New advances in the management of juvenile idiopathic arthritis: Non-biological therapy

M W Beresford and E M Baildam

doi:10.1136/adc.2008.144576

Updated information and services can be found at:
http://ep.bmj.com/cgi/content/full/94/5/144

These include:

References
This article cites 45 articles, 17 of which can be accessed free at:
http://ep.bmj.com/cgi/content/full/94/5/144#BIBL

Rapid responses
You can respond to this article at:
http://ep.bmj.com/cgi/eletter-submit/94/5/144

Email alerting service
Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Topic collections
Articles on similar topics can be found in the following collections
- Immunology (including allergy) (43359 articles)
- Rheumatology (325 articles)
- Epidemiologic studies (23414 articles)
- Child health (25921 articles)
- Artificial and donated transplantation (2256 articles)
- Oncology (606 articles)

Notes

To order reprints of this article go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to Archives of Disease in Childhood - Education and Practice go to:
http://journals.bmj.com/subscriptions/
New advances in the management of juvenile idiopathic arthritis—1: Non-biological therapy

M W Beresford,1 E M Baildam2

ABSTRACT
Juvenile idiopathic arthritis (JIA) is the most common paediatric rheumatic disease with significant long-term morbidity and mortality. Major advances have taken place in recent years in our understanding and the evidence base of JIA.

Key to this has been the serious collaborative efforts of clinicians, academics, scientists and the whole of the multidisciplinary team. This has led to the important recognition and development of specialised expertise for the management of patients, improvement in global outcome measures and aggressive treatment of the significant complications of JIA.

Important steps have taken place in optimising treatment of JIA. Clinical trials demonstrate that early use of intra-articular corticosteroid injections alone or in addition to other systemic treatments can have a long-lasting effect. Robust evidence has defined the importance of methotrexate as the first-line disease modifying anti-rheumatic drug in JIA. Newer treatment options in severe refractory disease are now available including stem cell transplantation.

This review focuses on the recent advances in non-biological therapies for treating JIA.

Juvenile idiopathic arthritis (JIA) is the commonest paediatric rheumatic disease with an annual incidence of 10/100 000 children in the United Kingdom.1 It is defined as arthritis of unknown aetiology beginning before the child’s 17th birthday and persisting for at least 6 weeks, and where known causes have been excluded.2 Significant progress in determining JIA aetopathogenesis has led to major advances in the management of JIA.

Fundamental to these developments is a robust classification system for a clinically heterogeneous group.3 The International League of Associations for Rheumatology (ILAR) taskforce on JIA classification provided the most recent consensus update.2 Table 1 summarises the subtypes of JIA and clinical features. Defining homogeneous groups facilitates research on cause, pathogenesis, epidemiology, outcome and therapeutic trials.

RECENT ADVANCES AND DEVELOPMENTS
Significant recent advances have improved the management of JIA (box 1).

There is growing importance given to a holistic approach to the care of JIA patients. This recognises the specific challenges and obligations of a multi-disciplinary team of specialised healthcare workers looking after children, adolescents and their families.3

A major shift in JIA outcome goals gives strong emphasis on early aggressive intervention and expectations that the inflammatory process will not only be controlled, but switched off. This is paralleled by an emergent focus on improving global, long-term clinical outcomes. Parameters used to assess these are no longer only limited to numbers of active joints. Key measures important to the child’s long-term health and welfare include joint damage, quality of life, social and health costs and impact of chronic disease on the health and psychosocial wellbeing of young people emerging into adulthood.

