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Etanercept: Anti-Tumor Necrosis Factor Therapy for Rheumatoid Arthritis

The Technology

Etanercept (Enbrel™, Immunex, Seattle, Washington), a tumor necrosis factor (TNF) antagonist, is the first of a new genetically engineered class of drugs for rheumatoid arthritis known as biologic response modifiers.[1,2] Etanercept is manufactured by Immunex Corporation and co-marketed in North America by Wyeth-Ayerst Laboratories under the trade-name Enbrel.[3]

In inflamed joints, the naturally occurring cytokine, TNF, attaches to cell surfaces of the immune system.[4] Binding triggers the production of inflammatory agents involved in joint destruction and the development of rheumatoid arthritis.[4,5] In healthy bodies, TNF is regulated by molecules called soluble TNF receptors.[5] Etanercept is a recombinant form of the human p75 TNF receptor fused to the Fc fragment of human immunoglobulin G1.[6] The resulting fusion protein mimics the action of soluble TNF receptors by binding TNF, thereby blocking the production of inflammatory agents.[6] Administered by subcutaneous injection, etanercept neutralizes TNF-mediated inflammation reducing the symptoms of severe arthritis.[7]

Regulatory Status

On November 2, 1998, the Centre for Biologics Evaluation and Research of the United States Food and Drug Administration (FDA) approved Enbrel™ as therapy to reduce the signs and symptoms of moderate to severely active rheumatoid arthritis.[1] As of September 10, 1999, etanercept has not been approved for use in Canada.[8]

Patient Group

Rheumatoid arthritis is a chronic, progressive, systemic autoimmune disorder. It is characterized by symmetric inflammation of the lining of the joints. This can result in damaged cartilage, bone, tendons and ligaments and can lead to inflammation of internal organs. Rheumatoid arthritis affects an estimated 293,000 Canadians, or 1 in 100 persons.[9] Striking all races and ethnic groups at any age, it commonly appears between the ages of 25 and 40, affecting women 2-3 times more often than men.[9] Many patients discontinue available therapies due to toxicity or inadequate efficacy. Etanercept is approved to reduce symptoms of moderate to severely active rheumatoid arthritis[1] and polyarticular course juvenile rheumatoid arthritis[10] in patients who respond inadequately to one or more disease-modifying anti-rheumatic drugs (DMARDs).

Current Treatments

Current treatments for rheumatoid arthritis include lifestyle changes to preserve joint mobility, medication to reduce inflammation and retard disease progression and surgical procedures to improve joint function.[9] When the disease is active, rest can reduce inflammation; when the acute flare is over, exercise is important to maintain mobility and strength.[11]

Conventional rheumatoid arthritis medications consist of cornerstone NSAIDS including aspirin, diclofenac, ibuprofen, and naproxen.[12] While physician and patient preference determine the agent of choice, a meta-analysis of DMARDs suggests that in early disease, antimalarials such as

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methotrexate, sulfasalazine, gold, cyclosporine and penicillamine are the most effective second-line drugs used to control inflammation.[13] Corticosteroids, including prednisone and methylprednisone, are reserved for active disease unresponsive to NSAIDs and DMARDs.[12]

Surgical procedures include joint replacement, tendon reconstruction, and synovectomy. Joint replacement is the most frequently performed surgery for rheumatoid arthritis. However, artificial joints may eventually need replacement. Tendon reconstruction and synovial tissue removal are frequently employed to restore hand function.[11]

Dosage and Potential Cost

Enbrel™ is supplied in a carton of four-dose trays containing 25 mg single-use vials of etanercept with 1 mL of sterile bacteriostatic water for each injection.[7] Etanercept may be self-administered following instruction and initial supervision by a qualified health care professional. Patients should consult physicians and pharmacists frequently regarding proper injection techniques and response to therapy.[6]

The recommended adult dosage for rheumatoid arthritis is 25 mg administered by subcutaneous injection twice weekly.[7] The dosage for juvenile rheumatoid arthritis is unclear; however, an open-label phase of a two-part study indicates administration of 0.4 mg/kg twice weekly for three months.[7] In the United States, the adult dosage corresponds to a cost of US $10,400 annually.[14]

Projected Rate of Diffusion

Administration of etanercept by subcutaneous injection, in contrast to oral medications, may prove difficult for rheumatoid arthritis patients lacking manual dexterity. This mode of administration may limit the diffusion of etanercept and place greater responsibility on administration by family members and health professionals.

