Drugs of the Future 2003, 28(12): 1182-1188

CCC: 0377-8282/2003

Pegsunercept

Anticytokine Therapy
Treatment of Rheumatoid Arthritis

Pegylated Soluble Tumor Necrosis Factor Receptor Type I
PEG-sTNF-RI

Recombinant (*E. coli*) form of the high-affinity p55 soluble tumor necrosis factor receptor type I (sTNF-RI) to which a 30-kD polyethylene glycol (PEG) molecule is attached

Pegylated (30 kilodaltons) L-methionyl-1-105-tumor necrosis factor receptor p55 (human)

CAS: 330988-75-5

EN: 280303

Abstract

Standard pharmacological interventions in rheumatoid arthritis involve administration of nonsteroidal antiinflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs). However, these agents may not influence the progression of damage to joints, and long-term tolerability and efficacy appear to be limited. Because rheumatoid arthritis is considered a disease of cytokine dysfunction, researchers have focused on the development of immune system-targeted therapies as an alternative, with particular emphasis on cytokine therapy as a promising therapeutic approach. The proinflammatory cytokine tumor necrosis factor α (TNF-α) is overexpressed in patients with rheumatoid arthritis and has been identified as having major pathological significance in the development and progression of the disease. Inhibition of TNF-α production or blockade of the interaction of TNF-α with its receptors is the focus of research for the development of therapies for rheumatoid arthritis. One such anti-TNF-α agent that has shown promise is the second-generation pegsunercept (PEG-sTNF-RI). Pegsunercept is a recombinant p55 monomeric, soluble TNF receptor type I linked to polyethylene glycol (PEG), which has been shown to have minimal immunogenicity, marked efficacy and minimal toxicity in animal models. Pegsunercept has shown efficacy alone and in combination with other antiarthritic agents in patients and continues to undergo phase II development for the treatment of rheumatoid arthritis.

Introduction

Rheumatoid arthritis is a chronic disease of unknown etiology that affects 1% of all Americans and about 7% of the world population. The disease is characterized by persistent autoimmune activity manifesting as symmetrical joint pain, inflammation, local injury of bone and cartilage, and pannus formation. Pain, stiffness, warmth, redness and swelling are experienced due to inflammation of the membranes lining the joints, especially the distal small joints in the hands, wrist and feet. Other manifestations and symptoms may also occur and include ocular inflammation, vasculitis, the appearance of rheumatoid nodules, cardiopulmonary disease, neurological dysfunction, splenomegaly, fever, fatigue, loss of appetite and anemia (1-3).

The cause of rheumatoid arthritis is unknown but both genetic and environmental factors are probably involved in the risk and development of the disease. Mutations in the major histocompatibility class (MHC) alleles HLA-DR1 and HLA-DR4 may increase susceptibility and contribute to progression of rheumatoid arthritis. The chronic inflammation that characterizes the disease can be due to inappropriate T-cell activation, cytokine modulation and/or membrane protein signaling. It is believed that the cascade leading to the development of rheumatoid arthritis is initiated when antigenic peptides present in the groove of the HLA-DR4 antigen, resulting in stimulation of CD4+ T-cells. These T-cells in turn activate macrophages, B-cells and synovial fibroblasts via direct cell-to-cell interactions and cytokines (*e.g.*, activated macrophages release IL-1β and TNF-α) and rheumatoid factors secreted by B-cells. These factors form immune complexes that activate complement and thus are responsible for inflammation. Joint destruction is due to the matrix metalloproteinases (MMPs) secreted by macrophages and synovial fibroblasts (1).

At present, the pharmacological or surgical treatment of rheumatoid arthritis attempts to maintain function, reduce pain and prevent irreversible joint damage. Typical pharmacological interventions generally involve administration of nonsteroidal antiinflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs

L.A. Sorbera. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

(DMARDs). However, although NSAIDs reduce pain and inflammation and improve mobility, they do not influence the progression of damage to joints. The DMARDs (*e.g.*, leflunomide), on the other hand, have been shown to have a significant effect on morbidity and mortality in patients with rheumatoid arthritis, and studies suggest that they control both pain and progression of disability even more effectively than NSAIDs. However, the long-term tolerability and efficacy of DMARDs appear to be limited and effects of these agents on articular, functional and radiographic outcomes in patients with rheumatoid arthritis have not been shown (1, 4).

