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New advances in the management of juvenile idiopathic arthritis—2: The era of biologicals

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.

The advent of biological therapies has opened a major new era in the medical management of JIA with recent trials published of etanercept, infliximab, adalimumab, abatacept, tocilizumab and anakinra. National and international collaborative clinical and research networks are ideally placed to enable future advances in the management of JIA and all paediatric rheumatic disorders.

This review follows on from Part 1 of a review of recent advances in non-biological therapies in JIA, and focuses on the significant new advances in biological therapies in managing JIA.

ETANERCEPT
The first multicentre, double-blind randomised controlled trial of a biological therapy in JIA was undertaken with etanercept (ETN) in children aged 4–17 years, with treatment resistant, active polyarticular JIA over 4 months.6 Patients received 0.4 mg/kg subcutaneously twice weekly for 3 months during an open-label active run-in phase. In a withdrawal-design trial of active responders, only patients who had at least an ACR Pedi30 response were then randomised to continue ETN or receive placebo in the double-blind phase of the trial.

Of 69 patients recruited, 51 (74%) were eligible for randomisation. Seven (28%) of 25 patients receiving ETN compared to 21 (81%) of the 26 who received placebo had a disease flare in the subsequent 4-month period (p = 0.003). Medium time to disease flare with placebo was 116 days with ETN (p < 0.001).

ETN has become an established part of managing JIA. The National Institute for Health and Clinical Excellence (NICE) granted its approval in March 2002 for use in children with JIA who have an inadequate response to, or find methotrexate (MTX) intolerable, under specific guidance.
**Pharmacy update**

**Table 1** Summary of biological therapies recently studied in JIA and their method of action

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>Soluble tumour necrosis factor (TNF) p75 receptor fusion protein that binds to and inactivates TNFα</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Chimeric human/mouse monoclonal antibody that binds to soluble TNFα and its membrane bound precursor neutralising its action</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Soluble fully human fusion protein of the extracellular domain of cytotoxic T-lymphocyte-associated antigen (CTLA)-4, linked to a modified FC portion of the human immunoglobulin G1. It acts as a co-stimulatory signal inhibitor by binding competitively to CD80 or CD86, where it selectively inhibits T-cell activation</td>
</tr>
<tr>
<td>Abatacept</td>
<td>A humanised immunoglobulin G1 monoclonal antibody which binds to TNFα and its membrane bound precursor inactivates TNFα</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>A humanised anti-human interleukin 6 (IL-6) receptor monoclonal antibody, Anakinra is an IL-1 receptor antagonist (IL-1 RA)</td>
</tr>
</tbody>
</table>

Compiled from Strand et al.¹

**Table 2** Summary of data from randomised placebo controlled trials of biological therapy in JIA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients</th>
<th>Dose</th>
<th>Open label</th>
<th>Randomisation, n (%)</th>
<th>Primary outcome after randomisation</th>
<th>Other outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>4–17 years. Treatment resistant, active polyarticular JIA</td>
<td>0.4 mg/kg SC twice weekly</td>
<td>All patients: 3-month active run-in (n = 69)</td>
<td>If ACR Pedi30 response, randomised to active or placebo n = 51 (74%)</td>
<td>After 4 months, disease flare: ETN 7/25 (28%), placebo 21/26 (81%), p = 0.003</td>
<td>Medium time to flare: ETN &gt;116 days vs placebo 28 days, p &lt; 0.001</td>
</tr>
<tr>
<td>Infliximab</td>
<td>4–17 years. Persistent polyarthritids despite MTX (oral or parenteral)</td>
<td>3 mg/kg IV throughout; or placebo followed by 6 mg/kg IV; continued MTX</td>
<td>NA</td>
<td>Initial 14 weeks active (3 mg/kg) vs placebo; then: active (3 mg/kg) vs active (6 mg/kg)</td>
<td>After 14 weeks, ACR Pedi30; active 63.8%, placebo 49.2%, p = NS</td>
<td>Secondary outcomes: not significant; better safety profile with less serious adverse events in higher dose (6 mg/kg)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>4–17 years. Polyarticular JIA, active disease despite NSAIDs; MTX naive or failed/ intolerant on MTX</td>
<td>24 mg/m² SC; maximum dose 40 mg. On or off MTX</td>
<td>All patients: 16 weeks’ active run-in (n = 85); off MTX n = 86; total n = 171</td>
<td>Completed and ACR Pedi30 response; randomised: on MTX: active (n = 38), placebo (n = 37); off MTX: active (n = 30), placebo (n = 29)</td>
<td>After 48 weeks, disease flare: off MTX: active 13/30 (43%) vs placebo 20/28 (71%), p = 0.03; on MTX: active 14/37 (38%) vs 24/37 (65%), p = 0.02</td>
<td>At 48 weeks: on MTX: greater percentage ACR Pedi30, Pedi50, Pedi70 and Pedi90 responses were significantly higher active (p &lt; 0.05); in those off MTX</td>
</tr>
<tr>
<td>Abatacept</td>
<td>6–17 years. JIA &gt;5 active joints, failed/ intolerant to &gt;1 DMARD (including anti-TNF therapy)</td>
<td>10 mg/kg IV, continued MTX, no other DMARD including anti-TNF</td>
<td>All patients, 4-month active run-in (n = 170)</td>
<td>If ACR Pedi30 response, randomised to monthly for 6 months or until disease flare: active (n = 60) vs placebo (n = 62)</td>
<td>After 6 months, disease flare: active 12/60 (20%) vs placebo 33/62 (53%), p = 0.0003</td>
<td>Similar adverse events; lower response rates in those previously failing anti-TNF therapy (ACR Pedi30 39% vs 76%)</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>2–19 years. Systemic-onset JIA resistant to conventional therapy</td>
<td>8 mg/kg IV every 2 weeks</td>
<td>All patients: 6-week active run-in (n = 56)</td>
<td>If ACR Pedi30 and CRP &lt;5 mg/l, randomised to continue active (n = 20) vs placebo (n = 23)</td>
<td>After 12 weeks, ACR Pedi30 plus CRP &lt;15 mg/l: active 16/20 (80%) vs placebo 4/23 (17%), p &lt; 0.0001</td>
<td>No deaths of macrophage activation syndrome</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; ETN, etanercept; IV, intravenous; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; SC, subcutaneous; TNF, tumour necrosis factor.

