The principles of pharmacological treatment of juvenile idiopathic arthritis

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Abstract

Juvenile idiopathic arthritis (JIA) is characterized by joints with swelling, pain, and limitation of movement. The main principle of treatment is to control this active arthritis in order to prevent permanent damage. This review describes the different types of JIA, a stepwise approach to treatment according to the level of disease activity, and the medications used.

Keywords biologics; corticosteroids; JIA; juvenile idiopathic arthritis; methotrexate; NSAIDs; sulfasalazine

Introduction

Juvenile idiopathic arthritis (JIA) is one of the most common paediatric rheumatological diseases in the United Kingdom with an annual incidence of 1/10,000 children. It is defined as arthritis of unknown aetiology, persisting longer than 6 weeks, with an onset before the age of 16 years.

The pharmacological management of JIA is a rapidly progressing field. In addition to long established drugs, including methotrexate, there are new and innovative biological therapies which have revolutionized the care of children with rheumatic diseases. Despite these advances in therapy, a significant proportion of affected children continue to suffer disability secondary to active disease. A good understanding of the various pharmacological treatment options enables more effective treatment.

Treatment objectives

The key aim of drug treatment is to achieve control of active arthritis and to enable a normal quality of life for the child. The ultimate objective is to prevent the irreversible joint and organ damage that active arthritis can cause. The possible implications of untreated or inadequately treated disease include impaired growth, significant disability, visual loss from complications of uveitis and an impact on the child's psychosocial development.

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Management of JIA may necessitate treatment for many years and is done in partnership with the child and family to help compliance. Studies in adult arthritis suggest a "window of opportunity" early in the disease course, when the institution of disease-modifying therapy has shown significant benefit. Therefore there may be a need for a more aggressive treatment approach early in the course of the disease to achieve complete disease control or even remission.

Outcome measures for assessing disease activity in JIA

A key to assessing response to treatment is having validated measures to disease activity. Originally developed to facilitate clinical trials, the American College of Rheumatology (ACR) Paediatric measures are used in routine clinical care to help assess efficacy of therapies.

The core set of outcome measures for JIA are:

- Physician global assessment of disease activity (10 cm visual analogue scale)
- Patient/parent assessment of overall well-being (10 cm visual analogue scale)
- Number of joints with active arthritis (joints with swelling not due to deformity or joints with limitation of motion with pain, tenderness or both)
- Number of joints with limitation of motion
- Functional ability based on Child Health Assessment Questionnaire (CHAQ) scores
- Erythrocyte sedimentation rate (ESR).

Responses are measured according to percentages of improvement or worsening of the variables. To meet a response termed ACR Pedi30, patients must have a 30% improvement from baseline in at least three of the six response variables, with no more than one of the six variables having worsened by 30% or more.

Therapeutic approaches

The International League Against Rheumatology (ILAR) has subdivided JIA into six subtypes (Table 1). Therapy and prognosis of each subtype varies.

The American College of Rheumatology (ACR) has recently published recommendations for the treatment of JIA, which cover the initiation and safety monitoring of the therapeutic agents used. These recommendations divide JIA into "five treatment groups", instead of the ILAR JIA categories. Features of poor prognosis and disease activity, which are specific for each group, are also taken into account (see Boxes 1–5).

The ACR five treatment groups include:

1. History of arthritis of four or fewer joints
2. History of arthritis of five or more joints
3. Active sacroiliac arthritis
4. Systemic arthritis with active systemic features (and without active arthritis)
5. Systemic arthritis with active arthritis (and without active systemic features).