This has led researchers to focus on the development of immune system-targeted therapies as an alternative. The various components of the immune system involved in the initiation and progression of rheumatoid arthritis (*e.g.*, cytokines, chemokines, T-cells, B-cells, monocytes, fibroblasts, dendritic cells, mast cells, neutrophils and adhesion molecules) are all potential targets of immunomodulatory therapy for rheumatoid arthritis. In particular, cytokine therapy appears to be very promising. Rheumatoid arthritis has been considered a disorder of cytokine dysregulation where the activity of proinflammatory cytokines increases, suppressing the action of those cytokines with antiinflammatory activity. Research is aimed at developing agents that neutralize proinflammatory cytokines such as interferon gamma, IL-1, IL-2, IL-6 and TNF-α (and possibly IL-15, IL-17 and IL-18), which are produced by activated T-cells in the synovium during the early stages of rheumatoid arthritis (1, 5-8).

The proinflammatory pleiotropic cytokine TNF-α has been identified as having major pathological significance in the development and progression of rheumatoid arthritis and other inflammatory autoimmune diseases. TNF-α is overproduced in patients with rheumatoid arthritis and has been identified in the synovial membrane, especially at the cartilage–pannus junction, of these patients. Its presence has been associated with more severe cases of the disease. TNF-α is involved in joint destruction since it can stimulate bone and cartilage resorption, induce inflammation and inhibit bone formation by suppressing bone collagen synthesis, and it has also been implicated as the cause of fatigue, malaise, fever, anemia and cachexia in patients with rheumatoid arthritis. TNF-α is a trimer of 3 identical subunits and signal transduction occurs when TNF-α binds to and dimerizes 1 of 2 cell-surface receptors: the p55 (TNF-RI) or the p75 (TNF-RII) subtype. There are naturally occurring TNF-α inhibitors which consist of the full-length 4 domain or truncated form of the extracellular region of TNF-RI and they are known as TNF-binding proteins (TNF-bp) or soluble TNF receptor (sTNF-RI). These molecules are active in human rheumatoid arthritic tissue, serum, synovial fluid and synovial explant cultures. Moreover, the presence of sTNF-RI correlates with rheumatoid arthritis disease activity. Thus, inhibition of TNF-α production or blockade of the interaction of TNF-α with its receptors is the focus of research for the development of therapies for rheumatoid arthritis (1, 8-12).

One such next-generation anti-TNF-α agent that has shown promise is pegsunercept (PEG-sTNF-RI). Pegsunercept is a recombinant methionyl p55 monomeric soluble TNF receptor type I linked to polyethylene glycol (PEG) that is an optimized form of the first-generation recombinant methionyl human TNF-binding protein pegylated dimer (PEG-rhTNF-bp), which was effective in reducing swollen and tender joints in patients with rheumatoid arthritis but found to be immunogenic and not suitable for chronic administration (13, 14). In contrast, pegsunercept exhibited minimal immunogenicity, marked efficacy and minimal toxicity in animal models. Pegsunercept was chosen for further development as a treatment for rheumatoid arthritis.

Pharmacological Actions

Pegsunercept was shown to bind with high affinity to recombinant human TNF-α *in vitro* (K_d = 557 pM) and to *Escherichia coli*- and CHO cell-derived sTNF-RI (K_d = 794 and 338 pM, respectively). The agent was demonstrated to be active in *in vitro* L929 cytotoxicity bioassays where the average specific activity of the agent was 0.88 ± 0.18 mg/mg and the average EC_{50} was 257.6 ± 62 ng/ml as compared to 1.2 ± 0.066 mg/mg and 0.94 ± 0.04 ng/ml, respectively, for PEG-rhTNF-bp. In addition, in rheumatoid arthritic explant synovial cell assays, pegsunercept (1 nM-10 μM) inhibited TNF-α-induced prostaglandin E_2 (PGE_2; IC_{50} = 25 nM) production at 24 in a concentration-related manner (10).

Pegsunercept was effective in several animal models of rheumatoid arthritis. In rats with adjuvant-induced arthritis, treatment with pegsunercept (9 mg/kg s.c. on days 9, 11 and 13 postinduction) reduced AUC values for paw swelling and bone resorption by 60 and 96%, respectively. Blood levels of the agent were maintained at 10-12 μg/ml and no antibody responses were observed. Similarly, in mice with developing type II collagen-induced arthritis, pegsunercept (3 mg/kg i.p. every 2 days) reduced clinical arthritis by 75%. Pegsunercept was not immunogenic in this model (15).

The effect of pegsunercept (10 mg/kg s.c. on days 8, 10 and 12 postinduction) on cytokine expression was examined in rats with adjuvant-induced arthritis. Pegsunercept significantly reduced paw volume as compared to untreated controls on days 13 and 17. Disease was shown to recur after cessation of treatment with the agent. Synovial expression of TNF, interferon gamma, IL-17 and IL-2 mRNA was not significantly altered by treatment as compared to controls. However, IL-4 and TNF-β expression was significantly increased on days 17 and 13, respectively, in pegsunercept-treated animals as compared to controls. It was suggested that increased expression of these cytokines may contribute to disease suppression seen with pegsunercept (16).

