BIOLOGICS & What You Need to Know

RheumNow

Biologic are given to improve how your immune system works & helps to control your disease. They are highly specific genetic copies of human proteins, given as injections or infusions and are distinctly different from conventional DMARDs like MTX.

Table 1. Differences	Biologics	Conventional DMARDs (MTX)
History (Time on market)	New (5-18 yrs)	Old (18-75yrs)
How manufactured	Recombinant human proteins made in cultures	Chemical manufacture
How they work	Specific inhibition of a protein or cell type	Often unclear; multiple mechanisms
How it is given	Intravenous infusion or subcutaneous injection	Oral pill
Cost	Very expensive (variable insurance coverage)	Cheaper (covered by most insurance)
Available cheaper version	Biosimilars	Generics

Who Should Take a Biologic (or Not)

- Those with moderate-severely active disease (seeTable 2)
- After adequate treatment with methotrexate (DMARD)
- Those who are unable to take methotrexate
- When signs, symptoms of aggressive disease are present
- DON'T start a biologic if you have active, serious infection

Questions to Ask Your Rheumatologist

Why is a biologic drug right for me? For my lifestyle?
How is the biologic given? Who will give it? How often?
Which is most effective? Which is safest?
What about my current arthritis medicines, do I continue?
Patient a$$istance programs or Copay cards

Do's	Don'ts
Take injx @ room temp Ask what are the rules for stopping the biologic	Stop drug until Rheum OKs Use live virus vaccines-Shingles Take more than 1 biologic Throw biologic in trash/toilet

The Real Risks for Biologic Drugs

COMMON >10%	UNCOMMON1-3%	RARE < 1/1000
Colds, upper respiratory infections, sinusitis, sore throat bronchitis, Injection site reactions (skin)	Hospitalizable infection, severe infusion reactions	TB, unusual infection, reactivation Shingles or Hepatitis B; Cancer (lymphoma, skin,lung)

Table 2. Indications and Use of Currently Approved Biologic Therapies — 👍 = FDA approved

Name	Enbrel	Remicade	Humira	Simponi	Cimzia	Rituxan	Orencia	Actemra	Kineret	Stelara	Cosentyx
Generic	Etanercept	Infliximab	Adalimumab	Golimumab	Certolizumab	Rituximab	Abatacept	Tocilizumab	Anakinra	Ustekinumab	Secukinumab
Target	TNF	TNF	TNF	TNF	TNF	B cells	T cells	IL-6	IL-1	IL-12/23	IL-17
Rheumatoid arthritis	👍	👍	👍	👍	👍	👍	👍	👍	👍		
Early RA*	👍	👍	👍	👍		👍	👍	👍			
Psoriasis	👍	👍	👍							👍	👍
Psoriatic arthritis	👍	👍	👍	👍	👍						👍
Ankylosing spondylitis	👍	👍	👍	👍	👍						👍
Juvenile arthritis	👍		👍				👍	👍			
Systemic JIA								👍			
Crohn's disease		👍	👍		👍						
Ulcerative colitis		👍	👍	👍							

Table 3. Biologics Approved for Specific Diseases	
Rheumatoid Arthritis	Enbrel, Remicade, Humira, Cimzia, Simponi, Kineret, Rituxan, Orencia, Actemra
Psoriasis	Enbrel, Remicade, Humira, Stelara, Cosentyx
Psoriatic Arthritis	Enbrel, Remicade, Humira, Simponi, Cimzia, Cosentyx
Ankylosing Spondylitis	Enbrel, Remicade, Humira, Simponi, Cimzia, Cosentyx
Colitis	Remicade, Humira, Cimzia, (UC only Simponi)
Juvenile Arthritis	Enbrel, Humira, Orencia, Actemra

Table 4. Biologics Groups by Class (mechanism of action)

TNF inhibitors	IL-1 inhibitor	IL-6 inhibitor	B cell blocker	T Cell blocker	IL-17 inhibitor	IL-12/23 inhibitor
Enbrel Humira Remicade Cimzia Simponi	Kineret Ilaris Arcalyst	Actemra	Rituxan Benlysta	Orencia	Cosentyx	Stelara

Table 5. How Frequently Biologics are Taken						
Daily	Weekly	Every 2 Wks	Every 4 Wks	Every 8 Wks	Every 12 Wks	Yearly
Kineret	Enbrel SC Orencia SC Actemra SC	Humira SC Cimzia SC Actemra SC	Simponi SC Orencia IV Actemra IV Cosentyx SC Benlysta IV	Remicade IV Simponi Aria IV	Stelara SC	Rituxan IV
SC: subcutaneous injection IV: intravenous infusion						

	Humira	**Enbrel**	**Remicade**	**Simponi**	**Simponi Aria**	**Cimzia**	**Rituximab** (Rituxan)	**Abatacept** (Orencia) **IV**	**Abatacept** (Orencia) **SC**	**Tocilizumab** (Actemra) **IV**	**Tocilizumab** (Actemra) **SC**
How Given	injection	injection	infusion	injection	infusion	injection	infusion	Infusion	Infusion or Injection	Intravenous Infusion	Subcutaneous injection
Recommended Loading Dose	No	No	Weeks 0, 2, 6 infusions	No	Weeks 0, 4	400 mg SC initially	No	Weeks 0, 2, 4	May give IV ← loading	Weeks	No
Usual Dose (mg)	40 mg	25 or 50 mg	3-5 mg/kg*	50 mg	2 mg/kg	200 mg	1000 mg	500, 750, 1000	150 mg	162 mg	162 mg
Given How Often	Every other week	Once a week	Every 8 weeks	Every 4 weeks	Every 8 weeks	Every 2wks or 400 mg every 4wks	2 infusions 2 weeks apart[&]	Every 4 weeks	Once a week	Every 4 weeks	Weekly if <220 lbs. or Every 2wks if >220 lbs.
Prefilled syringe	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	NA	Yes
Pen injector device	Yes (Humira Pen)	Yes (Sureclick)	NA	Yes	NA	No	NA	NA	No	NA	No
Onset of benefit[+]	2 -6 weeks	2 -6 weeks	2 -6 weeks	2 -6 weeks	2 -6 weeks	2 -6 weeks	4-8 weeks after 2nd infusion	4-6 weeks	4-8 weeks	4-8 weeks	4-8 weeks
Methotrexate needed? [$]	Suggested, not required	No	Yes	Yes	Yes	No	Suggested, not required	No	No	No	No
Type of Biologic	Antibody	Receptor	Antibody	Antibody	Antibody	Antibody	Antibody	Inhibitor	Inhibitor	Antibody	Antibody
Inhibits or Targets	TNF	TNF	TNF	TNF	TNF	TNF	B cells	T cells	T cells	IL-6 receptor	IL-6 receptor
Drug Half-Life*	12-14 days	4.25 days	9 days	14 days	14 days	14 days	19 days	13 days	13 days	11-13 days	5=13 days

