Etanercept and methotrexate for the treatment of rheumatoid arthritis

Nobuyuki Miyasaka
Tokyo Medical & Dental University, Graduate School, 1-5-45, Yushima, Bunkyo-ku, Tokyo, Japan
Tel.: +81 358 035 201
Fax: +81 356 840 057
miya.rheu@tmd.ac.jp

Rheumatoid arthritis (RA) affects approximately 1% of the population, resulting in disturbances of daily activity and quality of life. Tumor necrosis factor (TNF)-α has been implicated in the pathogenesis of RA, and the blockade of TNF-α with anti-TNF-α monoclonal antibodies (infliximab and adalimumab) and the soluble TNF-α receptor (etanercept) has caused a dramatic paradigm shift in the treatment of RA. Etanercept is a safe, highly effective biological agent in the treatment of RA. It can be used alone or with methotrexate, but the combination of the two is highly efficacious compared with monotherapy using etanercept. The most significant benefit of etanercept is to inhibit the progression of joint destruction. Although etanercept is well tolerated, its long-term safety, including the occurrence of malignant lymphoma, remains to be elucidated.

Keywords: etanercept, methotrexate, rheumatoid arthritis, tumor necrosis factor-α

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Rheumatoid arthritis (RA), which is characterized by the inflammation of multiple joints, not only deteriorates quality of life but can also shorten the lifespan of affected patients. Its pathological features are characterized by the formation of new blood vessels, inflammatory cell infiltration, and synovial proliferation. Abundant production of proteolytic enzymes, such as collagenase and metalloprotease, and inflammatory cytokines, including tumor necrosis factor (TNF)-α, causes the breakdown of cartilage and activation of osteoclasts, resulting in joint destruction.

The ultimate goals in the treatment of RA are to prevent joint damage, improve functional disability and decrease pain [1]. Conventionally, nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and disease-modifying antirheumatic drugs (DMARDs) have been widely used in combination to control disease activity, but insufficient results have been obtained to date. The benefit of early diagnosis and treatment of the disease have been stressed, but the process of joint destruction could not be completely controlled with conventional treatments. Methotrexate (MTX), which inhibits folate metabolism and upregulates adenosine production, is a potent and most commonly prescribed DMARD. There are more than 10 years of experience in which 370,000 patients have been treated with this drug. It can retard, but not completely prevent, joint destruction [2,3].

Overview of the market

The introduction of biological agents that block and/or neutralize inflammatory cytokines such as TNF-α, interleukin (IL)-1 and -6 have significantly altered the course of the disease and prevented joint damage [4]. Of note, the blockade of TNF-α has been shown to be remarkably effective in preventing the above-mentioned pathological processes, thus halting the progression of joint damage [5]. Among them, infliximab and adalimumab are both anti-human TNF-α monoclonal antibodies (mAbs) [6,7], and etanercept is a recombinant, soluble p75 receptor for TNF-α [8]. More than 370,000 patients have been treated with etanercept. In addition, abatacept (cytotoxic T-lymphocyte-associated antigen [CTLA]-4 immunoglobulin [Ig] fusion protein) and rituximab (chimeric anti-CD20 mAb) have both been shown to be useful in patients showing resistance to TNF-α-blocking treatment, and have recently been approved by the US FDA [9,10]. Furthermore, tocilizumab, a humanized anti-IL-6 receptor antibody for the control of IL-6 activity, will also be added to the biological agents used in the treatment of RA [11]. Other therapeutic agents to inhibit TNF-α production, such as polyethylene glycol (PEG)-conjugated anti-TNF-α mAb, and small molecules that can inhibit IL-17/-23 production and its signaling pathway, may also be developed in the near future.

Introduction to the compound

There are two distinct receptors for TNF-α, a 55- (p55) and a 75-kDa (p75) protein, and they exist as monomeric molecules on the cell surfaces and in soluble forms [12]. Etanercept is a recombinant dimeric protein of the extracellular ligand-binding portion of the human p75 TNF-α receptor linked to the Fc portion of human

IgG1. It is prepared by introducing the fusion gene into Chinese hamster ovary cells by recombinant DNA technology. Binding with human IgG1 elongates the plasma half-life. Compared with the naturally occurring, soluble TNF-α receptor, etanercept shows 50-fold greater binding to TNF-α, 100- to 1000-fold greater biological activity, and a five- to eightfold longer plasma half-life [12].

