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Guest Editors: Scott Kiker, Sean Murphy, Kayla Osbourn, Pharm.D. Candidates, Wesley Lindsey, Pharm.D.

Key Inforbits

- Introduction to Juvenile Idiopathic Arthritis
- Etiology and Pathogenesis
- Systemic Juvenile Idiopathic Arthritis
- Updated Recommendations for the Management of Systemic JIA
- New Juvenile Idiopathic Arthritis Medications

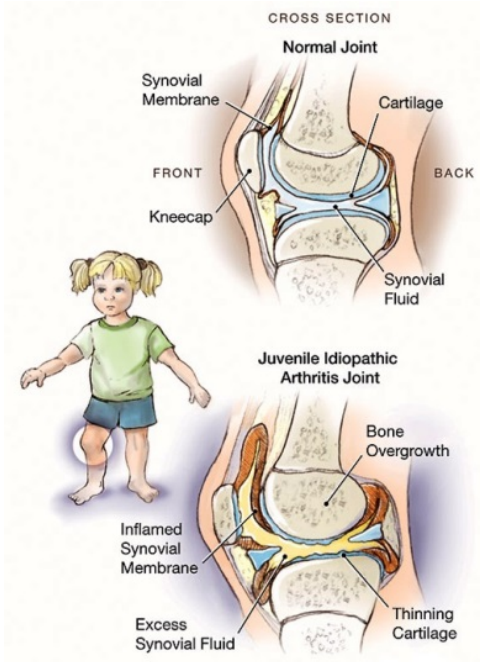
March is Juvenile Arthritis Awareness MONTH

Introduction

Juvenile Idiopathic Arthritis (JIA) refers to arthritis of unknown etiology that develops before age 16 and persists for 6 weeks or longer without other known causes.[1] JIA onset occurs most often between ages 2 and 4 years. It often carries on into adulthood and can cause long term complications such as physical disability. JIA is characterized by intra-articular swelling or presence of 2 or more of the following: limitation in range of motion, tenderness or pain on motion, and increased heat or erythema. The initial symptoms may be mild such as morning stiffness, a limp, becoming tired easily, or poor sleep. The CDC estimates that 294,000 children (1 in 250) in the United States are afflicted with JIA as of 2007.[2]

Etiology and Pathogenesis

There are 2 main components to the etiology of JIA: genetic susceptibility and an external trigger.[1] The genetic component to JIA is very complex and remains hard to define, but has been related to polymorphisms in tumor necrosis factor alpha (TNF-α), macrophage inhibitory factor (MIF), and Interleukins 6 and 1 (IL-6 and IL-1). External triggers can include infections by bacteria or viruses, joint trauma, abnormal levels of reproductive hormones, or an enhanced response to a foreign protein. Overall alterations in humoral and cell mediated immunity cause increased release of pro-inflammatory cytokines (TNF- α, IL-6, and IL-1).



http://www.urasociety.org/portals/0/juvenilearthritis.jpg

Systemic Juvenile Idiopathic Arthritis

Systemic JIA (SoJIA) makes up about 4-15% of JIA and is characterized by the following features:[1]

- Age <16 years
- ≥1 joint involvement for at least 6 weeks
- Fever for at least 2 weeks prior
  - Temperature spikes to 39°C on daily or twice daily basis
  - Rapid return to normal or below normal temperatures

    - May also have a faint, erythematous, macular rash
- One or more of following:
    - Fading red rash
    - Swollen lymph nodes
    - Enlarged liver or spleen
    - Inflammation of serous tissues (pleural, pericardial, peritoneal)

References

1. Wu EY, Van Mater HA, Rabinovich CE. Rheumatic Diseases of Childhood. In: Kliegman RM, Stanton BF, St Geme JW, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Elsevier Saunders;c2011.p.829-839
2. Childhood Arthritis. Centers for Disease Control and Prevention. [Updated 23 Oct 2013, cited 25 Feb 2014]. Available from: http://www.cdc.gov/arthritis/basics/childhood.htm

Updated Recommendations for the Management of Systemic JIA

An update of the JIA guidelines developed by the American College of Rheumatology (ACR) was recently published that focused on the management of systemic JIA.[1] Recommendations were made that addresses both the systemic features and symptoms of synovitis. Three types of systemic JIA include: 1) Active systemic features and varying degrees of synovitis, 2) No active systemic features and varying degrees of synovitis, 3) Systemic features concerning for macrophage activation syndrome (MAS). Treatment recommendations were based on the active joint count (AJC) and the physician global assessment (MD global) on a scale of 1-10 with 10 being the most severe disease. Stratification thresholds for AJC were ≤4 or >4 and for MD global ≥5 or <5.

Features Concerning for Macrophage Activation Syndrome (MAS)

MAS is a rare but potentially fatal complication of SoJIA that can occur at any time.[2] It can manifest as acute anemia associated with falls in platelet or white blood cell counts with high spiking fevers, as well as the typical symptoms of SoJIA. The erythrocyte sedimentation rate (ESR) falls, contradictory to typical JIA characteristics. This decrease in ESR can then be used to differentiate MAS from a flare of the SoJIA. Initial therapeutic options for patients who have features concerning for MAS include anakinra, calcineurin inhibitors such as cyclosporine and tacrolimus or systemic glucocorticoid therapy.[1] Depending on the severity of the clinical situation, monotherapy or combinations of these three are appropriate.