OUTCOME PARAMETERS FOR JIA
No single measure adequately quantifies outcome in JIA. Early JIA trials used a range of outcome variables, including composite scores of individual clinical parameters.5 Used initially for trials, a core set of criteria has been developed through
Table 1  ILAR classification of juvenile idiopathic arthritis (JIA) subtypes and clinical features of JIA

| Oligoarthritis | Arthritis of 4 or fewer joints within the first 6 months |
| Persistent     | Affecting not more than 4 joints throughout the disease process |
| Extended      | Extending to more than 4 joints after the first 6 months |
| Polyarthritis  | Arthritis of 5 or more joints within the first 6 months |
| RF positive    | Subdivided according to presence of rheumatoid factor (RF) |
| RF negative    | |
| Systemic arthritis | Arthritis with or preceded by (daily) fever for at least 3 days, accompanied by one or more of: |
|                | 1. Eosinophilic fibrinoid arthritis |
|                | 2. Lymphadenopathy |
|                | 3. Hepatomegaly and/or splenomegaly |
|                | 4. Arthritis (Mandatory exclusion of infective and malignant; arthritis may not be present early in course) |
| Psoriatic arthritis | Arthritis and psoriasis or arthritis with at least 2 of: |
|                | 1. Dactylytis |
|                | 2. Nail pitting or onycholysis |
|                | 3. Psoriasis in first-degree relative |
| Enthesitis-related arthritis | Arthritis and enthesitis or arthritis or enthesitis with 2 of: |
|                | 1. Sacro-iliac joint tenderness of inflammatory lumbo-sacral pain |
|                | 2. HLA B27 antigen |
|                | 3. Onset after age 6 years in a male |
|                | 4. Acute (symptomatic) anterior uveitis |
| Undifferentiated arthritis | Arthritis that fulfills criteria in no or more than 2 of the above categories |

Adapted from Petty et al2 and Brough and Cleary.4

Box 1 Key advances in the management of JIA

Specialised expertise in the management of JIA
- Recognition of holistic approach to management.
- The development of specialist paediatric rheumatology services at all children’s tertiary care hospitals.
- Established importance that care should be provided by a multi-disciplinary team comprising expert healthcare workers.
- Focus on the specific challenges of caring for wide range of ages from young children to adolescents, as well as their families.
- Shared care clinics for aggressive management of uveitis.
- Growing expectations and global outcomes.
- Major shift in management approach to early aggressive therapy inducing rapid remission.
- Increasing focus on improving long-term global health and welfare, such as the long-term cardiovascular risk from chronic inflammatory disease.
- Development of outcome measures acknowledging quality of life, social and health costs and the impact on the health and psychosocial wellbeing of children and adolescents emerging into adulthood.

Emerging evidence base for the treatment of JIA
- Growing evidence base through national and international collaborative efforts.
- Increased use of multiple intra-articular steroid injections.
- The advent of new biological agents.
- The use of stem cell transplantation in intractable disease.

Recognition and improved management of complications of JIA
- Better management of acute and chronic pain.
- Recognition of specific associated problems with JIA such as vitamin D deficiency, bone health, dental and orthodontic health, podiatry support, specialised hand function.

HEALTH-RELATED QUALITY OF LIFE AND JIA

Health-related quality of life (HRQOL) and disability indices are being actively developed and validated for use in JIA.3 The Childhood Health Assessment Questionnaire (CHAQ)22 is a widely used measure of disability in JIA (http://www.rheumatology.org/sections/pediatric/chaq.asp?aud=mem). The Child Health Questionnaire (CHQ), a generic measure quality of life, is increasingly used in JIA.23 24 PedsQL is a well validated reliable and sensitive measure of health-related quality of life in children with chronic disease.25 26 Robust measures of global and specific health-related outcome need to be developed, evaluated and refined for JIA to keep pace with development of new therapies and expectation from patients and families with JIA.3

ADVANCES IN THE TREATMENT OF JIA

Important steps have taken place in optimising treatment of JIA. Intra-articular injections of corticosteroids are used much earlier in the disease course.27 28 Rapidly effective they can be used solely intractable disease.

or in addition to other systemic treatments and can have a long-lasting effect. Robust evidence has defined the importance of methotrexate (MTX) as the first-line disease modifying anti-rheumatic drug (DMARD) in JIA. 20–22

INTRA-ARTICULAR INJECTIONS OF CORTICOSTEROIDS

For patients with oligoarticular JIA or the initial treatment of large joint involvement in polyarticular JIA, recent evidence has demonstrated the significant benefit of intra-articular injections of corticosteroids. 15–19 In contrast to adult practice, intramuscular (IM) corticosteroids are used in adolescent patients, but not often in view of painful injections and the lack of an evidence base in JIA. However, multiple simultaneous intra-articular steroid injections are used and it is likely that their effect is both direct on the joint and distant through a depot steroid effect.