Drug	Most Common Side Effects	Is there an Infection Risk	What about Cancer?	Really Rare/Serious Things that Happen
Orencia	10-30%: headache; nausea; upper respiratory infections (colds, sinusitis, bronchitis, sore throat); Injection site reactions	Common: Colds, URI, UTI Uncommon < 3% risk of serious infections - pneumonia, cellulitis, diverticulitis, acute pyelonephritis. Rare risk TB or hepatitis B	Overall, cancers on Orencia were same as those on placebo. Bu few more lung cancers seen on Orencia than placebo	Rarely worsening of COPD/Emphysema. Acute infusion reactions are rare (<1%) with low blood pressure, shortness of breath, rash, nausea, flushes, hives, cough, itching, wheezes
Actemra	10-30%: headache; nausea; upper respiratory infections (colds, sinusitis, bronchitis, sore throat); Injection site reactions. Low blood counts, high cholesterol or increased liver enzymes.	Common: upper respiratory infections (colds, sinusitis, bronchitis, sore throat Uncommon: (3-5 out of 100) serious infections (pneumonia, cellulitis, shingles, kidney, gastroenteritis, diverticulitis, sepsis) Rare risk of TB reactivation	The risk of cancer was the same (~1%) for on Actemra or placebo	Serious infusion reactions are rare (<0.2%). There is a rare risk of colon perforations (<3 per 1000 Actemra patients) usually occurring in RA patients with diverticulitis
Rituxan	<10% upper respiratory tract infections, nasopharyngitis (sore throat), urinary tract infections or bronchitis. Infusion reactions in up to 25% with first infusions and decrease with later infusions	Common: <10% upper respiratory tract infections, nasopharyngitis (sore throat), urinary tract infections or bronchitis. Uncommon: Serious infections (pneumonia, cellulitis) in 2% of patients. Reactivation of hepatitis B or other viral infections is rare	Rituxan is used to treat several blood cancers. It is not known to cause secondary cancers	Severe infusion reactions (< 1%), reactivation of hepatitis B, very severe skin reactions (Stevens-Johnson syndrome) or a very rare risk (1 in 30,000) of progressive multifocal leukoencephalopathy (PML).
Kineret	Injection site reactions, headache, upper respiratory infections (colds, sinusitis, bronchitis, etc.)	Common: upper respiratory infections (colds, sinusitis, bronchitis, etc.) Uncommon risk of serious infections < 5% (pneumonia, cellulitis, joint infections)	RA patients had a 3 fold higher risk of lymphoma (compared to general population)	Severe injection (skin) reactions are rare Staph infections have been rarely seen. Rarely, very low white blood cell counts
Enbrel Humira Cimzia Simponi	upper respiratory infections (colds, sinusitis, bronchitis, sore throat, etc.); injection site reaction, headache, injections site reactions (in the skin)	Common: Colds, URI, UTI Uncommon: ≤ 3% per year risk of serious infections (like pneumonia, cellulitis, etc.) TB is risk is between 1/500 and 1/2000. Fungal or opportunistic infections are even more rare than TB	Overall, no increased risk of all cancers; but certain cancers are more common with TNF inhibitor (skin or lung cancer, lymphoma, leukemia)and are 2-3 times more common than seen in normal people but same as other RA patients	Lymphoma risk is ~1 in 1000. Other very rare events include, severe anemia or very low blood counts, optic neuritis, multiple sclerosis, neurologic disorders, lupus, psoriasis, worsening of heart failure, hepatitis B reactivation, increased liver enzymes
Remicade	Infusion reactions (itching, hives, rash, nausea, headache), upper respiratory infections (colds, sinusitis, bronchitis, etc.)	Common: Colds, URI, sore throat, bronchitis, UTI Uncommon: ≤ 5% per year risk of serious infections (like pneumonia, cellulitis). TB is risk is 1/500 to 1/2000. Fungal or opportunistic infections are more rare	Overall, no increased risk of all cancers; but certain cancers are more common with TNF inhibitor (skin or lung cancer, lymphoma, leukemia)and are 2-3 times more common than seen in normal people but same as other RA patients	Rarely anaphylaxis (severe allergic reactions with swelling of lips, difficulty breathing, low blood pressure), Bacterial infection (cellulitis, pneumonia or joint infection), unusual infections (tuberculosis or fungal infections), optic neuritis or multiple sclerosis, nerve disorders, worsening of heart failure

Patient Guide to Biologics

Introduction - You are considering a "biologic" medicine to treat your condition. Don't let the term "biologic" scare you; all this means is that these medications are derived from animal or human proteins and not from chemicals Biologics are highly useful medications that have been extensively studied since the mid 1990's. Biologics were first approved by the Food and Drug Administration (FDA) in 1998 and since, have become popular treatments for many inflammatory conditions, including rheumatoid arthritis (RA), psoriasis, psoriatic arthritis (PsA), ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), inflammatory bowel disease or "colitis" (e.g., Crohn's disease or ulcerative colitis) and lupus (SLE) (see Table 2).

Each of these novel drugs took almost 10 years to develop at an average cost of nearly $1 billion dollars. By the time a biologic becomes FDA approved it will have been studied in several clinical trials ("drug studies"), in roughly 1000-4000 patients and been proven to have a track record of safety. This means that for each FDA approved biologic, the potential benefits have been shown to far outweigh the risks or safety concerns. It is important to know that your disease (e.g., RA) imposes far more risk and danger (if untreated) than any drug that would be offered to you.

How Biologics Work - Disease-modifying drugs (called "DMARDs") are medications that change the course of disease (not just cover-up signs of inflammation). Biologic drugs are one kind of DMARD. They are given to control inflammation or decrease an amplified disordered immune process. DMARDs may also come in the form of pills (oral drugs) and are called conventional (or synthetic) DMARDs (includes drugs like methotrexate [MTX], sulfasalazine, Plaquenil). Biologic DMARDs are different as they are usually given as injections or infusions. Biologic DMARDs differ from other conventional (pill) DMARDs (like methotrexate) the in 5 main ways:

Table 1. Differences	Biologics	Conventional DMARDs (MTX)
History (Time on market)	New (5-18 yrs)	Old (18-75yrs)
How manufactured	Recombinant human proteins made in cultures	Chemical manufacture
How they work	Highly specific inhibition of a normal human protein or cell type	Often unclear; usually multiple immune cells affected to lessen inflammation
How it is given	Intravenous infusion or subcutaneous injection	Oral pill
Cost	Very expensive (variable insurance coverage)	Cheaper (covered by most insurance)
Available cheaper version	Biosimilars	Generics

Biologics cost much more than most drugs because of the high cost of inventing, manufacturing and studying them. Biologics are genetic copies of natural human proteins that are manufactured to correct an over active immune response that doesn't turn off – and builds to cause an inflammation and damage to the joints, skin or gut. Thus, biologics can inhibit or interfere with a specific cell type (e.g., B cells) or immune substance (such as cytokines).

Cytokines are normal messenger molecules that help cells "talk" to each other. Cytokines deliver specific start or stop signals to guide the immune response. However, an excess of cytokines may cause certain diseases. Biologics differ in the cytokine it targets, such as tumor necrosis factor (TNF) or interleukins (IL), such as IL-1 or IL-6. TNF, IL-1 and IL-6 are inflammation messenger cytokines, meaning they can spark or amplify inflammation or an immune response. Biologic inhibitors of these cytokines would thus, reduce inflammation. For instance, Enbrel (etanercept) is one of several TNF inhibitor biologics. In the case of arthritis, the joint is on fire, TNF is the gasoline on the fire and Enbrel specifically removes the gasoline (TNF). By reducing inflammation or immune cell activity, biologic drugs can lessen symptoms and improve outcomes.