TB Screening

Annual tuberculosis (TB) screening in patients with JIA receiving immunosuppressive therapy who initially tested negative is no longer recommended if the patient remains at a low risk.[1] TB screening should be performed prior to initiating biologic therapy and repeated periodically when the risk of exposure is increased.

References

1. Ringold S, Weiss PF, Beukelman T, et al. 2013 Update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis. *Arthritis Rheum.* 2013 Oct;65(10):2499-512.
2. Wu EY, Van Mater HA, Rabinovich CE. Rheumatic Diseases of Childhood. In: Kliegman RM, Stanton BF, St Geme JW, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Elsevier Saunders;c2011.p.829-839

New Juvenile Idiopathic Arthritis Medications

	Canakinumab (Ilaris)[1]	Rilonacept (Arcalyst)[1,2]	Tocilizumab (Actemra)[1]
Mechanism of Action:	• Reduces inflammation • Binds to IL-1β and prevents interaction with cell surface receptors	• IL-1 inhibitor • Reduces inflammation by binding to IL-1β and preventing interaction with cell surface receptors	• IL-6 receptor antagonist • Causes a reduction in cytokine and acute phase reactant production during inflammatory process
Dosing:	• Patient must be ≥2 years old and weigh at least 7.5 kg • 4 mg/kg SubQ every 4 weeks • Maximum of 300 mg/dose	• 2.2-4.4 mg/kg SubQ on days 0, 3, 7, 14, and 21 of a treatment round • Maximum dose is 320 mg	• Patient must be ≥2 years old • <30 kg: 12 mg/kg every 2 weeks; ≥30 kg: 8 mg/kg every 2 weeks • Infused IV over 60 minutes • Do not initiate if: o Absolute neutrophil count is <2,000/mm^3 o Platelet count is <100,000/mm^3 o ALT or AST is >1.5 times upper limit of normal
Precautions:	• History of recurrent infections or cancer • Macrophage Activation Syndrome (MAS) • Should NOT be used in patients with active TB or with TNF-blockers	• History of recurrent infections • Cancer • Should NOT be used in combination with TNF-blocking agents	• Elevated liver enzymes • Decreased WBCs or platelets • Hyperlipidemia • Cancer • Risk for GI perforation • **BBW for serious and possibly fatal infections including TB**
Common Side Effects:	• Vertigo • Nausea or diarrhea • Gastroenteritis • Weight gain • Increased infections • Injection site reaction	• Antibody development • Increased infections • Injection site reaction • Upper respiratory tract infection	• Increased serum cholesterol • Increased ALT • Increased AST • Infusion-related reaction
Monitoring:	• Complete blood count • C-reactive protein • Serum amyloid A • Signs of infection • Weight • TB screening	• CBC • Lipid profile • C-reactive protein • Serum amyloid A • Signs of infection	• TB screening • Neutrophil and platelet counts • Liver function and lipid panel • Signs of infection • Signs of CNS demyelinating disorder
With all of these medications, patients should be current with all immunizations before initiating therapy, and live vaccines should not be given concurrently.			

References

1. Canakinumab, Rilonacept, and Tocilizumab. In: Lexi-Comp Online [AUHSOP Intranet]. Hudson, OH: Lexi-Comp, Inc. [updated Feb 1, 2014, cited 2014 Feb 25]. [about 15 p.]. Available from http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/1082879
2. Lovell DJ, Giannini EH, Reiff AO, Kimura Y, Li S, Hashkes PJ, et al. Long-term safety and efficacy of rilonacept in patients with systemic juvenile idiopathic arthritis. Arthritis Rheum. 2013 Sep;65(9):2486-96.

Updated Recommendations for Systemic JIA[1]

Medications	Comments
NSAIDs commonly used in practice	• Appropriate initial monotherapy for less complicated disease • Should never be used as monotherapy as initial treatment in patients with a global MD assessment ≥5 • Time to max response: 1 month
Systemic Glucocorticoids (Prednisone, methylprednisolone)	• Appropriate for initial monotherapy for patients with a global MD ≥5 • Time to max response: 2 weeks • Appropriate to use as adjunctive treatment
Intra-articular Glucocorticoids	• Appropriate to use as adjunctive treatment in patients with less than 4 active joints
Anakinra (Kineret)	• Appropriate first-line therapy in patients with a global MD ≥5 • Time to max response: 1 month
Canakinumab (Ilaris)	• Appropriate to initiate monotherapy after treatment failure with NSAIDs, glucocorticoids or anakinra
Tocilizumab (Actemra)	• Appropriate to initiate monotherapy after treatment failure with NSAIDs, glucocorticoids or anakinra
TNFα inhibitors (Adalimumab, etanercept, and infliximab)	• Monotherapy may be initiated after treatment failure with anakinra
Rilonacept (Arcalyst)	• Evidence supporting the use of rilonacept has been published since the development of the update

References

1. Ringold S, Weiss PF, Beukelman T, et al. 2013 Update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis. *Arthritis Rheum.* 2013 Oct;65(10):2499-2512.

Useful Websites:

The Arthritis Foundation: https://www.arthritis.org/

The American College of Rheumatology: http://www.rheumatology.org

The Nemours Foundation (A Children's Health System): http://kidshealth.org/

The American Academy of Pediatrics: http://www.healthychildren.org

The Last Dose

"The physician should not treat the disease but the patient who is suffering from it." ~Maimonides [Medieval philosopher, 1135-1204]

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