Using ENBREL® to Treat Rheumatoid and Psoriatic Arthritis

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Overview

This White Paper addresses the benefits of using etanercept, known by the product name of ENBREL® . Marketed by Amgen and Wyeth Pharmaceuticals, ENBREL is a fusion of two naturally occurring proteins and is used to treat patients diagnosed with rheumatoid arthritis (RA), juvenile rheumatoid arthritis (JRA), and psoriatic arthritis. Studies show that ENBREL provides more effective and rapid relief from arthritic symptoms over a sustained period of time than previously used treatments, such as disease-modifying antirheumatic drugs (DMARDs). Moreover, ENBREL has demonstrated the ability to inhibit the progression of joint and bone damage experienced by RA patients.

Rheumatoid arthritis

According to the Arthritis Foundation®, adult RA affects over 2.1 million Americans, mostly women (1.5 million women have RA compared to 600,000 men). Onset is usually in middle-age, but often occurs in the 20s and 30s.[1] RA symptoms include painful inflammation and stiffness of the joints, often accompanied by fatigue. Chronic RA can lead to progressive structural damage of the joints and bones, which can eventually cause disability and deformity.

Rheumatoid arthritis is an autoimmune disease, meaning that the normal immune response in the human body becomes pathogenic and starts attacking itself. ENBREL works by combining two naturally occurring proteins to control the body's overactive immune response and inhibit the pathological process, thereby reducing the painful joint inflammation and stiffness characteristic of arthritis, and often minimizing progressive joint and bone deterioration as well.

Juvenile Rheumatoid Arthritis

The most common form of arthritis in children is juvenile rheumatoid arthritis, which is characterized by chronic and destructive inflammation of joints and can also affect organs such as the eyes, heart lining and lymph nodes.[2] The FDA has approved ENBREL to treat pediatric patients suffering from polyarticular-course JRA (which affects five or more joints), who have shown minimal response to DMARDs, such as methotrexate.[3]

Psoriatic arthritis

Psoriatic arthritis is characterized by red, scaly skin lesions, in addition to joint inflammation and swelling. This disease is related to the skin condition psoriasis. In January, 2002, the FDA approved the use of ENBREL for sufferers of psoriatic arthritis, making it the first therapy specifically approved to treat signs and symptoms of active psoriatic arthritis.[4]

In all three types of arthritic patients, ENBREL helps patients regain vitality, the ability to perform routine activities, and a positive mental outlook.

A new class of drug

ENBREL falls into a new class of drug known as biological response modifiers, that is, it works solely by modifying naturally occurring biological responses. One of the fastest growing prescription drugs on the market, ENBREL is currently the only fully human biological therapeutic treatment being used to treat both moderate to severe RA and psoriatic arthritis. Since ENBREL's FDA approval and subsequent commercial availability in 1998, over 130,000 patients worldwide have been treated with the drug.[3]

According to Dr. Beth Seidenberg, Amgen's senior vice president of development, "patients receiving four years of chronic treatment with ENBREL experience long-term, significant inhibition of bone and joint damage. ENBREL has demonstrated the longest sustained inhibition of structural damage reported among all the biologic RA therapies currently approved by the FDA." [3]

Symptoms of Rheumatoid Arthritis

RA is characterized by inflammation of the synovial membranes lining the joints, causing redness, stiffness, and swelling. The synovial tissue called the pannus becomes enlarged and immune cells invade the joints. This can cause destruction of the adjacent articular structures of the joint, including the resorption of cartilage and bone tissues, and damage to ligaments and tendons. Destructive enzymes associated with cartilage and bone erosion are present at the onset of RA, creating a potential for joint damage very early in the disease--70% of RA patients have shown erosion on x-rays within 2 years of the onset of symptoms.[5]

Figure 1. Structural damage resulting from RA [5]

Tumor Necrosis Factor (TNF)

TNF is a naturally occurring cytokine that plays a key role in the body's normal inflammatory and immune response. When TNF is released by immune system macrophages and T cells in response to an immune reaction, it attaches to membrane-

bound TNF receptors on the surfaces of immune cells, triggering an inflammatory reaction.

In a healthy immune system, the body produces soluble TNF receptors that bind TNF. This binding action prevents excess TNF from attaching to the TNF receptors on the surfaces of immune cells, thus regulating the levels of TNF in the synovial membranes of the joints and controlling the immune response.