Chemistry

The molecular weight of etanercept is approximately 150 kDa, and it contains a total of 934 amino acid residues [13].

Pharmacodynamics

Etanercept, which can bind two molecules of TNF [12], inhibits the binding, of not only TNF-α, but also of TNF-β (lymphotoxin [LT]-α) to endogenous receptors, and thus neutralizes their biological activities, which in turn blocks their biological responses downstream, including IL-1 and -6 production, adhesion molecule expression and metalloprotease secretion. Namely, etanercept exerts its biological effects by serving as decoy receptors for both TNF-α and -β. Etanercept does not lyse TNF-α- or -β-expressing cells *in vitro,* with or without complement, in sharp contrast to anti-TNF-α mAbs [14]. A recent study has shown that infliximab binds to the Fc receptor and C1q to generate immunopreciptation, whereas etanercept does not [15].

Pharmacokinetics

In healthy volunteers, the time to peak concentration following a single subcutaneous injection of etanercept is approximately 50 h, with an average clearance of 132 ml/h [16]. It is speculated that etanercept binds with TNF-α, and these complexes are metabolized and excreted in bile and urine. A single subcutaneous injection of 25 mg of etanercept to 25 patients with RA yielded a plasma half-life of 102 ± 30 h (mean + SD) and a clearance of 160 ± 80 ml/h [17]. C_{max} was 1.1 ± 0.6 μg/ml and time to C_{max} was 69 ± 34 h in these patients. These patients showed a mean C_{max} of 2.4 ± 1.0 μg/ml after 6 months of twice-weekly 25-mg doses. A steady-state concentration of etanercept can be achieved approximately 2 weeks after the initiation of therapy [17]. Once-weekly administration of etanercept 50 mg in patients with active RA shows pharmacokinetics similar to 25 mg [18]. In addition, pharmacokinetics are not different between men and women and do not vary with age in adult patients [13]. Furthermore, concomitant use of MTX does not alter its pharmacokinetics [19].

Clinical efficacy

Etanercept monotherapy

Phase II/III trials

An initial study was conducted by examining 16 patients with active and refractory RA, in a double-blinded fashion [20]. Patients were assigned to different dose groups (0, 4, 8, 16 and 32 mg/m^2 of body surface area) and received an intravenous loading dose followed by subcutaneous twice-weekly injections for 29 days. Although no dose–response was observed, there was a significant improvement in decreasing total joint scores in etanercept-treated groups compared with placebo. No significant adverse effects were observed. In a multicenter, double-blind trial, 180 patients with RA who had inadequate response to DMARDs were randomly assigned to receive a subcutaneous injections of either a placebo or one of three doses of etanercept (0.25, 2 or 16 mg/m^2) twice weekly for 3 months [21]. Etanercept produced significant improvement in disease activity in a dose-dependent manner, and was well tolerated. Responses were rapid and sustained for 3 months. To confirm the benefit of the long-term use of etanercept and to simplify dosing, 234 patients with active RA resistant to DMARDs, including MTX, were analyzed in a randomized, controlled trial [22]. Patients were randomly assigned to receive placebo or 10 or 25 mg of etanercept twice weekly for 6 months. Etanercept significantly suppressed disease activity in a dose-dependent fashion. A significant number of patients exhibited improvement as early as 2 weeks after the initiation of therapy. At 6 months, 59% of the 25-mg group, 51% of the 10-mg group and 11% of the placebo group achieved a 20% American College of Rheumatology Response (ACR20). ACR70 was 15% in the 25-mg group, 9% in the 10-mg group and 1% in the placebo group.

