Abrocitinib, tralokinumab and upadacitinib for treating moderate-to-severe atopic dermatitis

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/LEXB9006.

Primary conflicts of interest: No competing interests were declared by Steven J Edwards, Charlotte Karner, Tracey Jhita, Samantha Barton, Gemma Marceniuk or Zenas Z N Yiu which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of the BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG. In the past 36 months, Miriam Wittmann has received research grants from AbbVie, the British Skin Foundation, Janssen, Lupus UK, Novartis, Pfizer Global and UCB. MW has received a consultancy fee from UCB for acting on an advisory board, and remuneration from various companies for carrying out educational lectures.

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Report reference: Edwards SJ, Karner C, Jhita T, Barton S, Marceniuk G, Yiu Z, Wittmann M. Abrocitinib, tralokinumab and upadacitinib for treating moderate-to-severe atopic dermatitis. BMJ Technology Assessment Group; 2021.

Published January 2024
DOI: 10.3310/LEXB9006

Scientific summary

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Health Technology Assessment 2024; Vol. 28: No. 4
DOI: 10.3310/LEXB9006

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Atopic dermatitis (AD), often referred to as atopic eczema, is a chronic relapsing inflammatory skin condition. One of the most common skin disorders in children, AD typically manifests before the age of 5 years, but can develop at any age. AD is characterised by dry, inflamed skin accompanied by intense itchiness (pruritus). As many as 1 in 5 children and 1 in 10 adults in the UK are estimated to have AD, with about 18% of cases of childhood AD categorised as moderate and 2% as severe. Of adults with AD, it has been reported that 5% of cases are severe. Of the people who need treatment for AD, 7% are estimated to have moderate-to-severe disease.

Atopic dermatitis is currently uncurable, and the goal of treatment is to improve symptoms and achieve long-term disease control. Those with moderate-to-severe AD that only partially responds to treatment, and those presenting with severe disease, are referred to secondary care for a more specialised therapy, where phototherapy [predominantly ultraviolet B (UVB)] is frequently the first treatment option. If phototherapy is unsuccessful, subsequent treatment typically constitutes systemic treatments.

Systemic treatment options available within the NHS for the management of AD in line with their marketing authorisations are ciclosporin A (CsA) in the first-line setting, and baricitinib and dupilumab as subsequent therapies. The three interventions for which an evaluation of the clinical and cost effectiveness in the treatment of moderate-to-severe AD form the basis of this report are abrocitinib, tralokinumab and upadacitinib. The clinical and cost effectiveness of these treatments at their recommended dose or doses versus treatment options available in the NHS for moderate-to-severe AD was evaluated in the positions in the treatment pathway proposed by the sponsoring company.

The proposed positions are:

- Abrocitinib:
  - second-line systemic therapy for adolescents
  - second-line systemic therapy for adults.
- Tralokinumab:
  - second-line systemic therapy for adults.
- Upadacitinib:
  - adolescents
  - first-line systemic therapy for adults
  - second-line systemic therapy for adults.

Objectives

The research objectives of the multiple technology appraisal (MTA) are to appraise the clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib within their marketing authorisations as alternative therapies for treating moderate-to-severe AD in the UK clinical setting compared to systemic immunosuppressants (first-line CsA or second-line dupilumab and baricitinib).

Methods

Studies were identified from an existing systematic review (search date 2019) and update searches of electronic databases (MEDLINE, EMBASE, CENTRAL) up to November 2021, from bibliographies of retrieved studies, clinical trial registers and evidence submissions provided by companies. Clinical studies and economic evaluations were included based on pre-specified inclusion criteria. Screening of title and abstracts to identify potentially relevant studies and evaluation of full-text publications were done independently by two reviewers. Data from included studies were extracted into a standardised data extraction form by one reviewer and validated by a second. Quality of included studies was assessed independently by two reviewers using standard checklists. Extracted data and quality assessment for each study were presented in structured tables. Where sufficient comparable data were available for an outcome measure, network meta-analysis (NMA) was performed using a Bayesian Markov Chain Monte Carlo simulation. The primary outcome of the review of clinical effectiveness was Eczema Area and Severity Index (EASI) 50 + Dermatology Life Quality Index (DLQI) ≥ 4 and EASI 75 was explored as a scenario. Treatment effects were analysed as odds ratios (ORs).

A de novo hybrid economic model was developed to assess the cost effectiveness of the three new drugs, comprising a short-term (1 year) decision tree component, to capture the treatment induction phase and treatment response assessments, followed by a long-term (lifetime), three-state Markov model. In consultation with clinical experts, the Evidence Assessment Group (EAG) selected baseline characteristics for the model from the upadacitinib trials, which were considered representative of the eligible patient population in England. Estimates of treatment response, based on the composite outcome of EASI 50 + DLQI ≥ 4 from the NMA of clinical effectiveness data, were used in the short-term model.

