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About Biologics

Anti-TNF

Description

Anti-tumor necrosis factor drugs are a class of drugs that have been used for more than 10 years. They are used worldwide to treat inflammatory conditions such as rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, Crohn's colitis, ankylosing spondylitis and psoriasis. These drugs are able to reduce inflammation and stop disease progression.

Fast Facts

Anti-TNF agents target an inflammation-causing substance called TNF.

These drugs can be used to treat several diseases, including RA, Crohn's and psoriasis.

They can alter the disease's effect on the body by controlling inflammation in joints, gastrointestinal tract and skin.

Uses

There are five anti-TNF drugs that have been approved by the U.S. Food and Drug Administration to treat moderate to severe RA that has not responded to one or more of the traditional disease-modifying anti-rheumatic drugs. To decrease side effects and costs, most patients with mild or moderate disease are treated with methotrexate before adding or switching to an anti-TNF agent.

Anti-TNFs can be used by themselves or in combination with methotrexate, hydroxychloroquine, leflunomide or sulfasalazine. Most clinical trials that had positive results in RA were done in patients taking methotrexate and an anti-TNF agent.

How It Works

TNF is a chemical produced by the immune system that causes inflammation in the body. In healthy individuals, excess TNF in the blood is blocked naturally, but in those who have conditions like RA,

higher levels of TNF in the blood lead to more inflammation, joint destruction and persistent symptoms. Anti-TNF Page 2

Dosing

The starting doses for RA are shown in **Table 1**. Anti-TNF medications may be given by injection under the skin (e.g., etanercept, adalimumab, certolizumab and golimumab) or by vein (e.g., infliximab). These medications must be kept in the refrigerator and warmed to room temperature before being injected. There are pamphlets and videos that can teach you how to give yourself an injection under the skin. Physicians, nurses, and pharmacists also are able to teach you.

The medicine can be injected into the thigh or abdomen. The site of injection should be rotated so the same site is not used multiple times. In the case of infliximab, the infusions are administered at a doctor's office or at an infusion center. These treatments could take up to 3 hours. Anti-TNF Page 3

TABLE 1: Comparison of anti-TNF drugs in RA Drug	**Usual Dosing Regimen**	**When to expect results**	**Methotrexate needed?**
Infliximab (*Remicade*®)	**Initially:** Given at the clinic or at an infusion center as an intravenous infusion (IV) at a dose of 3-5 mg/kg (according to body weight) at weeks 0, 2, and 6. **Maintenance:** IV infusions every 4-8 weeks. Dose may be increased to 5-10 mg/kg.	2-3 weeks	Yes
Etanercept (*Enbrel*®)	**Initially:** 50 mg once a week or 25 mg twice a week as a self-administered subcutaneous injection. **Maintenance:** Same	1-2 weeks	No
Adalimumab (*Humira*®)	**Initially:** 40 mg every other week as a self-administered subcutaneous injection. **Maintenance:** Same	2-3 weeks	Suggested, not required
Certolizumab (*Cimzia*®)	**Initially:** 400 mg on week 0, 2 and 4 as a self-administered subcutaneous injection. **Maintenance:** 200 mg every other	1-2 weeks	No

	week. *Note: Each 400 mg dose should be administered as 2 injections of 200 mg each.*		
Golimumab (*Simponi ®*)	**Initially:** 50 mg once per month as a self-administered subcutaneous injection. **Maintenance:** Same	1-2 weeks	Yes

Time to Effect

The time that it takes for the medication to have an effect may vary by patient. Most RA patients have reported a change in their symptoms after 2 or 3 doses.

Side Effects

The most common side effect seen with injectable drugs are skin reactions, commonly referred to as “injection site reactions.” The patients usually complain of a localized rash with burning or itching. These reactions can last up to a week. Infliximab has been associated with a severe allergic reaction with swelling of the lips, difficulty breathing and low blood pressure.

The most significant side effect is an increased risk for all types of infections, including tuberculosis (TB) and fungal infections. Some of these infections may be severe.

Patients should be tested for TB before starting therapy. The usual way of testing is with a skin test, but a blood test is also available. Hepatitis B testing may be recommended because unrecognized hepatitis B infection may worsen during treatment.

Anti-TNF medications should be stopped if the patient has a high fever or is being treated with antibiotics for an infection. Once the medication is stopped, it should not be restarted until the patient has discussed it with his or her doctor.

Long-term use of anti-TNF agents may increase the risk of cancers such as lymphoma and skin cancer. There are rare neurologic complications from the use of these medications. People who have a history of multiple sclerosis should not use them. People with significant heart failure should not be on anti-TNF therapy because of their heart disease could worsen.

Patients should talk to their doctors before getting any vaccines. Using these medications may make the vaccination less effective.

Refer to the package insert for more information.

Points to Remember:

Anti-TNF drugs are a new type of medication used to treat patients with inflammatory arthritis such as RA.

These therapies will not cure the disease, but they will make symptoms better and decrease further damage to joints.

