AU InforMed

Volume 10 Number 5 (Issue 256) *Monday, July 2, 2012*

Guest Editors: Jillian Blair Thomas and Michael Wayne Frye, Pharm.D. Candidates 2013

Key Inforbits

- Juvenile Idiopathic Arthritis Introduction and Diagnosis (JIA)
- Treatment Goals for JIA
- Treatment Options for JIA
- Non-Pharmacological Options to Aid JIA

July 1-31, 2012 is....
Juvenile Idiopathic Arthritis Awareness Month!

Juvenile Idiopathic Arthritis (JIA): Introduction and Diagnosis

Juvenile idiopathic arthritis (JIA) is one of the most common rheumatic diseases among children.[1-5] JIA is estimated to affect about 294,000 children and adolescents, approximately 1 in 1000 children, in the United States. Juvenile idiopathic arthritis is estimated to account for approximately 827,000 doctor's appointments and emergency room visits annually and about $128 billion annually in direct medical and indirect health care costs.[2,3,5]

Juvenile idiopathic arthritis (JIA) includes any form of arthritis that develops in children and adolescents before the age of 18.[2] Similar to rheumatoid arthritis, JIA is characterized by inflammation of the synovial tissue within the joint, leading to joint deformity and/or destruction.[5] Signs and symptoms can include: joint pain, swelling, and/or tenderness; limited range of joint motion; limited use of the joint; limited growth of bone and joint cartilage in the affected joint; and deformity of the joint as a result of destruction of bone and joint cartilage due to inflammation of the synovial tissue.[2,5]

Juvenile idiopathic arthritis (JIA) can present in many forms, depending mainly on the number and type of joints involved.[5] Polyarticular JIA is one of the most common forms of JIA. In this type of JIA, at least five (5) joints are affected. Females are more affected by polyarticular JIA than males. The joints that are most commonly affected by polyarticular JIA are the knee, wrist, and ankle in a symmetrical fashion. Oligoarticular or pauciarticular JIA is another common form of JIA. It is different from polyarticular JIA in that it affects less than five (< 5) joints. It affects the same joints as polyarticular JIA, but usually not in a symmetrical fashion. Eye inflammation, or uveitis, may be seen in oligo- or pauciarticular arthritis, usually in females that are positive for the presence of antinuclear antibodies. A more serious form of JIA is systemic onset JIA. This type of JIA is characterized by high spiking fevers that may last for long periods of time (e.g. weeks). Systemic JIA may also present with erythematous rash on the child or adolescent's thighs or chest. Males and females are equally affected by systemic onset JIA. Other types of JIA include psoriatic JIA, which involves JIA characterized by psoriasis, and

juvenile spondyloarthropies, which is characterized by arthritis affecting the spine and joints of the lower extremities.[2,4]

Diagnosis of juvenile idiopathic arthritis involves attaining a complete patient history and physical exam. Unfortunately, there is no one laboratory parameter or test used to diagnose JIA.[2] It is necessary to first rule out other possible causes of the patient's joint symptoms.[4] Laboratory parameters that may be useful are plasma monitoring for markers of inflammation and imaging (i.e. x-ray, MRI, etc.) to check for joint deformities.[2]

The type of JIA a patient is diagnosed with, level of disease activity, and presence or absence of features of poor prognosis are the main determinants of the course of treatment for a patient with JIA. JIA disease activity is classified as either low, moderate, or high. Features of poor prognosis can vary depending on the type of arthritis for which a patient is diagnosed. Arthritis of the hip or cervical spine, radiographic damage such as erosions or joint space narrowing, and positive rheumatoid factor (RF) or anti-cyclic citrullinated peptide antibodies are all examples of features of poor prognosis, with radiographic damage and arthritis of the hip being the most universal across types of JIA.[3] Only about one-third of patients with JIA experience complete disease remission, however, the majority of patients do not experience any long-term disability.[5]

Goals of Treatment

Primary Goals of Treatment:[2,5]