A comparison of etanercept and MTX in patients with early RA (disease duration of 3 years or less) was carried out by enrolling 632 patients (Early Rheumatoid Arthritis [ERA] trial) [23]. They were treated with either twice-weekly etanercept (10 or 25 mg) or weekly oral MTX (mean 19 mg/week) for 12 months. MTX was initially dosed at 7.5 mg/week and rapidly escalated to a maximum of 20 mg/week if there were any swollen or tender joints. Within the first 6 months, both etanercept groups had a

robust response in ACR20 and -50 compared with the MTX group, but by 12 months there was no statistically significant difference in ACR20, -50 and -70 between the etanercept and MTX groups. With regard to radiographic progression, the increase in erosion score during the first 6 months was 0.30 in the 25-mg etanercept group and 0.68 in the MTX group, and 0.47 and 1.03 at 12 months, respectively. Of the 25-mg etanercept group, 72% had no increase in erosion score, as compared with 60% in the MTX group. This trial was further extended to where the patients received 25 mg of etanercept twice weekly [24]. At year 5, ACR20, -50 and -70 scores were 65, 52 and 37%, respectively. Most of the patients in the MTX group decreased or discontinued MTX and the mean dose of MTX decreased from 17.6 mg/week at the beginning of the extension to 4.9 mg/week after 3 years. Furthermore, most patients in the etanercept groups did not receive MTX during the extension. Corticosteroid use was decreased from 8.6 mg/day at the beginning to 2.4 mg/day on average after 5 years of 25-mg etanercept treatment. This study suggests that etanercept has a potent effect in reducing the dosage of corticosteroids and MTX.

Patients involved in the ERA trial who were treated with 25-mg etanercept (mean disease duration 1 year) were compared to patients with established disease (mean duration 12 years) treated likewise to see whether early intervention with etanercept was more effective in improving disability as assessed by Health Assessment Questionnaire (HAQ) scores [25]. Etanercept treatment achieved rapid, sustained responses in both groups; however, patients with recent onset of the disease showed greater improvement in HAQ scores (56% in the recent onset group vs 39% in the long-standing group at year 3), supporting the finding that early intervention alters disease outcome.

Etanercept plus MTX

Phase II/III trials

In a double-blind study of concomitant MTX, 89 patients with active RA who had been treated with MTX for at least 6 months, received either etanercept 25 mg or a subcutaneous placebo twice weekly with MTX [26]. MTX was given for at least 6 months at a stable dose of 15–25 mg/week. The addition of etanercept to MTX resulted in rapid and sustained improvement and achieved ACR20 in 71% of patients and ACR50 in 39% of patients after 6 months. In contrast, ACR20 was 27% and ACR50, 3% in the placebo group. The median HAQ score improved from 1.5 to 0.8 in the etanercept plus MTX group, whereas it did not change significantly in the placebo group. A further open-label extension study was performed in 79 patients [27]. At year 3, ACR20, -50 and -70 were 77, 47 and 23%, respectively. Furthermore, corticosteroid dosage was decreased in 62% of the patients and 56% of the patients discontinued corticosteroids.

The remarkable effectiveness of the combination of etanercept and MTX was demonstrated in the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) [28]. In this study, 686 patients with RA who were resistant to one or more DMARDs other than MTX received one of the following three treatments for 2 years: MTX alone, 25 mg biweekly of etanercept alone, or 25 mg biweekly of etanercept plus MTX. The primary efficacy end point was the numeric index of the ACR response (ACR-N)–AUC over the first 24 weeks. The primary end point did not differ significantly between the MTX and etanercept monotherapy group; however, the etanercept plus MTX group had significantly higher ACR–AUC values than the two monotherapy groups. The proportion of patients achieving ACR50, a clinically meaningful efficacy, at 2 years was 71% in the etanercept plus MTX group as compared with 42% in the MTX monotherapy group and 54% in the etanercept group, indicating greater efficacy of the combination of etanercept and MTX. Moreover, the change in total Sharp score, the sum of the erosion score and joint space-narrowing score, at 1 year of treatment was -0.54 in the etanercept plus MTX group compared with +2.80 in the MTX monotherapy group and +0.52 in the etanercept group, suggesting the possibility that the combination inhibits the progression of joint destruction and may even heal the condition. In the TEMPO study, 2-year extended results recently demonstrated that etanercept in combination with MTX reduced disease activity, slowed radiographic progression and improved function more effectively that either monotherapy. No increase in toxicity was associated with combination treatment with etanercept and MTX [30].