Biologics must be given by intravenous infusion or subcutaneous injection (like an insulin shot). They are given this way because these complex proteins would not survive digestion by stomach acid enzymes if taken by mouth. Biologics are unique in that they are highly specific for their target and that inhibition of that target interferes with and turns down or off the uncontrolled immune system that drives the disease.

Table 2. Indications and Use of Currently Approved Biologic Therapies

= FDA approved

Name	Enbrel	Remicade	Humira	Simponi	Cimzia	Rituxan	Orencia	Actemra	Kineret	Ilaris	Stelara	Cosentyx
Generic	Etanercept	Infliximab	Adalimumab	Golimumab	Certolizumab	Rituximab	Abatacept	Tocilizumab	Anakinra	Canakinumab	Ustekinumab	Secukinumab
Target	TNF	TNF	TNF	TNF	TNF	B cells	T cells	IL-6	IL-1	IL-1	IL-12/23	IL-17
Rheumatoid arthritis	👍	👍	👍	👍	👍	👍	👍	👍	👍			
Early RA*	👍	👍	👍	👍		👍	👍	👍				
Psoriasis	👍	👍	👍								👍	👍
Psoriatic arthritis	👍	👍	👍	👍	👍							👍
Ankylosing spondylitis	👍	👍	👍	👍	👍							👍
Juvenile arthritis	👍		👍				👍	👍				
Systemic JIA								👍		👍		
Crohn's disease		👍	👍		👍							
Ulcerative colitis		👍	👍	👍								

*Studies done to prove the efficacy of this biologic in patients with early RA (usually with less than 1 year of symptoms)

Who Should Get a Biologic - Biologic agents are used as routine treatments for rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and inflammatory bowel disease (e.g., colitis). Most biologics are used to treat patients with moderate to severe disease that has not responded to an adequate course of usual or traditional drug therapy. For many diseases, a synthetic DMARD, like MTX, is typically the initial treatment for several reasons: they have been around a long time (their safety and benefits have been proven), they are cheaper and are easily taken. If the disease remains active despite DMARD or MTX treatment, then your doctor may consider using a biologic drug.

Biologics have been studied, developed and approved for use in patients with active disease and a poor response to MTX (or similar conventional DMARD). While biologics are newer, they have not been shown to be more effective than methotrexate alone. Biologics should be considered when:

- someone is unable to take methotrexate
- there is evidence of active disease (despite an adequate trial [more than 6 weeks] of MTX)
- signs or symptoms of aggressive disease and poorer outcomes are present.

If a biologic therapy is being considered, ask your physician to explain why such therapy is necessary (or not). No one biologic is superior to another and there are few studies that directly compare one biologic to another. Since all are proven be effective, the "right" biologic for you may be based on several factors:

- Your (patient) preference or doctor experience
- Your insurance may have a "preferred" list of biologics
- The drug with lowest risk to you (this may vary with each individual)
- The drug that best suits your lifestyle or preferences (for instance, you can choose IV infusions or injectables [prefilled syringes or pen-like autoinjectors])
- Other medical conditions (infections, hepatitis, skin conditions) that may steer you away from one biologic to get the best response at lowest risk
- Frequency of injections (some are given either daily, once weekly, once or twice monthly or every 8 or 12 weeks – see Table 5 and 7).

Biologic Choices - There are 9 approved biologics for RA, 6 for Psoriasis & PsA, 5 for Ankylosing Spondylitis and 5 for colitis. These fall into different classes based on how they work (or "mechanism of action"; MOA). Below are lists of available biologics according to the disease they treat (Table 2,3) and MOA (Table 4).

Table 3. Biologics Approved for Specific Diseases

Rheumatoid Arthritis	Enbrel, Remicade, Humira, Cimzia, Simponi, Kineret, Rituxan, Orencia, Actemra
Psoriasis	Enbrel, Remicade, Humira, Stelara, Cosentyx
Psoriatic Arthritis	Enbrel, Remicade, Humira, Simponi, Cimzia, Cosentyx
Ankylosing Spondylitis	Enbrel, Remicade, Humira, Simponi, Cimzia, Cosentyx
Colitis	Remicade, Humira, Cimzia, (UC only Simponi)
Juvenile Arthritis	Enbrel, Humira, Orencia, Actemra
Systemic JIA	Actemra, Ilaris
Lupus	Benlysta
Gout	Krystexxa

Table 4. Biologics Groups by Class (mechanism of action)

TNF inhibitors	IL-1 inhibitors	IL-6 inhibitor	B cell blockers	T Cells blocker	IL-17 inhibitor	IL-12/23 inhibitor
Enbrel Humira Remicade Cimzia Simponi	Kineret Ilaris Arcalyst	Actemra	Rituxan Benlysta	Orencia	Cosentyx	Stelara

Table 5. How Frequently Biologics Are Taken

Daily	Weekly	Every 2 Wks.	Every 4 Wks.	Every 8 Wks.	Every 12 Wks.	Yearly
Kineret SC	Enbrel SC Orencia SC Actemra SC	Humira SC Cimzia SC Actemra SC	Simponi SC Orencia IV Actemra IV Cosentyx SC Benlysta IV	Remicade IV Simponi Aria IV	Stelara SC	Rituxan IV

SC: subcutaneous injection IV: intravenous infusion

What? I have to Inject Myself? To many, the notion of giving yourself an injection seems extreme or undesirable. Biologics need to be given either by intravenous (IV) infusion or by injection. These injections do not go deep into muscle, instead they go into the subcutaneous fat just under the skin. Many people like you initially are scared or concerned about whether or not they can do this, but the majority find that after 1 or 2 injections, injections an easy thing to do with a lot less pain than you experience when getting blood drawn. Self-injection is not difficult or painful for most. Realize that there are more than 6 million Americans with diabetes who self-inject an insulin shot once or twice daily with ease and without complaint. Like insulin injections, your biologic injections may well be life-saving. If you have concerns about using injectable biologics, there are several options you should discuss with your doctor:

- You can receive training on how to give a subcutaneous (SC) injection from the clinic nurse, print materials (that come with the drug), online videos
- You can receive injections from someone else: a friend, spouse, care-giver or neighbor (they will need to have the same training)
- Some injections can be given less frequently in the clinic, by the clinic nurse
- Some biologics can be given as an injection or IV infusion – you could opt to receive monthly IV infusions instead of weekly or biweekly self-injections
- Some biologics come as "Pen" or autoinjectors (wherein you only need to press a button, you don't see the needle, and the injection is automatic)

Ask your doctor if you will take a biologic alone or in "combination" with methotrexate (MTX) or other DMARDs (e.g., Arava, Plaquenil) to maximize responses. When a biologic drug is started, your doctor will usually continue the previously used arthritis medicines (such as MTX, or nonsteroidal anti-inflammatory drugs [NSAIDs], prednisone, other pain medicines) until a good response is achieved. At the beginning, when your disease is most active, it is difficult to tell just how much medicine is needed to get control. Thus, it is common to use multiple medicines to achieve control or remission. Once this is achieved, you can discuss with your physician, which medicines, if any, may be reduced or stopped. Each class of biologic is discussed individually in the pages that follow. The following is a checklist of things that need to be done before or while on a biologic:

- Blood tests to ensure the safety of the biologic (blood counts [CBC], chemistry [liver, kidney] tests, inflammation labs [CRP or "sed rate"]
- A tuberculosis (TB) test (done as a blood test or a skin test called "PPD") - several biologics may rarely reactivate TB or increase TB risk
- Chest X-ray (especially if you already have lung disease or are having symptoms like cough, shortness of breath)
- Receive immunizations or have immunizations updated (you may receive many vaccines while on biologics – but you CANNOT receive live virus vaccines)
- Do not combine biologics or take more than one biologic drug at a time

How to Dispose of Biologic Syringes and Needles - Once a biologic injection is given, the syringe & needle or pen-like auto-injector needs to be safely disposed of into a puncture-resistant container for needles and syringes. These containers are called "sharps containers" and may be available from the clinic or pharmacy. Instead you can also use a large, washed-out, heavy plastic detergent or bleach bottle or wide-mouthed 2-liter soda bottle with screw caps. The syringes and "sharps" containers should be kept out of the reach of children. Syringes and injectors should not be reused or taken apart. Do not throw these in the garbage or in the toilet. Once a sharps container is full you can talk to the pharmacy, manufacturer or doctor's office about their disposal.

For More Biologic Information - You can also get more information about a biologic from the manufacturers website (example: *DRUGNAME.com*) or other sources below. Each biologic comes with prescribing information written for patients, usually referred to as a "Medication Guide". The Medication Guide has information about side effects, how to take the biologic, who should or should not take the biologic and more. Prescription medicines often come with a folded sheet of information about the drug. Note that at the end/bottom of that sheet you will find the "Medication Guide" written specifically for patients.

Table 6. Biologic information from the manufacturer

Generic name	Trade name	Manufacturers Website	Biologic Help Phone-line Number
Abatacept	Orencia	http://www.orencia.com/	1-800-ORENCIA
Adalimumab	Humira	https://www.humira.com/	1-800-4HUMIRA (1-800-448-6472).
Anakinra	Kineret	http://www.kineretrx.com/	1-866-547-0644
Belimumab	Benlysta	http://www.benlysta.com/	1-877-423-6597
Canakinumab	Ilaris	http://ilaris.com/	1-877-452-7471
Certolizumab	Cimzia	http://cimzia.com/	1-866-424-6942
Etanercept	Enbrel	https://www.enbrel.com/	1-888-4ENBREL (1-888-436-2735)
Golimumab	Simponi	http://www.simponi.com/	1-800-JANSSEN (1-800-526-7736)
Infliximab	Remicade	http://www.remicade.com/	1-800-JANSSEN (1-800-526-7736)
Pegloticase	Krystexxa	http://krystexxa.com/	1-888-579-7839
Rituximab	Rituxan	http://www.rituxan.com/	1-877-474-8892
Rilonacept	Arcalyst	http://arcalyst.com/	
Secukinumab	Cosentyx	http://www.cosentyx.com/	1-888-669-6682
Tocilizumab	Actemra	https://www.actemra.com/	1-800-ACTEMRA
Ustekinumab	Stelara	http://www.stelarainfo.com/	1-800-JANSSEN (1-800-526-7736).

Your rheumatologist or clinic may have additional patient education materials on recommended biologic drugs. This information may come in the form of pamphlets, handouts or videos from by the doctor, Arthritis Foundation or the manufacturer of that biologic.

For additional information please visit the following Web sites for patient information about rheumatoid arthritis or the use of biologic drugs:

- http://www.rheumatology.org/i-am-a/patient-caregiver/treatments
- http://www.arthritis.org/living-with-arthritis/treatments/medication/drug-guide/search-by-class.php?drugclass=Biologics
- http://www.uptodate.com/contents/rheumatoid-arthritis-treatment-beyond-the-basics
- http://www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis/ra-treatment/

Table 7. Comparison of Biologic Drugs for Rheumatoid Arthritis

Generic Name (Trade Name)	**Adalimumab** (Humira)	**Etanercept** (Enbrel)	**Infliximab** (Remicade)	**Golimumab** (Simponi)	**Golimumab** (Simponi Aria)	**Certolizumab** (Cimzia)	**Anakinra** (Kineret)	**Rituximab** (Rituxan)	**Abatacept** (Orencia) **IV**	**Abatacept** (Orencia) **SC**	**Tocilizumab** (Actemra) **IV**	**Tocilizumab** (Actemra) **SC**
How Given	Subcutaneous injection	Subcutaneous injection	Intravenous infusion	Subcutaneous injection	Intravenous infusion	Subcutaneous injection	Subcutaneous injection	Intravenous infusion	Intravenous Infusion	Infusion or Injection	Intravenous Infusion	Subcutaneous injection
Recommended Loading Dose	No	No	Weeks 0, 2, 6 infusions	No	Weeks 0, 4	400 mg SC initially	No	No	Weeks 0, 2, 4	May give IV ← loading	Weeks	No
Usual Dose (mg)	40 mg	25 or 50 mg	3-5 mg/kg*	50 mg	2 mg/kg	200 mg	100 mg	1000 or 500 mg	500, 750, 1000	150 mg	162 mg	162 mg
Given How Often	Every other week	Once a week	Every 8 weeks	Every 4 weeks	Every 8 weeks	Every 2 weeks or 400 mg q4wks	Daily	2 infusions given 2 weeks apart[&]	Every 4 weeks	Once a week	Every 4 weeks	Weekly if <220 lbs. or Every 2wks if >220 lbs.
Prefilled syringe	Yes	Yes	NA	Yes	NA	Yes	Yes	NA	NA	Yes	NA	Yes
Pen injector device	Yes (Humira Pen)	Yes (Sureclick)	NA	Yes	NA	No	No	NA	NA	No	NA	No
Onset of benefit[+]	2 -6 weeks	2 -6 weeks	2 -6 weeks	2 -6 weeks	2 -6 weeks	2 -6 weeks	4-8 weeks	4-8 weeks after 2nd infusion	4-6 weeks	4-8 weeks	4-8 weeks	4-8 weeks
Methotrexate needed? [$]	Suggested, not required	No	Yes	Yes	Yes	No	No	Suggested, not required	No	No	No	No
Type of Biologic	Antibody	Receptor	Antibody	Antibody	Antibody	Antibody	Receptor antagonist	Antibody	Inhibitor	Inhibitor	Antibody	Antibody
Inhibits or Targets	TNF	TNF	TNF	TNF	TNF	TNF	IL-1	B cells	T cells	T cells	IL-6 receptor	IL-6 receptor
Drug Half-Life*	12-14 days	4.25 days	9 days	14 days	14 days	14 days	6 hours	19 days	13 days	13 days	11-13 days	5=13 days

*Drug half-life: refers to how long it takes for the body to get rid of ½ the drug and indirectly measures of how long the drug stays in the body.

[&] Rituximab treatments may be repeated every 6-18 months; most patients need retreatment every 12 months

+ Onset: the time it takes for most patients to notice a significant change in symptoms indicating a good response to the biologic.

$ Although patients may receive these drugs with or without methotrexate, prescribing guidelines established by the FDA suggest that these biologics may be more effective or safer if used with background methotrexate therapy (this applies to Remicade, Humira, Simponi and Rituxan).