The applications for etanercept may expand as other uses are explored. On May 27, 1999, six months following initial approval, indications for etanercept were expanded for the treatment of polyarticular course juvenile rheumatoid arthritis.[10] Additional trials are being conducted to determine the effect of etanercept on early-stage arthritic disease. Studies are also underway to explore the therapeutic value of etanercept for other disease states with inflammatory components, including congestive heart failure, Wegener's Granulomatosis, and endometriosis.

Concurrent Developments

Promising agents for rheumatoid arthritis include other biological response modifiers ABX-IL8[15] and MDX-CD4[16] which target the inflammatory mediators interleukin-8 and CD4 respectively. Alternatives to NSAIDs for first line therapy include the cyclooxygenase-2 (COX-2) inhibitor celecoxib (Celebrex™, Searle), approved in Canada in April 1999[8] and refecoxib (Vioxx™, Merck Frosst), under fast-track review by Health Canada.[17] Additional options include the removal of immune complexes and antigens by apheresis using the Prosorba® column by Cypress Bioscience Inc.[18]

In September 1998, the FDA approved leflunomide (Arava®, Hoechst Marion Roussel) as the first oral treatment to slow the progression of active rheumatoid arthritis.[19] The recommended adult dosage of this DMARD for rheumatoid arthritis is 20 mg once daily, amounting to a cost of approximately US $2,940 annually.[14] In a double-blind, randomized, six-month, multicenter trial involving 358 rheumatoid arthritis patients, 56% of leflunomide treated patients showed a 20% improvement in symptoms.[20] This drug remains in the body for a long time and is not recommended for pregnant women or patients with liver disease.

The monoclonal TNF antibody remicade (Infliximab™, centocor) was approved as treatment for Crohn's disease by the United States Center for Biologics Evaluation and Research in August 1998.[21] It is in phase III trials for use in combination with methotrexate for the treatment of rheumatoid arthritis.

Assessing the Evidence

Table 1: Results of Clinical Trials with Etanercept

Clinical Trial	Active RA Patients	Therapy	% of Patients Achieving an ACR Response of:			% Reduction in Mean Tender Joint Count	Injection-site Reaction	Anti-double-stranded DNA Antibodies
			20%	50%	70%			
Moreland	n=78	E (25 mg)	59	40	15	56%	49%	4%
et al.[22]	n=76	E (10 mg)	51	24	9	44%	43%	9%
n_T=234	n=80	P	11	5	1	6%	13%	1%
Weinblatt	n=59	M + E (25 mg)	71	39	15	75%	42%	7%
et al.[23]								
n_T=89	n=30	M + P	27	3	0	39%	7%	3%

RA = rheumatoid arthritis ACR = American College of Rheumatology E = Etanercept
M = Methotrexate P = Placebo

The safety and efficacy of etanercept were assessed in two six-month, randomized, double-blind placebo-controlled clinical trials (Table 1). In one study, 234 rheumatoid arthritis patients inadequately responsive to DMARDs, were assigned to receive twice weekly subcutaneous injections of etanercept, 25 mg or 10 mg, or placebo.[22] Seventy percent of patients were female with a mean age of 52 years, a mean disease duration of 12 years, and had more than 12 tender and 10 swollen joints. Ninety percent of patients had prior methotrexate treatment and underwent a one month DMARD washout period prior to the study.

The primary efficacy end points were 20% and 50% improvement in disease activity at six months. Defined by the American College of Rheumatology (ACR), a 20% improvement specifies a 20% reduction in tender and swollen joint count and improvement in three of the following measures: patient and physician global assessments, pain, disability, and acute phase reactant measures.[24]

In comparison to placebo recipients, patients receiving etanercept showed significant improvement for all measures of rheumatoid arthritis activity. Of the patients receiving etanercept, 59% of the 25 mg group and 51% of the 10 mg group achieved a 20% ACR response; 40% and 24% respectively achieved a 50% improvement. In contrast, 11% of placebo recipients achieved a 20% ACR response, and 5% achieved a 50% improvement. While not prospectively defined as an endpoint, a 70% improvement was noted in 15% of patients receiving 25 mg, 9% of patients receiving 10 mg etanercept and only 1% of placebo recipients. Mean tender joint count was reduced by 56% in 25 mg and 44% in 10 mg etanercept recipients compared to 6% in the placebo group.[22]