Choice of corticosteroid

Triamcinolone hexacetonide (TH) and triamcinolone acetonide (TA) have been compared, where administered drug was selected dependent upon availability during the study period. 17–19 Prospective, blinded evaluation of 130 joints from 85 patients evaluated efficacy of both treatments. 25 A good response was defined as a decrease in their articular score of greater than 60%. The response rate was significantly higher with TH than with TA (81.4% versus 53.3%; p = 0.001) at 6 months and this difference was sustained to 24 months (60% versus 33.3%; p = 0.002).

A retrospective chart review of 85 patients defined the primary endpoint as time to relapse of arthritis in the affected joint. 19 Of 114 joints injected with TH, the mean time to relapse was 10.14 (SE 0.49) months, compared to 7.75 (0.49) months in 113 joints treated with TA (p<0.001). The average time to relapse for all joints injected was approximately 10.4 months for TH compared to 8.5 months for TA (p<0.02). 19

A double-blind randomised controlled trial (RCT) of intra-articular TH versus TA compared the affected joint to the joint symmetrically opposite used as a control. 19 Thirty-seven patients had 86 joints injected (68 knees, 16 ankles, 2 wrists). The rate of persistent or sustained response was significantly higher with TH than with TA at 6 months (89.7% vs 61.8%; p = 0.008), at 12 months (84.6% vs 48.7%; p = 0.001) and at 24 months (76.9 vs 38.5%; p = 0.001), respectively. These data indicate that TH offers a significant advantage over TA in the treatment of large joints affected by JIA, particularly in oligoarticular JIA. 19

Clinical effectiveness of joint injections

Remission with TH is longer with concomitant MTX treatment and use of general anaesthesia for the procedure. 24–26 It is less likely in the presence of antinuclear antibodies (ANA) positivity. 24 Earlier treatment optimises the chance of a protracted and possibly definitive response.24 Up to 70% of patients may remain in remission in the injected joint for at least a year and up to 40% for up to 2 years. 26 The procedure is generally well tolerated with few side effects noted. 27 In the RCT of TH versus TA, 2% of patients had subcutaneous atrophy at the injection site; families need to be told this can occur. There were no other significant associated complications including infection.

The long-term effects need prospective studies to evaluate adverse effects in children with JIA 27 and the effect of repeated injections. Inhaled nitrous oxide provides a safe and effective analgesia for intra-articular injection. 28 In younger children and those needing multiple joint injections, sedation or general anaesthesia is required. 27 Physiotherapy is

Box 2 Core set of outcome criteria for juvenile idiopathic arthritis

- Physician global assessment of disease activity (10-cm visual analogue scale).
- Parent/patient assessment of overall well-being (10-cm visual analogue scale).
- Functional ability (Childhood Health Assessment Questionnaire, CHAQ). 12
- Number of joints with limited range of movement.
- Number of joints with active arthritis.
- Parent/patient assessment of overall well-being.
- Presence of a physician global assessment of disease activity between 0 and 100.

Box 3 Definitions of disease remission and minimal disease activity in juvenile idiopathic arthritis

Preliminary criteria for “Disease remission” 18

- “Inactive disease” including the following: no active arthritis; no fever, rash, serositis, splenomegaly, or generalised lymphadenopathy attributable to JIA; no active uveitis; normal erythrocyte sedimentation rate or C-reactive protein; and a physician’s global assessment of disease activity rated at the best score possible for the instrument used.
  - Clinical remission on medication—6 continuous months of inactive disease on medication.
  - Clinical remission off medication—12 months of inactive disease off all anti-arthritis (and anti-uveitis) medication.

Preliminary definition of “Minimum disease activity” 13

- Presence of a physician global assessment ≤2.5 cm and a swollen joint count of zero in oligoarthritis.
- Presence of a physician global assessment ≤3.4 cm, a parent global assessment ≤2.1 cm and a swollen joint count of ≤1 in polyarthritis.
often used in conjunction with or following joint injections, although its role in this context needs to be formally evaluated. There are no studies of bed-rest post joint injection in childhood and it is not generally used.

