20 mg per week of MTX, strongly suggesting that etanercept is more effective than MTX in halting x-ray progression and that 20 mg per week on MTX is more effective than less than 20 mg per week of MTX in halting x-ray progression.

This trial demonstrated that in early rheumatoid arthritis, both high-dose MTX and etanercept 25 mg b.i.w. are effective in reducing the signs and symptoms of RA, improving patient function and slowing disease progression, as measured by x-ray changes. However, by 2 years, significantly more patients had a response to etanercept than MTX in each of these categories.

Etanercept versus MTX versus the combination of etanercept & MTX

The Trial of Etanercept and MTX with Radiographic Patients Outcomes (TEMPO) was a large RDBPCT three-arm trial to evaluate the clinical response and radiographic changes of etanercept versus MTX versus the combination of etanercept and MTX conducted in 642 patients [30]. The primary end points were clinical responses at 24 weeks and the change from baseline at 52 weeks in the TSS. At 52 weeks the ACR 20, 50 and 70 responses were 85, 69 and 43% for the combined MTX–etanercept group compared with 76, 48 and 24% for the etanercept monotherapy group and 75, 43 and 19%, respectively, for the MTX monotherapy group. The results indicate that although the ACR 20 responses were similar between the three groups, the depth of response was far greater with the combination group versus either monotherapy with 43% of the combination group achieving an ACR 70. The modified TSS was -0.54, 0.52 and 2.8 respectively for the combined, etanercept and MTX groups respectively. This would suggest that combination therapy with a TSS of -0.54 inhibited radiographic progression significantly more than etanercept (0.52 increase) versus MTX which had an increase of 2.8. This degree of inhibition of x-ray progression with the combination of etanercept and MTX should prevent future deformities, although this relationship between x-ray progression and disability has not yet been proven.

Dosing in RA

A Phase III trial was conducted to examine the safety, efficacy and pharmacokinetic profiles of 50 mg weekly versus 25 mg b.i.w. and placebo for 8 weeks [31]. The placebo group received placebo for 8 weeks followed by etanercept 25 mg b.i.w. for 8 weeks. At week 16, the ACR 20 response rates for etanercept subjects in the 50 mg weekly group and the 25 mg b.i.w. groups were 55 and 63%, respectively, which was not statistically significant. Individual etanercept concentration–time profiles for the two-dose regimens overlapped at weeks 1 and 8.

Etanercept in polyarticular course juvenile RA

Etanercept has been studied in polyarticular course juvenile rheumatoid arthritis (JRA) of any onset type in two phases [32]. In the first phase, 69 children were entered into an open-label study for 3 months with all patients receiving etanercept at 0.4 mg/kg sc. b.i.w. (maximum dose 25 mg b.i.w.). Patients had to be refractory or intolerant to MTX (≥ 10 mg/m^2/week). To be eligible for the second phase, which was the RDBPCT, patients had to respond to etanercept in Phase I with a ≥30% improvement in at least three of the six JRA core set criteria [33] and have ≥30% worsening in no more than one of the six criteria. The end point of Phase 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 one of the criteria with at least two active joints or two unit increase of global assessments.

Of the 69 patients entered into the 3 month open-label study, 64 (93%) completed and 51 (74%) met the requirements to enter Phase II as a responder. Response was rapid and observed as early as 2 weeks. At 3 months, in those 51 patients who met the definition of the ACR pediatric-30 response, approximately 90% satisfied the ACR pediatric-50 and 50% satisfied the ACR pediatric-70 response criteria. In Phase II, statistically significant differences in both the proportion who flared and the time to flare was demonstrated comparing those randomized to continue with etanercept compared with those randomized to placebo.

This trial demonstrated that etanercept at 0.4 mg/kg b.i.w. is efficacious in children for the signs and symptoms of JRA as well as function

measured by the Childhood Health Assessment Questionnaire (CHAQ). As joint x-rays were not carried out in this trial it is not known if the clinical response will correspond to decreased joint damage which is important in pediatric patients.