Although they increase the risk for infections, proper screening techniques and frequent doctor visits can minimize this risk.

Information to Discuss With Other Healthcare Providers

These medications are expensive (more than $10,000 per year) but they are covered by most health care insurance plans. Ask your doctor about prescription assistance plans that can help you to get the medication at a lower price or free of charge. Anti-TNF Page 5

For More Information

Your physician may have patient education material on anti-TNF drugs. The American College of Rheumatology has compiled this list to give you a starting point for your own additional research. The ACR does not endorse or maintain these Websites and is not responsible for any information or claims provided on them. It is always best to talk with your rheumatologist for more information and before making any decisions about your care.

ACR Factsheet on Rheumatoid Arthritis, Psoriatic Arthritis, and Spondyloarthritis

www.rheumatology.org/practice/clinical/patients/diseases_and_conditions/index.asp

The Arthritis Foundation

www.arthritis.org

Biologic response modifiers – also known as biologics – are genetically engineered medications that are used to control immune response. They are created from a living organism, such as a virus, gene or protein, to simulate the body's natural response to infection and disease. Biologics target proteins, cells and pathways responsible for the symptoms and damage of rheumatoid arthritis and other types of inflammatory arthritis.Biologics were previously used for people whose arthritis has not responded adequately to traditional disease-modifying anti-rheumatic drugs (DMARDs), but now they are the first line of defense. Here are the main types of biological drugs:

TUMOR NECROSIS FACTOR INHIBITORS (TNF-INHIBITORS)

Works by blocking a protein called tumor necrosis factor, which is made by white blood cells. TNF is the chemical messenger of inflammation, causing joint inflammation and destruction.

Drugs: Certolizumab (Cimzia); Etanercept (enbrel); Golimumab (simponi); Adalimumab (Humira); and Infliximab (Remicade).

INTERLEUKIN-6 (IL-6) BLOCKER

Tocilizumab (Actemra) is an antibody that blocks the spot when interleukin-6 (IL-6) attaches to cells, to prevent inflammation.

Drug: Tocilizumab, a human monoclonal antibody, is given intravenously for about an hour once a month.

BIOLOGIC TARGETING B CELLS

Rituximab (Rituxan), first used to treat Non-Hodgkin's lymphoma, wipes out B-lymphocytes, [a type of white blood cell] involved in inflammation."

Drug: Rituximab is a mix of mouse and human monoclonal antibodies that require two 4- to 6-hour infusions two weeks apart every six to 12 months.

TARGETING T-CELLS

Abatacept works by acting on T-cells [a type of white blood cell]. It attaches to the surface of inflammatory cells, blocking any communication between them.

Drug: Abatacept is a fusion protein. It is given by a 30-minute infusion every two weeks for three doses, then every four weeks.

INTERLEUKIN-1 (IL-1) BLOCKER

Interleukin -1 is a protein that is a major player in inflammation, and Anakinra (Kineret) blocks the action of IL-1.

Drug: Anakinra is a man-made form of a specific kind of protein secreted by the immune cells called Il-1 receptor antagonist.

TOFACITINIB – THE NEW DRUG

Tofacitinib (Xeljanz) is one in a new class of drugs that inhibits Janus kinases, enzymes key to inflammation. It differs from other biologics because it targets RA from inside, not outside, the cells. But like biologics, it has a single target, the Janus kinases.

Drug: Unlike other biologics, Tofacitinib is a small molecule drug and can be taken orally.

All biologics carry a risk of infection.

NEW DRUG FOR RA

The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use has recommended approval of Benepali, a biosimilar of etanercept (Enbrel, Immunex, and Amgen), for treatment of rheumatoid arthritis (RA), psoriatic arthritis, axial spondyloarthritis, and plaque psoriasis.

Benepali is from Samsung Bioepis, a joint venture between Samsung Biologics and Biogen. It will be available as a 50-mg solution for injection.

First Enbrel Biosimilar Recommended for Approval in Europe

The agency recommended Benepali for use in combination with methotrexate for the treatment of moderate to severe active RA in adults who have an inadequate response to DMARDs including methotrexate. Benepali can be used alone in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate, the EMA said. Benepali is also indicated for severe, active, and progressive RA in adults not previously treated with methotrexate. "Benepali, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function," the EMA said.

In psoriatic arthritis, Benepali is indicated for the treatment of active and progressive psoriatic arthritis in adults who fail to respond adequately to DMARDs. "Etanercept has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease," the EMA said.

In cases of axial spondyloarthritis and ankylosing spondylitis, Benepali is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy, the EMA said.

Benepali is also indicated for adults with severe nonradiographic axial spondyloarthritis with objective signs of inflammation, as indicated by elevated C-reactive protein and/or magnetic resonance imaging evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs.

And in plaque psoriasis, the indication is for adults with moderate to severe plaque psoriasis who fail to respond to, who have a contraindication to, or who are intolerant to other systemic therapy, including ciclosporin, methotrexate, or psoralen and ultraviolet A light.

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