A study using TNF-α knockout mice (TNF-$\alpha^{-/-}$) and membrane-bound TNF-α transgenic (TNF-α^{TgA86}) mice injected with *Mycoplasma pulmonis* or *Mycoplasma*

arthritidis to induce arthritis reported that TNF-$\alpha^{-/-}$ mice treated with pegsunercept had lower overall incidence/severity scores on days +7 postinfection as compared to vehicle-treated mice (0.8 vs. 1.6). In addition, TNF-α^{TgA86} mice treated with the agent had an ~ 50% reduction in severity scores as compared to vehicle-treated controls. Pegsunercept therefore successfully inhibited membrane-bound TNF-α-induced arthritis (17).

Additive and synergistic effects were observed in animal models of arthritis when pegsunercept was given in combination with several other agents. A study in rats with either adjuvant- or type II collagen-induced arthritis showed the enhanced benefit of combination treatment including pegsunercept and recombinant human IL-1 receptor antagonist (rhIL-1ra [anakinra] in hyaluronic acid). Rats with established adjuvant-induced arthritis treated with rhIL-1ra (100 mg/kg/day s.c.) or pegsunercept (3 mg/kg i.p. every 2 days) alone had reductions in AUC values for hind paw swelling of 25 and 29%, respectively. However, animals treated with the combination had a 70% reduction. Similarly, bone resorption was inhibited 56 and 14%, as evaluated histologically, in animals treated with pegsunercept and rhIL-1ra alone, respectively, in contrast to the 100% reduction observed in animals treated with the combination. Comparable results were obtained in rats with type II collagen-induced arthritis. Treatment with rhIL-1ra (30 mg/kg/day s.c.) or pegsunercept (1 mg/kg i.p. every 2 days) alone resulted in an approximate 60 and 16% reduction, respectively, in AUC for paw swelling as compared to the 73% reduction observed in combination-treated animals. Changes in body weight were similar in all groups (28).

Another study in rats with adjuvant-induced arthritis and examining the effects of rhIL-1ra (0.2, 1 or 5 mg/kg/h by s.c. infusion starting day 9 postinduction and continuing for 7 days) and pegsunercept (0.25, 1 or 4 mg/kg/day s.c.) demonstrated that treatment with either agent alone or in combination dose-dependently decreased bone erosion and osteoclast scores. Significant and similar 61-66 and 74% reductions in bone erosion and osteoclast counts, respectively, were seen with treatment at the highest doses alone and in combination. Thus, both agents protect bone integrity through regulation of osteoclast numbers (19).

Rats with adjuvant-induced arthritis were used to compare the effects of pegsunercept (0.3 or 3 mg/kg s.c. on days 9, 11 and 13 postinduction) and methotrexate (0.045, 0.06 or 0.075 mg/kg/day p.o. on days 1-14) alone and in combination. Animals treated with pegsunercept alone exhibited a 28 and 52% decrease in paw swelling for the respective doses and a 25 and 68% inhibition, respectively, of ankle bone resorption. Animals treated with methotrexate alone had reductions in paw swelling of 18, 51 and 84%, respectively, and reductions in bone resorption of 40, 76 and 98%, respectively. When the lower doses of methotrexate were combined with pegsunercept, additive effects were observed on paw swelling and bone resorption (20).

Combination therapy including pegsunercept and dexamethasone or indomethacin was shown to be beneficial in another study in rats with adjuvant-induced arthritis. Animals treated with pegsunercept (1 mg/kg s.c. on days 9, 11 and 13 postinduction) and dexamethasone (0.025 mg/kg/day p.o. on days 9-14 postinduction) alone had reductions in final paw weights of 25 and 25%, respectively, as compared to a reduction of 58% seen with combination treatment, and reductions in ankle bone resorption of 48 and 55%, respectively, were seen on pegsunercept and methotrexate alone as compared to 100% observed with combination treatment. When an inactive dose of dexamethasone (0.06 mg/kg) was combined with pegsunercept, a 39% inhibition in the AUC for paw swelling and a 39% reduction in bone resorption were observed. Slight additive effects on paw swelling were observed when indomethacin (0.5 or 0.25 mg/kg/day p.o. on days 9-14 postinduction) was combined with pegsunercept, although no additive effects were noted on bone resorption (21).

