Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

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

The Assessment group has presented the results of its economic modelling using the list prices for abatacept, adalimumab, etanercept and tocilizumab in this Assessment Report. A separate confidential appendix reporting the results incorporating the confidential patient access schemes for abatcept and tocilizumab has been prepared by the Assessment Group. The confidential appendix will not be released publically

ERRATUM

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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 'clinical remission off treatment' also included in a scenario analysis. The model cycles were three months in length to be consistent with timing between outpatient appointments in clinical practice. Patients discontinued treatment due to adverse events, 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 company submission to NICE. From these, nine full papers and 12 conference abstracts met the inclusion criteria. The included papers and abstracts collectively described four multi-centre 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 to16 weeks) in which participants had to achieve an American College of Rheumatology (ACR) Pedi 30 response to be eligible for entry to the randomised double-blind withdrawal phase of the study (16 to 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 sub-types of JIA was only reported for two of the trials, with polyarthritis being the predominant sub-type. 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 due to insufficient reporting.

Significantly fewer patients who continued to receive biologic DMARDs during the randomised withdrawal phase of the studies had arthritis flares compared to those receiving placebo in all four trials. Time to disease flare for participants receiving biologic DMARDs was statistically significantly longer (reported for abatacept, 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 to placebo, as were joint-related outcomes (reported for etanercept only) and pain in two out of three studies (etanercept and tocilizumab, not in abatacept). Not all studies reported a statistical comparison for

Table 10 Summary characteristics of included studies

	Abatacept	**Adalimumab**	**Etanercept**	**Tocilizumab**
Study details	AWAKEN, Ruperto et al.[57-60] Multi-centre withdrawal RCT at 45 centres in Europe (not UK), Latin America & USA	Lovell et al. 2008[61-64] Multi-centre withdrawal RCT at 31 centres in Europe (not UK) & USA	Lovell et al. 2000[42;65-67] Multi-centre withdrawal RCT at 9 centres in Canada & the USA	CHERISH, Brunner et al.[68-76] Multi-centre withdrawal RCT at 58 centres in Australia, Europe (inc. UK), Latin America, Russia & USA
Study phases[1]	16-week open-label lead-in **24-week randomised double-blind withdrawal** Open-label extension	16-week randomised open-label **32-week randomised double-blind withdrawal** Open-label extension	12-week open-label **16-week randomised double-blind withdrawal** Open-label extension	16-week open-label lead-in **24-week randomised double-blind withdrawal** Open-label extension
Intervention[2]	Abatacept: n=60 Abatacept 10 mg/kg at about 28-day intervals for 24 weeks or until disease flare	Adalimumab: n=38 Adalimumab 24 mg/m^2 BSA (to max. 40 mg) every other week for 32 weeks	Etanercept: n=25 Etanercept 0.4 mg/kg twice weekly until disease flare or for 16 weeks	Tocilizumab: n=82 10 mg/kg <30kg BW, n= 16; 8 mg/kg <30 kg BW n=11; 8 mg/kg ≥30kg BW n=55
Comparator[2]	Placebo n = 62	Placebo: n= 37 Placebo ≥10 mg/m^2 body surface area/week	Placebo: n = 26	Placebo: n=84 10 mg/kg <30kg BW, n=15; 8 mg/kg <30kg BW n=13; 8 mg/kg ≥30kg BW n=56
Key inclusion criteria	Age 6-17 years Active[3] JIA (extended oligoarticular, polyarticular, RF+ve or RF-ve, systemic without systemic manifestations) Inadequate response or intolerance to ≥1 DMARD including biological agents ACR Pedi 30 for entry to randomised double-blind phase	Age 4-17 years Active[3] polyarticular-course JIA (any onset type) Inadequate response to NSAIDs ACR Pedi30 at week 16 for entry to double-blind withdrawal phase	Age 4-17 years Active[3] JIA Inadequate response to NSAIDs and methotrexate at doses of ≤10 mg/m^2 body surface area/week	Age 2-17 years Active[3] polyarticular course or extended oligoarticular JIA (RF+ve or RF-ve) for ≥6months. Inadequate responses to or intolerant of methotrexate. Either never treated with biologics or had discontinued for a specified minimum period

