Biologics for the treatment of juvenile idiopathic arthritis: a systematic review and critical analysis of the evidence

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CRD summary
The authors concluded that evidence was insufficient to draw firm conclusions about the balance of risks and benefits of any biologic agent for treatment of juvenile idiopathic arthritis. These conclusions were suitably cautious in reflecting the limited evidence available and appear likely to be reliable.

Authors’ objectives
To assess the efficacy and safety of biologic agents for the treatment of juvenile idiopathic arthritis.

Searching
MEDLINE, EMBASE, The Cochrane Library and IPA were searched from 1990 to August 2006; search terms were reported. The Center for Drug Evaluation and Research database was searched to identify unpublished studies submitted to the US Food and Drug Administration. Reference lists of relevant reviews (and letters) were scanned and pharmaceutical manufacturers contacted in order to identify further studies. Studies published only as abstracts were excluded (authors were contacted to enquire about manuscripts).

Study selection
Studies of approved biologic agents (abatacept, adalimumab, anakinra, etanercept, infliximab, rituximab and tocilizumab) for treatment of juvenile idiopathic arthritis were eligible. Outcomes of interest were clinical improvement, functional capacity, quality of life, remission, radiographic outcomes and adverse events. Studies of efficacy had to be prospective; studies of adverse events could be retrospective or prospective.

Most included studies were of patients with polyarticular or systemic juvenile idiopathic arthritis. Etanercept (normally 0.4mg/kg) was the most frequently studied drug; infliximab and tocilizumab were also studied. Most studies allowed use of methotrexate. The outcomes assessed varied; American College of Rheumatology Paediatric 30 definition of improvement was used most frequently.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Two reviewers independently assessed trial study quality using US Preventative Services Task Force and Centre for Reviews and Dissemination criteria to result in ratings of good, fair or poor. Any differences were resolved by consensus or by a third senior reviewer. Observational studies were assessed using criteria outlined by Deeks et al. (but not detailed in the review).

Data extraction
It appeared that two reviewers independently extracted data.

Methods of synthesis
A narrative synthesis was presented, grouped by type of biologic agent.

Results of the review
The authors stated that 15 studies were included: one randomised controlled trial (RCT) (n=69), one non-RCT (n=24), 10 uncontrolled trials (n=497) and three case series (n=38, but not reported for one study). Details of related studies were tabulated. The RCT and non-RCT were both rated as fair quality. Three of the uncontrolled trials were rated as good quality, nine were fair and one was poor. All three case series were rated fair quality.

One RCT and six uncontrolled trials reported that etanercept improved symptoms; four of these studies suggested that
patients with systemic juvenile idiopathic arthritis had lower response rates than patients with polyarticular juvenile idiopathic arthritis. In the RCT, frequencies of adverse events did not differ between the etanercept and placebo groups.

There were three studies of infliximab; overall there was a suggestion of general efficacy, but also high rates of infusion reactions and adverse events. One of the two uncontrolled studies reported no additional benefit in patients who had failed etanercept.

Two small uncontrolled studies suggested that tocilizumab was efficacious.

**Authors’ conclusions**
Evidence was insufficient to draw firm conclusions about the balance of risks and benefits of any biologic agent for the treatment of juvenile idiopathic arthritis.

**CRD commentary**
The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify relevant studies were undertaken by searching electronic databases and by several other methods. Although studies published only as abstracts were excluded, brief summaries were provided in the results section. It was unclear whether the search included studies not published in English. Suitable methods were employed to reduce risks of reviewer error and bias for the relevant review processes. Study quality was assessed and was used in interpreting the results of the review, although no details of the particular assessment criteria used were stated. Sufficient study details were provided and an appropriate narrative synthesis of the data was undertaken.

The authors’ conclusions were suitably cautious in reflecting the limited evidence available and appear likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that findings from adult studies should be considered when determining the trade-offs between risks and benefits of biologic therapy for juvenile idiopathic arthritis. When considering use of biologics for juvenile idiopathic arthritis, clinicians should take account of the lack of evidence of long-term safety.

**Research:** The authors stated that high-quality RCTs were needed and clarification was required on the effect of earlier use of etanercept, use of biologics for rheumatoid uveitis prevention and whether high doses might be more beneficial than regular doses in patients with systemic juvenile idiopathic arthritis. Evaluation of the long-term safety of biologics should be made.

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