In addition to its antiarthritic efficacy, pegsunercept has also been shown to have other effects. A study using rats with peptidoglycan-polysaccharide polymer-induced arthritis examined the effects of pegsunercept at a dose of 4 mg/kg 3 times/week and the erythropoiesis-stimulating protein Aranesp® (darbepoetin alfa) at a dose of 3 or 6 μg/kg twice monthly alone and in combination on anemia associated with chronic disease in this model of relapsing arthritis. Animals treated with pegsunercept alone tended to have elevated mean hemoglobin (Hb) levels and significant reductions in mean paw edema. Mean Hb levels in animals treated with pegsunercept increased by 1.9 g/dl and those in rats treated with Aranesp® 3 and 6 μg/kg were elevated by a maximum of 0.4 and 1.3 g/dl, respectively, as compared to untreated anemic levels. Combination treatment significantly enhanced Hb levels by 1.3 and 1.9 g/dl for Aranesp® doses of 3 and 6 μg/kg, respectively, as compared to pegsunercept alone and by 2.9 and 3.7 g/dl compared to Aranesp® alone. In addition, combination therapy also induced more reticulocytes and red blood cells and increased total serum iron concentrations, corpuscular volume and corpuscular Hb as compared to either agent alone. Thus, the synergistic effects observed for the agents were mediated via enhanced erythropoietic responses, reduction of siderosis and enhanced red blood cell hemoglobinization (22).

Pegsunercept was effective in reducing the incidence of diabetes and insulitis in a study in nonobese diabetic (NOD) mice. Animals were treated with the agent (3 mg/kg s.c. every other day starting at 12 weeks of age for 8 weeks [study 1]; at 8 weeks of age for 12 weeks [study 2]; or at 8 weeks of age for 3 weeks with an injection of cyclophosphamide at week 9 to induce early diabetes onset [study 3]). In studies 1 and 2, pegsunercept significantly decreased the incidence of diabetes as compared to controls (29 and 19% vs. 85 and 69% for studies 1 and 2, respectively) and insulitis (14 and 13% vs. 100 and 86%, respectively). Treatment was also found to preserve

insulin content of islets and lower diabetes-induced increases in plasma glycerol and free fatty acid levels. In study 3, pegsunercept significantly decreased the incidence of cyclophosphamide-triggered diabetes from 66.6% to 23.1%. Thus, pegsunercept may be effective prophylactically and as treatment for human autoimmune diabetes (23).

Pharmacokinetics

The pharmacokinetics of pegsunercept have been determined in multiple-dose studies conducted in mice, rats, cynomolgus monkeys, baboons and chimpanzees. Absorption was slow after s.c. administration (t_{max} = 24-48, 36 and 12-48 h in rats, monkeys and chimpanzees, respectively). In primates, plasma pharmacokinetics, including plasma C_{max}, AUC and plasma clearance, of pegsunercept were both time- and dose-linear after multiple dosing. Systemic bioavailability in rats and monkeys after multiple s.c. dosing was 70 and about 100%, respectively. The volume of distribution in all species at steady state was < 200 ml/kg, suggesting that it is not distributed exclusively outside the plasma compartment. Elimination in all species except for mice was biphasic, with a significant amount eliminated in the α phase in higher species. Because plasma clearance in all species was less than the renal filtration rate, it was suggested that other routes are involved in elimination of pegsunercept. There was no accumulation in baboons after multiple i.v. dosing (0.2 mg/kg every 3 weeks x 3) or in monkeys after s.c. dosing (0.25-25 mg/kg s.c. twice weekly for 4 weeks). However, slight to moderate accumulation was noted in chimpanzees administered once- or twice-weekly s.c. doses (0.5 mg/kg x 4). No antibodies to pegsunercept were detected in any primate species (10, 24).

The plasma pharmacokinetics of pegsunercept (100-1000 μg/kg s.c. as a single injection on day 1 followed by 3 weekly injections 6 weeks later or only 3 bimonthly injections) were determined in a multicenter, randomized, double-blind, placebo-controlled, dose-escalation phase I study conducted in 81 subjects with active rheumatoid arthritis. The pharmacokinetics obtained appeared to be dose-independent for all doses tested and time-independent over 6-8 weeks at doses of 100-600 μg/kg. After single doses, plasma C_{max} values were reached at 48-96 h. Absorption was slow (absorption half-life = 27 h). Volume of distribution was limited (130 ± 42 ml/kg), and low clearance (1.1 ± 0.35 ml/h/kg) and long elimination half-life values were observed (82 ± 17 h). Although trough levels of the agent increased by 2-fold with weekly administration, no accumulation was observed with bimonthly dosing (25, 26).