DB, double-blind. LOM, limitation of motion. NSAIDs, non-steroidal anti-inflammatory drugs. RF, rheumatoid factor. +ve, positive. –ve, negative.
[1] the key phase of interest for efficacy outcomes is in bold text with lengths of phases reported in weeks for all studies for ease of comparison.
[2] during randomised double-blind withdrawal phase.
[3] Inclusion criteria for active disease were very similar for the adalimumab, etanercept and tocilizumab studies (key aspects were at least five swollen joints and at least three joints with LOM). The abatacept study required at least five active joints (with swelling or LOM accompanied by pain or tenderness) and active disease (at least two active joints and 2 joints with LOM)

double-blind withdrawal phase and an open-label extension phase. Enrolled participants all received adalimumab subcutaneously (24 mg per square metre of body surface area, to a maximum of 40 mg) every other week and methotrexate (at least 10 mg per square meter of body surface area per week) during the four-month lead-in phase. Those achieving an ACR Pedi 30 response were then eligible to be randomised in a 1:1 ratio to continued adalimumab plus methotrexate (n=38) or placebo plus methotrexate (n=37) (Table 10). The trial included two further study arms (adalimumab only and placebo only), but because the majority of participants in these arms had never received methotrexate, they do not meet the licenced indication and are not included in this report.

Patients were eligible for the trial if they were aged four to 17 years and had polyarticular-course JIA of any onset type. If systemic onset then patients had to be free of any systemic JIA manifestations for at least three months prior to study qualification.[77] Participants were required to have active disease (defined as five or more swollen joints and three or more joints with limited range of motion), had an inadequate response to NSAIDs, and had either not previously been treated with methotrexate or if previously treated with methotrexate, had had adverse events or an inadequate response. Exclusion criteria included clinically significant deviations in haematologic, hepatic or renal indicators; ongoing infection or a recent major infection that had required hospitalisation or intravenous antibiotics; recent receipt of live or attenuated vaccines. Patients who had previously been treated with other biologic agents at any time or who had received recent treatment with intravenous immune globulin, cytotoxic agents, investigational agents, DMARDs (other than methotrexate) or corticosteroids administered by intra articular, intra muscular or intravenous routes were also excluded from participation.

The primary outcome for the study (percentage of participants not receiving methotrexate who had a disease flare during the double-blind period) related to the two study arms that, as noted above, do not meet the licenced indication and are therefore not included in this report. Disease flare was reported for the two study arms relevant to this assessment and it was defined in different ways depending on the measure used: worsening of 30% or more in at least 3 of the 6 core criteria for JIA, and at least 30% improvement in no more than one of the criteria during the double-blind period; an increase of more than 30% on the 0-100 VAS if a global assessment was used; an increase in the number of active joints to at least two when the patient had none or only one if the number of active joints was used, with the same approach used for defining flare using joints with loss of motion. Outcomes were assessed every 12 weeks. The occurrence of adverse events was a secondary outcome.

Etanercept

The Lovell and colleagues (2000) RCT[42;65-67] was funded by the Immunex Corporation and consisted of three phases: an open-label lead-in phase of up to three months; a four-month double-blind

stable for eight or more weeks (methotrexate) or four or more weeks (oral glucocorticoids). Patients had to be treatment-naive for biologics or had discontinued for a specified minimum period. No other exclusion criteria were specified.

The primary outcome measure was proportion of participants with disease flare during the double-blind period (up to and including week 40 compared to week 16). Disease flare was defined as worsening of 30% or more in at least three of the six ACR core-response variables for JIA, and at least 30% improvement in no more than one variable during the double-blind period. Outcomes were assessed every four weeks. Secondary outcomes included the ACR Pedi 30/50/70/90 responses, the change from baseline in JIA core response variables and clinically inactive disease (physician global assessment indicating no disease activity plus the absence of all the following: joints with active arthritis, uveitis and erythrocyte sedimentation rate greater than 20 mm/hour.

Overview of the participants in the withdrawal phases of the included studies

For three of the four trials (abatacept,[57] adalimumab,[61] and etanercept[42]) baseline characteristics are provided for the participants who had achieved an ACR Pedi 30 and who were randomised to the double-blind withdrawal phase of each trial. The tocilizumab trial publication,[68] however, presented participant baseline characteristics for participants as randomised to the initial open-label lead-in phase, where three groups of participants all received the study drug (if body weight <30 kg then randomised to either 10 mg/kg or 8 mg/kg every 4 weeks; if body weight ≥30 kg then received 8 mg/kg every 4 weeks). Selected baseline characteristics are presented in Table 12, with the full set of characteristics available in the data extraction forms (Appendix 5). The mean age of trial participants reflected the differing entry criteria for the trials. Participants in the abatacept trial[57] (ages 6-17 years eligible) had the highest mean age (12-13 years) whereas those in the adalimumab[61] and etanercept trials[42] (ages 4-17 years eligible) had a slightly lower mean age (approximately 9-12 years) which was similar to those enrolled in the open-label phase of the tocilizumab study[68] (ages 2-17 eligible, mean age approximately 11 years). The majority of participants in all four studies were female (ranging from 67% in the etanercept study[42] to 80% in the adalimumab study[61]) and of white ethnicity (73% in the etanercept study[42] to 96% in the adalimumab study[61]). The proportion of patients across the sub-types of JIA were only reported for two of the trials (abatacept[57] and etanercept[42]). In these two trials polyarthritis was the predominant sub-type. In the abatacept trial just under 20% of patients had systemic JIA (without systemic manifestations),[57] whilst in the etanercept trial around a third had systemic JIA (with apparent systemic manifestations: spiking fever and rheumatoid rash).[42] The proportion of participants who were RF+ve ranged from 22% in the adalimumab study[61] to 29% in the tocilizumab study[68] and the duration of JIA from just under four years in the abatacept study[57] to approximately six years in the etanercept study.[42]

