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Etanercept

USAN

Antiarthritic
TNF-α Antagonist

TNFR:Fc
TNR-001
Enbrel™

1-235-Tumor necrosis factor receptor (human) fusion protein with 236-467-immunoglobulin G1 (human γ_1-chain Fc fragment)

CAS: 185243-69-0
CAS: 200013-86-1 (as enbrel)

EN: 213242

Description

Researchers have linked the cDNA encoding the extracellular portion of p75 TNFR with the DNA fragment encoding the Fc region of human IgG1 and expressed in a mammalian cell line. The resulting protein, TNFR:Fc (etanercept), is a dimer consisting of two TNFR molecules per Fc region. Etanercept binds TNF with high affinity similar to that observed for the surface-bound receptors and is an antagonist of TNF activity.

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive, systemic inflammatory disorder that results in substantial cases of morbidity and mortality (1-3). The disorder affects 2.5 million people in the U.S. who collectively make more than 9 million visits to physicians each year, reducing their earnings by more than $17 billion (4, 5).

Novel therapeutic targets are emerging as exciting and viable alternatives to traditional arthritis treatments with research efforts focused mainly on cytokine modulation as a therapeutic strategy for RA (6). Experimental and clinical evidence suggests that proinflammatory cytokines, particularly tumor necrosis factor (TNF), have an important role in the pathogenesis of RA (6, 7); administration of TNF antagonists to patients with RA has been shown to reduce symptoms (8-11). At present, two anti-TNF-α monoclonal antibodies, infliximab (Remicade™; Centocor) and CDP-571 (Celltech) are undergoing clinical trials for RA.

There are two known cell-surface TNF receptors (TNFRs): the 75 kDa receptor (p75) and the 55 kDa (p55) receptor (formerly referred to as p80 and p60, respectively) (12, 13). Soluble truncated versions of membrane TNFRs have been isolated and are thought to be involved in the regulation of TNF activity (14, 15). Moreover, soluble TNFRs are increased in sera and synovial fluid of patients with RA (16-20). Antagonism of TNF bioactivity via the use of soluble TNFRs has resulted in beneficial effects in preclinical animal studies (21-26). Scientists at Immunex constructed a recombinant human TNFR p75-Fc fusion protein (TNFR:Fc; etanercept) for therapeutic neutralization of TNF-α (22).

Pharmacological Actions

Etanercept is a potent antagonist of TNF biological activity both *in vitro* and *in vivo* and has been effective in many animal models of inflammation (24, 27). The preventive and therapeutic antiarthritic and immunosuppressant activities of etanercept were evaluated in a study using DBA/1 mice with bovine type II collagen-induced arthritis. Animals receiving the preventive treatment were injected i.p. with etanercept (50 μg) or saline on days 21-28 after immunization, while animals in the therapeutic group were administered either etanercept (50 μg) or human serum albumin (50 μg) i.p. for 14 days following time of disease onset. Etanercept preventive treatment significantly decreased the incidence (26% *vs.* 86% in controls) and severity of collagen-induced arthritis. Although the disease score increased in both control and therapeutic etanercept-treated animals at 7.5-10 weeks after disease onset, significantly more etanercept-treated animals progressed to a less severe disease state. Both preventive and therapeutic etanercept-treated animals displayed significantly lower arthritis indices and number

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Box 1: Efficacy and safety of etanercept in refractory rheumatoid arthritis (28).