Results from a double-blind, placebo-controlled, dose-escalating phase I study examining the pharmacokinetic interactions between pegsunercept (10, 30 or 60 mg/weekly s.c. or 800 μg/kg s.c twice weekly) and rhIL-1ra (100 mg s.c. daily on days 1-70) following multiple doses in 20 subjects with active rheumatoid arthritis, showed that coadministration did not alter the pharmacokinetics of either agent. Subjects were administered a single dose of pegsunercept on day 1 followed on day 15 by multiple dosing for 8 weeks. Steady-state levels of pegsunercept were found to increase with dose and frequency. Plasma C_{max} values for pegsunercept were dose-proportional and reached at 48-72 h postdosing. Clearance values for pegsunercept when coadministered with rhIL-1ra (1.28 ± 0.35 ml/h/kg) were similar to those obtained in another study in which pegsunercept was given alone (1.14 ± 0.35 ml/kg). Coadministration did not alter C_{max} or clearance values for rhIL-1ra (27).

Clinical Studies

The safety, efficacy and immunogenicity of pegsunercept (100, 300 or 600 μg/kg s.c. as a single dose followed by 3 weekly injections of the same dose 6 weeks later; 100, 300 or 600 μg/kg every 2 weeks x 3; or a single dose of 1000 μg/kg) were examined in a multicenter, double-blind, placebo-controlled, dose-escalating phase I trial conducted in 81 TNF receptor therapy-naïve patients with rheumatoid arthritis. Therapy with DMARDs was stopped at least 1 month before the study, although stable corticosteroids and NSAIDs were allowed. Pegsunercept was well tolerated. No serious adverse events were reported and those seen were similar in both treatment and placebo groups. Headache was the most common adverse event reported in 27 and 11% of the patients in placebo and pegsunercept groups, respectively. Flares occurred in 7 patients at 11-30 days after pegsunercept dosing, for which 3 patients discontinued. Mean tender/painful and swollen joint counts decreased in groups treated with pegsunercept. Four patients treated with pegsunercept had low-titer seroreactivity (1:400 or less; 3 and 1 patient had an IgM and IgG anti-pegsunercept response, respectively), although clinical assessment and pharmacokinetics were not altered in these patients; only 1 patient was seroreactive at the end of the study. It was concluded that pegsunercept was not immunogenic (25, 26, 28).

The safety and efficacy of pegsunercept (400 or 800 μg/kg s.c. weekly for 12 weeks) were examined in a multicenter, randomized, placebo-controlled phase II trial involving 194 subjects with rheumatoid arthritis for at least 6 months; DMARD therapy (stable for 8 weeks prior to entry) was allowed, including combination treatment with methotrexate + sulfasalazine or hydroxychloroquine or sulfasalazine + hydroxychloroquine. Only 2 serious adverse events unrelated to treatment were reported. The incidence of infection was slightly higher in patients receiving pegsunercept as compared to placebo (27% vs. 21%). Adverse events that were more frequent in pegsunercept-treated patients as compared to placebo were injection-site reactions (27% vs. 21%), diarrhea (8% vs. 3%), dizziness (6% vs. 3%) and nausea (6% vs. 3%). Treatment with pegsunercept did not affect laboratory parameters or vital signs, and no neutralizing antibodies

were detected. The American College of Rheumatology 20% (ACR20) response rate was significantly higher in patients receiving 800 μg/kg pegsunercept as compared to placebo (50% vs. 26%); no significant differences were observed, however, in ACR20 rates between the group receiving 400 μg/kg pegsunercept (33%) and placebo. At week 12, ACR20 rates were found to significantly increase with dose. Moreover, health-related quality of life as assessed using the SF-36 health survey was significantly improved in patients receiving either dose of the agent. In the groups receiving 800 and 400 μg/kg, 7 of 8 and 6 of 8 scales, respectively, were significantly improved over placebo (29, 30).

The safety and efficacy of pegsunercept (400, 800 or 1100 μg/kg s.c. twice weekly for 24 weeks) were confirmed in a randomized, double-blind, placebo-controlled phase II trial in 309 patients with active rheumatoid arthritis who also had received (for at least 16 weeks prior to study onset) and continued to receive methotrexate; no DMARDs were allowed 4 weeks before or during the study. The incidence of adverse events was similar in treatment and placebo groups except that injection-site reactions were more frequent in patients receiving pegsunercept (38, 36 and 50% for the respective pegsunercept doses vs. 30% on placebo). All doses of pegsunercept were significantly more effective than placebo since a significantly higher number of patients receiving pegsunercept achieved ACR scores at week 24 as compared to placebo (400, 800 and 1100 μg/kg, respectively, vs. placebo: ACR20 = 55, 68 and 49% vs. 26%; ACR50 = 33, 35 and 31% vs. 10%; ACR70 = 10, 25 and 10% vs. 3%) (31).