flare definitions based on global assessments and number of active joints. In all four studies, there were statistically significantly fewer arthritis flares in patients being treated with biologic DMARDs compared to those receiving placebo and in the three studies that reported time to disease flare this was statistically significantly longer in patients being treated with biologic DMARDs compared to those receiving placebo (Table 14).

Table 14 Disease flare during the randomised withdrawal phase

Study (Length: OL, RCT[1]), Outcome	**Intervention**	**Comparator**	
Abatacept[57] (4mo OL, 6mo RCT)	**ABA (n=60)**	**PBO (n=62)**	**p value**
Time to flare, median months	Not reached	6	0.0002
Disease flares, n (%)	12 (20)	33 (53)	0.0003
Disease flares, hazard ratio	0.31 (95% CI 0.16 to 0.59)		NR
Adalimumab[61] (4mo OL, 8mo RCT)	**ADA (n=38)**	**PBO (n=37)**	**p value**
Disease flares, n/N (%)	14/ 38 (37)	24/37 (65)	0.02
Time to onset of disease flare	>32 weeks	~20 weeks	0.03
Etanercept[42] (3mo OL, 8mo RCT)	**ETA (n=25)**	**PBO (n=26)**	**p value**
Disease flare, n (%) Corticosteroid use at baseline[3] Yes No	7 (28) 3/6 (50) 4/19 (21)	21 (81) 12/13 (92) 9/13 (69)	0.0031[2] 0.05
Time to flare, median days	>116	28	p<0.001
Tocilizumab[68] (4mo OL, 6mo RCTs)	**TCZ (n=82)**	**PBO (n=81)[4]**	**Difference[5] TCZ vs PBO (95% CI); p value**
Proportion with JIA flare, n (%)	21 (25.6)	39 (48.1)	–0.21 (–0.35, –0.08); 0.0024

ABA, abatacept. ADA, adalimumab. ETA, etanercept. mo, months. NR, not reported. OL, open-label. PBO, placebo. TCZ, tocilizumab.

[1] For ease of comparison lengths of open-label and RCT phases are presented as time in months (where originally presented in weeks value has been divided by 4, where originally presented in days value has been divided by 28)

[2] p<0.001 after adjustment for baseline characteristics in logistic regression model.

[3] Authors state that with the exception of corticosteroid use at base line (p=0.05), none of the baseline characteristics were significant predictors of flare rates (p>0.15).

[4] Of the 84 participants who achieved at least ACR Pedi 30 and were then randomised to placebo, three discontinued (1 insufficient therapeutic response, 2 due to adverse events). These three did not receive any study drug in the randomised part of the study and so were excluded from the analyses.

[5] Adjusted for baseline stratification factors (background use of MTX and oral glucocorticoids).

In the abatacept study,[57] by the end of the RCT period disease flare had occurred in 20% of patients receiving the study drug compared with 53% of patients receiving placebo (p=0.0003). Median time to disease flare was six months for the placebo group and statistically significantly greater compared to the abatacept group (p=0.0002), but authors state that insufficient events occurred in the abatacept group for this to be assessed. The risk of disease flare in patients randomised to continued abatacept during the RCT phase was just under a third of that for those receiving placebo (hazard ratio 0.31, 95% CI 0.16, 0.95, no p value reported).

Disease flare occurred in 37% of patients receiving adalimumab[61] compared with 65% of those receiving placebo (p=0.02) and the time to onset of disease flare was longer in the adalimumab group.

and infestations (44 - 45%). Adverse events were also reported under the headings of gastrointestinal disorders, general disorders and administration site conditions, nervous system disorders and respiratory, thoracic and mediastinal disorders (Appendix 5).