In an open label extension treatment trial, 58 of these 69 patients were continued on etanercept [34]. All patients received 0.4 mg/kg of etanercept. During the first year of the study MTX use was not permitted. At the completion of the first year, corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) were allowed without any restrictions, as was MTX. An interim analysis at 2 years showed 48 patients were still enrolled in the study with 43 patients completing at least 2 years of study. These patients had sustained efficacy, with 81% meeting the JRA 30, 79% meeting the JRA 50 and 67% meeting the JRA 70. The most common adverse events reported in this study were headache, abdominal pain, rhinitis, nausea, fever, accidental injury and rash. The infection rates were comparable with the placebo group in the initial study.

In another open-label trial in children with JRA of various types [35] which also demonstrated efficacy of etanercept of 61 patients enrolled, 12 patients developed severe side effects including neurologic disorders, retrobulbar optic neuropathy, weight gain, severe infection, cutaneous vasculitis, hemorrhagic diarrhea, uveitis flare and pancytopenia. Many of these side effects have not been reported in adults or patients treated with other anti-TNF agents.

Psoriatic arthritis

Etanercept became the first US Food and Drug Administration (FDA)-approved drug specifically for PsA in 2001 based on two trials [36,37,101]. The first study was a single center Phase II 3-month, RDBPCT with subjects treated either with etanercept 25 mg b.i.w. sc. or placebo [36]. Patients had to have active PsA defined as ≥3 swollen and tender joints with an inadequate response to NSAIDs and requiring immunomodulatory therapy. A subgroup was included to determine the response of plaque psoriasis to therapy if ≥3% of body surface area was involved. The primary end point was the psoriatic arthritis response criterion (PsARC) [12] with the ACR20 a secondary end point. The psoriasis end point was the percentage of subjects with at least 75% improvement in the Psoriasis Area and Severity Score (PASI) [38] at 12 weeks. There were 60 subjects who had psoriasis for a median of approximately 20 years and PsA for a median of 10 years. 87% of etanercept-treated subjects achieved a PsARC response as compared with 23% of placebo which was statistically significant with responses observed as early as 4 weeks and sustained for 12 weeks. Of etanercept subjects, 73% achieved an ACR20 response at 12 weeks versus 13% of placebo subjects which was statistically significant. In the plaque psoriasis subgroup, 26% of etanercept treated subjects achieved a 75% PASI improvement versus none of the placebo subjects. Subjects completing the Phase II study were permitted to enter a 6 month open label study of etanercept 25mg sc. b.i.w. The placebo subjects had rapid improvement and the original etanercept subjects continued to improve.

A Phase III RDBPCT was performed with 205 subjects [37] required to have ≥3 swollen and tender joints. The mean duration of psoriasis was 19 years and mean duration of arthritis was 9 years. Approximately 50% were receiving concomitant MTX. The primary end point was the ACR20 at 12 weeks. Of subjects, 59% in the etanercept group and 15% in the placebo group achieved an ACR 20 which was statistically significant at 12 weeks. An ACR 50 was achieved in 38% of subjects in the etanercept group at 6 months and ACR 70 in 10%. By the PsARC criteria, 72% of the etanercept group and 31% of the placebo group met criteria for clinical response which was statistically significant at 3 months.

Plaque psoriasis

Both a Phase II and III trial have been performed in patients with plaque psoriasis. The Phase II trial enrolled 112 subjects with chronic psoriasis in a 24 week RDBPCT evaluating etanercept as monotherapy at 25 mg sc. twice weekly [39]. The primary end point was a 75% improvement in the PASI score at 12 weeks. Subjects had to have at least 10% of body surface area involved with plaque psoriasis and have failed at least one previous systemic psoriasis therapy. Of the subjects in the etanercept group, 30% attained a 75% improvement in PASI compared with 2% in the placebo group. At 24 weeks 56% had a 75% improvement in PASI compared with 5% in the placebo group.