The long-term safety of pegsunercept (400 or 800 μg/kg s.c. weekly or 300 or 600 μg/kg twice weekly) was demonstrated in an open-label extension study involving 502 patients with rheumatoid arthritis who had participated in the above phase II trials. The average duration of treatment was 7 months, with 86 patients discontinuing for nonadministrative reasons. Pegsunercept was considered to be safe and well tolerated. One death occurred due to respiratory distress syndrome following the last pegsunercept dose. Serious adverse events were reported in 53 patients, of whom 9 discontinued. However, only 1 of these 9 patients was concluded to have treatment-related adverse events (anemia, ecchymosis and malignant lymphoma). Of the 51 patients with injection-site reactions, only 23 were considered related to pegsunercept. No changes in laboratory parameters or vital signs were observed and no neutralizing antibodies were detected. Improvements in ACR scores seen in the initial phase II trials continued to be observed in this extension study (32).

The safety of combination therapy including pegsunercept (10, 30 or 60 mg weekly or 800 μg/kg twice weekly for 8 weeks) and rhIL-1ra (100 mg/day for 8 weeks) was studied in a multicenter, double-blind, placebo-controlled, dose-escalating phase I trial in 20 patients with rheumatoid arthritis. Stable corticosteroids and NSAIDs, but not DMARDs, were allowed. Two patients given combination therapy discontinued early for joint pain. A similar incidence of adverse events was observed in the combination and placebo groups, including injection-site reactions, gastrointestinal (GI) complaints and respiratory complaints. Four serious adverse events were reported in the combination therapy group, although none resulted in withdrawal or were treatment-related. The incidence of mild to moderate infectious episodes was higher in the combination therapy group as compared to placebo (6 vs. 1 case) although no serious infectious episodes were seen (33).

An open-label phase II trial enrolling 22 patients with active rheumatoid arthritis compared the effects of combination pegsunercept (800 μg/kg twice weekly for 31 weeks) + rhIL-1ra (100 mg/day for 31 weeks) with rhIL-1ra monotherapy. After 4 weeks of treatment, ACR20, ACR50 and ACR70 responses were seen in (combination vs. monotherapy) 73% vs. 27%, 27% vs. 0% and 9% vs. 0% of patients, respectively. Following a mean of 31 weeks of treatment, ACR20, ACR50 and ACR70 responses were seen in 64% vs. 36%, 64% vs. 9% and 46% vs. 0% patients, respectively; ACR50 and ACR70 rates were significantly higher in the combination group. Health assessment questionnaire (HAQ) scores were significantly improved in a similar manner in both combination and monotherapy groups; 82 and 55% of the patients in the combination and monotherapy groups, respectively, showed clinical improvements at the final follow-up. Analysis of arthroscopic synovial biopsies of inflamed knee joints and blood samples from 4 patients receiving combination therapy and 3 receiving monotherapy showed alterations in inflammation parameters and synovial genes involved in cartilage degradation (*e.g.*, significant reductions in MMP-1 and MMP-3 gene expression) in 6 of 7 samples at 4 weeks, indicative of a clinical response. Analysis of radiographs of hands and feet before and after treatment from 8 patients in the combination group and 7 patients in the monotherapy group showed a strong tendency (p=0.053) towards improvements in the rate of progression (34, 35).

Pegsunercept continues to undergo phase II development for the treatment of rheumatoid arthritis (36).

Source

Amgen, Inc. (US).

References

1. Prous Science Drug R&D Backgrounders: *Rheumatoid arthritis (online publication)*. Updated December 11, 2003.

2. Shmerling, R.H. *Rheumatoid arthritis.* Drugs Today 1998, 34: 649-53.

3. Matteson, E.L. *Current treatment strategies for rheumatoid arthritis.* Mayo Clin Proc 2000, 75: 69-74.

4. Cush, J.J. *Rationale and risks of novel immunomodulatory therapies in rheumatoid arthritis.* Drugs Today 1999, 35: 287-94.

5. Kavanaugh, A. *An overview of immunomodulatory intervention in rheumatoid arthritis.* Drugs Today 1999, 35: 275-86.

6. Ribbens, C., André, B., Kaye, O. et al. *Increased synovial fluid levels of interleukin-12, sCD25 and sTNF-RII/sTNF-RI ratio delineate a cytokine pattern characteristic of immune arthropathies.* Eur Cytokine Netw 2000, 11: 669-76.

7. Brennan, F.M., Maini, R.N., Feldmann, M. *Role of pro-inflammatory cytokines in rheumatoid arthritis.* Springer Semin Immunopathol 1998, 20: 133-47.

8. Firestein, G.S., Zvaifler, N.J. *Anticytokine therapy in rheumatoid arthritis.* New Engl J Med 1997, 337: 195-7.

9. Williams, R.O., Feldmann, M., Maini, R.N. *Cartilage destruction and bone erosion in arthritis: The role of tumour necrosis factor α.* Ann Rheum Dis 2000, 59(Suppl. 1): i75-80.

