



## Biologic Treatments for Rheumatoid Arthritis

(also known as cytokine inhibitors, TNF inhibitors, IL-1 inhibitor, or Biologic Response Modifiers)

### Description

Biologics are new class of drugs that have been used since 1998 and have been studied for almost 10 years. Overall, they have been given to more than 600,000 people worldwide. A “biologic” drug copies the effects of substances naturally made by your body's immune system. Biologic agents are genetically engineered drugs – meaning that human genes that normally guide the production of these natural human immune proteins (i.e., an antibody to TNF) are used in non-human cell cultures to produce large amounts of a biologic drug. These drugs are given to lessen inflammation by interfering with biologic substances that cause or worsen inflammation. These new biologic agents can specifically affect some of the abnormalities of the immune system that lead to the joint inflammation and other abnormalities seen in rheumatoid arthritis and so help treat its symptoms.

### Uses

Biologic agents have been approved by the FDA to treat moderate to severe rheumatoid arthritis that has not responded to an adequate trial of one or more of the traditional disease modifying antirheumatic drugs (DMARDs). Because of their expense and side effects, most people with mild to moderate rheumatoid arthritis are treated with [methotrexate](#) before a biologic agent is used unless they are unable to take [methotrexate](#) because of side effects or other conditions.

Biologic agents may be used alone, but are often given in conjunction with other DMARDs (e.g., [methotrexate](#), [leflunomide](#), [hydroxychloroquine](#), [sulfasalazine](#)), to increase the benefit and limit potential side effects. When patients start biologic agents, they usually also remain on their current dose of nonsteroidal anti-inflammatory (NSAID) and/or corticosteroid (i.e., prednisone) medicines. Some of the TNF inhibitors have been approved for use in [juvenile arthritis](#), Crohn's colitis, [psoriatic arthritis](#), ankylosing spondylitis and psoriasis.



### How it works

Currently available biologic agents act as inhibitors of the cytokines IL-1 or TNF. Cytokines are messenger molecules made by many of the body's cells that act to excite other immune system cells. Interleukin-1 (L-1) and tumor necrosis factor (TNF) are made in large amounts in rheumatoid arthritis and other forms of inflammation. In these diseases, TNF or IL-1 act to increase inflammation, similar to the effect of gasoline on a fire. However, in rheumatoid arthritis TNF or IL-1 (the gasoline) acts to excite the inflamed joint (the fire). Hence, these cytokines amplify and worsen inflammation and joint damage. Biologic agents were made to specifically attach to TNF or IL-1 and inhibit or inactivate them. [Table 1](#) compares the different biologic drugs used in rheumatoid arthritis.

### Dosing

For rheumatoid arthritis, the starting doses have been established by large clinical trials and are shown in Table 2. Biologic agents must be given by an injection under the skin (etanercept (brand name Enbrel), adalimumab (brand name Humira) and anakinra (brand name Kineret)) or by intravenous (IV) infusion (infliximab (Remicade)). These medications must be stored in a refrigerator and warmed to room temperature prior to use. Patient education information and videos are available for the self injectable medicines. A nurse or physician can teach you about the medicine and how to give the injections. It often helps to bring a spouse or friend with you to learn how to do the injections. You can inject the medicine in the front of your thighs or abdomen. Injection sites should be rotated so that the same site is not used repeatedly. Most patients who fear self-injection are usually able to give these injections repeatedly with mild or no discomfort. Remicade infusions are either done through an IV line in the doctor's office or specialized infusion centers. These treatments usually take 2-3 hours, during which time the patient can rest, read, watch TV or do office work without discomfort.

### Time to effect

Biologic agents usually work quickly to relieve the symptoms and swelling associated with rheumatoid arthritis. Although the studies show that most patients will improve within 4-6 weeks of treatment, most patients receiving Enbrel, Humira, or Remicade will notice marked improvement after the first or second injection.

### Side effects

The most common side effects seen with the injectable medicines include skin reactions, which are called "injection site reactions." Skin reactions to injection occur in less than 30% of patients, and such patients usually complain of localized rash, burning, or itching at the site of injection. With Enbrel and Humira these skin reactions may last up to a week. Kineret injection skin reactions may last for 10-14 days before fading away without scar.

The most significant side effect of these medications is an increase the risk of all types of infections, including tuberculosis (TB). Before starting an anti-TNF medication a TB skin test is usually done. Treatment with these agents should be stopped while you have an active infection and are taking an antibiotic or if you have a high fever. Remicade can cause allergic reactions. There are rare neurologic complications from the anti-TNF medications and people with multiple sclerosis should not use them. (See [table 2](#) and package insert). People with significant congestive heart failure should not take the anti-TNF agents.



### Points to remember

Biologic agents represent a new kind of treatment for patients with inflammatory arthritis, like rheumatoid arthritis. They are expensive (usually over \$12,000 per year in the US), generally effective, well tolerated and quite safe in most patients, but do increase the risk of infections. Their safety can be enhanced by proper screening procedures (e.g., TB skin test) and periodic monitoring of blood tests by your doctor. Patients should request and read educational materials (including videos) from the doctor who prescribes these medicines. Watching instructional videos and having another person give you these injections can minimize the fear of self-injection.