Table 7. Drug Safety Concerns with Biologic Drugs for Rheumatoid Arthritis

Drug	Most Common Side Effects	Is there an Infection Risk	What about Cancer?	Really Rare/Serious Things that Happen	Safety Monitoring
Orencia	10-30%: headache; nausea; upper respiratory infections (colds, sinusitis, bronchitis, sore throat); Injection site reactions	Common: Colds, URI, UTI Uncommon < 3% risk of serious infections - pneumonia, cellulitis, diverticulitis, acute pyelonephritis. Rare risk of reactivation of TB or hepatitis B	Overall, cancers on Orencia were same as those on placebo. But a few more lung cancers seen on Orencia than placebo	Rarely worsening of COPD/Emphysema. Acute infusion reactions are rare (<1%) with low blood pressure, shortness of breath, nausea, flushing, urticaria, cough, itching, rash, wheezing.	No special monitoring of blood tests required; most physicians will do periodic (every 3-6mos) labs to ensure safety – CBC, chemistry. Patients should avoid pregnancy.
Actemra	10-30%: these side effects are a bit more than usually occur in healthy people, thus may be from the drug: headache; nausea; upper respiratory infections (colds, sinusitis, bronchitis, sore throat); Injection site reactions. Low blood counts, high cholesterol or increased liver enzymes.	Common: upper respiratory infections (colds, sinusitis, bronchitis, sore throat Uncommon: (3-5 out of 100) serious infections like pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis. Rare risk of TB reactivation	The risk of cancer was the same (~1%) for on Actemra or placebo	Serious infusion reactions are rare (<0.2%). There is a rare risk of colon perforations (<3 per 1000 Actemra patients) usually occurring in RA patients with diverticulitis	Lab tests to check blood counts (CBC) and Liver enzymes monthly x 2, then every 3 months. and cholesterol/ lipids should be checked at 4 and 8 weeks, then every 6 months.
Rituxan	<10% upper respiratory tract infections, nasopharyngitis (sore throat), urinary tract infections or bronchitis. Infusion reactions in up to 25% with first infusions and decrease with later infusions	Common: <10% upper respiratory tract infections, nasopharyngitis (sore throat), urinary tract infections or bronchitis. Uncommon: Serious infections (pneumonia, cellulitis) are seen in 2% of patients. Reactivation of hepatitis B or other viral infections rarely occurs	Rituxan is used to treat several blood cancers. It is not known to cause secondary cancers	Severe infusion reactions (< 1%), reactivation of hepatitis B, very severe skin reactions (Stevens-Johnson syndrome) or a very rare risk (1 in 30,000) of progressive multifocal leukoencephalopathy (PML).	Patients should be monitored for infusion reactions. Vaccines should be updated and tests for hepatitis should be done before the first infusion. Blood counts (CBC) should be done every 3-6 months.
Kineret	Injection site reactions, headache, upper respiratory infections (colds, sinusitis, bronchitis, etc)	Common: upper respiratory infections (colds, sinusitis, bronchitis, etc.) Uncommon risk of serious infections < 5% (pneumonia, cellulitis, joint infections, etc.)	RA patients had a 3-fold higher risk of lymphoma (compared to general population)	Severe skin reactions are rare Staph infections have been rarely seen. Rarely, very low white blood cell counts	Blood cell counts (CBC) should be done 1 month after starting then every 6 months
Enbrel Humira Cimzia Simponi	upper respiratory infections (colds, sinusitis, bronchitis, sore throat, etc); injection site reaction, headache, injections site reactions (in the skin)	Common: Colds, URI, UTI Uncommon: ≤ 3% per year risk of serious infections (like pneumonia, cellulitis, etc) TB is risk is between 1/500 and 1/2000. Fungal or opportunistic infections are even more rare than TB	Overall, no increased risk of all cancers; but certain cancers are more common with TNF inhibitor use (skin cancer, lymphoma, leukemia, lung cancer) and were 2-3 times more common than the general population but not higher than other RA patients	Lymphoma risk is ~1 in 1000. Other very rare events include, severe anemia or very low blood counts, optic neuritis, multiple sclerosis, neurologic disorders, lupus, psoriasis, worsening of heart failure, hepatitis B reactivation, increased liver enzymes	Monitor for symptoms of infection or TB; repeat TB test once & if risk changes. Most physicians will do periodic (every 3-6mos) labs to ensure safety – CBC, liver enzymes, chemistry. Patients should avoid pregnancy.
Remicade	Infusion reactions (itching, hives, rash, nausea, headache), upper respiratory infections (colds, sinusitis, bronchitis, etc)	Common: Colds, URI, sore throat, bronchitis Uncommon: ≤ 5% per year risk of serious infections (like pneumonia, cellulitis, etc.) TB is risk is between 1/500 and 1/2000. Fungal or opportunistic infections are even more rare than TB	Overall, no increased risk of all cancers; but certain cancers are more common with TNF inhibitor use (skin cancer, lymphoma, leukemia, lung cancer) and were 2-3 times more common than the general population but not higher than other RA patients	Rarely 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	Monitor for symptoms of infection or TB; repeat TB test once & if risk changes. Blood cell counts (CBC) and chemistry tests for liver function should be done initially and every 3-6 months

TNF Inhibitors: there are 5 FDA-approved TNF inhibitors (also called "anti-TNF" or "TNF blockers") - Enbrel, Remicade, Humira, Cimzia, Simponi

How they work: TNF inhibitors to inhibit a specific protein called tumor necrosis factor (TNF). In patients with RA or psoriasis, high levels of TNF may be found in the joints, skin and circulation. TNF is a normal messenger molecule but when made in excess causes or worsens inflammation, similar to the effect of gasoline on a fire. Hence, TNF (the gasoline) acts to excite the inflamed joint or skin (the fire). These biologic durgs (see above) are given to reduce the inflammation.

Indication: All of the TNF inhibitors have been approved for use in patients with moderate to severe, active RA, not responding to MTX or other DMARD therapy. Enbrel and Humira are approved for use in juvenile arthritis (JIA). These biologics may be used in those with many swollen joints and signs of aggressive disease (nodules, elevated "sed rate", positive tests for rheumatoid factor or CCP antibodies or joint damage by X-ray). These drugs may be used alone or in combination with MTX or other DMARDs. TNF inhibitor therapy often works best when used in combination with methotrexate.

How it is given: TNF blocking drugs must be given either by an injection under the skin (Enbrel, Humira, Simponi, Cimzia) or by intravenous (IV) infusion (Remicade). Enbrel is given once weekly, Humira and Cimzia are given every 2 weeks and Simponi every 4 weeks. These medications must be stored in a refrigerator and warmed to room temperature prior to use. Information about this biologic, how it is given and the side effects can be found in the MEDICATION GUIDE (found on the manufacturers website or attached to the box the medicine comes in). A nurse or physician can teach you about how, when and where to give the injection into the subcutaneous fat. Self-injection uses a small, skinny 25 or 27-gauge needle (like an insulin syringe & needle) and is supplied as either a prefilled syringe or automatic injector device. It may help to bring a spouse or friend with you when learning how to do the injections. You should rotate the injection sites between your right and left thigh or lower abdomen. Infliximab (Remicade) is given as an IV infusion in the doctor's office or at designated infusion centers. Infliximab treatments are initially given at weeks 0 (start), 2 and 6, and then are usually given every 6 to 8 weeks. Infusions take 2-3 hours to administer. <u>During this time the patient can rest, read, watch TV or do office work without discomfort</u>. Some centers prefer to pre-medicate their infliximab patients with acetaminophen (Tylenol) and antihistamine (eg, Benadryl or Zyrtec) to reduce the low risk of allergic reactions during the infusion.

