Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people: systematic review and economic evaluation

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Scientific summary

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Scientific summary

Background

Psoriasis is a chronic inflammatory disease of the skin and joints and typically results in red, scaly and flaky skin, also known as plaque psoriasis.

Existing psoriasis guidance for all age groups [National Institute for Health and Care Excellence (NICE) clinical guideline CG153 in England)] recommends traditional topical therapies as first-line therapy. Second-line therapies include phototherapy and non-biological systemic agents. Third-line therapy includes systemic biological therapies. Although there is currently no childhood-specific treatment pathway, CG153 highlights special considerations for children {e.g. referral to a specialist at presentation; avoidance of very potent corticosteroids, photochemotherapy [psoralen plus UVA light (PUVA)] and acitretin}.

Adalimumab (HUMIRA®, AbbVie, Maidenhead, UK), etanercept (Enbrel®, Pfizer, New York, NY, USA) and ustekinumab (STELARA®, Janssen Biotech, Inc., Titusville, NJ, USA) are the biologics currently licensed in children, although the exact populations included in these licences vary.

Objective

The aim of this study was to determine the clinical effectiveness and cost-effectiveness of adalimumab, etanercept and ustekinumab within their respective licensed indications for the treatment of plaque psoriasis in children and young people.

Methods

Clinical review and network meta-analysis

Studies were identified through searches of the literature and regulatory sources, direct requests for clinical study reports and contact with European psoriasis registries. Searches were carried out on 24/25 May 2016 and updated during September 2016. The following databases were searched: EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database, NHS Economic Evaluation Database (NHS EED), PubMed and Science Citation Index.

Studies of children and/or young people with moderate to severe plaque psoriasis, in whom topical or systemic therapies or phototherapies were inadequate, inappropriate or not tolerated, were eligible for inclusion.

Relevant interventions were adalimumab, etanercept and ustekinumab and relevant comparators included alternative biological therapies with relevant marketing authorisation (adalimumab, etanercept or ustekinumab) and their biosimilars, non-biological systemic therapy, topical therapy and biological treatments used outside their marketing authorisation.

Data on effectiveness, adverse effects, patient-centred outcome measures, health service costs and cost-effectiveness were eligible for inclusion.

Randomised controlled trials (RCTs) were eligible for the review of clinical efficacy. To address longer-term measures of efficacy and drug survival, published analyses based on large and long-term data sets were also considered.

The results of the included studies were presented in a series of structured tables, summarised narratively and subjected to critical appraisal. A naive indirect treatment comparison of adalimumab and etanercept was initially conducted based on the available placebo-controlled RCT data in children with psoriasis. A network meta-analysis (NMA) framework incorporating adult data was developed to allow the effectiveness data in children and young people to be connected and to inform the economic model.

Cost-effectiveness review

A systematic review was undertaken to identify published evidence on the cost-effectiveness of adalimumab, etanercept and ustekinumab, and relevant comparators, for the treatment of psoriasis in children and young people. This included the company submissions from Janssen Biotech, Inc. (ustekinumab) and AbbVie (adalimumab); Pfizer, the manufacturer of etanercept, did not submit any evidence. Additional hand-searching of published documents associated with previous NICE technology appraisals of psoriasis in adults was carried out. The aim was to examine existing decision-analytic models to identify important structural assumptions, highlight key areas of uncertainty and outline the potential issues associated with generalising evidence from the adult population to a population of children and young people.

Economic modelling

A de novo decision-analytic model was developed to estimate the cost-effectiveness of adalimumab, etanercept and ustekinumab compared with each other and with either methotrexate or best supportive care (BSC), depending on the position of the intervention in the management pathway. Before systemic therapy methotrexate was considered the relevant comparator (as the current standard of care), whereas after systemic therapy BSC was considered the most relevant comparator. The cost-effectiveness model took the form of a cohort Markov model and the time horizon was extended until individuals reached 18 years of age, when separate NICE recommendations for the use of the interventions in adults apply. Outcomes were expressed using quality-adjusted life-years (QALYs) and costs use a NHS and Personal Social Services perspective.

To reflect differences in marketing authorisation by age and the positioning of treatment in the pathway, the cost-effectiveness analysis considered three separate populations:

1. Children and young people aged 4–17 years, with adalimumab as the only licensed intervention for the treatment of severe plaque psoriasis in individuals inadequately controlled by, or intolerant to, topical therapy and phototherapies, that is, as an alternative to systemic therapies.
2. Children and young people aged 6–11 years, with adalimumab and etanercept used for the treatment of severe plaque psoriasis in individuals inadequately controlled by, or intolerant to, systemic therapies or phototherapies.
3. Children and young people aged 12–17 years, with adalimumab, etanercept and ustekinumab used for the treatment of severe plaque psoriasis in individuals inadequately controlled by, or intolerant to, systemic therapies or phototherapies.