A Phase III trial of 24 weeks in duration involving 672 subjects evaluated three doses of etanercept: 25 mg four times weekly (q.w.), 25 mg b.i.w. and 50 mg b.i.w. versus placebo [40]. Patients were required to have stable plaque

psoriasis involving at least 10% of the body surface area, a minimal PASI score of 10 and had previously received phototherapy or systemic psoriasis therapy at least once, or were a candidate for therapy. At week 12, placebo subjects began double-blind treatment with etanercept 25 mg sc. weekly. The primary end point was the proportion of subjects in each group that attained an improvement of 75% in the PASI at week 12. This was achieved in 49% of patients treated at 50 mg b.i.w. compared with 34% in the 25 mg b.i.w. group, 14% in the 25 mg OW group versus 4% in the placebo group (which was statistically significant for all groups vs. placebo) with response seen as early as week 2. By week 24 there was a 75% improvement in 25% of the 25 mg weekly group, 44% in the 25 mg b.i.w. group and 59% in the 50 mg b.i.w. group. The placebo group was switched to the active drug at 25 mg b.i.w. at week 12 and demonstrated similar results to the original 25 mg b.i.w. group at week 12.

Ankylosing spondylitis

Prior to the approval of etanercept for the treatment of AS, NSAIDs were the only approved therapy. Early reports from open-label and small placebo-controlled studies suggested that TNF blockers may be effective in seronegative spondyloarthropathies. An open-label study of 10 subjects with resistant spondyloarthropathies including clinical and magnetic resonance imaging (MRI) findings showed marked improvement in both clinical and MRI images using etanercept 25 mg sc. twice weekly at 6 months [41].

The first RDBPCT of etanercept in AS involved 40 subjects who received either placebo or etanercept 25 mg twice weekly for 4 months with a 6 month open-label extension [42]. Patients had to meet the modified NY criteria for AS [43]. The primary end point was a 20% improvement at week 16 in three of five response criteria (subject global assessment, nocturnal spinal pain, duration of morning stiffness, Bath ankylosing spondylitis function index [BASFI] [44] and swollen joint score). At 24 weeks 80% of the etanercept group and 30% in the placebo group ($p = 0.004$) showed improvement in the primary end point. In a retrospective analysis, the ankylosing spondylitis assessment score (ASAS)-20 score [45] (which had not been developed at the time this study was conducted) was calculated and the study showed ASAS-20, -50 and -70 scores of 85, 50 and 25% compared with placebo 30, 15 and 10% respectively [46].

Based on these results, two large Phase III RDBPCTs were initiated which compared placebo with etanercept 25 mg b.i.w. The larger study evaluated 277 subjects for 24 weeks [47] while the smaller study enrolled 84 subjects for 12 weeks [102]. The primary end point of both studies was the ASAS-20 score at 12 weeks. Subjects were balanced for demographics, medications and disease activity in both studies. The ASAS-20, -50 and -70 scores at 12 weeks in the larger study were 83, 62 and 40% compared with placebo at 27, 13 and 7%. The ASAS-20, -50 and -70 scores at 24 weeks were maintained at 80, 58 and 39%. In the smaller study at 12 weeks the ASAS-20, -50 and -70 scores were 60, 49 and 24%, compared with placebo at 23, 10 and 10%, respectively.

Another small Phase II trial was conducted which evaluated etanercept 25 mg b.i.w. versus placebo with 15 patients in each group [48]. Patients were allowed to continue NSAIDs but were not allowed DMARDs or steroids. The first 6 weeks was placebo-controlled. The placebo group was then subsequently treated with etanercept at 25 mg b.i.w. for an additional 3 months. The results demonstrated that etanercept was effective by every response criteria measured. At 6 weeks during the placebo control part the ASAS 20 score was 78.5% for etanercept compared with 25% for placebo and for ASAS 50, 42.9 versus 12.5% (both $p < 0.01$).

