

Practical Aspects of New Therapies for Children With Juvenile Rheumatoid Arthritis

by Richard Vehe, M.D., and Patricia Erickson, C.P.N.P.

Juvenile rheumatoid arthritis (JRA)* and similar diseases, such as spondyloarthropathies, affect approximately 300,000 children in the United States each year. There are many categories of JRA; the most common forms are pauciarticular, polyarticular and systemic. Types of spondyloarthropathies include enthesitis-arthritis syndrome, reactive arthritis and psoriatic arthritis (see sidebar).

Because nonsteroidal anti-inflammatory drugs (NSAIDs) and immune-suppressive medications can relieve pain and block inflammation, they're mainstays of JRA treatments. Physical and occupational therapy also can benefit patients with JRA. Moreover, new medications (called *biologic agents*) — and the general increase in pediatric drug trials — have dramatically improved treatment for JRA and other rheumatic diseases. Biologic agents have been used since 1998 and were studied for almost 10 years before that.

When primary-care providers are caring for a child on biologic agents, we recommend collaboration with a rheumatologist to enhance patient safety. Such safety precautions include not using biologic agents in combination with antibiotics and certain vaccinations. This article highlights some of the common biologic agents that physicians use to treat JRA and spondyloarthropathies. It also discusses some of the practical issues that would be beneficial for primary-care providers to know.

What Are Biologic Agents?

Biologic drugs (genetically engineered medicines) copy the effects of substances that a person's immune system naturally makes. The manufacturing of traditional pharmaceuticals occurs through synthetic means, whereas the development of biologic agents occurs using proteins derived from living cells. Biologic agents can interfere with the cascade of events characteristic of JRA, interrupting the

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*The preferred international term for JRA is juvenile idiopathic arthritis, or JIA.

Types of JRA

The main categories of JRA are:

• Pauciarticular JRA

This form affects four or fewer joints — usually the knees, ankles or elbows. It's often asymmetric, affecting a particular joint on just one side of the body. The most common form of JRA, it affects more girls than boys.

• Polyarticular JRA

This form affects five or more joints — typically small joints (such as those in the hands and feet) and weight-bearing joints (such as the knees, ankles and feet). Polyarticular JRA is often symmetric, affecting similar joints on both sides of a child's body.

• Systemic JRA

Also known as Still's disease, systemic JRA can affect many areas of the body, including joints and internal organs. The least common form of JRA, it generally causes spiking fevers and a rash of pale red spots, often on the trunk or limbs.

Spondyloarthropathies

Types of spondyloarthropathies include:

• Enthesitis-Arthritis Syndrome

This disorder generally causes inflammation in larger joints of the lower extremities (such as the hips). It often features prominent pain at the entheses (the points where tendons and ligaments attach to bones). If the condition spreads to the back, the disease is called juvenile ankylosing spondylitis.

• Reactive Arthritis

This disorder usually develops after a respiratory or gastrointestinal illness (such as shigella, salmonella or Yersinia-associated diarrhea). In addition to causing arthritis, the condition can result in inflamed eyes, rashes and fever.

• Psoriatic Arthritis

With psoriatic arthritis, a red rash with a silvery scale might occur on the back of the elbows, on the front of the knees or elsewhere. This type of arthritis, which can affect large or small joints in a variety of patterns, resembles many other forms of juvenile arthritis.

Although JRA and the spondyloarthropathies are the most common causes of chronic arthritis in children, other diseases — including systemic lupus, juvenile dermatomyositis and mixed connective-tissue disease — also can cause arthritis.

ongoing immune attack and inflammation. The biologic agents act on different parts of the inflammatory system, evoking specific, targeted effects.

Treatment With Biologic Agents

Physicians often prescribe biologic agents for patients who haven't responded to an adequate trial of one or more of the traditional, disease-modifying, antirheumatic drugs (DMARDs), which include methotrexate, leflunomide, hydroxychloroquine and sulfasalazine. Physicians might prescribe biologic agents independently of or in conjunction with DMARDs. When patients start taking biologic agents, they typically remain on their current dose of NSAIDs for symptomatic relief of pain and stiffness.

The most commonly used biologic agents act as inhibitors of the cytokines interleukin-1(IL-1) or tumor necrosis factor (TNF). Cytokines are messenger molecules sent from one type of cell to another. Each type of cytokine binds to its unique receptors, thereby stimulating immune-system cells. Rheumatoid arthritis and many other forms of inflammation cause the body to manufacture large amounts of IL-1 and TNF, which in turn increase inflammation, similar to the effect of pouring gasoline on a fire. By design, biologic agents specifically attach to cytokines or their receptors, and thereby specifically block TNF or IL-1 from binding to and stimulating cells of the immune system.

Biologic Agents for Treating JRA

The most common biologic agents that rheumatologists prescribe to treat JRA are:

- Adalimumab (Humira®)
- Anakinra (Kineret®)
- Etanercept (Enbrel®)
- Infliximab (Remicade®)

Side Effects

Biological agents are specifically targeted, making them more precise and more predictable than traditional medicines. Therefore, they tend to produce fewer side effects and undesirable consequences. Side effects depend on many factors, such as the type of biologic agents, dosage, method of administration, dosage schedule, and body's reaction to the biologic agents.

For injectable medicines, the most common side effects are injection-site reactions. Skin reactions to injections occur in up to 40 percent of patients, who usually complain of a rash, burning and/or itching at the site of

the injection. With adalimumab and etanercept, skin reactions can last up to a week. Skin reactions to anakinra injections can last 10 to 14 days before fading away.