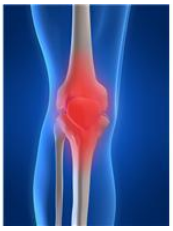
- Minimize destruction of joints due to inflammation and prevent further joint damage
- Maintain and appropriately treat the patient's pain
- Preserve the current or restore range of motion (ROM)
- Promote healthy growth and development of the patient's joints
- Improve and maintain the patient's quality of life (QOL)

Treatment Options: Pharmacologic Agents

The main drug classes and their role in the treatment of JIA are:[3,5,6,7,8]

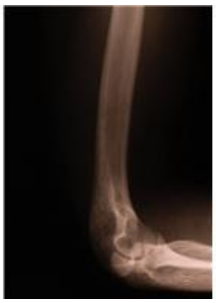
- Glucocorticoids
  - Mechanism of action (MOA): suppress leukocyte migration and reduce capillary permeability to decrease inflammation; also suppresses the immune system
  - Intra-articular injections
    - Use of these agents is recommended for patients with active arthritis regardless of other treatments the patient may be on
    - Triamcinolone hexacetonide is the recommended agents because it has shown to be the most efficacious
    - Symptom improvement should be seen for at least 4 months after injection and can be repeated as needed
  - Systemic agents
    - Recommended as monotherapy or in combination with other agents for patients with systemic arthritis and active fever
- Non-steroidal anti-inflammatory drugs (NSAIDs)
  - MOA: inhibit cyclooxygenase (COX)-1 and COX-2 which results in decreased prostaglandin production and reduced inflammatory response
  - Monotherapy is inappropriate for patients with active arthritis

    - Monotherapy is acceptable during the evaluation period for patients presenting with suspected systemic arthritis
    - Can be used in combination with other agents for all types of JIA
- Non-biologic disease modifying anti-rheumatic agents (DMARDs)
    - Methotrexate
        - MOA: inhibits dihydrofolate reductase and thymidylate synthase to ultimately inhibit DNA synthesis
        - Initiation of therapy is recommended within the first 1-2 months after diagnosis regardless of disease severity except in patients with systemic arthritis with active fever but no signs of active arthritis
        - Continue methotrexate when a tumor necrosis factor (TNF)-alpha inhibitor is added to therapy
    - Leflunomide
        - MOA: inhibits dihyroorotate dehydrogenase to ultimately inhibit RNA and protein synthesis
        - Treatment can be initiated in patients with a history of arthritis in at least 5 joints with high disease activity or moderate disease activity with features of poor prognosis
        - Methotrexate is favored over leflunomide
    - Sulfasalazine
        - MOA: inhibits prostaglandin synthesis to decrease inflammatory response
        - May be used after an adequate trial of glucocorticoid injections and NSAIDs for patients with enthesitis-related arthritis with moderate or high disease activity
    - Hydroxychloroquine
        - MOA: may inhibit neutrophil and eosinophil migration and prostaglandin synthesis leading to anti-inflammatory effects
        - Initiation of monotherapy is inappropriate for patients with active arthritis
        - Use not recommended in pediatric patients[6,7]
    - Combination of non-biologic DMARDs
        - May or may not provide additional benefit over methotrexate monotherapy



- Biologic DMARDs
    - Tumor necrosis factor- alpha (TNF-α) inhibitors
        - Includes adalimumab, etanercept, and infliximab
        - MOA: reduce inflammatory response by binding TNF-α and preventing its interaction with TNF receptors
        - May be added to therapy after a 3-6 month trial of methotrexate or leflunomide at the maximum tolerated dose if arthritis is still active
        - For patients with enthesitis-related or active sacroiliac arthritis, may start a TNF-α inhibitor after a 3-6 month trial of sulfasalazine if arthritis is still active
        - If a patient receives an agent for 4 months and still has moderate or high disease activity, it is appropriate to switch to another agent within the class
    - Abatacept
        - MOA: modulates T-cell costimulation by binding CD80/86 and preventing interaction with CD28 on antigen presenting cells