**Box 1 Key points—etanercept**

- Etanercept is licensed for use in children with JIA in the UK and has NICE approval.
- Etanercept has a 77% response rate.
- Systemic-onset JIA disease responds less well than polyarticular disease.
- 36% of patients reach full clinical remission.
- There is a low serious adverse event rate of 0.029 per patient-year.
- There is a UK BSPAR-run etanercept drug registry and all paediatric patients on etanercept should be registered.

(http://www.nice.org.uk/nicemedia/pdf/JIA-PDF.pdf) This included recommendations that administration should be in specialist units including clinical nurse specialist with continued monitoring of toxicity and clinical efficacy over time.

**Long-term safety and efficacy profile of etanercept**

The long-term safety and efficacy of ETN is now being reported from this original cohort and other prospective studies. Following the initial trial, up to 8 years of continuous ETN therapy has shown no cases of tuberculosis, opportunistic infections, malignancies, lymphoma, lupus, delimitating disorders or deaths.¹¹ An ACR Pedi70 response or higher was achieved by 100% of patients with 8 years of data (n = 11) and 61% at their last observation. These data indicate that ETN continues to be efficacious and safe, but reflects very few patients. In the UK children receiving ETN for JIA are enrolled in a prospective study of safety and efficacy as part of a prerequisite of NICE’s approval.¹² National biologics registries such as the BSPAR Biologics and New Drug Registry (http://www.bspar.org.uk/pages/home.asp) aim to determine the real-world long-term clinical effectiveness and safety of ETN in JIA, as is taking place with adult-based registries.¹³

The Dutch National Register of 146 JIA patients (median follow-up 2.5 years/patient: range 0.3–7.3) reported that 77% of patients met ACR Pedi30 criteria in the initial 3 months of treatment.¹⁴ For the majority of patients this improvement was sustained with 56% of patients meeting remission criteria and a low serious adverse event rate (0.029 per patient-year).
Infliximab is given by intravenous infusion at 0, 2, 4 and then 8 weekly intervals and the intravenous route may be preferred by some patients. The higher dose of infliximab (6 mg/kg) has a more favourable safety profile.

**Box 2 Key points—infliximab**

- Infliximab is given by intravenous infusion at 0, 2, 4 and then 8 weekly intervals and the intravenous route may be preferred by some patients.
- The higher dose of infliximab (6 mg/kg) has a more favourable safety profile.

**Adverse events and infliximab**

Infliximab was generally well tolerated. Of particular note was that the safety profile of infliximab at 3 mg/kg was less favourable than that at 6 mg/kg. There were more occurrences of serious adverse events, infusion reactions, antibodies to infliximab and newly induced anti-nuclear antibodies and antibodies to double-stranded DNA in the 3 mg/kg regime. The higher dose regimen of infliximab achieved better maintenance of drug levels and is now used in paediatric rheumatology practice.