**SYSTEMIC CORTICOSTEROIDS**

With the introduction of MTX and more recently biological therapies, use of long-term oral corticosteroids has declined in the management of JIA. This is predominantly because of their significant deleterious effects with long-term use, particularly on bone health and growth. Indications for their ongoing use are now primarily for severe systemic features associated with systemic-onset JIA, for induction of remission in early aggressive treatment of polyarticular disease or as a bridging medication until other treatments become effective. Periodic pulses of intravenous methylprednisolone (IVMP) (30 mg/kg per dose, maximum 1 g) can be used in place of high-dose daily oral corticosteroids and may result in lower cumulative steroid burden. High-dose intravenous steroids may be life-saving in secondary haemophagocytic lymphohistiocytosis. There are no randomised trials of dosage, schedules or reduction regimens when oral or IV or IM corticosteroids are used to “bridge the gap” while MTX is being commenced.

**METHOTREXATE**

The importance of MTX in the management of JIA is now clearly established. Although not licensed for use in childhood, MTX provides the mainstay of long-term disease-modifying therapy in JIA and is used as first-line agent in polyarticular-presenting JIA. It can be used alone, but more commonly with an initial course of IVMP and/or appropriate intra-articular corticosteroid injections to achieve rapid disease control and then maintenance.

**Evidence for the use of methotrexate in JIA**

The initial double-blind placebo controlled trial of oral MTX in resistant JIA compared doses of 10 mg/m²/week against 5 mg/m²/week or placebo over 6 months. It demonstrated a significant therapeutic advantage of the higher dose regimen, with 63% of children showing positive response compared to 32% in lower-dose MTX and 36% with placebo. Woo and colleagues subsequently focused on patients with systemic or extended oligoarticular JIA with persistent active arthritis despite non-steroidal anti-inflammatory drugs (NSAIDs) and either oral or local steroid therapy, respectively. A multicentre, double-blind, placebo-controlled crossover trial consisted of an initial 4-month active/placebo treatment period (followed by a 2-month washout period) and a second 4-month placebo/active treatment period (and further 2-month washout). The initial dosage was 15 mg/m²/week given orally which could be increased to 20 mg/m²/week after 2 months if there was no improvement on clinician’s global assessment (blinded to treatment). Combined data from both subgroups demonstrated a significant clinical improvement during MTX treatment ($p = 0.006$). In the extended oligoarticular arthritis patients, three of five core outcome variables (erythrocyte sedimentation rate, physician’s and parent’s global assessment of disease activity) improved significantly. In systemic patients, only the two global assessments showed significant change not including the systemic feature score. While this study demonstrated that higher doses of MTX are effective in JIA, optimal dosing and particularly the management of systemic-onset disease remains a concern.

Some children responded only partially or did not respond to lower doses of MTX and preliminary reports indicated higher doses may be effective. To address this, a Paediatric Rheumatology International Trials Organisation (PRINTO)-led trial took place in children newly started on standard doses of MTX (mean 10 mg/m²/week; range 8–12.5 mg/m²/week administered by oral, intramuscular or subcutaneous route) failing to respond following a 6-month screening phase. Eligible children had a diagnosis of JIA with polyarticular disease course (>5 active joints). Children with rheumatoid-factor positive polyarticular JIA, psoriatic arthritis and enthesitis-related arthritis were excluded. Following the open-labelled screening phase, the trial investigated the subsequent effect of randomising non-responders to receive an additional 6 months of subcutaneous or intramuscular MTX at either an intermediate (15 mg/m²/week) or a higher dose (30 mg/m²/week) regimen. The primary outcome for the trial was the ACR Pedi30. The intermediate dose MTX (15 mg/m²/week) demonstrated additional benefit to children ($p < 0.05$); higher dose MTX was not associated with additional therapeutic benefit. There was no difference in safety profile between the dosing regimens.