        - Recommended for patients that have received more than one TNF-α inhibitor sequentially and still have moderate or high disease activity or low disease activity with features of poor prognosis
        - May switch to abatacept after a 4 month trial of a TNF- α inhibitor if patient still has high disease activity or moderate disease activity with features of poor prognosis
    - Rituximab
        - MOA: binds CD20 on B cells and mediates cell lysis, leading to the depletion of B cells
        - Option for patients who have received a TNF-α inhibitor and abatacept sequentially and still has high disease activity or moderate disease activity with features of poor prognosis
        - May be more appropriate for patients who are RF-positive
    - Anakinra
        - MOA: Interleukin-1 (IL-1) receptor antagonist
        - Mainly used for patients with systemic arthritis
        - Recommended for all patients with systemic arthritis…
            - With active fever and features of poor prognosis
            - Maintain or develop active fever while receiving systemic glucocorticoids



        - May be added on to therapy for patients with systemic arthritis without active systemic features who received methotrexate or methotrexate plus either a TNF-α inhibitor or abatacept and still have moderate or high disease activity
        - May be less appropriate to start later in the disease course compared to soon after disease onset

Dosing Information for Agents Used for the Treatment of JIA[5-8]

Drug	Trade Name	Recommended Dose
Glucocorticoids*		
triamcinolone hexacetonide	Aristospan®	Large joints (hip, knee, shoulder, etc.): 40 mg or 1 mg/kg given as an intra-articular injection Small joints (elbow, ankle, etc.): 20 mg or 0.5 mg/kg given as an intra-articular injection Maximum dose= 60 mg
prednisone	Prednisone Intensol®	0.5-2 mg/kg/day PO given as 1-4 divided doses
NSAIDs*		
ibuprofen	Advil®; Motrin®; Addaprin®; I-Prin®; Proprinal®; Ultraprin®	30-50 mg/kg/day PO given as divided doses Q 6-8h Start at lower end of range and titrate up as needed Maximum dose: 2.4 g/day
naproxen	Aleve®; Anaprox®; Naprosyn®; Naprolean®; Mediproxen®	Children >2 yo: 10 mg/kg/day PO given as 2 divided doses Maximum dose: 15 mg/kg/day
Non-biologic DMARDs		
methotrexate	Rheumatrex®; Trexall®	10 mg/m^2 given once weekly either orally or as an intramuscular injection
leflunomide	Arava®	100 mg loading dose PO for 1-3 days followed by:

		10 mg PO daily for patients weighing 10-19.9 kg 15 mg PO daily for patients weighing 20-40 kg 20 mg PO daily for patients weighing >40 kg
sulfasalazine	Azulfidine®; Azulfidine EN-tabs®	Children ≥6 yo: 30-50 mg/kg/day PO given in 2 divided doses Initial dose should be one-quarter to one-third of expected maintenance dose. Titrate weekly until maintenance dose is reached. Max dose: 2 g/day
hydroxychloroquine	Plaquenil®	Use not recommended in pediatric patients 3-6 mg/kg PO daily has been studied in clinical trials
Biologic DMARDs		
adalimumab	Humira®	Children 15-29.9 kg: 20 mg given subcutaneously every other week Children ≥30 kg: 40 mg given subcutaneously every other week
etanercept	Enbrel®	0.8 mg/kg given subcutaneously once per week or 0.4 mg/kg given subcutaneously twice weekly Maximum dose: 50 mg weekly
infliximab	Remicade®	3-10 mg/kg IV infusion given at week 0, week 2, and week 6, then Q 4-10 weeks Give in combination with methotrexate
abatacept	Orencia®	Children ≥6 yo and <75 kg- 10 mg/kg infusion Children ≥6 yo and ≥75 kg- dose based on body weight 75-100 kg- 750 mg infusion >100 kg- 1000 mg IV infusion Given at week 0, week 2, week 4, then Q 4 weeks
rituximab	Rituxan®	1000 mg IV infusion on days 1 and 15; repeat at 6-12 months as needed Give in combination with methotrexate
anakinra	Kineret®	1-2 mg/kg daily given by subcutaneous injection Maximum daily dose: 100 mg

*The glucocorticoids and NSAIDs listed in the chart are examples of commonly used agents, but are not the only agents from these classes that can be used in the treatment of JIA. The American College of Rheumatology specifically recommends triamcinolone hexacetonide due to its efficacy.[3]