Study Design	Randomized, dose-finding, double-blind, placebo-controlled clinical trial
Study Population	Patients with refractory rheumatoid arthritis (n = 16)
Intervention Groups	Etanercept, 4 mg/m^2 i.v. + 2 mg/m^2 s.c. 2x/week x 4 weeks (n = 3) Etanercept, 8 mg/m^2 i.v. + 4 mg/m^2 s.c. 2x/week x 4 weeks (n = 3) Etanercept, 16 mg/m^2 i.v. + 8 mg/m^2 s.c. 2x/week x 4 weeks (n = 3) Etanercept, 32 mg/m^2 i.v. + 16 mg/m^2 s.c. 2x/week x 4 weeks (n = 3) Placebo x 4 months (n = 4)
Adverse Effects	Adverse reactions (mild injection-site reactions) in 8 patients
Endpoints	Improvement rate, painful joint score at 31 days: P, 23%; etanercept, 45% Improvement rate, swollen joint score at 31 days: P, 25%; etanercept, 40% Improvement rate, morning stiffness at 31 days: P, -12%; etanercept, 58%
Significance of Results	At 4 weeks of treatment, a mean improvement of 45% was observed in patients treated with etanercept compared to 22% in those on placebo. C-reactive protein levels decreased in all patients on active treatment. No serious adverse events were recorded
Conclusions	Etanercept is a safe, well-tolerated drug significantly active in the treatment of refractory rheumatoid arthritis

Source: Prous Science CTLine database.

of involved joints as compared to control animals. Anti-type II collagen responses to collagen were significantly reduced in both therapeutic and preventive etanercept-treated animals, suggesting a possible immunosuppressive action of etanercept. Proliferation responses to type II collagen and ConA were similar for both treated and untreated animals. However, proliferation responses to LPS were significantly less in both preventive and therapeutic etanercept-treated groups as compared to controls (24).

Clinical Studies

The pharmacokinetics and safety of etanercept were evaluated in RA patients. Sixteen patients received single i.v. loading doses of either 4, 8, 16 or 32 mg/m^2 or a placebo, followed by 8 maintenance doses of 2, 4, 8 or 16 mg/m^2 s.c. or a placebo twice a week x 4, respectively, for each loading dose. A 45% improvement in total pain and total joint scores and a 30% decrease in C-reactive protein (CRP) levels were observed in etanercept-treated patients as opposed to a 22% improvement and 13% decrease in CRP in patients receiving the placebo. Mild injection site reactions were noted with etanercept treatment, although no serious side effects were observed in treated patients (28) (Box 1).

A double-blind, multicenter study examined efficacy and tolerability of etanercept treatment in patients with refractory RA. One hundred and eighty patients received a s.c. injection of 0.25, 2, or 16 mg/m^2 etanercept or a placebo twice a week for 3 months. Dose-dependent decreases in disease activity were noted in etanercept-treated patients. After 3 months, 75% of patients receiving 16 mg/m^2 showed improvements in inflammatory symptoms as compared to only 14% in the placebo group. In addition, a greater decrease in the number of tender or swollen joints was observed in the treated group. Mild upper respiratory tract symptoms and mild injection site reactions were evident in etanercept-treated patients; however, no observed dose-limiting toxic effects nor serum anti-etanercept antibodies were detected (29) (Box 2).

Phase II/III randomized, double-blind, placebo-controlled studies examined the efficacy of etanercept in RA patients receiving methotrexate therapy and demonstrated that etanercept-treated patients exhibited a significant decrease in disease activity with an increase in functional ability (30).

In addition to studies demonstrating the efficacy of etanercept in the treatment of RA, the fusion protein has also been suggested to be a possible adjuvant immunomodulator in the subacute period following kidney transplant. The safety of etanercept treatment was examined in a study in which 16 renal allograft patients underwent OKT3 induction therapy (2.5 mg x 12 days), which included intraoperative administration of azathioprine (3 mg/kg i.v.) and methylprednisolone (3 mg/kg, 1 h prior to OKT3 treatment). Patients received etanercept (0, 4, 8 or 16 mg/m^2) 1 h prior to OKT3 treatment on days 0 and 3. Serum cytokine levels, creatinine and C-reactive protein were similar for all groups. A significantly higher incidence of infection 3 months post-transplant was observed in etanercept-treated patients as compared to controls (83% *vs.* 25%), in addition to trends toward increased rejection rates (42% *vs.* 25% for treated and control groups, respectively). However, symptom scores for

Box 2: Efficacy and safety of etanercept in patients with rheumatoid arthritis (29).

