Current Management of Juvenile Idiopathic Arthritis

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Introduction

Juvenile Idiopathic Arthritis (JIA) is the most common form of chronic rheumatic disease in children. There is wide variation in the epidemiological studies of JIA in different countries. It is estimated that the overall prevalence of JIA is from 0.07 to 4.01 per 1000 children. From most outcome studies of JIA, active disease often persists into adult life in all subtypes of JIA. Several long-term studies conducted from 1960s to 1990s showed that 31% to 55% patients with JIA have active disease when followed for at least 10 years. Persistently active disease is associated with poor outcome and long term disability. Thus, the current management of JIA is to diagnose early, treat early and be aggressive earlier in order to limit permanent disability. This article focuses on the current medical therapies of JIA.

Definition

JIA is defined as presence of arthritis (swelling or effusion, limitation of range of motion, tenderness or pain on motion, and increased heat) in one or more joints. The age at onset is less than 16 years old. The duration of arthritis lasts for 6 weeks or longer and other causes of arthritis (e.g. septic arthritis, malignancy) are excluded.

Classification

JIA is a new ILAR (International League Against Rheumatism) classification of juvenile arthritis. (Table 1)

Treatment

A. Multi-disciplinary Approach

A coordinated multi-disciplinary team care consisting of paediatric rheumatologist, nurse specialist, social worker, physical therapist, occupational therapist, orthopaedic surgeon and clinical psychologist is the key to success of management of JIA. Uveitis is an important extra-articular complication in children with JIA. Children with JIA should have regular slit-lamp screening by ophthalmologists. The aims of treatment are to preserve cartilage, control pain and preserve range of motion, muscle strength and function; to manage systemic complications; to facilitate normal nutrition, growth, and physical and psychological development.

B. Medical Therapy

Non-steroidal Anti-inflammatory Medications (NSAIDs)

Traditional NSAIDs are the first line therapy for all types of JIA. Naproxen is effective in management of joint inflammation in a dose of 15-20 mg/kg/day in two divided doses. Other NSAIDs include ibuprofen (35 mg/kg/day in 4 divided doses), tolmetin (25-30 mg/kg/day in 3 doses) and diclofenac (3-5 mg/kg/day in 4 doses). Other NSAIDs have specific indications but are not officially approved for use in children.

Disease Modifying Anti-Rheumatic Medications (DMARDs)

a. Methotrexate (MTX)

Methotrexate remains the remission-inducing agent of first choice for persistent and active arthritis. Most paediatric rheumatologists will initiate methotrexate therapy early in the disease course, sometime within 8 weeks of initiation of NSAID therapy. The starting dose is usually 15 mg/m²/week per oral route. Daily folic acid supplementation (1 mg/day) may alleviate the side effects of nausea, vomiting, gastrointestinal upset and mucosal stomatitis without compromising the therapeutic effect. If the response is inadequate, it could be stepped up with an increment of 2.5 mg/week. Subcutaneous route is advised if the dose reaches 20 mg/week or more.

Most studies have demonstrated no severe liver damage in children taking methotrexate for extended periods. There is no clear evidence that methotrexate increases the risk of malignancy in children. In our hospital, a retrospective study (from 1996 to 2005) of 40 children with JIA was performed to review the treatment outcome and adverse effects associated with use of MTX. We concluded that MTX was safe and well tolerated in the majority of patients, but treatment response varied with different JIA subtypes. Methotrexate is teratogenic and adolescent patients are advised about prevention of pregnancy and total abstinence from alcohol drinking. Patients should be informed of the nature, toxicities, precautions, expected duration of therapy and education of subcutaneous injection technique.

b. Leflunomide

Methotrexate is the mainstay of therapy, but recently, combination DMARD therapy such as methotrexate and leflunomide has been shown to have better clinical outcomes when methotrexate monotherapy fails. Headache, diarrhoea, abdominal pain, elevated liver enzymes, reversible hair loss and skin rash are the reported side effects. Leflunomide is teratogenic and patients should not take alcohol to minimise hepatotoxicity.
c. Corticosteroid: Systemic Corticosteroid
Moderate or high dose systemic corticosteroid therapy should be reserved for patients with systemic arthritis with severe systemic symptoms that cannot be controlled with NSAID, such as macrophage activation syndrome, symptomatic serositis and myocarditis. Systemic corticosteroid is not recommended for all other subtypes of JIA.

Intra-articular Corticosteroid Injection
Intra-articular corticosteroid is a safe and effective treatment in managing synovial inflammation in a child with monoarticular or oligoarticular arthritis. It is sometimes indicated in treatment of particular symptomatic joints in a child with polyarticular arthritis. It provides sustained anti-inflammatory effect on synovium lasting for 4 to 6 months in most cases. It has been shown by magnetic resonance imaging studies that intra-articular steroid therapy resulted in significant suppression of inflammation and pannus formation while cartilage integrity is well preserved.

d. Sulphasalazine (SSZ)
SSZ has been shown to be effective in children with oligoarthritis or spondylitis at doses 30-50 mg/kg/day (maximum dose 2000 mg/day). The adverse effects are gastrointestinal intolerance, rash, leukopenia and hypogamma-globulinaemia.