Time to effect: The TNF inhibitors are remarkable for their quick responses. Many patients feel improvement after the first few treatments. Joint symptoms and swelling often improve within 2-6 weeks of starting treatment and maximal responses are seen by weeks 12-16. Studies show that roughly 60% will be "responders" to anti-TNF therapy. If no response is seen in the first 2-3 months, many rheumatologists will increase the dose, increase the frequency or switch to another biologic drug.

Side Effects: The most common side effects seen with the TNF inhibitors are skin reactions during or after the injection ("injection site reactions"), which occur in less than 5-30% of patients. The most common injection reactions include skin stinging or burning during the injection, rash, itching or hives (welts). Reactions may also occur during infliximab intravenous infusions; with few patients complaining of headache, fever, rash, chest tightness, itching or low blood pressure. Non-serious infections may occur with the TNF inhibitors - bronchitis, sinusitis, sore throat or urinary tract infections. There is a small but significant risk of serious infections, including pneumonia, joint or skin infections (cellulitis) that may occur in <5% of patients. Tuberculosis (TB) and unusual "opportunistic" infections are rare. A TB blood test or skin test (called a "PPD") must be done before starting a TNF inhibitor. There is a less than 1 in 1000 risk of developing lymphoma (lymph node cancer), lung or skin cancers while taking TNF inhibitor therapy. However, RA patients (not on TNF blockers) also have a higher risk of these same cancers. It is unclear if using these biologics will increase the risk of cancer above that imposed by the inflammatory disease (RA) itself. There are <u>very rare</u> complications of TNF inhibitor use, including drug-induced lupus, severe skin reactions, Shingles, and neurologic conditions like multiple sclerosis or optic neuritis. People with poorly controlled congestive heart failure should not take the anti-TNF agents. If any of these side effects concern or apply to you, discuss them with your physician before you decide to not take the medicine. Note: not treating uncontrolled, chronic inflammation associated with a disease like RA has vastly higher risks and bad outcomes compared with the few scary, dangerous, rare or very rare risks associated with TNF inhibitors.

Costs: TNF inhibitors are very expensive. Even with insurance coverage, copays on these medicines may vary widely but may be unaffordable to some. Financial assistance may be available as patient assistance programs or copay card programs through the manufacturer. Those with very low income may be eligible to receive free medicine from the manufacturer or special foundations – ask your doctor or call the company help line.

Patient instructions: TNF inhibitor biologics are only available by prescription and can be given as a self-administered subcutaneous injection or IV infusion. Tell your doctor about side effects that worry you, bother you or do not go away. Do not take any "live" virus vaccines (like the Shingles vaccine) while on a TNF drug. Your doctor needs to know if you have a current active infection, fever, open sores or wounds, or if you are taking another biologic treatment. Prior to beginning treatment tell your doctor if you've had a recent hospitalization, have a history of recurrent infections, pneumonia, tuberculosis, positive TB skin tests (PPD), lung problems (like emphysema, COPD), uncontrolled heart failure, hepatitis or liver disease, multiple sclerosis, HIV, serious medical problems, or plan to become pregnant or undergo major surgery.

Kineret (Anakinra)

How it works: Kineret is a genetic replica of a naturally produced antagonist (blocker or inactivator) of interleukin-1 (IL-1). IL-1 is a cytokine (intracellular messenger) that acts to promote inflammation in the joints, skin, etc. IL-1 increases inflammation, similar to the effect of gasoline on a fire. Thus, IL-1 (the gasoline) acts to excite the inflamed joint (the fire). Kineret is very specific and only blocks IL-1.

Indication: Kineret is approved for use in adult patients with moderate to severely active RA, after failing an adequate trial of MTX or other DMARD therapy. Kineret is also approved for use in children with CAPS (Cryopyrin-Associated Periodic syndromes) or NOMID (Neonatal-Onset Multisystem Inflammatory Disease). Kineret is not FDA approved for, but is often used to treat, very rare conditions like Still's disease (systemic juvenile idiopathic arthritis) and other autoinflammatory diseases.

How it is given: Kineret is given once daily as an injection under the skin (subcutaneous injection). It must be stored in a refrigerator and warmed to room temperature (for 15-30 minutes) prior to use. Information about this biologic, how it is given and the side effects can be found in the MEDICATION GUIDE (found on the manufacturers website or attached to the box the medicine comes in). A nurse or physician can teach you about how, when and where to give the injection into the subcutaneous fat. Self-injection uses a small, skinny 25 or 27-gauge needle (like an insulin syringe and needle) and is supplied as a prefilled syringe.

Time to effect: Kineret may take weeks to months before patients begin to notice improvement. In RA, Kineret begins to work usually after week 4 and before week 12. In many patients skin reactions will occur from the start but will resolve after 4 weeks. During this period no clinical improvement will be expected, but once the skin reactions subside, the clinical benefits become noticeable. Responses to Kineret may be much faster in CAPs or systemic JIA (Still's disease). Not every patient will respond to Kineret therapy. If no response is seen in the first 2-3 months, many rheumatologists will usually switch to another drug.

Side Effects: The most common side effects seen with Kineret are skin reactions, often called "injection site reactions" or "ISRs". Skin reactions to the Kineret injection can be seen in 30-70% of patients. These appear as round, red, nonpainful spots usually within 2 days of the injection and may last up to 2 weeks before they become faint, flaky and fade away without leaving a scar. Rarely do they cause burning, or itching. Also common is the small risk of nonserious infections - like bronchitis, sinusitis, sore throat or urinary tract infections. Such infections are common in all of us, but may be more frequent with inflammatory diseases (like RA), prednisone use or Kineret use. Less than 5% of patients may develop a serious infection. Many of the rare, serious side effects seen with the TNF inhibitors (like Enbrel or Humira) are not seen with Kineret – especially, TB, opportunistic infections, heart failure, Shingles, lupus, or multiple sclerosis. If any of these side effects concern or apply to you, discuss them with your physician before you decide to not take the medicine. Note: not treating uncontrolled chronic inflammation associated with a disease like RA has vastly higher risks and bad outcomes compared with the few scary, dangerous, rare or very rare risks associated with Kineret use.

Costs: Kineret (and other biologic therapies) are very expensive and may not be affordable to those without insurance. Even with insurance coverage, copays on these medicines may vary widely and sometimes make them unaffordable. Patients should discuss the cost of therapy with their physician. Financial assistance may be available as patient assistance programs or copay card programs through the manufacturer. Those with very low income may be eligible to receive free medicine from the manufacturer.

Patient instructions: Kineret is only available by prescription and must be given as a self-administered subcutaneous injection. Tell your doctor about side effects that worry you, bother you or do not go away. You should not take any "live" virus vaccines (like the Shingles vaccine) while on Kineret. Your doctor needs to know if you have problematic injection skin reactions, current or recurrent infection, fever, sores or wounds, or if you are taking another biologic treatment. Tell your doctor if you've had a recent hospitalization, have a past history of recurrent infections, pneumonia, other serious medical problems, or plans to become pregnant or undergo major surgery.

