The clinical effectiveness and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis: a systematic review and economic evaluation

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Scientific summary

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Background

The term juvenile idiopathic arthritis (JIA) encompasses all forms of arthritis of unknown cause with onset prior to 16 years of age and with symptoms that persist for > 6 weeks. Suggested incidence (1.6 to 23 per 100,000) and prevalence rates (3.8 to 400 per 100,000) vary widely. The disease is characterised by joint pain, swelling and a limitation of movement which is caused by an inflammation of the synovial membrane of the affected joints. Left untreated, this inflammation causes a progressive erosive arthritis, which may potentially lead to disability and growth restriction. However, disease severity and long-term outcomes are variable both between different JIA subtypes and between different individuals with the same JIA subtype. At onset, the particular subtype of JIA will be diagnosed according to the presenting features as oligoarthritis, polyarthritis, enthesitis-related JIA (ERA), psoriatic arthritis (PA), systemic-onset JIA or undifferentiated arthritis. Polyarticular-course JIA applies to patients who at a particular point in time 6 months or more after the onset of disease (JIA of any onset type) have five or more active joints. Polyarticular-course JIA can typically include rheumatoid factor-positive (RF+) and rheumatoid factor-negative (RF−) polyarthritis, extended oligoarthritis (EO), ERA, PA and systemic JIA (providing that there have been no active systemic symptoms during the previous 6 months).

The treatment of JIA includes non-steroidal anti-inflammatory drugs, intra-articular corticosteroids and disease-modifying antirheumatic drugs (DMARDs), of which methotrexate is the most common conventional (non-biologic) DMARD used in the UK. Clinical practice now favours earlier treatment with biologic DMARDs, where indicated.

Objectives

The aim of this multiple technology appraisal is to assess the clinical effectiveness and cost-effectiveness of the biologic DMARDs etanercept (Enbrel®, Pfizer), abatacept [Orencia®, Bristol-Myers Squibb (BMS)], adalimumab (Humira®, AbbVie) and tocilizumab (RoActemra®, Roche), in combination with methotrexate, where permitted, in the treatment of JIA. It updates and extends a previous National Institute for Health and Care Excellence (NICE) technology appraisal (TA) of etanercept conducted in 2002 (NICE TA35). The licensed indication for etanercept has broadened since 2002 and three newer biologic DMARDs have been licensed. This appraisal includes all subtypes of JIA, with the exception of systemic JIA with active systemic features or persistent oligoarticular JIA.

Methods

Clinical effectiveness systematic review

Electronic bibliographic resources including MEDLINE, EMBASE, The Cochrane Library and the Database of Abstracts of Reviews of Effects were searched for published studies from inception to May 2015 for English-language articles. Bibliographies of included articles and systematic reviews were also searched for additional studies, as were company submissions (CSs) to NICE. An expert advisory group was contacted to identify additional published and unpublished evidence.
Titles and abstracts were independently screened for eligibility by two reviewers using inclusion criteria that were defined a priori. Inclusion criteria were applied to full texts by one reviewer and checked by a second reviewer. Inclusion criteria were as follows:

- **Population**: patients with JIA including polyarthritis (both RF+ve and RF–ve, and EO, both onset and course), ERA and PA.
- **Intervention**: the biologic DMARDs abatacept, adalimumab, etanercept and tocilizumab (in combination with methotrexate where permitted), evaluated within their licensed indication. Studies of biologic DMARDs without concomitant methotrexate were permitted if patients were intolerant to it or if treatment with methotrexate was inappropriate.
- **Comparators**: DMARDs such as methotrexate (best supportive care if DMARDs are not tolerated), as well as abatacept, adalimumab, etanercept and tocilizumab compared with each other.
- **Outcomes**: disease activity, disease flares, physical function, joint damage, pain, corticosteroid reducing regimens, extra-articular manifestations (such as uveitis), body weight and height, mortality, adverse effects of treatment and health-related quality of life (HRQoL).
- **Design**: randomised controlled trials (RCTs). Non-randomised studies could be considered where RCT data were not available.

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer. Differences in opinion were resolved by discussion at each stage or in consultation with a third reviewer where necessary.

Data were synthesised through narrative reviews with tabulation of the results of included studies. An adjusted pairwise indirect comparison of the four biologic DMARDs was presented.

**Economic evaluation**
A systematic review of cost-effectiveness studies and a systematic review of HRQoL studies was conducted to identify relevant evidence to inform the economic evaluation. Studies were included in the systematic review of cost-effectiveness if they were full economic evaluations (cost-effectiveness, cost–utility, cost–benefit or cost–consequence analyses).