Once-weekly administration of etanercept 50 mg in patients with active RA was compared with etanercept 25 mg twice weekly in efficacy, safety and pharmacokinetics, in a multicenter, randomized, double-blind, placebo-controlled trial [18]. Approximately half of the patients in

each group were receiving concomitant MTX. There were no differences between 50-mg weekly and 25-mg biweekly doses of etanercept in the above-mentioned end points.

Safety & tolerability

Etanercept was well tolerated and serious adverse effects were uncommon in clinical trials [18–26,29]. Combined treatment with etanercept and MTX does not alter the incidence and severity of adverse effects [27,28]. Long-term safety of etanercept was observed even in elderly patients [31,32]. However, caution should be observed as a series of adverse effects have been reported in postmarketing surveillance.

Injection-site reactions

Injection-site reactions, which include erythema, edema and itching, occur in approximately 40% of patients treated with etanercept [21–29]. However, they are generally mild and discontinuation of the drug is not necessary in most cases. The reactions continue for 3–5 days, however, most resolve without medication. The topical application of H1-antihistamines or corticosteroids is infrequently required.

Infections

RA patients are known to have an increased risk of developing infections [33]. In addition, TNF-α-blocking treatment is associated with a higher frequency of infections and infliximab is believed to carry a higher risk of infections than etanercept [34,35]. However, a very recent study – Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) – carried out in Germany, showed that the relative risks of serious infections were 2.2 for patients receiving etanercept and 2.1 for those taking infliximab, compared with controls who were treated with conventional DMARDs [36]. The most common infection is of the upper respiratory system, but any type of infection can occur. Patients with underlying conditions, such as diabetes mellitus, coexistent pulmonary disease and advanced age, have a higher risk of serious infection.

There is considerable evidence that links reactivation of latent tuberculosis (TB) infection to the use of TNF-α-blocking agents [37,38]. TNF-α plays a central role in TB infection and in the immunopathology of TB [39]. The risk of developing TB is greater with infliximab – 47.6 cases/100,000 receiving infliximab versus 20.7 cases receiving etanercept/100,000 [40]. The development of active TB occurs later in patients with etanercept therapy than in those taking infliximab (median time, 11 vs 3 months) [41]. However, half of the patients receiving etanercept showed extrapulmonary TB, including miliary TB. Careful history taking and TB skin test and chest radiography are essential for TB screening [40]. Prophylactic treatment with isoniazid should be performed for latent TB [42,43]. Rifampicin can be used as second-line prophylaxis.

Malignancy

There is no overt association of malignancies with TNF-α-blocking treatment. Askling and colleagues reported that risk of solid tumors in RA patients treated with TNF-α-antagonists were not increased [44]. However, recent study disclosed an unexpected increase of solid tumors in patients with Wegener's granulomatosis treated with etanercept and glucocorticosteroids plus cytotoxic agents [45]. Of note, an increased risk of malignant lymphoma in active RA patients has been reported [46], and it has been disputed whether TNF-α blockade further accelerates the development of malignant lymphoma [47,48]. A total of 26 cases of malignant lymphoma, including 18 involving etanercept and eight involving infliximab, were reported to the US FDA [47]. The interval between the development of malignant lymphoma and the initiation of anti-TNF-α treatment was a median of 8 weeks. Among these cases, regression of lymphoma was observed following discontinuation of anti-TNF-α treatment [48]. In this respect, Wolfe and colleagues reported that the standard incidence ratio (SIR) of lymphoma is 2.9 (95% confidence interval [CI]: 1.4–4.5) in patients receiving anti-TNF-α treatment (etanercept and/or infliximab) and 1.7 (95% CI: 0.9–3.2) in patients not receiving anti-TNF-α treatment or MTX, respectively [48]. In a very recent report from the South Swedish Arthritis Treatment Group (SSATG), registering 757 patients treated with either etanercept or infliximab, SIR of having malignant lymphoma was 11.5 (95% CI: 3.7–26.9) and 1.3 in the comparison group (95% CI: 1.08–1.76) [47]. Further analysis should be performed to establish a causal relationship between the risk of malignant lymphoma and exposure to anti-TNF-α treatment [49].