**Effectiveness of methotrexate**

Methotrexate takes 6–12 weeks to become effective after commencing treatment or after dose increase and its effect may continue to increase for 9–12 months. The ACR Pedi30 response rate using standard treatment (mean 10 mg/m²/week) is approximately 72%. Using parenteral administration, ACR Pedi30, Pedi50 and Pedi70 response rates in children not responding to standard dose but treated with 15 mg/m²/week are approximately 65%, 55% and 45%, respectively. Children with JIA have a poorer HRQOL. Although no functional outcome was assessed in the trial of intermediate-dose versus high-dose MTX, in a separate study, MTX has been shown to significantly improve all health-related quality of life health concepts, particularly the physical ones. Improvements in HRQOL were paralleled with improved measures of disease severity. However, the presence of marked disability at the start of
Withdrawal of methotrexate

Having demonstrated the efficacy of MTX in JIA, when is it safe to withdraw MTX without precipitating a disease flare? Relapses leading to escalation of treatment should be avoided. The optimal time for withdrawal is difficult as up to 60% of patients flare on discontinuing MTX. Preliminary data indicate longer duration of MTX treatment after inducing remission does not generally improve the status of remission in JIA. The PRINTO trial of “Methotrexate withdrawal in JIA” which has completed recruitment is keenly awaited. A literature review of 550 reported cases treated with sulfasalazine indicated that it was effective in most cases. Poor efficacy indicates it should not be used in systemic-onset arthritis where its use has been associated with macrophage activation syndrome.

LEFLUNAMIDE

In a controlled study comparing leflunamide, a pyrimidine synthesis inhibitor, with methotrexate (n = 94) in polyarticular juvenile arthritis, significantly more children responded to MTX (ACR Pedi30 response 89%), although 68% responded to leflunomide. Adverse effects include alopecia, diarrhoea, nausea, rash and hepatotoxicity. Most patients responsive to leflunomide maintain response at 2 years. No differences in adverse effects were noted between MTX and leflunamide.

There are no controlled studies of ciclosporin A in JIA but it is used in treating severe systemic JIA, especially where there are features of macrophage activation syndrome. Hydroxychloroquine may be useful in older patients with severe needle phobia.

STEM CELL TRANSPLANTATION

Autologous stem cell transplantation (ASCT) has been used in the last decade to treat unresponsive, severe JIA, or JIA only controlled at an unacceptable steroid cost. The BSPAR guidelines define referral procedures.

Intensive immunosuppression followed by ASCT resulted in sustained complete remission or marked improvement in 15 of 22 patients with progressive refractory JIA followed up over a median period of 80 months. Of 20 surviving patients, eight reached complete clinical remission, seven were partial responders and five experienced a relapse of their disease (up to 7 years after ASCT in one patient). The procedure is associated with significant morbidity and risk of mortality. Viral infections may have contributed to the development of macrophage activation syndrome (MAS), leading to death in two patients. These complications led to amendment of the protocol, to ensure less profound T cell depletion, better control of systemic disease before transplantation, antiviral prophylaxis after transplantation, and slower tapering of corticosteroids. No additional ASCT-related deaths were observed among the 11 patients who received the modified protocol.

More recently, alternative regimens of immunosuppression with ASCT have had favourable outcomes. Four patients followed over 4–5 years are in drug-free full remission. Allogeneic transplant with an HLA-matched family donor was reported in two JIA cases. Initial, often dramatic clinical response noted in all seven patients recently reported can be followed by significant sustained benefit including improved quality of life; catch-up growth and withdrawal of immunosuppressive therapy in over 50% of patients. The procedure
is not without its mortality risk and patients may relapse even years later. Follow-up studies continue to evaluate its long-term outcomes.

SUMMARY
The management of JIA has evolved considerably in recent years with significant advances in our understanding and the evidence base of this the commonest paediatric rheumatic disease. Key to this has been the collaborative efforts of clinicians, academics, scientists and the whole of the multidisciplinary team. Such concerted efforts will enable further major advances in the management not just of JIA. Trials are needed to determine optimum management of JIA with both the newer biological therapies but also of established medications and related therapies.

Competing interests: None.

Provenance and peer review: Commissioned, externally peer reviewed.

REFERENCES