Non-Pharmacological Recommendations

Proper patient education about the disease is a critical part of successfully treating JIA. While this is true, many patients may not be of age to fully understand the nature of the patient education. Therefore, the aim of the patient education, in these cases, should be focused on educating the guardian/caregiver. Other recommendations that may be helpful in successfully managing JIA include:[2,5]

- Getting adequate physical activity on a scheduled basis to maintain ROM and minimize stiffness of affected joint(s)
- Heat and cold therapy and massage therapy may have beneficial effects on joint inflammation, pain control, and quality of life
- Splints or orthotics may be helpful in relieving pain and promoting proper joint health
- Maintaining proper nutrition, as there is a potential for weight loss due to loss of appetite, general fatigue, or jaw stiffness

- Attending regularly scheduled eye care for prevention/maintenance of uveitis and dental care appointments to properly manage jaw stiffness
- Weight bearing exercise can help prevent bone loss, but should be avoided during times of joint inflammation
- Physical or occupational therapy may be an option to aid in restoration of ROM or to improve flexibility of affected joints
- Surgery may be an option for some patients

Non-pharmacologic therapies play an important role in the treatment of JIA. Implementation of these therapies can help maintain joint flexibility and ROM and prevent future disability.[5]

References:

1. Dueckers G, Guellac N, Arbogast M, et al. Evidence and consensus based GKJR guidelines for the treatment of juvenile idiopathic arthritis. Clin Immunol. 2012;142:176-93.
2. Arthritis Foundation[Internet]. Atlanta: Arthritis Foundation; c2012. Juvenile arthritis: the basics about this disease that affects 300,000 children in the U.S. [cited on 5 Jun 2012]. Available from: http://www.arthritis.org/juvenile-arthritis.php.
3. Beukelman T, Patkar NM, Saag KG, et al. 2011 American college of rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res. 2011 Apr;63(4):465-82.
4. Hull RG. Guidelines for the management of childhood arthritis. Rheumatology. 2001;40:1309-12.
5. Chen SW, O'Callaghan RE, Reta AM. Chapter 44: Rheumatoid arthritis. In: Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BR. Koda-Kimble and Young's applied therapeutics: the clinical use of drugs. 10th ed. Pennsylvania: Wolters Kluwer; c2013. p.1002-38.
6. Methotrexate, Leflunomide, Anakinra, Rituximab, Abatacept, Hydroxychloroquine, Sulfasalazine, Triamcinolone (systemic), Adalimumab, Etanercept, Infliximab, Ibuprofen, Naproxen, Prednisone. In: Lexi-Comp Online {AUHSOP Intranet]. Hudson, OH: Lexi-Comp, Inc. [updated 2012, cited 2012 Jun 6]. Available from: http://online.lexi.com/lco/action/home.
7. Triamcinolone hexacetonide (intra-articular), Methotrexate, Leflunomide, Sulfasalazine, Hydroxychloroquine sulfate, Abatacept, Rituximab, Anakinra, Adalimumab, Etanercept, Infliximab, Prednisone, Ibuprofen, Naproxen. In: Drug Facts and Comparisons (Facts and Comparisons eAnswers) [AUHSOP Intranet]. St. Louis: Wolters Kluwer Health [updated 2012, cited 2012 Jun 6]. Available from: http://online.factsandcomparisons.com/index.aspx.
8. Leflunomide, Prednisone, Methotrexate, Hydroxychloroquine. In: Clinical Pharmacology [AUHSOP Intranet]. Tampa, FL: Gold Standard/Elsevier [c2012, cited 2012 Jun 6]. Available from: http://www.clinicalpharmacology-ip.com/.

The last "dose" …

Energy and persistence conquer all things.
Benjamin Franklin (US author, diplomat, inventor, physicist, politician, printer and signer of the Declaration of Independence [1706 - 1790])

An electronic bulletin of drug and health-related news highlights, a service of …
Auburn University, Harrison School of Pharmacy, Drug Information Center
• Phone 334-844-4400 • Fax 334-844-8366 • http://www.pharmacy.auburn.edu/dilrc/dilrc.htm
Bernie R. Olin, Pharm.D., Director
Archived issues are available at: http://pharmacy.auburn.edu/dilrc/au_informed.htm