In RA patients however, there is an inadequate supply of TNF soluble receptors to bind TNF, resulting in abnormally elevated TNF levels in the synovial fluid. The increased levels of TNF at the pannus-cartilage junction activate the production of destructive enzymes in the joints, leading to progressive tissue, joint, and bone deterioration.[6]

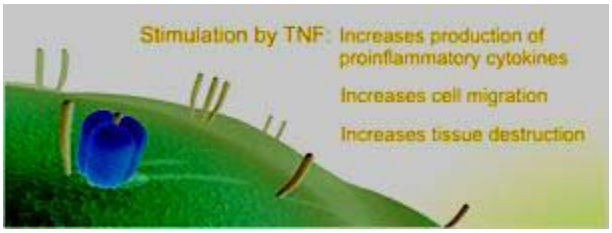

Figure 2. TNF (blue) stimulating membrane-bound TNF receptors on the cell surface. 6

How ENBREL works

ENBREL is a recombinant soluble cell receptor that combines two naturally occurring TNF cytokine receptors to target RA at the cellular level. ENBREL supplements the body's insufficient supply of naturally occurring TNF soluble receptors, thus restoring the body's natural balance between TNF and TNF soluble receptors and controlling synovial tissue inflammation.

Each molecule of ENBREL binds two TNF molecules, thus preventing excess TNF from binding to the cell surface TNF receptors. It has been shown that the dimeric structure of ENBREL gives it a greater affinity for TNF and makes it up to 1,000 times more potent in neutralizing TNF than the body's naturally occurring soluble receptors.[7]

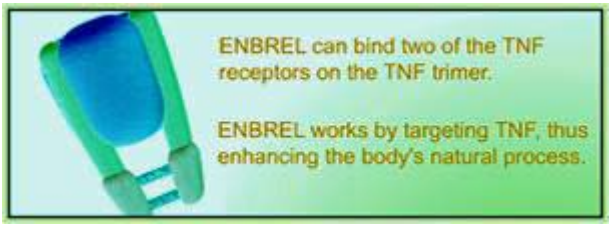

Figure 3. ENBREL (blue) binds with two molecules of excess TNF (green). 7

ENBREL works in co-operation with the body. Because the components of ENBREL occur naturally in humans, the body does not generate neutralizing antibodies against it, which could reduce its efficacy. DMARDs, on the other hand, usually work by suppressing the immune system, which can lead to other health complications.

JRA patients exhibit elevated levels of another cytokine closely related to TNF called lymphotoxin (LT) alpha in elevated levels in their synovium, in addition to elevated levels of TNF. ENBREL binds both proteins to inhibit them from attaching to cell-surface TNF receptors.

ENBREL pharmacological description and function

ENBREL (etanercept) is a dimeric fusion protein consisting of the extra-cellular ligand-binding protein of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFRs) linked to the F_c portion of human IgGI. The F_c component of ENBREL contains the C_H2 domain, the C_H3 domain and the hinge region, but not the C_H1 domain of IgGI. ENBREL is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. It consists of 934 amino acids and has an apparent molecular weight of approximately 15 kildaltons.[8]

Two distinct receptors for TFN (TFNRs), a 55 kilodalton protein (p55) and a 75 kildalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF is dependent upon binding to either cell surface TFNR. ENBREL is a dimeric soluble form of the p75 receptor that can bind to two TNF molecules. ENBREL prevents the binding of both TNF and TNF_β (lymphotoxin alpha LT_α) to cell surface TNFRs, rendering TNF biologically inactive.[8]

Medical studies and clinical trials

A variety of studies involving RA and psoriatic arthritis patients indicate a significant improvement in signs and symptoms for patients using ENBREL over a sustained period of time. The following are the results of a few of these studies, followed by links to more specific study and clinical trial information.

These studies are based on the definition for patient improvement set by the American College of Rheumatology (ACR). That is, the patient must show at least a 20% improvement in tender and swollen joint counts, as well as a 20% improvement in three of the five remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute phase reactant.[9] These results are defined as an ACR response of 20.

Long-term studies on RA patients using ENBREL (reported June, 2002)

In an ongoing Immunex study of 629 patients who had failed to respond to DMARDs, and who were now using ENBREL as monotherapy, more than 70 % of the patients showed a consistent and sustained ACR response of at 20 or higher, regardless of age, longevity, or severity of RA.

