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Key Inforbits

- Juvenile Idiopathic Arthritis (JIA) Introduction
- Subtypes of JIA
- Pharmacologic Treatment and Goals of Therapy
- Non-pharmacological Therapy
- New and Emerging Treatments
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What is Juvenile Idiopathic Arthritis (JIA)?

Juvenile idiopathic arthritis (JIA), formerly known as juvenile rheumatoid arthritis, is defined as arthritis lasting greater than six weeks before the age of 16 in children and adolescents.[1,2] JIA is the most common type of arthritis in children and affects approximately 1 in every 1,000 children.[1] It involves inflammation of the joints (arthritis) that can cause subsequent joint pain, tenderness, stiffness, swelling, warmth, fever, fatigue, and decreased mobility.[2,3] It can affect any joint, but is most common in the knees, hands, and ankles. JIA may affect an individual for a short period of time, and the child may achieve remission. In other cases, it is a lifelong disease that requires treatment into adulthood. The body's immune system mistakenly attacks some of its own healthy cells and tissue resulting in inflammation and associated symptoms. Inflammation from JIA can damage the joints, eyes, or even affect the internal organs. The term "idiopathic" indicates that the origin is not known. Newer therapies specifically target potential molecules of interest, e.g. tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and Janus kinase (JAK). There are multiple types of JIA that all share the same "arthritic" symptoms but have a defining characteristic to distinguish between each other.

Subtypes of JIA[2]

Table 1: Subtypes of JIA

Type	Defining characteristic(s)
Systemic	• Joint swelling or pain in multiple joints, fevers, erythematous rash, and possible visceral involvement • Complicated by macrophage activation syndrome • If left untreated can cause multi-organ dysfunction and become fatal • Least common, but most severe
Oligoarticular	• Involves 1 to 4 joints, usually large joints such as the wrists or knees • Usually asymmetric, on one side of the body • May also affect the eyes causing uveitis • Most common type of JIA, usually females 8 years old and younger
Polyarticular	• Involves at least 5 small or large joints • Usually symmetric, and may involve the neck, spine, or jaw • Rheumatoid factor may be present, usually more aggressive/erosive • May develop into adult rheumatoid arthritis later • Affects females more than males
Enthesitis-related	• Mainly affects lower limb joints such as the sacroiliac joint, spine, pelvic bone, and hip. May affect the shoulder or possibly the internal organs. • Similar to spondylarthritis in adults • Diagnosed usually between ages 8 to 15, more common in males
Psoriatic	• Affects asymmetric large and small joints and is accompanied by a scaly red rash behind the ears, at the elbows, or on the scalp. • Other symptoms are nail pitting and dactylitis. • Theoretically may be inherited from a first degree relative who may have psoriasis
Undifferentiated	• Inflammation is present in one or more joints, but symptoms/characteristics don't meet the criteria to fit one specific type, or the criteria has been fulfilled by more than one subtype and cannot be differentiated

Pharmacological Treatment & Goals of Therapy

There is no cure for JIA, but the disease can be effectively controlled. The goals of treatment in JIA are to maintain joint function and mobility, prevent future joint or organ damage, relieve symptoms, and improving the child's quality of life.[3,4]

Initial Therapy[2-5] is usually monotherapy or a combination of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids to reduce inflammation and/or suppress the immune system during the evaluation period for diagnosis.

Conventional Synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs)[2-5]

Traditional DMARDs are used to slow or stop the disease that causes inflammation in the joints and usually take weeks to months to start working. Initiation of a DMARD is recommended as soon as a diagnosis is determined or after one to two months of ineffective therapy from NSAIDs and/or corticosteroids. One DMARD may not work alone, and combination therapy is an alternative. However, combination therapy may not provide additional benefit over methotrexate monotherapy. Methotrexate is the most frequently used DMARD.

