Conventional and biologic therapies – towards personalised pharmacotherapy for juvenile idiopathic arthritis

The management of juvenile idiopathic arthritis (JIA) is aimed at rapid joint inflammation control. Standard therapies remain the first line treatment but biologics offer an effective alternative for patients suffering from ongoing inflammation. An improved understanding of the biological characteristics of JIA sub-types will in future allow for increasingly personalised treatment regimens.

In Finland, some 2,300 children are affected by JIA and about 150 new cases are diagnosed each year. Outcomes have improved over the past decade, thanks largely to the availability of more effective therapies.

The same treatments are used to control joint inflammation in both child and adult patients. Pharmacotherapy for children affected by JIA are tailored to their individual needs wherever possible and are determined by levels of inflammatory activity as well as disease sub-type and severity.

Pharmacotherapy aims for remission

The treatment of JIA has changed significantly in the past decade, due in large part to the new scientific and clinical data available on biologic therapies. The aim of clinicians now is to achieve complete remission by suppressing all active inflammation.

Achieving symptomatic relief and preventing long-term joint damage are no longer considered sufficient clinical objectives. Previously, inflammation was partially or temporarily controlled in up to 20−30% of children with JIA. In the era of biologic therapies, the proportion of patients with an insufficient response to treatment now stands at only a few per cent.

New guidance highlights the need for standard and biologic therapies

Two new sets of recommendations for the treatment of JIA (Kröger et al. 2012 and Beukelman et al. 2011) have been published recently. The recommendations are broadly similar in content, barring some interesting differences.

The American guidelines provide an assessment of appropriate therapeutic interventions based on a systematic literature review. The assessment of treatment efficacy is focused on classifying inflammatory activity as well as well-known indicators for poor prognosis. The Finnish guidelines also take into account clinical experience as well as quality-of-life considerations.

In Finland, the use of combination disease modifying antirheumatic drug (DMARD) therapies (Table 1) has become established clinical practice over the past two decades although there is little published evidence on the benefits of combination therapies in the treatment of JIA. The American guidelines do not support the use of combination therapies in the treatment of JIA due to the lack insufficient evidence-based data is available on their safety and efficacy.

The use of glucocorticoids is not recommended in the United States except in the treatment of systemic onset JIA previously known as Still's Disease. In Finland, glucocorticoids are used in the systemic treatment of polyarthritis as well as in cases of oligoarthritis associated with erosion of the articular surface or poor prognosis and affecting no more than four joints. When used, they are prescribed in conjunction with standard arthritis therapies, usually in low doses and on alternate days, to prevent adverse effects.

Glucocorticoids are used as part of combination therapies in circumstances, where pain and morning stiffness are otherwise poorly controlled or in the short-term when long-term therapies have not achieved the desired clinical response. Their use has become established practice in other parts of Europe too, despite the lack of convincing scientific evidence on glucocorticoid therapy for this indication. However, long-standing clinical experience suggests that their use is both effective and safe.

Table 1. Treatment of JIA in Finland in 2011 (based on Kröger et al. 2012).

Oligoarthritis (<4 joints)
Intra-articular glucocorticoid injections and regular NSAIDs.
If more than 2 injections (2 joints or 2 injections in the same joint) are required in a period of less than 4 to 6 months, DMARD to be added: • Most commonly methotrexate (MTX) (10–)15 mg/m2/once weekly, alternatively salazopyrine or leflunomid. Methotrexate with folic acid 4–5 mg/weekly. • Salazopyrine in cases of HLA-B27 positive or enthesitis-related arthritis. • Hydroxychloroquine for mildly-active JIA only.
Polyarthritic (>4 joints) JIA or erosive or poor prognosis oligoarthritis
Single intra-articular glucocorticoid injections as required.
MTX 15–20 mg/m2/weekly (+ folic acid); parenteral if required (s.c.); alternatively leflunomid or salazopyrine.
Systemic glucocorticoid for initial treatment or management of acute flare-ups (e.g. predisolone 0.2–0.5mg/kg/od). Calcium and Vit D replacement recommended for all patients on glucocorticoids.
If response to MTX (or alternative DMARD) insufficient: • Combination therapy: MTX (+ folic acid), another DMARD and low dose glucocorticoid alternate mornings or • TNF inhibitor (etanercet, adalimumab, infliximab, certolizumab, golimumab) with MTX (+ folic acid).
If no response to TNF inhibitor: • Iternative TNF inhibitor, abatacept, tosilizumab or rituximab.
Systemic onset JIA
Glucocorticoid injections in single joints as required.
Systemic glucocorticoid, e.g. predisolone 1–2 mg/kg/od according to severity.
Articular symptoms: MTX (+ folic acid) and TNF inhibitor as required.
Glucocorticoid resistance: tosilizumab or anti-IL-1 therapy (anakinra, kanakinumabi).