Adalimumab[61]

There were 234 AEs in the adalimumab group (12.8 per patient-year) and 155 AEs in the placebo group (10.3 per patient-year) during the eight-month double-blind period. No statistical comparisons in AEs between treatment groups were reported. Only one serious AE possibly related to study drug was reported and this was gastroduodenitis which occurred in one patient in the placebo group. The most common AEs were related to injection-site reactions [ADA: 73 events (4.0 events per patient year); PBO: 57 events (3.8 events per patient year)]. Other reported AEs were contusion, nasopharyngitis, upper respiratory tract infection, viral infection, vomiting and excoriation (Appendix 5). No AE lead to the discontinuation of the treatment drug (Table 20). Sixteen percent of patients (27/171) had at least one positive test for anti-adalimumab antibody during the open-label and double-blind phases (methotrexate: 5/85 -6%, No methotrexate: 22/86 - 26%), but this did not lead to a greater rate of discontinuation of the study drug, nor did it increase the incidence of serious AEs. The study authors state that there was no occurrence of opportunistic infections, malignant conditions, demyelinating diseases or lupus-like reactions.

Etanercept[42]

Two patients who received etanercept needed hospitalisation for serious AEs (one for depression and a personality disorder, and the other for gastroenteritis-flu syndrome). It is not clear at what point in the trial these events occurred. One patient withdrew after the first dose of etanercept (presumably at the start of the open-label period) because of urticaria. There were only two reported injection-site reactions during the double-blind phase of the trial, one in each treatment group (Table 20). All other AEs were reported to be of mild-to-moderate intensity, with no significant difference in the frequency of AEs between the treatment groups during the double-blind phase. There were no laboratory abnormalities requiring urgent treatment in the etanercept group. No patient had persistent elevations in autoantibodies or had signs or symptoms of another autoimmune disease. Two patients tested positive for non-neutralising antibody to etanercept.

Tocilizumab[68]

The safety population consisted of all patients who received ≥1 dose of study medication. During the double-blind period, the total number of patients with at least one AE was 58 in the tocilizumab group (454.7 AEs per 100 patient-years) and 60 in the placebo group (514.4 AEs per 100 patient years). The most frequently reported AE in both treatment groups was nasopharyngitis (TCZ: 17%, PO 11%). Other reported AEs occurring were headache, upper respiratory infection, cough, pharyngitis, nausea,

diarrhoea, rhinitis, vomiting, abdominal pain, oropharyngeal pain, and rash (Appendix 5). Two AEs led to drug discontinuation, one in each treatment group (TCZ: increased blood bilirubin level; PO: gastroenteritis) and 3.7% of patients in each treatment group had ≥1 serious AE. One patient in the tocilizumab group suffered with ≥1 infectious serious AE. Rates of serious AEs per 100 patient-years were similar between groups (TCZ: 9.3; PO: 10.9), while the rate of infections serious AEs per 100 patient-years was 3.1 for the tocilizumab group. Other reported serious AEs, included pneumonia, upper limb fracture, uveitis, psychosomatic disease, enterocolitis and complicated migraine, with one case in each category and varying by treatment group (Appendix 5).

Table 20 Adverse events (AEs)

Study, Outcome	**Intervention**	**Comparator**	
Abatacept[57] (during 6-month DB period)	**ABA (n=60)**	**PBO (n=62)**	**p value**
Total serious AEs, n (%)	0	2 (3)	0.50
Total AEs,[1] n (%)	37 (62)	34 (55)	0.47
Adalimumab[61] (during 8-month DB period)	**ADA (n=37; 15 Pt-yrs)**	**PBO (n=38; 18.3 Pt-yrs)**	
Any AE, n of events (n of events per patient-year)	234 (12.8)	155 (10.3)	
Serious AEs, possibly related to study drug,[2] n of events (n of events per patient-year)	0	1 (0.1)	
AEs leading to the discontinuation of the drug, n	0	0	
Etanercept[42] (time period unclear unless stated below)	**ETA (n=25)**	**PBO (n=26)**	
Hospitalisation for serious AEs, n	2	0	
Injection-site reactions during the 4-month double-blind period, n	1	1	
Most common AEs - injection-site reaction, no. of events (no. of events per patient-year)	57 (3.8)	73 (4.0)	
Tocilizumab[68] (during 6-month DB period)	**TCZ[4] (n=82)**	**PBO[4] (n=81)**	
Serious AEs and AEs occurring ≥5% of patients, n (%)			
Duration in study (years)	32.33	27.41	
Patients with ≥1 AE	58 (70.7)	60 (74.1)	
Total no. of AEs[5]	147	141	
Rate of AEs per 100 patient-years	454.7	514.4	
Serious AEs			
Patients with ≥1 serious AE	3 (3.7)	3 (3.7)	
Rate of serious AEs per 100 patient-years	9.3	10.9	
Patients with ≥1 infectious serious AE	1 (1.2)	0	
Rates of infectious serious AEs per 100 pt-years	3.1	0	
AEs leading to study drug discontinuation	1 (1.2)[6]	1 (1.2)[7]	