Results

Clinical effectiveness review

Of the 2386 non-duplicate records identified, nine studies (three RCTs and six observational studies) were included in the clinical effectiveness review.

Efficacy data from pivotal randomised controlled trials

One RCT was identified for each of the biologics of interest. The etanercept and ustekinumab trials included 12 weeks of follow-up and used a placebo as the comparator, whereas the adalimumab trial was of 16 weeks' duration and included methotrexate as the comparator. The risk of bias was low for most domains in each study.

Although only older children and adolescents (aged 12–17 years) were included in the ustekinumab trial, the median age of children did not differ greatly across the three trials as relatively few younger children were recruited. Across the three RCTs, only 11 children aged < 6 years received biological treatment.

All three trials used a composite measure of disease severity incorporating baseline Psoriasis Area and Severity Index (PASI), Physician Global Assessment (PGA) and body surface area measurements. Average PASI scores ranged from 18.3 to 21.2, with 93–100% of participants having a PGA score of > 3 (mild/moderate disease). Although adalimumab and etanercept are licensed for 'severe chronic plaque psoriasis' and ustekinumab is licensed for 'moderate to severe plaque psoriasis', on average, measures of disease duration and the component measures of severity did not appear to differ markedly between the trials.

In total, 29.8% and 42.7% of participants in the adalimumab and ustekinumab trials, respectively, had received prior systemic therapy and 56.8% of participants in the etanercept trial had received either prior systemic therapy or phototherapy.

A similar proportion of participants in the adalimumab and ustekinumab trials had received some form of biological treatment prior to enrolment (9.6% and 10.8% respectively). No participants recruited to the etanercept trial had previously been treated with a biologic.

Adalimumab

One multicentre RCT (M04-717) found that adalimumab at the licensed dose of 0.8 mg/kg (up to 40 mg) led to significantly greater responses than methotrexate for the outcomes of PASI 50 and PASI 75 but not PASI 90 at 16 weeks. PGA 0/1 response rates were non-significantly higher for adalimumab than for methotrexate. The benefits of half-dose adalimumab were not statistically greater than those for methotrexate. Evidence on quality of life was inconsistent across different measures, possibly because of baseline imbalances on the Pediatric Quality of Life Inventory (PedsQL™). In children and young people, adalimumab did not appear to be associated with an increase in adverse events relative to methotrexate over 16 weeks, although the possibility of rare adverse events cannot be entirely excluded. The trial did not provide any comparative evidence for children aged 4–6 years of age.

Etanercept

One multicentre RCT (20030211) found etanercept to be significantly more effective than placebo in improving the severity of plaque psoriasis, based on PASI 50, 75 and 90 and PGA 0/1 response rates at 12 weeks. Improvements in health-related quality of life were larger for etanercept than for placebo but reached statistical significance only when measured using the Children's Dermatology Life Quality Index (CDLQI).

Adverse event rates were mostly similar in the etanercept and placebo groups at 12 weeks, with no serious adverse events observed for either treatment. However, a higher observed rate of infections among participants receiving etanercept was of borderline statistical significance. Relatively few young children (9% aged < 8 years; 4.3% aged < 6 years) were included in the study.

Up to 6 years of open-label follow-up (20050111) found that the proportions of PASI and PGA responders were stable over time, although only 36% of participants were available at the latest follow-up point. The proportion of participants withdrawing because of lack of efficacy is unknown. Through 264 weeks of follow-up, withdrawals because of adverse events were infrequent and no deaths or malignancies were observed.

Ustekinumab

One multicentre trial (CADMUS) in children aged 12–17 years found that both the standard dosage and the half dosage of ustekinumab were significantly more effective than placebo in improving the severity of plaque psoriasis, based on PASI 50, 75 and 90 and PGA 0/1 responses at 12 weeks. Both ustekinumab dosages also led to significantly greater improvements in health-related quality of life, measured using the CDLQI and PedsQL.

Among participants originally allocated to ustekinumab, PASI and PGA effects observed at 12 weeks appeared to be largely sustained at 52 weeks, with few withdrawals because of lack of efficacy.

There were no notable adverse effects associated with ustekinumab, although the number of observations was small and the longest follow-up time was only 60 weeks. Few participants withdrew because of adverse effects.

Efficacy data from network meta-analyses

The treatment effects for the interventions were assumed to be exchangeable across age as no statistically significant differences were identified in PASI response outcomes by age within the trials. The wider network including evidence from adult trials facilitated an indirect comparison of adalimumab, etanercept and ustekinumab. The NMA results – adjusted for differences in population and placebo response rates – demonstrated that ustekinumab is the most effective intervention, followed by adalimumab, etanercept and methotrexate.