NSAIDs, intra-articular glucocorticoid injections and conventional therapies

NSAIDs, most commonly naproxen and ibuprofen, are used in the treatment of JIA for pain control and to alleviate stiffness. As they do not influence long-term outcomes, NSAIDs are almost always used in conjunction with intra-articular glucocorticoid injections, except in the least severe cases. This is the first line therapy for monoarthritis and oligoarthritis in particular.

If joint inflammation is not controlled with the administration of a limited number of glucocorticoid injections, the patient will usually be commenced on a DMARD therapy. Methotrexate is the most common and most closely studied form of DMARD. In terms of patient compliance, an additional benefit is that methotrexate is administered once weekly.

In certain circumstances, sulphasalazine and leflunomid may be nearly as effective as methotrexate. Sulphasalazine has been used in HLA-B27 positive patients in particular. These patients suffer from a JIA subtype affecting the entheses, the sites of tendon and ligament attachment to bone.

In recent years, there has been a reduction in the use of azathioprine and hydroxychloroquine to treat JIA. There is a lack of convincing evidence for their effectiveness and following the introduction of biologic agents, their role in the treatment of JIA remains unclear.

Biologics are used when conventional therapies are not enough

The indications for biologic therapies are chronic active polyarthritic (affecting more than four joints) JIA with a poor response to conventional DMARDs or monoarthritis with erosion of the articular surface. Normally, several conventional DMARDs and combination therapies are attempted prior to the commencement of biologic agents.

Biologic therapies are normally used in combination with methotrexate or another conventional therapy. Results from a number of studies indicate that biologic therapies may be more effective when used in combination with methotrexate than without. Methotrexate is also thought to inhibit or suppress antibody production against the biologic agent. This may result in the longer-term effectiveness of the biologic therapy.

First biologics are TNF inhibitors

Tumour necrosis factor (TNF-alpha), interleukin 1 (IL-1) and interleukin 6 (IL-6) are the key cytokines that induce and maintain the inflammatory process in JIA.

TNF inhibition was the mechanism of action for the first biologic treatments for rheumatoid arthritis. Etanercept and infliximab were introduced in the late 1990s. Etanercept is a soluble TNF receptor, which inhibits the binding of free TNF-alpha and TNF-beta. Infliximab, on the other hand, is a monoclonal TNF antibody.

Adalimumab, the third TNF inhibitor, was made available sometime after the introduction of the first two therapies. Adalimumab is an entirely humanised monoclonal TNF antibody. Anakinra, an IL-1 receptor antagonist, was brought into clinical use in the late 1990s.

Current experience suggests that all three TNF inhibitors discussed above achieve similar efficacy in long-term use. However, no comparative studies of the three inhibitors have been performed. It should also be noted that only infliximab and adalimumab have been found to be effective in the treatment of chronic iritis associated with JIA

Certolizumab and golimumab are new TNF inhibitors recently introduced to clinical practice. They have been shown to be as effective as other TNF inhibitors. It is assumed that the same applies to the treatment of JIA. Clinical trials investigating the use of these therapies in the treatment of JIA are currently ongoing.

New biologics target IL-1 or IL-6

The new generation of biologic agents for rheumatoid arthritis are antibodies inhibiting white cell activity or targeting IL-6 or IL-1. Of these, the most commonly used is abatacept, a selective costimulation modulator that inhibits T-lymphocyte activation.

Rituximab is an antibody targeting the B-cell surface antigen CD20. Rituximab is also used in the treatment of systemic lupus erythematosus (SLE) and lymphoma.

Currently, abatacept, rituximab and tocilizumab, an IL-6 receptor antibody, are used in the treatment of severely active JIA, where one or more TNF inhibitors have proved ineffective.

Systemic onset JIA

High dose systemic glucocorticoid continues to be used in the treatment of systemic onset JIA. If a sufficient therapeutic response is not achieved or the treatment has to be discontinued due to side effects, IL-1 and IL-6 inhibitors can be used. Both anakinra, the IL-1 receptor antagonist, and tosilizumab, the monoclonal IL-6 receptor antibody, have achieved excellent results in the treatment of this relatively rare subtype of JIA.

The latest agent is canakinumab, a long-acting anti-IL-1 antibody. It is currently licensed for the treatment of autoinflammatory cryopyrin-associated periodic syndrome (CAPS). Clinical trials investigating the use of canakinumab in the treatment of systemic onset JIA are underway.

The signs of systemic onset JIA include high fever, skin rash, hepatosplenomegaly, lymphadenopathy and pericardial and pleural effusion. If it is associated with arthritis, it can be treated as polyarthritis. Treatment options include both conventional therapies, particularly methotrexate, as well as TNF inhibitors.

Timing drug therapy in JIA

Conventional drug therapies are first line treatments in the management of JIA. However, it is estimated that approximately one third of all children affected by JIA require biologic agents.

At the moment it is not clear, when is the best time in the course of the disease to commence biologic therapy. Preliminary data suggests that commencing treatment as early as possible may lead to earlier remission in children with polyarthritic JIA. However, there is currently no evidence available on the long-term benefits of early commencement.

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