Table 2: csDMARDs

Medication	Mechanism of Action	Frequency
Hydroxychloroquine [Plaquenil]	Unknown immunomodulator that may inhibit neutrophil and eosinophil migration and prostaglandin synthesis	Once or twice a day (oral)
Leflunomide [Arava]	Pyrimidine synthesis inhibitor – inhibits dihydroorotate dehydrogenase to inhibit RNA and protein synthesis	Once a day (oral)
Methotrexate [Rheumatrex]	Inhibits dihydrofolate reductase and thymidylate synthase to inhibit DNA synthesis	Once a week (oral, SQ)
Sulfasalazine [Azulfidine]	Inhibits leukotriene and prostaglandin synthesis to decrease inflammatory response	Twice a day (oral)
Abbreviations: DNA, deoxyribonucleic acid; RNA, ribonucleic acid; SQ, subcutaneous.		

Biologic DMARDs (bDMARDs)[2-5]

Newer DMARDs have been developed to target specific mechanisms, instead of suppressing the whole immune system to slow disease progression. Continued disease activity after two months of methotrexate therapy prompts for initiation of anti-tumor necrosis factor (TNF) agents or another biologic if a TNF-α inhibitor is contraindicated.

Table 3: bDMARDs

Drug Class	Medication	Mechanism of Action	Frequency
TNF-α Inhibitors	Adalimumab [Humira]	Bind to tumor necrosis factor cytokines to prevent TNF receptor binding by T-cells and macrophages	Every 2 weeks (SQ)
	Etanercept [Enbrel]		Once or twice a week (SQ)
	Golimumab [Simponi]		Every 4 weeks (SQ)
	Infliximab [Remicade]		Every 4 to 8 weeks (IV)
B-cell Inhibitor	Rituximab [Rituxan]	Binds CD20 on B-cells; mediate cell lysis, causing B-cell depletion	Every 24 weeks (6 months) (IV)
IL- Inhibitors	Anakinra [Kineret]	Selectively binds to and inhibits IL-1	Once a day (SQ)
	Canakinumab [Ilaris]		Every 4 weeks (SQ)
	Secukinumab [Cosentyx]	Selectively binds to IL-17A cytokine to inhibit IL-17	Every 4 weeks
	Tocilizumab [Actemra]	Binds to soluble and membrane bound IL-6 receptors to inhibit IL-6 signal pathway	Every 1 to 2 weeks (SQ) Every 4 weeks (IV)
	Ustekinumab [Stelara]	Binds to the p40 subunits of IL-12 and IL-23 cytokines	Every 12 weeks (SQ)
Co-stimulation Modulator	Abatacept [Orencia]	Modulates T-cell co-stimulation by binding CD80/CD86 and preventing interaction with CD28 on antigen presenting cell	Once a week (SQ) Every 4 weeks (IV)
JAK inhibitors	Tofacitinib [Xeljanz]	Inhibits JAK, thus prevents the activation of STATs	Twice a day (oral)
Abbreviations: IL, interleukin; JAK, Janus kinase; IV, intravenous; SQ, subcutaneous; STATs, signal transducer and activator of transcription; TNF-α, tumor necrosis factor alpha			

Non-pharmacological Therapy

Although there are several treatment options used for patients with JIA, there are a few nonpharmacologic therapies that may also be beneficial in alleviating symptoms. These recommendations include:

Rest: During active phases of JIA, adequate rest is useful to reduce inflammation and combat fatigue.[6] Encourage the patient to utilize a consistent sleep routine and create a comfortable sleep environment.
Heat treatments: Applying heat pads or taking warm baths can alleviate stiffness and relax muscles.[6]
Exercise: Low-impact and joint friendly exercise is recommended to ease joint stiffness and pain.[6] Some examples include swimming, biking, and walking. Encourage the patient to engage in physical activity they enjoy, such as sports or playing with friends, to promote overall well-being.
Vaccines: It's important for all children, including those with JIA, to stay up-to-date with vaccinations recommended by the ACIP and AAP schedules.[4] An annual inactivated influenza vaccine is strongly recommended. However, live attenuated vaccines are not recommended for children receiving immunosuppressive treatments.
Nutrition: A healthy, age-appropriate diet is strongly recommended.[4] While there isn't a specific diet proven to treat JIA, evidence supports a balanced, nutrient-dense diet for all children. Foods rich in omega-3 fatty acids (such as fatty fish), fruits, vegetables, and whole grains may help reduce inflammation.[6] Conversely, foods high in fat, sugar, and processed ingredients should be limited.
Physical and Occupational Therapy: Physical and occupational therapy are conditionally recommended to maintain joint range of motion, improve strength, address functional deficits, enhance endurance, prevent injury, and promote participation in daily activities.[4]

New and emerging Treatments

New treatment options are currently being explored for JIA. One class of drug, JAK inhibitors, are currently being recommended by the European League Against Rhematism.[7] JAK inhibitors such as baricitinib, upadacitinib, and filgotinib have shown to be efficacious in reducing symptoms of JIA. JAK inhibitors should be used with caution as there is an elevated risk of serious infections, malignancies, and blood clots.

Artificial intelligence (AI) is currently being utilized in developing algorithms that use clinical data, imaging studies, and biomarkers to aid in the diagnosing of JIA.[7] Further implementation involving the use of electronic health records (EHR) has shown a positive predictive value of 97% when diagnosing JIA. AI not only has the potential to aid physicians in diagnosing JIA but may also aid in monitoring the treatment for these patients. Algorithms are currently predicting treatment response of various therapies utilizing patient's EHR with an accuracy of 72.22%. "Several biomarkers are currently under investigation in the context of JIA research" and with the expansion of these biomarkers, drug therapy can be specifically targeted, and treatment efficacy may increase. These advancements, coupled with the implementation of AI and machine learning, are promising for the future treatment for JIA.

International Perspective from Thailand

Various studies have shown that JIA in Asia differs from that in Western countries due to several factors, including ethnic, socioeconomic, and geographic differences.[8] This means that Thailand will have different disease outcomes compared to the US. However, ACR guidelines are still used for standard treatment. In systemic therapy, treatment typically begins with IV pulse prednisolone at a dosage of 1-2 mg/kg/day for 3-5 days, followed by a switch to oral therapy based on disease severity. NSAIDs are usually prescribed for patients with mild symptoms lasting 1-2 weeks. Additionally, we use DMARDs (such as methotrexate, sulfasalazine, and hydroxychloroquine) to delay disease progression in the long term, similar to their use in rheumatoid arthritis. Moreover, biologic agents are also used to treat patients with JIA who do not respond to conventional medications. Examples of these drugs available in Thailand include anti-TNF agents (such as etanercept, infliximab, and adalimumab), anti-IL-6 agents (such as tocilizumab), and T-cell regulatory agents (such as abatacept). Anti-IL-1 agents (such as anakinra and canakinumab) are also used. However, most of these drugs are expensive, and some insurance plans, like the Universal Coverage Scheme that insures Thai citizens, do not cover all of them. Some patients must pay for these medications themselves, limiting their access to proper treatment. Nevertheless, many effective drugs are being added to the coverage list. We hope that these biologic agents will soon be available to every patient.

Summary

Appropriate treatment of JIA is important to decrease disease activity in children who have been so diagnosed. There are several treatment options available that can be utilized and should be individualized. Additionally, there are also non-pharmacologic options that can help alleviate symptoms and improve quality of life in those who are affected. In comparison, Thailand also uses the same treatment methods as the United States, but some products are more difficult to obtain due to insurance restrictions. New technology is currently being investigated to aid in diagnosing and treating patients with JIA, and we hope the benefits of this technology will be seen in the near future.

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The last "dose" …

"The good physician treats the disease; the great physician treats the patient who has the disease" —

Sir William Osler, 1849 to 1919 [Canadian physician and the "father of modern medicine"]

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