An open-label follow-up study was conducted of 119 patients from the original group, who had now been using 25 mg of ENBREL twice weekly for five years. Results showed that:

- 71% of patients achieved an ACR response of 20
- 48% of patients achieved an ACR response of 50
- 27% of patients achieved an ACR response of 70 [10]

A second open-label study was conducted at Johns Hopkins University of 161 patients diagnosed with early RA and who had been taking 25 mg of ENBREL twice weekly as monotherapy for three years. The results showed that:

- 77% of patients achieved an ACR response of 20.
- 58% of patients demonstrated no radiographic progression of structural damage.[10]

Psoriatic Arthritis (reported January, 2002)

A 24-week, multicenter, randomized, double-blind, placebo-controlled phase 3 study assessed the efficacy and tolerability of ENBREL versus placebo in 205 patients with psoriatic arthritis. Data was not only evaluated by ACR rate but also by the psoriasis area and severity index (PASI) index, which measures improvement in both the amount of psoriatic plaque occurring throughout the body and the severity of the skin disease. After 12 weeks of being treated with 25 mg of ENBREL twice weekly:

- 59 % of 101 patients receiving ENBREL achieved an ACR response of 20 compared to 15 % of 104 patients receiving placebo.
- 38 % of 101 patients receiving ENBREL achieved an ACR response of 50 compared to 4 % of 104 patients receiving placebo.
- 11 % of 101 patients receiving ENBREL achieved an ACR response of 70 compared to 0 % receiving placebo.

Similar results were seen at 24 weeks. The results of this study were similar to those seen in an earlier, single-center, randomized, placebo-controlled study of 60 patients with psoriatic arthritis. [4]

ENBREL vs. Methotrexate (reported November, 2000)

A study was conducted at Johns Hopkins University on 632 patients with early RA using either ENBREL (10 to 25 mg twice weekly subcutaneously) or methotrexate orally (mean, 19 mg per week) over a 12-month period. Bone erosion and joint-space narrowing were measured radiographically and scored with use of the Sharp scale. On this scale, an increase of one point represents one new erosion or minimal narrowing.

Compared with patients who received methotrexate, patients treated with ENBREL showed a more rapid rate of improvement (decreased symptoms and inhibited joint damage), with significantly more patients having 20 %, 50 %, and 70 % improvement in disease activity during the first six months.

Among patients who received the 25-mg dose of ENBREL, 72 % had no increase in the erosion score, as compared with 60 % of patients in the methotrexate group. This group of patients also had fewer adverse events and fewer infections than the group that was treated with methotrexate.[11]

Links to studies and clinical trials

For more detailed information concerning ENBREL clinical trials and studies, visit the following links:

- ENBREL® (etanercept) Product Information document, No. 10662-12, Issue date 10/02 (PDF)
- About ENBREL - Tolerability Profile
- Arthritis Foundation® - Conditions and Treatment, "TNF Inhibitors Show Promise in Early Treatment of RA"
- Arthritis Foundation® - Resources, "Arthritis Foundation Statement on ENBREL for Psoriatic Arthritis
- "A Comparison of Etanercept and Methotrexate in Patients with Early Rheumatoid Arthritis," New England Journal of Medicine, Vol. 343:1586-1593, Nov. 30, 2002, No. 22
- Frequently Asked Questions - Clinical Trials FAQs
- Amgen Press Release, February 19, 2003, "Amgen Submits ENBREL® Four-Year Data Supporting Long-Term Inhibition of Bone and Joint Damage in RA" (PDF)

- ENBREL in the News, January 16, 2002, "ENBREL® (etanercept) Is First Therapy Approved for Treatment of Psoriatic Arthritis"

Side effects and adverse reactions

ENBREL is generally well-tolerated. The most common side effects experienced by patients using ENBREL in clinical trials are injection site reactions (ISRs), infections, and headaches. In clinical trials conducted on both RA and psoriatic arthritis patients, only ISRs (redness, pain, itching, swelling, bruising) occurred more frequently than that of a placebo.[3] [12]

For detailed information regarding potential side effects, adverse reactions, and precautions when using ENBREL, visit the following links:

- Amgen Press Release, February 19, 2003, "Amgen Submits ENBREL® Four-Year Data Supporting Long-Term Inhibition of Bone and Joint Damage in RA" (PDF)
- ENBREL® (etanercept) Product Information document, No. 10662-12, Issue date 10/02 (PDF)
- About ENBREL - Indications and Important Treatment Considerations
- About ENBREL - Tolerability Profile

Treatment and dosage information

ENBREL is the first biological TNF-inhibitor that can be used to treat rheumatoid and psoriatic arthritis without any other drug treatment. However, ENBREL provides physicians with increased flexibility in determining patient treatment in that it can be used in conjunction with symptomatic medications such as glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), and analgesics. ENBREL can also be used combination with methotrexate in adult patients who do not adequately respond to methotrexate alone.

ENBREL is indicated for the following groups of people to treat arthritic signs and symptoms:

- Adult patients with moderate to severe active RA.
- Pediatric patients four years or older with moderate to severe active polyarticular-course JRA who have not shown an adequate response to one or more DMARDs.
- Patients with psoriatic arthritis. [8] [13]

Recommended Dosage

- For **adults** with rheumatoid or psoriatic arthritis, the recommended dosage is 25 mg twice weekly, administered 72 to 96 hours apart.