A cost–utility decision-analytic model was developed to compare the cost-effectiveness estimates of biologic DMARDs versus methotrexate. The model used a Markov approach to estimate the costs and health benefits for patients with JIA. The model consisted of three health states: on treatment (with biologic DMARD), off treatment and death, with a further health state of ‘clinical remission off treatment’ also included in a scenario analysis. The model cycles were 3 months in length to be consistent with timing between outpatient appointments in clinical practice. Patients discontinued treatment owing to adverse events (AEs), inefficacy of the treatment or remission. The model also included the cost and disutility of disease flares. The perspective of the analysis was that of the NHS and Personal Social Services. The model used a time horizon of 30 years and discount rates of 3.5% for costs and health benefits. The outcome of the economic evaluation is reported as cost per quality-adjusted life-year (QALY) gained.

**Results**

**Clinical effectiveness**
From 2554 references screened on title and abstract, 56 full texts were retrieved. One further conference abstract was identified from a pharmaceutical CS to NICE. From these, nine full papers and 12 conference abstracts met the inclusion criteria. The included papers and abstracts collectively described four multicentre RCTs, with one RCT each evaluating abatacept, adalimumab, etanercept and tocilizumab. Only the tocilizumab study included UK participants. All four studies were described as being withdrawal trials starting with an open-label lead-in phase (12–16 weeks) in which participants had to achieve an American College of Rheumatology (ACR) Pediatric (Pedi)-30 response level to be eligible for entry to the randomised...
double-blind withdrawal phase of the study (16–32 weeks), followed by an open-label extension (OLE). All studies used a placebo as the comparator. With the exception of the etanercept trial, the majority of patients in the trials received methotrexate in addition to the biologic DMARD or placebo. The distribution of patients across the subtypes of JIA was reported for only two of the trials, with polyarthritis being the predominant subtype. The other two trials appeared to include patients with polyarticular-course JIA. Overall, the quality of the RCTs was reasonable, with a low risk of bias for most domains, but some aspects were rated as unclear, primarily owing to insufficient reporting.

Significantly fewer patients who continued to receive biologic DMARDs during the randomised withdrawal phase of the studies had arthritis flares than those receiving placebo in all four trials. Time to disease flare for participants receiving biologic DMARDs was statistically significantly longer (reported for adalimumab and etanercept). A greater proportion of those treated with biologic DMARDs achieved ACR Pedi responses of ≥30 and had inactive disease (reported for abatacept and tocilizumab only). Generally, the individual ACR Pedi core variables (reported for abatacept, etanercept and tocilizumab) were improved by biologic DMARDs when compared with placebo, as were joint-related outcomes (reported for etanercept only) and pain in two out of three studies (etanercept and tocilizumab, not abatacept). Not all studies reported a statistical comparison for each of these outcomes. Three studies (adalimumab, etanercept and tocilizumab) reported mortality, with no treatment-related deaths. Differences in HRQoL between trial arms reported in one study (abatacept) were not statistically significant. The proportions of AEs and serious adverse events (SAEs) were generally similar between the treatment groups. One study (tocilizumab) reported subgroup data, albeit without statistical comparisons between treatment groups. None of the studies reported data for outcomes such as corticosteroid dose reduction, extra-articular manifestations (such as uveitis), height or weight for the randomised withdrawal phase of the trials.

An adjusted indirect comparison suggests that the four biologic DMARDs appear to be similar in terms of disease flare and ACR Pedi-50 and -70 responses, with wide confidence intervals and clinical heterogeneity between the trials.

There were differences across the trials in the eligibility criteria for the OLE phase, and in how the results were reported. In some studies, it was not possible to differentiate between participants treated continuously with a biologic DMARD (i.e. from open-label lead-in and randomised withdrawal phase) and those who received placebo before being offered a biologic DMARD at entry to the OLE. Generally, patients’ ACR responses remained constant over time or even increased after the double-blind phase. Limited data for adalimumab and tocilizumab reported in abstracts at week 104 appear to support the positive effect of these drugs on growth, but the use of different outcome measures prevents a comparison between the drugs.

In addition to the four RCTs, seven relevant ongoing trials were identified and summarised in this report (three investigating adalimumab and four investigating etanercept).

There is limited evidence for the clinical effectiveness of biologic DMARDs in specific JIA disease subtypes. An observational study (CLIPPER) assessing the safety and efficacy of etanercept in children and adolescents with EO JIA, ERA and PA found variations in response to treatment between JIA disease subtypes (commercial-in-confidence information has been removed). By week 96, similar ACR Pedi-90 (62–72%) and ACR Pedi-100 (51–60%) responses were achieved by participants with different JIA subtypes, and proportions of patients with inactive disease varied between 29% (ERA and PA) and 37% (EO).