Wegener's granulomatosis

A group of 20 subjects with Wegener's granulomatosis (WG) were evaluated in a 6 month open-label study in which etanercept was added to conventional therapy [49]. All subjects met the ACR criteria for Wegener's [50] and had active disease as defined by the Birmingham Vasculitis Activity Scale for WG (BVAS/WG) [51] within 1 month of their baseline visit. All subjects were treated with etanercept 25 mg b.i.w. sc. Of the 20, 16 had limited disease and four had severe disease at baseline. Of the 20, six received a new immunosuppressive at baseline while the other 14 continued on their preexisting immunosuppressives. Due to the heterogeneity of the subject population and the differences in treatment regimens, this study was designed to evaluate safety rather than efficacy. The most frequent adverse events were ISRs. There were two serious adverse events; elevated liver transaminases in one subject and neutropenia in five subjects thought to be related to concomitant immunosuppressives.

There seemed to be efficacy in that the mean BVAS/WG decreased from 3.6 to 0.6 and the mean dose of prednisone was reduced from 19 mg to 7.4 mg. At 6 months, five subjects were in remission and two subjects discontinued steroids. These results suggested that there did not appear to be safety concerns and there may have been efficacy with etanercept.

There is an ongoing RDBPCT evaluating etanercept in the treatment of WG in which the trial design and demographics of the subject population have been reported [52,53].

Uveitis

Reiff and colleagues studied 10 children with treatment resistant, chronically active uveitis in a 6-month open-label study [54]. Of the patients, seven 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 subjects had failed treatment with topical steroids, MTX and/or cyclosporin. The subjects were treated with 0.4 mg per kg sc. b.i.w. for 3 months and if no improvement was noted, the dose was increased to 25 mg sc. b.i.w. for the next 3 months. Such a dose increase was required in seven of the 10 subjects. At baseline 18 eyes in the 10 children were involved. Of the 18 eyes examined for anterior chamber density, 10 improved or remitted by 3 months. Intraocular pressure and visual acuity were unchanged. Increase of etanercept to 25 mg b.i.w. led to no further improvement. A uveitis flare occurred in five of the 18 eyes while on etanercept while three went into remission. The only adverse events noted were ISRs. These results would indicate a limited role for etanercept in the treatment of resistant chronic uveitis in children.

Foster and colleagues evaluated 20 adults with uveitis in a RDBPCT taking MTX to prevent relapse in whom it was desired to taper the MTX [55]. The dose of etanercept was 25 mg b.i.w. MTX was tapered at 2.5 mg/wk commencing 2 weeks after the first dose of study drug. The primary outcome measure was recurrence of uveitis. There was no difference between the placebo and etanercept groups observed with an equal number of patients remitting and flaring.

Crohn's disease

A RDBPCT of 8 weeks duration involving 43 patients with moderate-to-severe Crohn's disease was initiated to evaluate the effectiveness of etanercept 25 mg b.i.w. versus placebo [56]. Concomitant stable doses of prednisone, budesonide, azathioprine, 6-mercaptopurine, MTX, mycophenolate mofetil, antibiotics and 5-aminosalicylates were allowed. Etanercept was not as effective as placebo in inducing a clinical response thus indicating no role for this dose of etanercept in Crohn's disease.

Postmarketing surveillance

As discussed below, the only safety and tolerability issues that were revealed in the clinical trials were ISR and an increase in URI. The major safety and tolerability issues were all found in postmarketing surveillance.

Safety & tolerability

The safety of etanercept has been studied in clinical trial patients for more than 5 years and the observations of 2054 patients with a total of 5549 patient-year therapy has been reported [57]. Safety data from a postmarketing trial registry, which includes 1685 patients initially starting etanercept, has also been reported [58]. In the March 2003 FDA safety review of anti-TNF-α agents, the total number of patients observed in clinical trials with etanercept was 3839 with 8336 patient-years exposure. It is estimated that commercial exposure as of July 31, 2003 was more than 202,000 patients [103].