- For **pediatric patients** (ages 4 to 17) with active polyarticular-course JRA, the recommended initial dose is 0.4 mg/kg twice weekly 72 to 96 hours apart (up to a maximum of 25 mg per dose). [8]

Administration

ENBREL comes in single-use 25 mg-vials and is administered as a subcutaneous injection in the thigh, abdomen, or back of the upper arm—rotating sites is recommended. This permits ENBREL to directly enter the blood stream. (Because of it protein nature, stomach acids would break down pills taken orally.)

Initially, ENBREL should be administered under the care and supervision of a physician or healthcare professional. However, adult patients or caregivers may perform injections at home once they have received proper training for dosage measurements and injection techniques. Routine laboratory monitoring is not required. [8] [14]

Information for Pharmacists

ENBREL is supplied as a sterile, white, preservative-free lyophilized powder for subcutaneous administration after reconstitution and is packaged in a carton containing four dose trays (NDC 58406-425-34). Each dose tray contains one 25 mg vial of ENBREL, one syringe containing 1 mL sterile Bacteriostatic Water for Injection (BWFI), USP (0.9% benzyl alcohol), one plunger, two alcohol swabs, and a dating sticker for the vial of ENBREL. Reconstitution with the supplied BWFI yields a multiple-use, clear, and colorless solution of ENBREL with a pH of 7.4 $\pm$ 0.3. Each vial of ENBREL contains 25 mg ENBREL, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine. [8]

For more pharmaceutical information, including reconstitution instructions, refer to the Immunex ENBREL Product Information document at:
ENBREL® (etanercept) Product Information document, No. 10662-12, Issue date 10/02 (PDF)

Summary

Since its approval in 1998, the biological response modifier known as ENBREL (etanercept) has helped relieve the symptoms of rheumatoid arthritis, juvenile RA, and psoriatic arthritis in thousands of patients much more effectively and quickly than disease-modifying anti-rheumatic drugs such as methotrexate. In addition, studies and clinical trials with RA patients treated with ENBREL over a four-year period have shown sustained inhibition of progressive joint and bone deterioration, with minimal side-effects. ENBREL can be easily and conveniently injected by adult patients or caregivers at home, without clinical laboratory monitoring.

For more information

- On ENBREL, go to:
  www.enbrel.com
- On RA, go to:
  http://www.arthritis.org/conditions/DiseaseCenter/ra.asp
- On JRA, go to:
  http://www.arthritis.org/conditions/DiseaseCenter/jra.asp
- On psoriatic arthritis, go to:
  http://www.arthritis.org/conditions/DiseaseCenter/psoriatic_arthritis.asp
  www.psoriasis.org
- On types of drugs used to treat arthritis, go to:
  http://www.arthritis.org/conditions/DrugGuide/types.asp
- On insurance coverage and reimbursement for patients who use ENBREL, go to:
  http://www.enbrel.com/hcp/reimbursement/requirements.jsp
- On free products and services for patients offered through *Enliven* services for patients who use ENBREL, go to:
  www.enbrel.com and select *Enliven* Online.

References

[1] Arthritis Foundation® - Disease Center

[2] Arthritis Foundation® - Research

[3] Amgen Press Release, February 19, 2003, "Amgen Submits ENBREL® Four-Year Data Supporting Long-Term Inhibition of Bone and Joint Damage in RA"

[4] ENBREL in the News, January 16, 2002, "ENBREL® (etanercept) Is First Therapy Approved for Treatment of Psoriatic Arthritis"

[5] The Science of RA - Pathogenesis

[6] The Science of RA - Role of TNF

[7] The Science of RA - Mode of Action

[8] ENBREL® (etanercept) Product Information document, No. 10662-12, Issue date 10/02 (PDF)

[9] American College of Rheumatology Preliminary Definition of Improvement in Rheumatoid Arthritis, Reprinted from Arthritis and Rheumatism, vol. 38, No. 6, June 1995

[10] Amgen Press Release, June 14, 2002, "New Data Presented on ENBREL® (etanercept), Only Fully-Human TNF Soluble Receptor, Demonstrates Sustained Efficacy and Tolerability Up to 5 Years"

[11] "A Comparison of Etanercept and Methotrexate in Patients with Early Rheumatoid Arthritis," New England Journal of Medicine, Vol. 343:1586-1593, Nov. 30, 2002, No. 22

[12] About ENBREL - Tolerability Profile

[13] About ENBREL - Indications and Important Treatment Considerations

[14] ENBREL® Explained - "Why Must ENBREL Be Injected?"