Evidence from observational studies suggests that biologic DMARDs can improve uveitis symptoms, such as intraocular inflammation, in children with JIA. Adalimumab appears to be more effective than etanercept in improving uveitis.
Four pharmaceutical companies made submissions in support of their drugs to NICE. Only one of these (Pfizer, etanercept) provided a systematic review of clinical effectiveness. This was judged to be of a good standard. None of the submissions included any relevant RCTs that were additional to those identified in this assessment report.

**Cost-effectiveness**

The systematic review of published economic evaluations identified 388 potentially relevant publications. Of these, four studies (described in five publications) met the inclusion criteria. The studies were conducted in the UK, the Netherlands, Canada and the Russian Federation. There were two cost–utility studies, one cost-effectiveness study and one cost–consequence study. The studies were assessed for quality and generalisability to the UK but all contained limitations in the methodological quality or generalisability to the UK NHS. The study conducted in the UK was the assessment report for the previous NICE appraisal for etanercept in children with JIA (NICE TA35). The systematic review of HRQoL identified two studies reporting health-state utility values for patients with JIA.

In terms of the CSs to NICE, Roche (the manufacturer of tocilizumab) constructed a Markov state-transition model that compared tocilizumab with adalimumab in children with JIA. The base-case results conclude that tocilizumab is of similar effectiveness and is less expensive than adalimumab. Two companies, BMS (the manufacturer of abatacept) and Pfizer (the manufacturer of etanercept) assumed that the biologic DMARDs were equivalent in clinical effectiveness. They submitted cost analyses to compare the biologic DMARDs. BMS concluded that abatacept was the least costly treatment option and that tocilizumab was slightly cheaper than adalimumab. Pfizer concluded that for most ages, etanercept is the biological treatment with the lowest acquisition cost compared with tocilizumab and adalimumab. AbbVie (the manufacturer of adalimumab) did not submit an economic analysis and cited a number of methodological limitations to producing an economic model. Two companies, Roche (tocilizumab) and BMS (abatacept) submitted a confidential patient access scheme discount.

The independent model developed for this assessment report modelled one line of biological treatment for the comparison of adalimumab, etanercept and tocilizumab versus methotrexate. From this model, the incremental cost-effectiveness ratios (iCERs) for adalimumab, etanercept and tocilizumab versus methotrexate are estimated at £38,127, £32,526 and £38,656 per QALY gained, respectively, using the list price drug acquisition costs. Abatacept is licensed for second-line biological therapy after discontinuation of an antitumour necrosis factor. Abatacept was compared with methotrexate as a second-line biological treatment, following etanercept as the first-line biologic. In this analysis, abatacept had an ICER of £39,536 per QALY gained.

The model results are most sensitive to changes in the HRQoL utility values. The changes to the clinical effectiveness parameters, such as treatment discontinuation and disease flare had minimal effect on the model results. The differences in cost-effectiveness of the biologic DMARDs are primarily the effect of the differences in the drug acquisition cost.

**Discussion**

Biologic DMARDs (plus methotrexate where indicated) are superior to placebo (plus methotrexate where indicated) across a number of outcome measures in children with JIA who have had an insufficient response to previous treatment. Owing to the withdrawal trial design, results of the double-blind phase are applicable only to patients who have already achieved an initial (low) degree of benefit from a biologic DMARD. Long-term treatment effectiveness in terms of ACR Pedi response appears to be sustained for all four included RCTs and the occurrence of AEs is generally similar between biologic DMARD and placebo-treated patients. SAEs seem to be uncommon and the long-term safety profile of the biologic DMARDs is relatively favourable. An incremental analysis and the costs and health benefits of the four biologic DMARDs was not presented, as the DMARDs were similar in effects and costs.
There was insufficient evidence for all input parameters to permit a cost-effectiveness subgroup analysis for each of the respective types of JIA within the scope of the appraisal. The modelled patient population is people with JIA, although it is primarily relevant to those with polyarticular-course JIA.

The strengths of this assessment include the use of standard methods for evidence synthesis and economic modelling, and the transparent reporting of the scope and methods a priori in a published protocol. Limitations include the lack of head-to-head trial comparisons of biologic DMARDs, necessitating an indirect comparison, and the lack of available data to inform the economic evaluation, particularly HRQoL utility estimates (which were the most influential parameters of cost-effectiveness), long-term discontinuation rates and the long-term impact of treatment on disease progression. Assumptions have been made where possible based on best available evidence and expert opinion.

Conclusions

Implications for service provision
Given that biologic DMARDs are currently used in the treatment of JIA, any recommendation supporting their use is unlikely to have significant implications for service provision (e.g. in terms of changes to infrastructure, staff training).

Suggested research priorities
Randomised head-to-head comparisons of biologic DMARDs are necessary to establish comparative effectiveness. Trials should be sufficiently powered, with long-term follow-up of safety and efficacy, and should include an economic evaluation to assess cost-effectiveness.

Study registration
This study is registered as PROSPERO CRD42015016459.

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