Study Design	Prospective, multicenter, randomized, dose-finding, comparative, double-blind, placebo-controlled clinical trial
Study Population	Patients with rheumatoid arthritis (n = 180)
Intervention Groups	Etanercept (TNR), 0.25 mg/m^2 s.c. 2x/week x 3 months (n = 46) Etanercept (TNR), 2 mg/m^2 s.c. 2x/week x 3 months (n = 46) Etanercept (TNR), 16 mg/m^2 s.c. 2x/week x 3 months (n = 44) Placebo x 3 months (n = 44)
Withdrawals [causes]	One patient was withdrawn due to a mild injection-site reaction after active treatment
Adverse Effects	Adverse reactions (mild injection-site reactions, mild upper respiratory tract symptoms) were more frequent in groups TNR2 and TNR16; one patient died on placebo
Endpoints	Swollen joint count (change) at 3 months; P, -5; TNR0.25, -5; TNR2, -7; TNR16, -13 Tender joint count (change) at 3 months: P, -7; TNR0.25, -8; TNR2, -15; TNR16, -17 Pain intensity (change) at 3 months: P, -0.3; TNR0.25, -1.3; TNR2, -2.1; TNR16, -3.3 (mm on a VAS score) Health Assessment Questionnaire score (change) at 3 months: P, -5; TNR0.25, -13; TNR2, -15; TNR16, -31 Improvement rate, swollen joints: P, 24%; TNR0.25, 26%; TNR2, 32%; TNR16, 58% Improvement rate, tender joints: P, 28%; TNR0.25, 25%; TNR2, 46%; TNR16, 64%
Significance of Results	Etanercept produced a significant improvement in all measures of disease activity, the maximal improvement being observed after 16 mg twice weekly. Adverse events were limited to mild injection-site reactions and mild upper respiratory tract symptoms
Conclusions	Etanecerpt showed excellent efficacy in rheumatoid arthritis patients, while being safe and well tolerated

Source: Prous Science CTLine database.

treated patients tended to be less than those of controls. Adverse effects were similar for both groups. The results indicated that etanercept treatment in renal transplant patients receiving OTK3 therapy was well tolerated and may offer some improvement of symptoms. Since TNF-α has been shown to be involved in acute rejection processes, the authors concluded that etanercept may also be used as an adjuvant immunomodulator in the subacute period after transplant (31).

Since studies have shown that TNF-α levels are elevated in patients with advanced heart failure, a double-blind phase I trial examined whether administration of etanercept was beneficial to such patients. Twelve patients with advanced heart failure and mean TNF-α plasma levels of 6.3 ± 0.5 pg/ml received 1 or 4 mg/m^2 i.v. etanercept or a placebo. An 85% decrease in plasma TNF-α was observed and maintained for 14 days postinfusion in etanercept-treated patients. In addition, treated patients had significantly increased 6-min walk times and a 1.4 ± 0.1-fold improvement in symptoms with maximum responses occurring on days 7-14 after etanercept infusion; left ventricular ejection was not affected by etanercept treatment. Thus, etanercept treatment was well tolerated and may be associated with an improved functional state and quality of life in patients with advanced heart failure (32).

Enbrel™ has been unanimously recommended for approval by the FDA Arthritis Advisory Committee for use alone in patients with RA who have failed other disease-modifying antirheumatic drugs, and also in combination with methotrexate. If approved by the FDA, this drug will be the first new approach to the treatment of RA in over a decade. Pending FDA review and approval, Immunex and the Wyeth-Ayerst division of American Home Products will comarket Enbrel™ in North America, while Wyeth-Ayerst and affiliates will market the product outside North America.

Manufacturer

Immunex Corp. (US); Wyeth-Ayerst Labs. (US).

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