e. Cycloporine A (CsA)
There are no controlled trials on the use of CsA in JIA treatment. A few open studies suggest that it may have a role in the treatment of systemic symptoms of systemic-onset JIA and steroid sparing effect but less convincing efficacy for arthritis control. The usual dose is 3-5 mg/kg/day. Adverse effects include hypertension, hand tremor, impaired renal function, gingival hyperplasia and hypertrichosis.

f. Combination DMARD Therapy
If conventional treatment with a single DMARD fails to adequately control clinical symptoms or to prevent disease progression, combination DMARD therapy is indicated. In such cases, rheumatologist referral is strongly recommended.

g. Biologic Agents
It has been shown that tumour necrosis factor and other cytokines like interleukin 1 and interleukin 6 are important mediators of joint and synovial inflammation. Targeted monoclonal antibody therapies have been developed recently.

i. TNF Inhibitors
Etanercept, a TNF receptor antagonist, is the first biologic to be approved by the FDA for use in JIA. In a randomised, prospective, placebo-controlled trial in children who had severe JIA not controlled by methotrexate, etanercept induced a rapid, significant improvement in the clinical and laboratory features of JIA. The median improvements ranged from 40% to 95%. Etanercept is well tolerated in children, with headache, upper respiratory tract infections, and injection site reactions being the toxicities reported most commonly. Rare but serious infections such as sepsis and varicella meningitis have been reported. Other infections, such as TB, histoplasmosis, and listeriosis, have been reported in people taking anti-TNF-alpha drugs. Neurologic disorders, retrobulbar optic neuropathy, cutaneous vasculitis, and pancytopenia have been reported. Data on the long-term toxicity of etanercept are not available. Other anti-TNF-alpha biologics such as infliximab and adalimumab have been given to children who have JIA, with improved response.

ii. Anti-IL-6
Anti-IL-6R, termed tocilizumab, has been tried in children who had systemic arthritis with some success.

iii. Anakinra
i. Anakinra is a recombinant form of agonist to interleukin-1 receptor (IL-1Ra) and its use in arthritis treatment is associated with reduction in mononuclear cell infiltration of the synovial membrane. A few anecdotal reports indicate good responses to the use of anakinra (IL-1 receptor antagonist) in JIA.

h. Thalidomide
1. Thalidomide is a potential agent that looks promising in treatment of inflammatory joint disease.

C. Autologous Stem Cell Transplantation (ASCT)
Despite the emergence of new therapeutic agents which appear to be more effective in treating JIA, there are still some patients who remain resistant to medical therapies. Autologous stem cell transplantation has been considered in recalcitrant cases. Drug-free remissions of disease have been reported, but the procedure carries a significant mortality risk, usually from macrophage activation syndrome. Stem cell transplantation should be performed only after all other treatment options have failed. In our hospital, we have performed autologous stem cell transplantation for two patients. One is in complete remission with follow up more than 6 years and the other relapsed 9 months after transplantation, and remission is achieved with combination therapy of leflunomide, cyclosporine and thalidomide. At present, this treatment should be considered experimental and should be reserved for those patients who have most severe disease unresponsive to standard treatment.

Conclusion
Progress in achieving international consensus concerning the classification of JIA has been made. There are many promising developments in the understanding and improved treatment options in JIA. In order to prevent long term disability, earlier and more aggressive therapy is advised for those with persistent arthritis. A multidisciplinary team approach is very important in management of JIA. It is hoped that with increased awareness of the long term morbidity of JIA and the availability of new treatment options in JIA, the outcome of patients with JIA could be further improved.
# Table 1 ILAR Classification of JIA

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<tr>
<th>Category</th>
<th>Criteria</th>
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<tr>
<td>Systemic arthritis</td>
<td>Arthritis: daily fever for at least 2 weeks evanescent nonfixed erythematous rash generalised lymphadenopathy hepato/splenomegally arthritis</td>
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<tr>
<td>Oligoarthritis</td>
<td>Arthritis of one to four joints during the first 6 months of disease.</td>
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<tr>
<td>o Persistent</td>
<td>Affects no more than four joints throughout the disease course.</td>
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<tr>
<td>o Extended</td>
<td>Affects more than four joints after the first 6 months.</td>
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<tr>
<td>Polyarthritis (*RF-negative)</td>
<td>Affects five or more joints in the first 6 months of disease. Tests for RF are negative.</td>
</tr>
<tr>
<td>Polyarthritis (*RF-positive)</td>
<td>Affects five or more joints in the first 6 months of disease.</td>
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<tr>
<td>Enthesitis-related arthritis</td>
<td>Arthritis and enthesitis or arthritis or enthesitis with at least two of sacroiliac tenderness and/or inflammatory spinal pain human leukocyte antigen (HLA) B27-positive, family history in a first- or second-degree relative of medically confirmed HLA B27-associated disease.</td>
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<tr>
<td>Psoriatic arthritis</td>
<td>Arthritis and psoriasis or arthritis and at least two of: dactylitis, nail abnormalities, family history of psoriasis in at least one first-degree relative.</td>
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<tr>
<td>Other</td>
<td>Arthritis of unknown cause persisting for at least 6 weeks that either does not fulfill criteria for any categories or fulfills criteria for more than one category</td>
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* RF=rheumatoid factor

## References


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