In addition to injection-site reactions, possible side effects of anakinra, adalimumab and etanercept are frequent headaches and upper respiratory infections (such as colds and sinus infections). Patients taking infliximab, an intravenous infusion medication, might experience chest tightness, shortness of breath, nausea, weakness, dizziness, hives, an itchy rash, and stomach pain. Because infliximab can cause an allergic reaction, patients receiving this medication undergo monitoring in a clinic or hospital setting.

The most significant side effect of biologic agents is an increased risk of other types of infections, including reactivation of latent tuberculosis (TB). Before starting an anti-TNF medication, physicians typically request a TB skin test to make sure the patient doesn't have a "silent" TB infection. Physicians should delay treatment with biologic agents if patients have an active infection that requires an antibiotic or if such patients experience a high fever. Close monitoring should follow.

Precautions and Monitoring

The precautions for children who take biologic agents are almost the same for each agent. The information below lists — for each drug — laboratory tests and vaccines that physicians recommend when monitoring patients.

Table 1: Safeguards When Using Biologic Agents

	Adalimumab	Anakinra	Etanercept	Infliximab
Influenza vaccine recommended	Yes	Yes	Yes	Yes
Complete blood-count tests	Yes	Yes	Yes	Yes
Liver-function tests	Yes	No	Yes	Yes
Initial TB test	Yes	Yes	Yes	Yes

Children who take biologic agents should not have live-virus vaccines (such as the measles, mumps and rubella vaccine, the nasal mist influenza vaccine, and the varicella vaccine).

Table 2: Comparisons of Biologic Agents

	Adalimumab	Anakinra	Etanercept	Infliximab
Inhibits what?	TNF	IL-1	TNF	TNF
Type of biologic	Antibody	Receptor antagonist	Receptor	Antibody
Administration method	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection	Intravenous infusion

Pediatric rheumatologists have become more aggressive in treating JRA with medication because of the risk of irreversible joint or eye damage in children whose inflammation is only partially controlled. Controlling the inflammatory process with medication preserves function, prevents joint deformity, decreases pain, and leads to normal growth and development. Biologic agents have been shown to repress swelling and inflammation and prevent joint destruction in children with JRA. Safety can be enhanced for children taking these medications by being aware of side effects and following safety recommendations.

Treating JRA at Gillette

As a regional referral center, Gillette serves patients from throughout Minnesota and the Upper Midwest. Each year, more than 300 new patients undergo comprehensive evaluations to aid in diagnosing and treating their conditions. Our comprehensive pediatric rheumatology team includes physicians, nurses, nurse practitioners, physical and occupational therapists, orthotists and psychologists. Together, we help patients develop physically and emotionally while learning to manage their conditions.

Richard Vehe, M.D., is a pediatric rheumatologist and medical director of the Center for Pediatric Rheumatology at Gillette Children's Specialty Healthcare and the Pediatric Rheumatology Program at the University of Minnesota. He sees patients who have a broad range of rheumatic and related inflammatory conditions, including juvenile rheumatoid arthritis.



Vehe received his medical degree from Washington University in St. Louis, Mo. He completed a pediatric residency at the University of Minnesota and a fellowship in pediatric rheumatology at the University of Washington, Children's Hospital and Medical Center, and Virginia Mason Research Center, all in Seattle.

Vehe has been on Gillette's staff since 1993. He is also an assistant professor in the University of Minnesota's Department of Pediatrics.

Patricia Erickson, C.P.N.P.,

is a certified pediatric nurse practitioner at Gillette Children's Specialty Healthcare. For the past 12 years, Erickson has provided care to patients who have juvenile rheumatoid arthritis and other rheumatic conditions. She is program manager for Gillette's Center for Pediatric Rheumatology.



Erickson received her bachelor's and master's degrees from the College of St. Catherine in St. Paul. She received her pediatric nurse practitioner certification from the Pediatric Nursing Certification Board in August 2006.

She is a member of the Association of Rheumatology Health Professionals, Arthritis Foundation, Minnesota chapter of the National Association of Pediatric Nurse Practitioners, and Sigma Theta Tau International Honor Society of Nursing.

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Gillette Children's Specialty Healthcare
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Gillette Welcomes New Physicians

Patrick Graupman, M.D., a pediatric neurosurgeon, sees patients with spina bifida, epilepsy, brain tumors and craniofacial disorders at Gillette Children's Specialty Healthcare. Graupman's subspecialty interests are hydrocephalus and spinal disorders — conditions that he also treats at Gillette.

After completing his medical degree at the University of Minnesota School of Medicine in Minneapolis, Graupman completed a neurosurgery residency there. He completed a pediatric neurosurgery fellowship at University of Colorado Children's Hospital of Denver.

To refer a patient to Graupman, call 651-229-3944 or 800-719-4040 (toll-free).

Robert Wagner, M.D., a family medicine physician, has joined Gillette Lifetime Specialty Healthcare as medical director of adult services. Wagner has outpatient and inpatient care responsibilities that include presurgical evaluation and discharge planning, consultation, and integrative-care management for nonsurgical patients.

Wagner also helps Gillette Lifetime staff establish and maintain community-based primary care for our patients. He provides selected, direct patient-care services that include gynecology, wound care, tube feeding, medication management and pulmonary assessment.

After receiving his medical degree from the University of Minnesota in Minneapolis, Wagner completed a family medicine residency at St. Paul Ramsey Medical Center (now Regions Hospital). Before joining Gillette, he served as section head of family medicine at Regions Hospital. He is board-certified in family medicine and a member of the Minnesota Academy of Family Physicians and the American Academy of Family Physicians.

To refer a patient to Wagner, call 651-229-3944 or 800-719-4040 (toll-free).

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