Cost-effectiveness evaluation

Cost-effectiveness reported in existing published studies and manufacturer submissions

No previously published cost-effectiveness studies of adalimumab, etanercept or ustekinumab for psoriasis in children and young people were identified. One economic model was discussed as part of the All Wales Medicines Strategy Group advice for the use of etanercept within NHS Wales.

None of the companies participating in this appraisal submitted an economic model.

Cost-effectiveness results from de novo modelling

The de novo model generated incremental cost-effectiveness ratios (ICERs) for the three populations according to age and position of the intervention in the treatment pathway. Results were generated for a base case and for separate scenarios:

1. In the evaluation of adalimumab as an alternative to systemic therapy, the ICER for adalimumab compared with methotrexate was £308,329 per QALY.
2. In the evaluation of adalimumab and etanercept after failed systemic therapy in those aged 6–11 years, adalimumab was more effective but also more costly than etanercept and BSC. Based on a fully incremental analysis, the ICER for etanercept compared with BSC was £71,903 per QALY whereas the ICER for adalimumab compared with etanercept was £174,519 per QALY. The individual pairwise ICER for adalimumab compared with BSC was £115,825 per QALY.
3. In the evaluation of ustekinumab, adalimumab and etanercept after failed systemic therapy in those aged 12–17 years, ustekinumab was the most effective and most costly treatment, followed by adalimumab, etanercept and BSC. Based on a fully incremental analysis, etanercept was extendedly dominated by adalimumab (i.e. etanercept produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy of adalimumab), the ICER for adalimumab compared with BSC was £110,430 per QALY and the ICER for ustekinumab compared with adalimumab was £201,507 per QALY. The individual pairwise ICERs for etanercept, adalimumab and ustekinumab compared with BSC were £137,059, £110,430 and £116,568 per QALY respectively.

Using utility values from an adult population brought the ICER for etanercept compared with BSC under a threshold of £30,000 per QALY in children and young people aged 6–11 years. The ICERs for ustekinumab and adalimumab were reduced significantly but remained above the £30,000 per QALY threshold.

Under the assumption of no health benefits for BSC, the ICERs were reduced substantially but remained quite high, with the lowest ICER being £56,430 per QALY for etanercept compared with BSC.

If the average number of days hospitalised per annum was increased from 0 days to 6.49 days based on a study in adults, the ICERs for the interventions reduced significantly; however, the only ICER that fell below the £30,000 threshold was for the use of etanercept compared with BSC in children and young people aged 6–11 years. If the average length of hospitalisation per annum was increased significantly to 26.6 days per annum based on a very high-need adult population, the biological treatments were all considered cost-effective compared with BSC in individuals who have failed systemic therapy.

Discussion

Although the number of included participants and trial follow-up periods were limited, this systematic review included the best available evidence on the efficacy and short- to medium-term safety of adalimumab, etanercept and ustekinumab that was directly relevant to the decision problem.

Very little evidence on efficacy or safety was available for young children. The ustekinumab trial restricted inclusion to participants aged > 12 years and the adalimumab and etanercept studies included few children aged < 8 years. Only 11 children aged 4–5 years were included across all of the RCTs of biologics for psoriasis.

The review of cost-effectiveness evidence in this population, and the absence of economic models submitted by the manufacturers involved in this appraisal, highlight the challenges involved in evaluating the cost-effectiveness of biological interventions in children and young people with plaque psoriasis. The fundamental challenge is the limited clinical evidence base for short- and long-term outcomes. A key strength of this evaluation was that it went beyond the scope of the appraisal by bringing together evidence from the adult population to support an economic evaluation in children and young people. However, inevitably the results are subject to a number of uncertainties.

Conclusions

The paucity of clinical and economic evidence to inform the cost-effectiveness of biological treatments in children and young people has imposed a number of strong assumptions and uncertainties. Health-related quality-of-life gains associated with treatment and the number of hospitalisations in children and young people are areas of considerable uncertainty.

Based on the economic assessment, the majority of ICERs for the use of biologics in children and young people were above NICE's usual cost-effectiveness threshold and were reduced significantly only by adopting combined assumptions that align with those made in the management of psoriasis in adults.

Suggested research priorities

- The continued collection of data through registries of biological therapies for individuals aged < 18 years is warranted to enable safety, patterns of treatment switching, the impact on comorbidities and long-term withdrawal rates to be investigated.
- Adequately powered RCTs could substantially reduce the uncertainty surrounding the effectiveness of biological treatments in biologic-experienced populations of children and young people. In particular, evidence for the comparative clinical effectiveness and safety of adalimumab and etanercept in younger children is currently lacking.
- Further research is needed on the resource use and costs associated with BSC.

Study registration

This study is registered as PROSPERO CRD42016039494.

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