ABA, abatacept. ADA, adalimumab. AE, adverse event. DB, double-blind. ETA, etanercept. MTX, methotrexate. no, number. PBO, placebo. Pt-yrs, patient years. NR, not reported. TCZ, tocilizumab.
[1] AEs that occurred in ≥5% of patients in the open-label and double-blind phases.
[2] Serious AEs were death or any event that was life-threatening; required hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability, congenital anomaly, or spontaneous or elective abortion; or required medical or surgical intervention to prevent another serious outcome.
[3] After 1st dose of etanercept (responded to oral antihistamines).
[4] AE data on open-label TCZ escape therapy were excluded
[5] Multiple occurrences of the same AE in one individual were counted.
[6] Increased blood bilirubin level, highest total bilirubin reading, 50μmol/L (normal range, 3–24μmol/L); 2 consecutive readings >51mmol/L mandated withdrawal per protocol. The event resolved without sequelae.
[7] Gastroenteritis occurred 46 days after the last of five doses of placebo.

appeared to be more effective than these two comparators in terms of ACR Pedi 50 and ACR Pedi 70 responses. Therefore, there was no consistent ranking of treatment comparisons across these outcome measures. The indirect comparisons were generally not statistically significant, and confidence intervals were wide so caution is advised in the interpretation of these results. Furthermore, the etanercept trial[42] appears to have some differences from the other trials which may confound the results, namely the absence of methotrexate background therapy and the longer duration of JIA disease. There was also a noticeably higher rate of flares in the placebo arm of that trial compared to the other three trials (81% compared to 48% – 65%) which may account for the bigger treatment effect seen. Taking the above limitations into account an overall interpretation of the results of the indirect comparison is that, due to the absence of statistically significant differences between the biologic DMARDs, currently they appear to be similar in treatment effectiveness. This accords with the conclusion reached by Otten and colleagues who suggested that the short-term efficacy of the biologic DMARDs in polyarticular course JIA seem similar.[79] Furthermore, the clinical advisors to the assessment group felt that these data generally reflect clinical experience in that when used for the same indication in the same population effectiveness was likely to be similar. However there was also a recognition that for individual patients and potentially for particular sub-groups of JIA patients differential effects of each biologic DMARD might be apparent but these differential effects have not yet been captured by current trial data.

4.1.4 Summary of the systematic review of clinical-effectiveness

- Four multi-centre RCTs, one each evaluating abatacept, adalimumab, etanercept and tocilizumab met the inclusion criteria of this review. Only the tocilizumab RCT included UK patients. Seven additional RCTs (3 for adalimumab and 4 for etanercept) are described as ongoing (details summarised in section 4.3 'Ongoing trials' below).
- Each RCT had three phases, an open-label lead-in period, a randomised withdrawal period, and an open-label extension. The lengths of the lead-in and randomised phases varied between studies (open-label lead-in: 12 to 16 weeks; randomised double-blind withdrawal phase 16 to 32 weeks). In each study patients had to achieve an ACR Pedi 30 response during the initial open-label phase in order to be eligible for entry to the randomised double-blind withdrawal phase, Hence results are only applicable to patients who have already achieved an initial (low) degree of benefit from a biologic DMARD.
- The quality of the included RCTs was reasonable overall, with a low risk of bias judged for most items, although some aspects were rated as unclear, mainly due to a lack of reporting.
- Disease flare: this was the primary outcome in all four RCTs, with definitions broadly consistent between the studies. Patients who continued to receive biologic DMARDs during the randomised withdrawal phase of the studies had statistically significantly fewer arthritis

flares compared to those receiving placebo in all four studies, while time to disease flare reported in three studies (abatacept, adalimumab and etanercept) was statistically significantly longer in those treated with biologic DMARDs.