Injection site reactions

ISRs occurred in 37% of subjects enrolled in controlled trials, were generally mild-to-moderate and self-limiting. Erythema and/or itching are the most common complaints. The reactions tend to occur early in treatment and resolve with time [IMMUNEX CORPORATION: ENBREL® (ETANERCEPT) PACKAGE INSERT (2003)].

Infection

During the development of etanercept there was a great deal of concern about bacterial infections because of the role of TNF-α in the response to infection. During the double-blind and open-label clinical trials, the incidence of infections in patients treated with etanercept, when adjusted for length of therapy was similar to those subjects treated with placebo [IMMUNEX CORPORATION: ENBREL® (ETANERCEPT) PACKAGE INSERT (2003)]. The most common type of infections reported were URIs, which occurred at a rate of approximately 20%. The type of infections and response to therapy was similar to those patients treated with placebo in the clinical trials. The rate of serious infection was similar between the etanercept and

placebo groups and similar to what has historically been observed in patients with RA [59]. No opportunistic infections were reported in the clinical trials, including tuberculosis [IMMUNEX CORPORATION: ENBREL® (ETANERCEPT) PACKAGE INSERT (2003)].

In postmarketing surveillance however, there were early reports of serious infections, some of which were fatal. The associated risk factors for the development of serious infections were diabetes, chronic pulmonary disease and any patient who has recurrent or active infections for any cause. There was an update to the label in the USA which states that if a subject develops a new infection while on etanercept, they should be monitored closely. Etanercept should be discontinued if the subject develops a serious infection or sepsis. It is also stated that etanercept should not be initiated in subjects with active infections, including chronic or localized infections, or those patients with recurrent infections [IMMUNEX CORPORATION: ENBREL® (ETANERCEPT) PACKAGE INSERT (2003)]. Once the infection has been treated the patient can be restarted on etanercept.

Postmarketing, there have been reports of the development of tuberculosis in 36 patients, as well as the development of other opportunistic infections [60–64]. For this reason, physicians should perform a purified protein derivative (PPD) for tuberculosis and chest x-ray prior to the institution of etanercept. If the PPD is positive and the patient does not have active tuberculosis, then concomitant treatment with isoniazid (INH) should be considered. If the chest x-ray demonstrates the presence of opportunistic infection, then alternative therapy should be considered.

In a 24 week RDBPCT in 242 subjects with RA, taking background MTX, a study was conducted which compared etanercept alone 25 mg b.i.w. and etanercept 25 mg q.w. with anakinra 100 mg daily or etanercept 25 mg b.i.w. and anakinra 100 mg daily [104]. The primary end point was an ACR 50 response. The study showed a 0, 3.7 and 7.4% incidence of infection in the etanercept 25 mg b.i.w. alone, etanercept 25 mg q.w. plus anakinra 100 mg daily and etanercept 25 mg b.i.w. and anakinra 100 mg daily groups respectively. The combination of etanercept and anakinra did not result in a higher ACR 50 score compared with etanercept alone. Thus, there appeared to be no clinical benefit and a clinically significant increased incidence of serious infections when etanercept was combined with anakinra.

Development of malignancy

The second area of concern during the development of etanercept was the development of malignancy. In the double-blind and open -abel studies there have been no differences in the development of malignancies in patients treated with etanercept than expected from the SEER database [65] with 57 observed malignancies versus 55 predicted [IMMUNEX CORPORATION: ENBREL® (ETANERCEPT) PACKAGE INSERT (2003)]. It has been demonstrated that patients with RA have an increased risk of developing lymphoma compared with the normal but not RA population [66,105]. A nested case study has been performed and determined that RA patients with high inflammatory activity had the highest risk of lymphoma with an odds ratio (OR) of 25.8; patients with moderate inflammation had an odds ratio of 5.33 and those with low inflammatory activity had an odds ratio of around two [67]. In the clinical trials of etanercept there were nine patients who developed lymphoma with an OR of 3:47 [103]. Post marketing there have been 70 lymphomas reported [68,69]. It is not yet clear whether the development of lymphoma will become a significant problem as more patients are exposed to etanercept for a longer period of time.