Stepwise pharmacological treatment using the ACR 2011 recommendations

The exact timing and factors leading to the progression from one JIA medication to the next are not strictly defined. The recently published ACR 2011 recommendations, although not universally

ILAR classification of JIA subtypes

Oligoarticular	1–4 joints affected in the first 6 months of the disease Subdivided into persistent oligoarticular/extended oligoarticular Extended oligoarticular is >4 joints affected after first 6 months
Polyarticular	Five or more joints affected during the first 6 months Subdivided into rheumatoid factor positive/negative
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least two of: dactylitis, nail pitting or onycholysis, psoriasis in a 1st degree relative
Enthesitis related arthritis	Arthritis and enthesitis, or arthritis or enthesitis with two of: sacroiliac joint tenderness of inflammatory lumbosacral pain, HLA-B27 antigen positive, onset after age of 6 years in a male, acute (symptomatic) anterior uveitis, history of HLA-B27 associated disease in 1st degree relative
Systemic arthritis	Arthritis with or preceded by daily fever for at least 3 days, accompanied by at least one of: evanescent erythematous rash, generalized lymphadenopathy, hepatomegaly or splenomegaly or both, serositis.
Other undifferentiated arthritis	

Table 1

Features of poor prognosis and disease activity for a history of arthritis of four or fewer joints

Features of poor prognosis

- Arthritis of the hip or cervical spine
- Arthritis of the ankle or wrist AND marked or prolonged inflammatory marker elevation
- Radiographic damage (erosions or joint space narrowing by radiograph)

Disease activity levels

Low disease activity (must satisfy all)

- One or fewer active joints
- Erythrocyte sedimentation rate or C-reactive protein level normal
- Physician global assessment of overall disease activity <3 of 10
- Patient/parent global assessment of overall well-being <2 of 10

Moderate disease activity (does not satisfy criteria for low or high activity)

- One or more features greater than low disease activity level AND fewer than three features of high disease activity

High disease activity (must satisfy at least three)

- Two or more active joints
- Erythrocyte sedimentation rate or C-reactive protein level greater than twice upper limit of normal
- Physician global assessment of overall disease activity ≥7 of 10
- Patient/parent global assessment of overall well-being ≥4 of 10

Box 1

adopted, provide a framework of when to progress through the steps. The initial two steps in the pharmacological treatment of JIA are usually NSAIDs and intra-articular steroid injections, which may be repeated as required.

Patients with four or fewer joints involved may not require methotrexate at presentation unless there is high disease activity or poor prognostic features. Methotrexate is started if the joint flares within 4 months of the intra-articular steroid injection or if more than three injections are needed in 12 months. Anti-TNF (etanercept) may be appropriate to be added when there is high disease activity after 6 months of maximum methotrexate (10–15 mg/m^2 subcutaneously weekly) or if there are poor prognostic factors and moderate/high disease activity after 3 months of maximum methotrexate. If the response to anti-TNF is inadequate after 4–6 months a change in biologic may be considered.

Patients with five or more joints involved usually have methotrexate started at diagnosis unless there is low disease activity and no poor prognostic features. When there are low activity levels not responding to 6 months of methotrexate, or moderate or high activity levels not responding to 3 months maximum methotrexate, addition of anti-TNF may be appropriate. If there is persistent moderate or high activity after 4 months a change in biologic may be appropriate for example to a 2nd anti-TNF, or in cases not responsive to anti-TNF the T-cell regulator abatacept.

The choice of medication for patients with systemic JIA depends on the presence or absence of ongoing systemic features. It is routine practice in the UK to use systemic corticosteroid as the first step. A biologic (anti-IL-6/IL-1) may be required for ongoing systemic features. Methotrexate is prescribed for ongoing joint symptoms without ongoing systemic features and if there is inadequate response to methotrexate anti-TNF or anti-IL-6/IL-1 biologic may be used.

The ACR 2011 recommendations for the group of children with active sacroiliac arthritis recommend that anti-TNF may be started after a trial of methotrexate or sulfasalazine for 3–6 months, or in the presence of high disease activity or features of poor prognosis after an adequate trial of NSAIDs.

Anti-inflammatory medications

Non-steroidal inflammatory drugs (NSAIDs)

NSAIDs have an analgesic and anti-inflammatory effect. They inhibit cyclooxygenase and thus reduce prostaglandins. Prostaglandins amplify the physiological mechanisms of pain and mediate the vasodilation of inflammation.

NSAIDs are suitable for most children from the onset of symptoms, prior to JIA being diagnosed. NSAIDs may sometimes be used as JIA monotherapy, but only for about 8 weeks, and usually only for children with less than four joints involved, low disease activity and no predictors of poor prognosis. Naproxen is