- ACR Pedi: a greater proportion of patients receiving biologic DMARDs during the randomised withdrawal phase of the studies achieved ACR Pedi responses of ≥30 compared with placebo-treated patients, with differences statistically significant in all but two instances where p-values were reported. The proportion of biologic DMARD-treated patients with inactive disease was more than twice that of placebo-treated patients in the two studies (abatacept and tocilizumab) reporting this outcome.
- ACR Pedi core variables: in the three studies reporting this outcome (abatacept, etanercept and tocilizumab) results were generally in favour of treatment with biologic DMARDs when compared to placebo.
- Joint related outcomes: one study (etanercept) reported additional joint outcomes without statistical comparisons. All outcomes favoured etanercept when compared to placebo.
- Pain: three studies reported pain (abatacept, etanercept and tocilizumab). A statistically significant difference in the mean change from baseline favoured the tocilizumab group. While pain scores were lower for those receiving biologic DMARDs in the remaining two studies, differences between treatment groups were not statistically significant in the abatacept study and no statistical comparison reported in the etanercept study.
- Mortality: no treatment-related deaths were reported in the three studies reporting this outcome (adalimumab, etanercept and tocilizumab).
- Outcomes not reported by the included RCTs for the randomised withdrawal phase of the trials were corticosteroid reducing regimens, extra-articular manifestations (such as uveitis), height and weight.
- HRQoL: reported by the abatacept study (abatacept) only, with differences between treatment groups for the physical and psychosocial summary scores not statistically significant. Those treated with abatacept had improved scores for 14 of the 15 CHQ subscales compared to 6 out of 15 for placebo-treated patients.
- AEs: during the randomised withdrawal phase of the trials the proportions of AEs and serious AEs were generally fairly similar between the biologic DMARDs and the placebo groups.
- Sub-group analyses: the tocilizumab study reported data for sub-groups but no statistical comparisons between treatment groups were reported.
- OLE: all four studies included an OLE phase. There were differences in eligibility criteria between studies and in how data were presented. Only results for ACR Pedi, AEs and growth are included in this report.
- OLE ACR Pedi:

Table 65 Deterministic sensitivity analysis for abatacept versus methotrexate only

Abatacept vs methotrexate	High CI	Low CI	Range
Base case ICER: £39,536			
Utility, treatment, long-term	£31,529	£52,995	£21,467
Discount rate costs	£30,512	£50,137	£19,625
Utility treatment 15-27 months	£32,110	£51,430	£19,319
Discount rate benefits	£49,908	£31,906	£18,002
Utility no treatment	£50,345	£32,549	£17,796
Start age	£42,187	£33,234	£8,952
On biologic DMARD cost	£43,094	£35,978	£7,117
Off biologic DMARD cost	£35,978	£43,094	£7,117

[1] After treatment for more than 27 months with biological DMARD

5.7.2 Scenario analysis

We conducted several scenario analyses to investigate uncertainty for specific aspects of the modelling. The results of these analyses are presented for the first line biologics.

i) Discontinuation of treatment due to clinical remission

Patients with clinical remission off medication are at high risk of relapse. Baszis and colleagues[160] conducted a retrospective chart review in a cohort of 171 patients with JIA (of a range of sub-types but predominantly polyarticular course) in the United States treated with TNFα antagonists. They found that 12 months after stopping treatment only 33% still had clinical remission. Similarly, a retrospective chart review of 437 JIA patients from centres in the United States and Italy by Wallace and colleagues[161] estimated that 6% of patients, that had discontinued methotrexate therapy with clinical remission, had persistent remission after five years off treatment.

The rate of discontinuation of biologic treatment varies between studies. In a retrospective observational study Tynjala and colleagues, patients receiving etanercept were followed up for four years and 10% of patients had discontinued treatment due to inactive disease. In the study by Baszis and colleagues[160] 80% of patients discontinued TNFα antagonist treatment due to inactive disease. We varied the discontinuation rate between that seen by Tynjala and colleagues[145] (used in the base case) and Baszis and colleagues[160].

We assumed a relapse rate from Baszis and colleagues[160] of 67% for that analysis and 40% relapse rate as seen in Wallace and colleagues[161] for the 'Tynjala and colleagues' analysis. We assumed no patients on the methotrexate only arm would discontinue as fewer patients on methotrexate would be in remission.