**Box 3 Key points—adalimumab**

- Subcutaneous injections only every 2 weeks.
- It is particularly effective with concomitant MTX therapy.
- There is a limited EMEA licence for paediatric use (>12 years only).
occurred in 65% on placebo, compared to 57% receiving adalimumab (p = 0.02). At 48 weeks, the percentage of patients treated with MTX who had ACR Pedi30, Pedi50, Pedi70 and Pedi90 responses were significantly greater for those receiving adalimumab than those receiving placebo (p<0.05). Open-label extension of the studies showed sustained responses for up to 104 weeks of treatment.

Adverse events and adalimumab
Serious adverse events occurred in 14 patients. The most frequently reported were infections and injection site reactions. Seven serious adverse events were serious infections, although no deaths, malignant conditions, opportunistic infections, tuberculosis, demyelinating diseases or lupus-like reactions were reported. Sixteen per cent had at least one positive test for anti-adalimumab antibodies, predominantly in those not receiving MTX. Not statistically powered to detect differences between patients receiving and not receiving MTX, the proportions of patients with ACR Pedi30, Pedi50, Pedi70 and Pedi90 responses were higher in those treated in combination with MTX.

ABATACEPT
Not all patients with JIA respond or respond adequately on anti-TNF therapy; some relapse while on treatment or are intolerant of it.20 21 Adult trials of RA demonstrate that abatacept improves disease and health related quality of life (HRQOL) and inhibits structural damage in patients not responding to DMARDs, including anti-TNF therapy.7

Abatacept trial in JIA
A double-blind randomised control withdrawal trial of 190 patients, aged 6–17, with active JIA (≥five active joints), and inadequate response to or intolerance to at least one DMARD, including anti-TNF therapy has recently been published.7 All patients were given 10 mg/kg of abatacept as a 30-minute intravenous (IV) infusion on days 1, 15, 29, 57 and 85 of a 4-month open-labelled phase. Sixty-seven per cent of patients demonstrated an ACR Pedi30 response, similar across disease subtypes. ACR Pedi50, Pedi70 and Pedi90 response rates were 50%, 28% and 13%, respectively, while 13% of patients had inactive disease after the lead-in phase. Maximum benefit extended after 6 months of treatment. Patients showed a clinical benefit after restarting abatacept. Those previously failing anti-TNF therapy showed poorer response rates compared to biologically naive patients. Follow-up of this study to date is 1 year; long-term follow-up is very important.

One-hundred and seventy completed this lead-in phase. 47 patients did not meet predefined ACR Pedi30 response. During the double-blind phase of the trial, 60 were randomised to receive abatacept 10 mg/kg IV monthly for 6 months or until flare of their disease, while 62 received placebo. Primary endpoint was flare of arthritis (ACR30).

Twelve of 60 (20%) abatacept-treated patients had disease flare, compared to 33/62 (53%) of patients treated with placebo (p = 0.0008). Frequency of adverse events did not differ significantly between treatment groups. Just two serious adverse events were reported, both in controls (haematoma and varicella encephalitis). No serious or opportunistic infections were seen.

TOCILIZUMAB
Systemic-onset JIA (SoJIA) is characterised by spiking fever, erythematous skin rash, serositis and hepatosplenomegaly with highly associated morbidity and mortality.22 SoJIA is often resistant to standard JIA treatments. Steroids used to control systemic symptoms are associated with significant side effects, such as osteoporosis and growth failure. Both MTX23 24 and the anti-TNF therapies show limited efficacy with SoJIA and do not significantly lower the risk of macrophage activation syndrome (or secondary haemophagocytic lymphohistiocytosis).22 23

The role of interleukin 6 (IL-6) in the pathogenesis of SoJIA is established and an open-label, single-dose, ascending dose trial of tocilizumab in severe SoJIA showed it to be dramatically effective in clinical and laboratory responses observed by 48 hours post-infusion. ACR Pedi30 was achieved in 11/18 patients while eight achieved ACR Pedi50 improvement.24

A double-blind, placebo-controlled, withdrawal phase III trial of efficacy and safety in patients with severe SoJIA has been published.19 Fifty-six children, aged 2–19 years with disease refractory to conventional treatment were given three doses of tocilizumab at 8 mg/kg every 2 weeks, during a 6-week open-label lead-in phase. Those children achieving an ACR Pedi30 response and C-reactive protein (CRP) <5 mg/l were randomly assigned to receive placebo or continue tocilizumab for a further 12 weeks or until withdrawal if rescue medication was required, in a double-blind phase.