Neurologic events

Treatment with TNF-α antagonists is rarely associated with demyelinating and neurological events including multiple sclerosis, optic neuritis,

transverse myelitis of new onset, or exacerbation [50,51]. Of the 19 patients with neurological events identified from the US FDA database, 17 received etanercept and two infliximab [51]. Discontinuation of the drug resulted in partial or complete resolution of the symptoms. It should be pointed out that patients with known demyelinating disease should avoid etanercept treatment and those treated with TNF-α-antagonists should be closely monitored for developing neurological symptoms.

Heart failure

Heart failure is not uncommon among RA patients [52] and etanercept may exacerbate congestive heart failure [53]. It is therefore recommended that etanercept should not be used in patients with New York Heart Association (NYHA) grade 3/4 congestive heart failure [40]. However, a recent report indicates that anti-TNF therapies may ameliorate heart failure in RA [54].

Hematological abnormalities

Rare cases of hematological abnormalities, including neutropenia, lymphocytopenia and aplastic anemia have been reported [55].

Immunogenicity & autoantibody production

Etanercept consists entirely of a human sequence and immunogenicity is low [56]. Consequently, induction of anti-etanercept antibodies is significantly uncommon. This may explain why etanercept has rare instances of anaphylaxis, dose increment and shortening the interval of administration, a clear-cut difference from infliximab, a mouse–human chimeric mAb. However, formation of antinuclear antibodies and anti-dsDNA antibodies are sometimes associated with the use of etanercept. Development of lupus-like syndrome is, however, rare [2,23,26,28,57]. Induction of anticardiolipin antibodies is also reported [58].

Vaccinations

Patients on TNF-α antagonists should avoid receiving live vaccines. Antibody responses to pneumococcal vaccination are not impaired in patients receiving etanercept [59]. When live vaccines are required, they should be given 4 weeks prior to starting treatment [60].

Pregnancy

There are no detailed clinical studies of etanercept in pregnancy or lactation. TNF-α antagonists are classified into class B (no evidence of risk in humans; either animal findings show risk but human findings do not, or, if no adequate human studies have been performed, animal findings are negative) of pregnancy risk by the US FDA. A preliminary report suggests that the use of TNF inhibitors does not increase materno–fetal complications [61,62].

Others

Elevated liver function tests have been observed in controlled clinical trials conducted with etanercept [28]. Cutaneous manifestations such as rash, vasculitits, cutaneous lupus during etanercept treatment have been described in the literature [63–65].

Table 1. Characteristics of TNF inhibitors.

	Etanercept	Infliximab	Adalimumab
Structures	Recombinant TNF receptor–Fc fusion protein	Chimeric (mouse–human) anti-TNF mAb	Fully human anti-TNF mAb
Route of administration	s.c. injection	i.v. injection	s.c. injection
Recommended dose	25 mg twice weekly or 50 mg/week	3–10 mg/kg every 4–8 weeks	40 mg every 2 weeks
Concomitant MTX required	No	Yes	No
Half-life	4.8 days	8–9.5 days	11–13.7 days
In vitro *complement fixation*	No	Yes	Yes
In vivo *lysis of TNF-expressing cells*	No	Yes	Yes
Binding to Fc receptors	No	Yes	yes
Antigenicity	No	Yes	Yes

i.v.: Intravenous; mAb: Monoclonal antibody; MTX: Methotrexate; s.c.: Subcutaneous; TNF: Tumor necrosis factor.