10. Edwards, C.K. III. *PEGylated recombinant human soluble tumour necrosis factor receptor type I (r-Hu-sTNF-RI): Novel high affinity TNF receptor designed for chronic inflammatory diseases.* Ann Rheum Dis 1999, 58(Suppl. 1): I73-81.

11. Grell, M., Wajant, H., Zimmermann, G., Scheurich, P. *The type 1 receptor (CD120a) is the high-affinity receptor for soluble tumor necrosis factor.* Proc Natl Acad Sci USA 1998, 95: 570-5.

12. Cope, A.P., Maini, R.N. *Soluble tumor necrosis factor receptors in arthritis.* J Rheumatol 1995, 22: 382-4.

13. Moreland, L.W., McCabe, D.P., Caldwell, J.R. et al. *Phase I/II trial of recombinant methionyl human tumor necrosis factor binding protein PEGylated dimer in patients with active refractory rheumatoid arthritis.* J Rheumatol 2000, 27: 601-9.

14. Kohno, T., Baker, S., Frazier, J. et al. *Assessment of the major antigenic epitopes of the recombinant human soluble p55 TNF type I receptor: Design of a novel monomeric non-immunogenic analog, sTNF-RI.* J Interferon Cytokine Res 1998, 18(5): Abst 6.17.

15. Bendele, A.M., McComb, J., Gould, T., Chlipala, L, Frazier, J., Colagiovanni, D., Edwards, C.K. III. *Comparative efficacy of sTNF-RI, a novel monomeric, recombinant soluble TNF type I receptor, to dimeric sTNF-RI and sTNFRII IgG1 Fc fusion proteins in animal models of rheumatoid arthritis.* J Interferon Cytokine Res 1998, 18(5): Abst 5.06.

16. Bush, K.A., Walker, J.S., Kirkham, B.W. *Effect of PEG sTNF-RI treatment on cytokine expression in rat adjuvant arthritis.* 64th Annu Meet Am Coll Rheumatol (Oct 29-Nov 2, Philadelphia) 2000, Abst 997.

17. Edwards, C.K. III, Chlipala, E.S., Dinarello, C.A., Reznikov, L.I., Moldawer, L.L., Bendele, A.M. *Clinical and histopathological characterization of arthritis in male and female tumor necrosis factor-α knockout (TNF-$\alpha^{-/-}$) and membrane-bound TNF-α transgenic (TNF-α^{TgA86}) mice injected with Mycoplasma pulmonis or Mycoplasma arthritidis.* 63rd Annu Meet Am Coll Rheumatol (Nov 13-17, Boston) 1999, Abst 296.

18. Bendele, A.M., Chlipala, E.S., Rich, W.R., Edwards, C.K. III. *Combination benefit of treatment with recombinant human interleukin-1 receptor antagonist (IL-1ra) and pegylated recombinant human soluble tumor necrosis factor receptor type I (PEG sTNF-RI) in animal models of rheumatoid arthritis.* Ann Rheum Dis 2000, 59(Suppl. 1): Abst POS-350.

19. Bolon, B., Morony, S., Capparelli, C., Hu, Y.-L., Giuseppe, C., Duryea, D., Feige, U. *IL-1ra and PEG sTNF-RI reduce osteoclast numbers in rats with adjuvant arthritis.* 64th Annu Meet Am Coll Rheumatol (Oct 29-Nov 2, Philadelphia) 2000, Abst 1002.

20. Bendele, A.M., McComb, J., Gould, T. et al. *Effects of PEGylated soluble tumor necrosis factor receptor type I (PEG sTNF-RI) alone and in combination with methotrexate in adjuvant arthritic rats.* Clin Exp Rheumatol 1999, 17: 553-60.

21. Bendele, A.M., McComb, J., Gould, T. et al. *Combination benefit of PEGylated soluble tumor necrosis factor receptor type I (PEG sTNF-RI) and dexamethasone or indomethacin in adjuvant arthritic rats.* Inflamm Res 1999, 48: 453-60.

22. Stoney, G., Sutherland, W., Cooke, K., Duryea, D., Tarpley, J., del Castillo, J., Molineux, G. *Novel erythropoiesis stimulating protein (Aranesp™) enhances pegylated soluble tumor necrosis factor receptor type 1 (PEGsunercept) alleviation of anemia of chronic disease (ACD) in a rodent model of relapsing arhritis.* Eur Leag Against Rheum Congr (June 12-15, Stockholm) 2002, Abst AB0015.

23. Wang, J.-L., Qian, X., Chinookoswong, N., Lu, J., Chow, G., Theill, L., Shi, Z.-Q. *PEGylated soluble TNF receptor-1 reduces insulitis and incidence of spontaneous and cyclophosphamide induced diabetes in NOD mice.* Diabetes 2001, 50(Suppl. 2): Abst 1095-P.