Orencia (Abatacept)

How it works: Orencia is a "fusion protein" genetically engineered to specifically interfere with the way "T cells" work in diseases like rheumatoid arthritis (RA). T cells (one of several types of white blood cells) are the 4 star generals of the immune system. They direct other types of cells and guide the immune response. Orencia decreases the activity of T cells decreases the intense inflammation seen in RA and juvenile idiopathic arthritis (JIA).

Indication: Orencia is approved for use in adults with moderate to severe, active RA, not responding to MTX or other DMARDs. It is also approved for use in children (over 6 yrs of age) with moderate to severe, active, juvenile idiopathic arthritis (JIA) that involves many joints. It is indicated in those with many swollen joints, and signs of aggressive disease (nodules, elevated "sed rate", positive tests for rheumatoid factor or CCP antibodies or joint damage by X-ray). Orencia may be used alone or in combination with MTX or other DMARDs. Orencia is usually used in combination with methotrexate.

How it is given: Orencia is given either as an injection under the skin (once a week) or by intravenous (IV) infusion once a month. Orencia syringes must be stored in a refrigerator and warmed to room temperature (for 15-30 minutes) before use. Information about this biologic, how it is given and the side effects can be found in the MEDICATION GUIDE (found on the manufacturers website or attached to the box the medicine comes in). A nurse or physician can teach you about how, when and where to give the injection into the subcutaneous fat. Self-injection uses a small, skinny 25 or 27-gauge needle (like an insulin syringe and needle) and is supplied as a prefilled syringe. It may help to bring a spouse or friend with you when learning how to do the injections. You should rotate the injection sites between your right and left thigh or lower abdomen. Orencia may also be given as IV infusions in the doctor's office or a designated infusion center. The dose given is based on your weight. Treatments are initially given at weeks 0 (start), 2 and 4, and then every 4 weeks. A startup infusion (weeks 0, 2, 4) may also be given to those choosing weekly Orencia injections. Infusions take 30 minutes. Pre-medication (with acetaminophen (Tylenol) or antihistamines) are only needed in those who show allergic reactions with or after the infusion.

Time to effect: Most who respond to Orencia will feel improvement in the first 4-8 weeks and have maximal responses by weeks 12-16. However, studies show that roughly 60% will "respond" to Orencia. If no response is seen in the first 2-3 months, many rheumatologists will switch to another biologic drug.

Side Effects: The most common side effects seen with Orencia are headaches, nausea, upper respiratory tract infections or nasopharyngitis (sore throat). Skin reactions from the injection ("injection site reactions") occur in less than 3% of patients. The injection site reaction symptoms may include a skin stinging sensation during the injection, itching or hives (welts) or bruising at the site of injection. Reactions may also occur during Orencia intravenous infusions; these were seen in up to 9% of patients. Common complaints include headache, fever, rash, chest tightness, itching, high or low blood pressure. Serious infusion reactions are rare (< 1%). Nonserious infections (bronchitis, sinusitis, sore throat, influenza) were common (5-13%). There is a small but significant risk of serious infections, including pneumonia, joint infections, skin infections (cellulitis) or kidney infections (pyelonephritis); these were seen in 3% of patients. There is a very rare risk of reactivating tuberculosis (TB) or hepatitis B with Orencia use. Thus, a hepatitis blood test and a TB blood test or skin test (called a "PPD") must be done before starting Orencia. Rarely, a flare of COPD (emphysema) was seen. The risk of cancer was the same (~1%) for patients who took Orencia or placebo (fake or no medicine) in large drug studies. However, there were a few more lung cancers in patients who received Orencia in studies. RA patients (not on Orencia) may have a higher risk of some cancers (lymphoma, lung or skin cancer) that is related to chronic uncontrolled inflammation. It is unclear if using these Orencia or other biologics will increase the risk of cancer above that imposed by the inflammatory disease (RA) itself. Note: not treating uncontrolled, chronic inflammation associated with a disease like RA has vastly higher risks and bad outcomes compared with the few scary, dangerous, rare or very rare risks associated with Orencia use.

Costs: Orencia is very expensive and may not be affordable to those without insurance. Even with insurance coverage, copays on these medicines may vary widely and sometimes make them unaffordable. Medicare patients are eligible for infusion treatment with Orencia. Patients should discuss the cost of therapy with their physician. Financial assistance may be available as patient assistance programs or copay card programs through the manufacturer. Those with very low income may be eligible to receive free medicine from the manufacturer.

Patient instructions: Orencia is only available by prescription. Tell your doctor about side effects that worry you, bother you or do not go away. Your doctor needs to know if you a current or recurrent infection, fever, sores or wounds, or if you are taking another biologic treatment. You should not take any "live" virus vaccines (like the Shingles vaccine) while on Orencia. Tell your doctor if you've had a recent hospitalization, have a past history of recurrent infections, pneumonia, COPD, TB, hepatitis B, other serious medical problems, or plans to become pregnant or undergo major surgery.

Rituxan (Rituximab)

How it works: Rituxan is a genetically engineered antibody directed against a specific marker (antigen) on B cells called CD20. B cells are one of several types of "white blood cells" in your circulation. B cells make antibodies. Antibodies are the "arrows" of the immune system and are very specific for their target. The body's immune system uses antibodies to protect against infection and invasion by foreign substances. B cells are hyper-active in autoimmune and inflammatory disorders and Rituxan is used to target (bind to and inactivate), stop or interfere with B cells, so that they can no longer drive inflammatory disease. Rituxan can also be used to target and remove excessive numbers of CD20 B cells seen with certain kinds of blood cancer.

Indication: Rituxan is approved for use in adult patients with moderate to severely active rheumatoid arthritis (RA), after failing an adequate trial of MTX or other DMARD therapy. Rituxan has also been FDA approved for use in patients with certain forms of systemic vascular inflammation ("vasculitis") including granulomatosus with polyangiitis (GPA or Wegener's granulomatosis) and microscopic polyangitis. Rituxan is approved for use in Non-Hodgkin's Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL) as well.

How it is given: Rituxan is given as an intravenous (IV) infusion through an IV catheter in the doctor's office or a designated infusion center. Information about this biologic, how it is given and the side effects can be found in the MEDICATION GUIDE (found on the manufacturers website or attached to the box the medicine comes in). In RA, Rituxan is usually given along with methotrexate or another conventional DMARD. Treatments include 2 infusions of 500 or 1000 mg given 2 weeks apart. Rituxan infusions are longer than other biologics and take 4-5 hours to administer. Pre-medication (with acetaminophen [Tylenol], IV steroids and antihistamines) is commonly given to avoid allergic reactions associated with the infusion. These 2 infusions are called a "course". A repeat "course" of Rituxan can be given again in 6 or 12 months or when the response goes away or is lost.

Time to effect: Many patients feel somewhat better immediately following the first or second infusions, but this is often due to the high dose of IV steroids given with the Rituxan infusion. Those who will ultimately respond to Rituxan will feel improvement starting 4-8 weeks after the second infusion and will have maximal responses by weeks 12-16. Not every patient will respond to Rituxan. Studies show that roughly 50-60% will "respond" to Rituxan. If no response is seen in the first 3-4 months, most rheumatologists will either repeat with another course (2 more infusions) or switch to another biologic drug.