Adding etanercept to methotrexate therapy significantly improved all measures of disease activity in a second study involving 89 patients with active rheumatoid arthritis.[23] Patients with inadequate response to a stable dose of 15 to 25 mg per week of methotrexate were randomly assigned to receive either 25 mg of etanercept or placebo subcutaneously twice weekly, while continuing methotrexate treatment. Of patients receiving etanercept plus methotrexate, 71% achieved a 20% ACR response; 39% a 50% response, and 15% achieved a 70% improvement in symptoms. In contrast, 27% of those receiving methotrexate plus placebo achieved a 20% ACR response and 3% achieved a 50% improvement. Etanercept plus methotrexate subjects had a median number of seven tender and six swollen joints versus 17 and 11 experienced by the methotrexate plus placebo group.[23]

Etanercept was also found to benefit patients with polyarticular course juvenile rheumatoid arthritis refractory to methotrexate. In an open-label part of a two-part trial, 69 rheumatoid arthritis patients, aged 4 to 17 years, received 0.4 mg/kg of etanercept twice weekly for three months. Of 54 patients for whom 3-month data was available, 76% achieved a 30% improvement in symptoms of the disease.[7]

Adverse Effects

The most common adverse event associated with the use of etanercept was mild injection-site reaction. Injection-site reactions developed in 49% percent of patients receiving 25 mg of etanercept[22] and 42% of those receiving etanercept plus methotrexate (Table 1).[23] Most patients who had injection-site reactions had five or fewer events during the study.[22,23] In contrast, only 13% of patients receiving placebo[22] and 7% receiving placebo plus methotrexate[23] developed injection-site reactions. Additional adverse effects of etanercept therapy included headache, sinusitis, rhinitis, and diarrhea.[22]

Malignancies (~0.94%)[7] and infections (~0.12%)[11] were the most common serious adverse events observed in rheumatoid arthritis patients participating in controlled and open label trials of etanercept. Abdominal pain (17%) and vomiting (14.5%) were reported in patients with juvenile rheumatoid arthritis. It is recommended that children be updated with all immunizations prior to initiating treatment with etanercept, as two pediatric patients developed varicella infection.[7] Most patients tested negative for autoantibodies (Table 1); however, the impact of long-term etanercept therapy on fertility, autoimmune disease, or malignancy development remains to be evaluated.[7]

Five months following adoption of the drug in the US, 30 of an estimated 25,000 patients (~0.1%) treated with etanercept developed serious infections.[11] Several patients had sepsis, six of whom died within six to sixteen weeks from initiation of treatment. Of these patients, many had a history of chronic or recurrent, pre-existing infections, diabetes mellitus, congestive heart failure or other conditions which predisposed them to infection. As a result, the FDA issued a warning not to initiate etanercept treatment in patients with active, chronic or localized infections, or a history of recurring infections or underlying conditions predisposing to infections.[11] Patients who develop a new infection while undergoing etanercept treatment should be monitored closely, those with serious infection or sepsis are recommended to discontinue treatment.[12]

Implementation Issues

The evidence assessed in this brief is based primarily on two clinical trials,[22,23] a limited number of participants and short-term safety and efficacy data. While data from longer term studies are needed to determine the efficacy and effectiveness of etanercept therapy, long term placebo-controlled trials for rheumatoid arthritis are generally considered unethical.[27]

Canadian clinical and economic data comparing methotrexate and etanercept alone versus etanercept in combination with methotrexate would be necessary before informed predictions could be made on its cost-effectiveness in our health care system. While the direct costs of this therapy are high, if etanercept controls the disease more effectively than current treatments, or earlier in the progression of the disease, it may have incremental cost-effectiveness. In addition, factors such as the timing of initial treatment, adverse effects, and the possibility that anti-TNF therapies may reduce the patient's defense against infection and malignancy, must also be taken into consideration prior to implementation.

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