7 DISCUSSION

7.1 Statement of principal findings

7.1.1 Clinical-effectiveness

The systematic review of clinical-effectiveness conducted for this report found that biologic DMARDs are superior to placebo (with methotrexate where permitted) across a number of outcome measures in children with JIA (predominantly polyarticular course) and who had an insufficient response to previous DMARD treatment. With the exception of the etanercept trial the majority of patients in the trials received methotrexate in addition to the biologic DMARD/placebo. Biologic DMARD-treated patients had fewer arthritis flares, longer time to disease flare (applicable to abatacept, adalimumab and etanercept), were more likely to achieve a treatment response as defined by the ACR Pedi criteria, and to have inactive disease (only measured in the abatacept and tocilizumab trials). The latter outcome can be considered to be most clinically significant as absence of disease activity (e.g. no joints with active arthritis, physician's global assessment) is a key treatment goal. Treatment was associated with reduced pain scores, though this was only reported as statistically significant in one study (tocilizumab). HRQoL as measured by the CHAQ appeared to be higher for treated patients, though this was not always statistically significant.

The percentage of patients achieving ACR Pedi 30 in the open-label lead-in phases of the RCTs ranged from 65% to 94% across the trials. It should be acknowledged that due to the withdrawal design of the RCTs, in which only patients achieving an ACR Pedi 30 response during the open-label lead-in phase are eligible for randomisation, the results of the double-blind randomised phase of the trials are therefore only applicable to patients who have achieved an initial degree of treatment benefit. The effects seen during the double-blind period in the placebo group may not necessarily be the same for a placebo group who had not received a biologic DMARD prior to randomisation. However, expert clinical opinion suggests that ACR Pedi 30 can be considered an inadequate or partial response threshold, and higher rates, such as ACR Pedi 70 or above are considered more clinically significant. In this respect the patients responding to ACR Pedi 30 in the open-label lead-in phase (and eligible to be randomised) may not necessarily be considered atypical of patients eligible for treatment in clinical practice, as both would have active disease.

The clinical significance of the ACR Pedi 30 results of the randomised phases of the trials may also be questioned. ACR Pedi 30 response rates varied from 63% to 80% across the trials and declined with increasing response thresholds. Nonetheless, at ACR Pedi 70 (the highest threshold for which data were available across all four RCTs) the response rate varied from 44% to 65% and remained

This report is subject to certain limitations. The lack of head-to-head trials meant performing an indirect comparison of the biologic DMARDs, which is subject to a number of caveats due to heterogeneity between the trials (e.g. patient characteristics; treatment duration).

Limited HRQoL data were available for children with JIA, with none of the RCTs of biologic DMARDs reporting health utility data. The model results were based upon one Dutch registry study for patients treated with etanercept. It was necessary to make assumptions about the quality of life of patients treated with other biologic DMARDs. Due to the scarcity of the HRQoL data, it was not possible to link effectiveness data from the RCTs, in terms of ACR Pedi or CHAQ score, to a HRQoL utility measure. Furthermore, no HRQoL data were identified to inform the estimate of disutility of disease flare or the caregiver burden.

There were limited data available for the long-term discontinuation rates for patients for some of the biologic DMARDs and it was necessary to assume that the discontinuation rates for the biologic DMARDs were the same as each other.

The economic analysis has compared biologic DMARDs against methotrexate only, for patients with an insufficient response to previous methotrexate. The NICE scope also includes best supportive care (e.g. NSAIDS, corticosteroids) as a comparator in patients who cannot tolerate a DMARD (e.g. methotrexate) but this has not been included in the analysis due to lack of available data to make a comparison with best supportive care. Such patients would likely be offered a biologic DMARD rather than receiving best supportive care, therefore this comparison is not necessarily clinical relevant.

The model consists of a simple structure that does not incorporate the natural history of the disease in terms of long-term disease progression. JIA causes joint disease requiring joint operations and is associated with other co-morbidities. It is unclear from the current evidence how biologic DMARDs affect the natural history of the disease and the occurrence of these outcomes.

7.3 Uncertainties

The RCTs included in our systematic review of clinical-effectiveness did not report the impact of treatment on extra-articular manifestations. Uveitis is the most common of these manifestations and if not identified and adequately controlled can lead to permanent vision loss. Current guidance is to treat JIA patients with uveitis that has not responded to steroids or methotrexate with either adalimumab or infliximab which are both anti-TNF drugs (of

these, only adalimumab is within the scope of this assessment).[29] The guidance[29] states that etanercept is not suitable for the treatment of JIA patients with uveitis.

Furthermore, no HRQoL utility values for the impact of uveitis on the health-related quality of life in children with JIA were identified in our systematic review of quality of life. The paucity of good quality evidence for the effectiveness of biologic DMARDs means that the clinical and cost-effectiveness of treating JIA patients with uveitis is currently uncertain. However, it could be assumed that if biologic DMARD treatment of uveitis is effective in reducing sight impairment in addition to improving general JIA symptoms then the cost-effectiveness estimates generated in the independent economic evaluation in this assessment report would be improved. The SYCAMORE RCT of adalimumab in combination with methotrexate for JIA associated uveitis (funded by the NIHR HTA programme and Arthritis Research UK) has recently completed recruitment and will include an assessment of cost-effectiveness.[87]

The lack of available suitable published cost-utility models, necessitated building a new model which aimed to resemble clinical practice, but also utilise the effectiveness data from the RCTs. The design of the RCTs does not necessarily represent clinical practice (e.g. there wouldn't be a lead-in phase with a biologic DMARD).