Neurologic

Mohan and colleagues identified 17 patients with neurologic events suggestive of demyelination following administration of etanercept [70]. This report included data from a period between November 1998 and May 2000, representing 55,313 persons per year exposure. New symptoms were identified in nine patients, suggestive of a demyelination disorder. This compares with the natural incidence of 4–6 cases per population of 100,000 per year. Although it is still unclear whether there is a direct relationship to etanercept, it is suggested that etanercept not be used in patients with or who develop evidence of a demyelinating disease.

Congestive heart failure

Two trials of etanercept in 2048 patients have been completed [71,72]. One trial compared placebo with etanercept 25 mg q.w. versus etanercept 25 mg b.i.w., while the other compared placebo with etanercept 25 mg b.i.w. to etanercept 25 mg thrice weekly (t.i.w.). The primary end point was improvement in mortality from congestive heart failure (CHF). The trials were terminated early because of lack of efficacy. There were no significant differences in adverse events or serious infections in any of the groups.

There was, however, a trend towards worsening of CHF in patients treated with the higher dose of etanercept. For this reason, caution should be exercised in treating patients with significant CHF with etanercept.

Pregnancy

There is no published data on pregnancy, as pregnant subjects were excluded from all the trials and subjects had to be on adequate birth control [IMMUNEX CORPORATION: ENBREL® (ETANERCEPT) PACKAGE INSERT (2003)].

Use in previous malignancy

There is no published data on the use of etanercept in subjects with malignancy [IMMUNEX CORPORATION: ENBREL® (ETANERCEPT) PACKAGE INSERT (2003)].

Use in patients with hepatitis C

An open-label study of 21 patients with hepatitis C who had no viral load and were treated with etanercept (18 patients) or with infliximab (three patients), demonstrated that these patients did not increase their viral load during therapy with either agent [73].

Rare adverse events

There are a few reports of rare adverse events which include the development of atrial fibrillation, leukocytoclastic vasculitis, diabetes mellitus and autoimmune skin rashes [74–77]. It is not known if these are true adverse events of etanercept.

Regulatory affairs

Etanercept is approved for use in the USA for the treatment of RA in patients with early disease including DMARD-naïve patients, in combination with MTX and in DMARD failures. Its use has also been approved as monotherapy in polyarticular JRA patients who have failed one DMARD, PsA, psoriasis and AS. It is not approved for the treatment of Crohn's disease. Etanercept is also approved in many countries for the treatment of RA in DMARD failures and in combination with DMARDs as well as polyarticular course JRA, but is not universally approved for DMARD-naïve patients, PsA and AS. A treating physician should therefore ascertain the country specific guidelines for use.

Conclusions

Etanercept has been shown to be an effective medication for the treatment of RA, polyarticular JRA, PsA and AS. Its safety profile to date has been favorable, although the development of lymphomas, serious infections, CHF and demylinating diseases needs to be to be monitored. Etanercept has had a significant positive impact on patients that has not been observed previously [78]. No other medications for these diseases have had as dramatic an effect other than the introduction of steroids.