Highlights

- Etanercept is a recombinant dimeric protein of the human p75 tumor necrosis factor (TNF)-α receptor linked to the Fc portion of human immunoglobulin (Ig)G1.
- Etanercept inhibits binding of TNF-α and -β, thus neutralizing their biological activities as decoy receptors.
- Half-life in plasma is approximately 100 h and clearance rate is 160 ± 80 ml/h.
- Once-weekly administration of 50 mg etanercept has pharmacokinetics similar to those of 25 mg biweekly in patients with active rheumatoid arthritis (RA).
- Recommended dosage of etanercept for adult RA patients is 50 mg/week by subcutaneous injection.
- Etanercept can be used alone or in combination with methotrexate (MTX).
- Concomitant use of MTX does not alter its pharmacokinetics.
- Etanercept, both in monotherapy and in combination therapy with MTX, induces rapid clinical improvement within 2 weeks, and its efficacy is prolonged.
- Etanercept significantly ameliorates the functional status of patients.
- Etanercept treatment significantly inhibits the progression of joint damage.
- Etanercept in combination with MTX is significantly better in reducing disease activity, improving functional disability, and retarding radiographic progression in comparison with MTX or etanercept alone.
- Dosage reduction of corticosteroids and MTX can be achieved with use of etanercept.
- Etanercept is well tolerated in the majority of patients.
- Adverse reactions to etanercept include injection site reactions and opportunistic infections.
- The rate and severity of adverse effects in etanercept treatment is equivalent to or better that treatment with infliximab or other biologics.
- A causative relationship between etanercept therapy and the development of malignant lymphoma remains to be clarified.

Regulatory affairs

On the basis of these results, etanercept was approved as a treatment for RA by the US FDA in November 1998. Indications for RA are reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA. Etanercept can be used alone or in combination with MTX. It has also been approved by the US FDA for psoriatic arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis and moderate-to-severe chronic stable psoriasis.

Expert commentary

A comparison of TNF-α antagonists is presented in **Table 1**. Etanercept is remarkably effective in treating RA patients resistant to conventional treatment. The improvement obtained by etanercept is rapid and sustained over the long term. Furthermore, etanercept can significantly prevent progression of joint damage. Etanercept can be used alone and is also useful in treating patients showing intolerance to MTX. However, its efficacy is better when used in combination with MTX. Combination treatment with etanercept and MTX induced remission in a significant proportion (35%) of patients in the TEMPO study [28]. With the advent of biologics, a critical time or window of opportunity has been found for inducing remission. During this period, rheumatoid inflammation is particularly sensitive to treatment. The window of opportunity for etanercept remains to be clarified. Targeting patients with recent onset of disease and treating them with a combination of etanercept and MTX will make it possible to answer this question. Remission can not only be clinical and radiological, but also drug-free. Etanercept can be beneficial when infliximab has failed and *vice versa* [66,67]. Although severe adverse effects of etanercept are infrequent, physicians should be careful in determining the eligibility of patients and should consider the potential risks and benefits of etanercept therapy. Close monitoring of adverse effects, including infections, is mandatory.

Outlook

At present, it is difficult to predict the efficacy of etanercept prior to treatment. Genetic polymorphisms may contribute to clinical response and studies to identify responders to etanercept are currently ongoing [68,69]. Furthermore, some patients still show resistance to anti-TNF-α therapy. Other problems of etanercept in RA include its long-term safety in various countries. Pharmacoeconomic analyses of etanercept have just begun and preliminary studies indicate that its cost–effectiveness may be acceptable [70,71].

Abatacept shows sustained clinical benefit in RA patients who had inadequate response to anti-TNF therapy and was approved by the US FDA in December, 2005. Rituximab, an anti-CD20 mAb, is also effective in treating patients refractory to anti-TNF treatment and was approved by the US FDA in January 2006 [10]. The anti-IL-6 receptor, tocilizumab, is efficacious in inhibiting radiographic progression [11].

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Affiliation

Nobuyuki Miyasaka, MD,
Professor of Medicine & Rheumatology,
Tokyo Medical & Dental University,
Graduate School, 1–5-45, Yushima,
Bunkyo-ku, Tokyo, Japan
Tel.: +81 358 035 201
Fax: +81 356 840 057
miya.rheu@tmd.ac.jp