The model has not incorporated the impact of biologic DMARD treatment on disease progression, and assumes that the HRQoL of patients treated with methotrexate is constant over time. The results therefore may under-estimate the cost-effectiveness of treatment.

The model has assumed that treatment is equally effective for subsequent lines of biologic DMARD treatment as for the first line of treatment. If effectiveness is seen to be reduced in subsequent lines of therapy for particular switching regimens then cost-effectiveness may be reduced compared to the results presented in this report (relating to abatacept as 2nd line treatment, and the scenario analysis of three lines of treatment).

The model has been modelled with a 30 year time horizon in the base case analysis. There is a lack of long-term outcome data for JIA patients. In addition, there are often differences in the management of JIA patients as adults, than as children which may affect patient outcomes. However, there are little empirical data available on the management of adult patients with JIA.

ACR Pedi response[1] week 48 (%) 30 50 70 90	 63 63 63 42	 38 38 27 27	 p=0.03 p=0.03 p=0.002 p=0.17
Physical function	NR	NR	
Joint damage	NR	NR	
Pain	NR	NR	
Corticosteroid reducing regimens	NR	NR	
Extra-articular manifestations (such as uveitis)	NR	NR	
Body weight and height	NR	NR	
Mortality	See comments AEs		
Health-related quality of life	NR	NR	

Comments: NR, not reported.
[1] A patient who had a flare according to the protocol definition was classified as having no response (ACR Pedi <30) from that point forward, regardless of the patient's ACR Pedi response at that time.

Adverse Events, no. of events (no. of events per patient-year)	**ADA (+MTX) (n=37; 15 Patient-yrs)**	**Placebo (+MTX) (n=38; 18.3 Patient-yrs)**	**p-value**
Any AE	234 (12.8)	155 (10.3)	
Most frequently reported AEs			
Related to injection-site reaction	73 (4.0)	57 (3.8)	
Contusion	12 (0.7)	7 (0.5)	
Nasopharyngitis	5 (0.3)	6 (0.4)	
Upper respiratory tract infection	6 (0.3)	5 (0.3)	
Viral infection	7 (0.4)	3 (0.2)	
Vomiting	4 (0.2)	2 (0.1)	
Excoriation	10 (0.6)	1 (0.1)	
Serious AEs, possibly related to study drug[1]	0	1 (0.1) - Gastroduodenitis	
AEs leading to the discontinuation of the drug	0	0	

Comments: no occurrence of deaths, opportunistic infections, malignant conditions, demyelinating diseases or lupus-like reactions. [1]Serious adverse events were death or any event that was life-threatening; required hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability, congenital anomaly, or spontaneous or elective abortion; or required medical or surgical intervention to prevent another serious outcome.

(27/171 (16%) had at least 1 positive test for anti-ADA antibody during the open-label and double-blind phases (MTX: 5/85 (6%), No MTX: 22/86 (26%), but development of anti-ADA antibody did not lead to a greater rate of discontinuation of the study drug, nor did it increase the incidence of serious AEs)

First 104 weeks of open-label extension phase[61]

ACR Pedi at 104 weeks of OLE, %	**OLE phase (n=128)[1]**
30	89%[2]
50	86%[2]
70	77%[2]
90	59%[2]
100	40%

Comments:
[1]Only 71/128 (55%) of this group received methotrexate during the open-label and double- blind phases of the study and meet the licenced indication for adalimumab (ie. the 128 includes participants not receiving methotrexate in the two study arms that do not meet the licenced indication).
[2] Data extracted from figure using Engauge software. Data available for earlier time points in OLE (weeks 8, 16, 24, 56, 104) but not data extracted. For missing values the last observation was carried forward.

Post-hoc analysis - OLE,[64] n(%)	**ADA**		**Placebo**		**p-value[2]**
	week 48	**week 88**	**week 48**	**week 88**	
Minimal disease activity[3]	19 (76)	26 (83.9)	15 (62.5)	14.0 (50.0)	
Minimal disease activity[3] with normal	17 (68.0)	24 (77.4)	15 (62.5)	14 (50.0)	