24. Martin, S., Frazier, J., Seely, J. et al. *A genetically modified tumor necrosis factor receptor I (sTNF-RI) that does not elicit antibody response in primates.* Arthritis Rheum 1998, 41: S58.

25. Martin, S.W., Sommers, J., Macri, M.J. et al. *The pharmacokinetics of subcutaneous injections of pegylated recombinant methionyl soluble tumor necrosis factor-type I receptor (PEG sTNF-RI) in subjects with active rheumatoid arthritis.* 63rd Annu Meet Am Coll Rheumatol (Nov 13-17, Boston) 1999, Abst 50.

26. Caldwell, J.R., Davis, M.W., Jelaca-Maxwell, K. et al. *A phase 1 study of pegylated soluble tumor necrosis factor receptor type I (PEG sTNF-RI [p55]) in subjects with rheumatoid arthritis (RA).* Ann Rheum Dis 2000, 59(Suppl. 1): Abst POS-391.

27. Martin, S.W., Nguyen, L., Stouch, B.J. et al. *Pharmacokinetics (PK) of anakinra and pegylated soluble tumor necrosis factor receptor type I (pegsunercept) were not altered after combination treatment in subjects with rheumatoid arthritis (RA).* Eur Leag Against Rheum Congr (June 12-15, Stockholm) 2002, Abst FRI0155.

28. Davis, M.W., Frazier, J.L., Martin, S.W., Edwards, C.K. III *Non-immunogenicity of a pegylated soluble tumor necrosis factor receptor type I (PEG sTNF-RI [p55]).* Ann Rheum Dis 2000, 59(Suppl. 1): Abst POS-390.

29. Schiff, M., Furst, D., Fleischmann, R., Macri, M., Joh, T., Edwards, C.K. III, Davis, M.W. *The efficacy and safety of pegylated recombinant methionyl human soluble tumor necrosis factor receptor type I (PEG sTNF-RI; p55) in a randomized, placebo-controlled, clinical study of patients with rheumatoid arthritis (RA).* Annu Eur Congr Rheumatol (EULAR) (June 13-16, Prague) 2001, Abst FRI0059.

30. Tesser, J.R., Schiff, M.H., Davis, M.W., Woolley, J.M. *PEG sTNF-RI improves health-related quality of life in patients with rheumatoid arthritis.* Annu Eur Congr Rheumatol (EULAR) (June 13-16, Prague) 2001, Abst OP0084.

31. Sarzi-Puttini, P., Thomson, G., Sheldon, E., Roschmann, R., Liu, T., Lee, D., Solinger, A. *Efficacy and safety of PEGylated recombinant methionyl human soluble tumor necrosis factor receptor type I: A phase 2 study in patients with rheumatoid arthritis.* 67th Annu Meet Am Coll Rheumatol (Oct 23-28, Orlando) 2003, Abst 205.

32. Schiff, M., Furst, D., Cohen, S. et al. *The long-term safety of pegylated recombinant methionyl human soluble tumor necrosis factor type I (pegsunercept): An extension study for rheumatoid arthritis patients completing previous pegsunercept clinical studies.* Eur Leag Against Rheum Congr (June 12-15, Stockholm) 2002, Abst FRI0085.

33. Caldwell, J.R., Offenberg, H., Furst, D. et al. *A phase I safety study of combination treatment with pegylated soluble tumor necrosis factor receptor type I (PET STNF-RI) and anakinra (interleukin-1 receptor antagonist, IL-1RA) in patients with rheumatoid arthritis.* Eur Leag Against Rheum Congr (June 12-15, Stockholm) 2002, Abst FRI0087.

34. Rooney, T., Madigan, A., Greenan, L. et al. *Combination therapy with anakinra and PEGylated soluble tumor necrosis factor receptor type I (pegsunercept) in rheumatoid arthritis (RA): Preliminary analysis of clinical, functional, synovial tissue, and radiographic outcomes from a phase II, open-label, mode of action study.* 67th Annu Meet Am Coll Rheumatol (Oct 23-28, Orlando) 2003, Abst 211.

35. Edwards, C.K. III, Williams, A., Fitzpatrick, V.D. et al. *Combination therapy with anakinra (r-metHuIL-1ra) and PEGylated soluble tumor necrosis factor receptor type I (PEG sTNF-RI) in rheumatoid arthritis (RA): Cluster analysis and microarray mRNA expression profiles of patient synovium and peripheral blood mononuclear cells (PBMC).* 66th Annu Meet Am Coll Rheumatol (Oct 25-29, New Orleans) 2002, Abst 1468.

36. *Product pipeline.* Amgen Web Site November 14, 2003.