Side Effects: RA patients who receive Rituxan will have a very different (and milder) side effect experience compared to those who take Rituxan for cancer (NHL, CLL) where the killing of many cancer cells causes many more side effects. In RA, the most common side effects are upper respiratory tract infections, nasopharyngitis (sore throat), urinary tract infections or bronchitis – these are seen in $\leq$ 10% of patients. Serious infections (pneumonia, cellulitis) are seen in 2% of patients. Infusion reactions can occur in 15-25% of first infusions and decrease with subsequent infusions. Symptoms of an infusion reaction include fever, chills, shaking, itching, hives, rash, lip swelling (angioedema), cough, chest pain or tightness, wheezing and changes in blood pressure. Very rare complications of Rituxan include severe infusion reactions (< 1%), reactivation of hepatitis B, very severe skin reactions (Stevens-Johnson syndrome) or a very rare risk (1 in 30,000) of a fatal brain infection called progressive multifocal leukoencephalopathy (PML). People with chronic or active viral infections (shingles, herpes, CMV, parvovirus, hepatitis, etc.) should not take Rituxan as it may worsen such infections. If any of these side effects concern or apply to you, discuss them with your physician before you decide to not take the medicine. Note: not treating uncontrolled, chronic inflammation associated with a disease like RA has vastly greater risks and bad outcomes compared with the few scary, dangerous, rare or very rare risks associated with Rituxan use.

Costs: Rituxan is very expensive and may not be affordable to those without insurance. Even with insurance coverage, copays may vary widely and sometimes make the drug unaffordable. Medicare patients are eligible for infusion treatment with Rituxan. Patients should discuss the cost of therapy with their physician. Financial assistance may be available as patient assistance programs or copay card programs through the manufacturer. Those with very low income may be eligible to receive free medicine from the manufacturer.

Patient instructions: Rituxan is only available by prescription and must be given as an IV infusion by an experience infusion center. Tell your doctor about side effects that worry you, bother you or do not go away. Your doctor needs to know if you a current or recurrent infection, fever, sores or wounds, or if you are taking another biologic treatment. You should not take any "live" virus vaccines (like the Shingles vaccine) while on Rituxan. Tell your doctor if you've had a recent hospitalization, have a past history of recurrent infections, pneumonia, TB, hepatitis B, other serious medical problems, or plans to become pregnant or undergo major surgery.

Actemra (Tocilizumab)

How it works: Actemra is a genetically engineered antibody that blocks the receptor for interleukin-6 (IL-6). IL-6 is a cytokine (messenger between cells) that acts to increase inflammation in the joints. IL-6 acts just like gasoline on a fire. Thus, IL-6 (the gasoline) excites the inflamed joint (the fire). Actemra is very specific and only blocks IL-6. An excess of IL-6 can make inflammation worse. Actemra acts to reduce inflammation.

Indication: Actemra is approved for use in adult patients with moderate to severely active rheumatoid arthritis (RA), who have failed an adequate try of MTX or other DMARD therapy. Actemra is also approved for use in children (over age 2 years) with moderate to severely active, polyarticular (many joints) juvenile idiopathic arthritis (JIA) and children (over age 2 years) with active "Still's disease" or systemic juvenile idiopathic arthritis.

How it is given: Actemra is given either as an injection under the skin (either once a week or every 2 weeks, depending on your weight) or by intravenous (IV) infusion once a month. Actemra syringes must be stored in a refrigerator and warmed to room temperature (for 15-30 minutes) before use. Information about this biologic, how it is given and the side effects can be found in the MEDICATION GUIDE (found on the manufacturers website or attached to the box the medicine comes in). A nurse or physician can teach you about how, when and where to give the injection just under the skin - into the subcutaneous (SC) fat. Self-injection uses a small, skinny 25 or 27-gauge needle (like an insulin syringe) and comes as a prefilled syringe. It may help to bring a spouse or friend with you when learning how to do the injections. You should rotate the injection sites between your right and left thigh or lower abdomen. Actemra can also be given as an IV infusion, through an IV catheter in the doctor's office or a designated infusion center. Treatments are given every 4 weeks and take 60 minutes to administer. Pre-medication is seldom needed and is only given in patients who show allergic reactions with or after the infusion

Time to effect: Those who will respond to Actemra will feel improvement 4-8 weeks after starting treatment and will have maximal responses by weeks 12-16. But, not every patient will respond to Actemra. Studies show that roughly 50-60% will "respond" to Actemra. If no response is seen in the first 2-4 months, most rheumatologists will either increase the dose of Actemra or switch to another biologic drug.

Side Effects. The most common side effects seen with Actemra are headaches, nausea, upper respiratory tract infections or nasopharyngitis (sore throat), headache, hypertension, or increased liver tests. Skin reactions from the injection ("injection site reactions") occur in 7-10% of patients. Injection site reactions may cause a skin stinging sensation, itching or hives (welts) or bruising at the site of injection. Reactions may also occur during Actemra intravenous infusions; these were seen in up to 8% of patients and may include symptoms of headache, fever, rash, chest tightness, itching, high or low blood pressure. Serious infusion reactions are rare (<0.2%). Several unique side effects seen with Actemra use include a 2-3% risk of low blood cell counts (white blood cells or platelets), increased liver enzymes (20-30%) increased cholesterol and lipid levels (20%) and a rare risk of colon perforations (<3 per 1000 Actemra patients) usually occurring in RA patients with diverticulitis. Nonserious infections (bronchitis, sinusitis, sore throat) may also be seen with Actemra (5-8%). An important side effect is a small but significant risk (3-5 out of 100 persons on Actemra) of serious infections, including pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis or sepsis (blood poisoning). There is a rare risk of reactivating tuberculosis (TB) or other opportunistic infections with Actemra use. Thus, a TB blood test or skin test (called a "PPD") must be done before starting Actemra. The risk of cancer was the same (~1%) in those who took Actemra or placebo (fake or no medicine) in large drug studies. RA patients (not on Actemra) may have a higher risk of some cancers (lymphoma, lung or skin cancer) that is related to chronic uncontrolled inflammation. It is unclear if using Actemra will increase the risk of cancer above that imposed by RA itself. Note: not treating uncontrolled, chronic inflammation associated with a disease like RA has vastly higher risks and bad outcomes compared with the few scary, dangerous, rare or very rare risks associated with Orencia use.

Costs: Actemra is very expensive and may not be affordable to those without insurance. Even with insurance coverage, copays may vary widely and sometimes make the drug unaffordable. Medicare patients are eligible for infusion treatment with Actemra. Patients should discuss the cost of therapy with their physician. Financial assistance may be available as patient assistance programs or copay card programs through the manufacturer. Those with very low income may be eligible to receive free medicine from the manufacturer.

Patient instructions: Actemra is only available by prescription and must be given as an infusion or injection. Tell your doctor about side effects that worry you, bother you or do not go away. Your doctor needs to know if you a current or recurrent infection, fever, sores or wounds, or if you are taking another biologic treatment. You should not take any "live" virus vaccines (like the Shingles vaccine) while on Actemra. Tell your doctor if you've had a recent hospitalization, have a past history of recurrent infections, pneumonia, TB, diverticulitis or colon perforations, low blood counts, other serious medical problems, or plans to become pregnant or undergo major surgery.