Expert opinion

In patients with newly diagnosed RA, it is most reasonable to institute therapy with MTX. Although the initial dose differs amongst rheumatologists, it is our opinion that the most effective dose of MTX is 20 mg per week [28] which is where we start therapy (and, anecdotally, have not seen any significant differences in side effects from initiating therapy with a lower dose). If the patient has an excellent response, then we continue MTX monotherapy. If the patient has not had an excellent response by 8–12 weeks, then we consider the addition of a biologic. As shown in the TEMPO trial [30], the combination of etanercept and MTX seems to give a much better depth of response and x-ray progression also seems to be dramatically slowed with this combination. It is important to initiate the anti-TNF therapy as early as possible as patient function is determined both by inflammation and structural damage. The earlier inflammation is brought under control and the less structural damage that occurs, the more functional the patient will remain over time [78].

If the patient is initially seen on MTX (or another DMARD) and still has active disease, the addition of etanercept has also been shown to be effective [24]. We do not believe that the combination of MTX with another DMARD or when used in triple therapy is as efficacious as the combination with a biologic.

Patients who have failed multiple DMARDs have also benefited from the addition of etanercept [21,23]. With the above in mind, one should consider the addition of etanercept to the regimen of any patient with any disease activity – it is never too early or too late.

In patients with polyarticular course JRA, the efficacy of etanercept has been demonstrated [31,34]. Etanercept should be added early in order to prevent joint damage and functional declines which can occur early in JRA and may be life-long.

In patients with AS, etanercept is the medication of choice. No DMARD has shown to be as effective as etanercept and treatment with NSAIDs for years, although helpful, may delay but not prevent progression.

Etanercept is effective in PsA for both the spinal and peripheral arthritis. It is clear that 100 mg per week for the first 12 weeks and then 50 mg per week is the most effective dose for the skin disease as demonstrated in the clinical trials. Although there is little doubt about the efficacy of etanercept, caution needs to be observed and cannot be understated.

Careful screening for tuberculosis should be undertaken and if found, proper procedures should be followed to prevent the development of active tuberculosis. Similar caution should be observed with respect to other opportunistic infections. Physicians and patients should also observe extreme caution with respect to infections. If the patient does develop a serious infection, then treatment should be withheld until the infection is fully treated and resolved before etanercept is reinstituted.

It appears that malignancies other than lymphoma are not a problem with etanercept. However, time will tell whether this is true. Lymphoma occurs in patients treated with etanercept but it appears to occur at the same frequency as seen in patients with RA not treated with anti-TNF agents. The next 10 years should demonstrate whether the early, aggressive use of etanercept will decrease, increase or not affect the incidence of lymphoma.

Until we have more data, etanercept should be used with caution or not at all in patients with demyelinating disease or CHF.

Outlook

There are a number of medications in clinical trials whose mechanism of action differ from etanercept. Examples include rituximab and anti-BAFF that affect B-cells specifically, medications that block the costimulatory molecule, block interleukin (ILN)-1 or other ILNs and oral medications that block p38 mitogen-activated protein kinases or TNF-α converting enzyme. The clinical trials of these medications will hopefully determine whether these medications are more effective than etanercept, work in a different population, have a better safety profile or are cheaper. It is conceivable that at least one of these compounds will successfully complete clinical trials and have at least one of the advantages listed above.

Highlights

- Rheumatoid arthritis (RA), juvenile rheumatoid arthritis (JRA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are diseases which affect a significant percentage of the population, are very disabling and shorten longevity.
- Nonsteroidal anti-inflammatory drugs (NSAIDS) are somewhat effective in controlling symptoms but do not slow disease progression.
- Traditional disease-modifying anti-rheumatic drugs (DMARDs) are effective in a small number of patients in producing remission, have significant tolerability and toxicity issues which limit their usefulness and slow x-ray progression in RA but not to the same extent as etanercept.
- Etanercept is effective in most patients with any stage RA, children with polyarticular course JRA and patients with PsA and AS to degrees not seen with traditional DMARDs and does not have the tolerability or toxicity issues of traditional DMARDs, although caution should be exercised with respect to active and latent tuberculosis, opportunistic infections, lymphoma, demyelinating diseases and congestive heart failure.

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