### For more information

Your physician may have patient education material on biologic drugs. This information may come in the form of either pamphlets or videos written by either the Arthritis Foundation or the manufacturers of that product. For additional information please visit the following Web sites for patient information about rheumatoid arthritis or the use of biologic drugs:

ACR Factsheet on Rheumatoid Arthritis [www.rheumatology.org/public/factsheets/ra.asp](http://www.rheumatology.org/public/factsheets/ra.asp)

The Arthritis Foundation <http://www.arthritis.org>

**Table 1:** Comparison of Biologic Drugs in RA

	<b>Adalimumab (Humira)</b>	<b>Anakinra (Kineret)</b>	<b>Etanercept (Enbrel)</b>	<b>Infliximab (Remicade)</b>
<b>Inhibits what?</b>	TNF	IL-1	TNF	TNF
<b>Type of biologic</b>	Antibody	Receptor antagonist	Receptor	Antibody
<b>Drug Half-Life *</b>	12-14 days	6 hours	5 days	9 days
<b>How given</b>	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection	Intravenous infusion
<b>Given how often</b>	Every other week	Daily	Every week or twice weekly	Every 8 weeks
<b>Onset of benefit +</b>	2 -4 weeks	4-6 weeks	2-4 weeks	2-4 weeks
<b>Methotrexate needed? §</b>	Suggested, not required	No	No	Yes

\* Drug half-life: refers to how long it takes for the body to get rid of 1/2 the drug and indirectly measures of how long the drug stays in the body.

+ Onset: the time it takes for most patients to achieve a good response.

§ Although patients may receive these drugs with or without methotrexate, prescribing guidelines established by the FDA suggest that patients treated with Remicade (and possibly Humira) should also receive background methotrexate therapy.



**Table 2:** Biologic Drugs in RA: What are the side effects, doses, monitoring (testing) and costs?

Drug	Common Adverse Effects	Rare/Serious Toxicities	Safety Monitoring	Usual Dosing Regimens	Annual Cost*
Adalimumab (Humira®)	Injection site reactions, upper respiratory infections (colds, sinusitis, bronchitis, etc)	Bacterial infection (e.g., pneumonia or joint infection), unusual infections (tuberculosis or fungal infections), optic neuritis or multiple sclerosis, nerve disorders, worsening of heart failure	Initially, blood cell counts (CBC) and skin test for tuberculosis.  With continued use: CBC and chemistry tests for liver function every 3-6 months	Initially: 40 mg given once every two weeks as a self-administered subcutaneous injection.  Maintenance: same (40 mg subcutaneous every other week)  ** comes in a prefilled syringe	\$14,522
Anakinra (Kineret®)	Injection site reactions, headache, upper respiratory infections (colds, sinusitis, bronchitis, etc)	Pneumonia, skin or joint infections, very low white blood cell counts	Blood cell counts (CBC) every month x 6 months, then once every 3-6 months	100 mg given once a day as a self-administered subcutaneous injection. May be used with an automatic injector device (called Simpleject)  ** comes in a prefilled syringe	\$12,800
Etanercept (Enbrel®)	injection site reactions, upper respiratory infections (colds, sinusitis, bronchitis, etc)	Bacterial infection (e.g., pneumonia or joint infection), unusual infections (tuberculosis or fungal infections), optic	Initially, blood cell counts (CBC) and skin test for tuberculosis.  With continued	Initially: 50 mg given once a week or 25 mg given twice weekly as a self-administered subcutaneous injection.	\$15,436



Drug	Common Adverse Effects	Rare/Serious Toxicities	Safety Monitoring	Usual Dosing Regimens	Annual Cost*
		neuritis or multiple sclerosis, nerve disorders, worsening of heart failure	use: CBC and chemistry tests for liver function every 3-6 months	Maintenance: same  ** comes in prefilled syringe or can be mixed from power before use.	
Infliximab (Remicade®)	Infusion reactions (itching, hives, rash, nausea, headache), upper respiratory infections (colds, sinusitis, bronchitis, etc)	Anaphylaxis (severe allergic reactions with swelling of lips, difficulty breathing, low blood pressure), Bacterial infection (e.g., pneumonia or joint infection), unusual infections (tuberculosis or fungal infections), optic neuritis or multiple sclerosis, nerve disorders, worsening of heart failure	Initially, blood cell counts (CBC) and skin test for tuberculosis.  With continued use: CBC and chemistry tests for liver function every 3-6 months	Initially: given in the clinic or doctors office as an intravenous (IV) infusion at a dose of 3-5 mg/kg (according to your body weight) at weeks 0, 2, 6.  Maintenance: IV infusions every 4-8 weeks. If needed the dose may be increased to 5-10 mg/kg.	\$13,940-\$30,287

**Created December 2004**

Written by John J. Cush, MD and Reviewed by the American College of Rheumatology Communications and Marketing Committee.

*This patient fact sheet is provided for general education only. Individuals should consult a qualified health care provider for professional medical advice, diagnoses and treatment of a medical or health condition.*

© 2010 American College of Rheumatology