At the end of the open-labelled lead-in phase, ACR Pedi30, Pedi50 and Pedi70 responses were achieved in 51 (91%), 48 (86%) and 38 (68%) patients, respectively. Of 43 patients continuing the double-blind phase 4/23 (17%) patients in the placebo group maintained ACR Pedi50 response, with a CRP concentration of less than 15 mg/l compared to 16/20 (80%) in the tocilizumab group (p<0.0001). At the end of 48-week open-label extension, ACR Pedi50, Pedi50 and Pedi70 responses were achieved by 47 (98%), 45 (94%) and 43 (90%) of 48 patients. No deaths or cases of macrophage activation syndrome occurred. Two serious adverse events in the open-label phase included an anaphylactoid reaction and a gastrointestinal haemorrhage.

A further phase III trial of tocilizumab in SoJIA has just been initiated (http://clinicaltrials.gov/ct2/home).
INTERLEUKIN-1 RECEPTOR ANTAGONIST (ANAKINRA)

Along with IL-6, IL-1 has also been shown to have a key role in SoJIA. Anakinra is an IL-1 receptor antagonist (IL-1 RA), which has been reported anecdotally to have a marked efficacy for the treatment of SoJIA and adult-onset Stills disease (AoSD). A prospective study has explored the safety and efficacy of anakinra in 20 SoJIA and 15 adult-onset patients. Of the 20 JIA patients, five achieved ACR Pedi50 response in the 6 months with a decrease in steroid dose of between 15% and 78% in 10 cases. Where complete response took place it was dramatic, although 10/20 SoJIA patients were non-responders. Clinical systemic features including fever and rash were resolved in 14 out of the 20 patients in the first 3 months. Other case series indicate that some children show an excellent response to anakinra with resolution of both systemic and joint disease. In a series of 22 patients with SoJIA treated with anakinra, 10 had a dramatic complete response while 11 had an incomplete or no response. Trials of anakinra in SoJIA are ongoing (http://clinicaltrials.gov/ct2/).

UVEITIS ASSOCIATED WITH JIA

The treatments for uveitis associated with JIA are currently not based on randomised controlled trial data. However, the philosophy of early detection, early and persistent treatment in clinics shared with ophthalmologists and paediatric rheumatologists is leading to integrated and intensive treatment. Screening guidelines produced jointly by BSPAR and the Royal College of Ophthalmologists for the early detection of JIA-associated uveitis aim to reduce the incidence of visual impairment among patients with JIA and allow early intervention (http://www.bspar.org.uk/downloads/clinical_guidelines/BSPAR_guidelinesEyeScreening_2006.pdf).

Methotrexate appears to be an effective treatment for uveitis as well as for arthritis. Methotrexate is discontinued for arthritis treatment possibly stimulating a uveitis flare.

The rationale for anti-TNF therapy JIA-associated uveitis

Animal models of uveitis indicate a potential role of anti-TNF therapy in uveitis related to JIA. Review of infliximab and adalimumab have demonstrated significant efficacy in controlling uveitis associated with seronegative spondyloarthropathies and JIA. However, ETN has failed to show a similar treatment effect. Review of 280 reported cases treated with biologicals concluded that infliximab may be more effective that ETN. However, as adalimumab blocks the interaction of TNFα with both the p55 and p75 receptors it may be more effective in uveitis than either of the other two anti-TNF drugs.

Fourteen children with uveitis (nine JIA-associated and five idiopathic) were treated with adalimumab for an average of 18.1 months. Inflammation decreased in 21/26 eyes (80.8%), four eyes remained stable (15.4%), and one worsened (3.8%) (p<0.001) and no significant adverse events occurred.

A robust evidence base for the use of anti-TNF therapy in JIA-associated uveitis is urgently needed.

THE WAY FORWARD: IMPROVING THE EVIDENCE BASE

Newer biologicals are continually being developed and will be used in JIA. The challenge is to undertake, in a timely manner, trials specifically designed to demonstrate quality, safety and efficacy in JIA, and adapting formulations for paediatric administration.

Recent trials of biologicals in JIA have come about through significant international collaborative efforts. In the UK the National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN) (http://mcrn.org.uk/) aims to facilitate clinical trials in children. Similar networks are developing in other European Union nations. Integrated national research networks supported by multidisciplinary collaborative expertise such as the UK MCRN/arc Paediatric Rheumatology Clinical Studies Group provide a unique opportunity to improve the evidence base for the management of JIA and are in an excellent position to collaborate with international paediatric rheumatology-specific trial networks.

SUMMARY

The management of JIA has evolved considerably in recent years. Key to this has been the collaborative efforts leading to important clinical trials of newer biological therapies. Such concerted efforts will enable further major advances in the management not just of JIA but of all rheumatic disorders of childhood.

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