Conditional discontinuation data (defined as people whose condition responded to treatment at week 16 but withdrew from treatment for any reason at week 52) were used to estimate week-52 outcomes as well as long-term treatment discontinuation. Conditional discontinuation data were provided by the companies. Where there was a paucity of data, the EAG adopted a drug class approach to fill the gaps, where upadacitinib was used to inform Janus kinase inhibitors and tralokinumab was used to inform monoclonal antibodies. Additionally, in the long-term model treatment, waning assumptions were applied to all treatments as patients may lose response to treatment over time and these were informed by assumptions accepted in the NICE technology assessment of dupilumab for treating moderate to severe atopic dermatitis (TA534).

Rates of adverse events and flare (based on the use of rescue medication) associated with each treatment were obtained from the companies, and where data gaps existed, a similar drug class approach was adopted for the missing data. Utilities based on drug class were obtained from key trials of upadacitinib and tralokinumab. Costs were obtained from standard UK sources. Probabilistic, one-way and scenario analyses were carried out to assess parameter uncertainty.

Results

The EAG identified 23 studies of relevance to the MTA. Most of the studies included in the assessment of clinical effectiveness were considered to be well-conducted and well-designed Phase III randomised controlled trials (RCTs), and, as such, are at an overall low risk of bias. However, the identified studies predominantly included mixed populations of people with moderate-to-severe AD, with some studies comprising both adolescents and adults, as well as a combination of people receiving systemic therapy as a first-line or second-line regimen. Thus, data informing the NMAs for the populations and outcomes of interest to the MTA are predominantly derived from post hoc subgroups.

There were considerable amounts of uncertainty, and the vast majority of results were not statistically significant. However, there were consistent trends across the outcomes (EASI 50 + ΔDLQI ≥ 4 and EASI 75), interventions (combination therapy or monotherapy) and populations (adults in the first- or second-line setting and adolescents).

Treatment with abrocitinib 200 mg leads to a better response, assessed as either EASI 50 + ΔDLQI ≥ 4 or EASI 75, than dupilumab, whereas there was less of a difference in the effectiveness between dupilumab and abrocitinib 100 mg with some comparisons showing a benefit in favour of dupilumab and others favouring abrocitinib 100 mg. Both doses of abrocitinib were more effective than baricitinib 4 mg (EASI 75 for adults in the second-line setting) and in the adolescent population, both doses of abrocitinib were more effective than dupilumab (EASI 75). Although significantly better than placebo, tralokinumab treatment was numerically, but not statistically significantly, less effective than treatment with either dupilumab or baricitinib 4 mg (response assessed as either EASI 50 + ΔDLQI ≥ 4 or EASI 75). Similar to abrocitinib, treatment with upadacitinib 30 mg led to a better response (assessed as either EASI 50 + ΔDLQI ≥ 4 or EASI 75) than dupilumab, whereas there was less of a difference in the effectiveness between dupilumab and upadacitinib 15 mg with some comparisons showing a benefit in favour of dupilumab and others favouring upadacitinib 15 mg. Both doses of upadacitinib were more effective than baricitinib 4 mg (EASI 75 for adults in the second-line setting). In the adolescent population, upadacitinib 15 mg was more effective than dupilumab (EASI 75).

The National Institute for Health and Care Excellence (NICE) typically considers interventions a cost-effective use of the NHS resources if the incremental cost-effectiveness ratio (ICER) sits within a £20,000–30,000 threshold. The decision rule is reversed if an intervention is less costly and less effective (south-west quadrant), such that if the ICER is >£20,000–30,000 threshold, it can be considered a cost-effective use of NHS resources.

For the adolescent population analyses, both doses of abrocitinib and upadacitinib 15 mg were less costly and more effective than dupilumab, resulting in dominant probabilistic ICERs. For the adult second-line monotherapy population, upadacitinib 15 mg is less costly and more effective than dupilumab (dominant) and tralokinumab was less costly and less effective than dupilumab (south-west quadrant ICER of £409,271).

For the adult second-line combination therapy population, compared with dupilumab, abrocitinib 100 mg, upadacitinib 15 mg and tralokinumab were associated with south-west quadrant probabilistic ICERs of £58,920, £204,598 and £285,653, respectively.

Compared with dupilumab, the following were not considered a cost-effective use of NHS resources with ICERs above £30,000 threshold commonly used by NICE: upadacitinib 15/30 mg (adult first-line combination therapy), abrocitinib 100/200 mg and upadacitinib 30 mg (adult second-line monotherapy), and abrocitinib 200 mg and upadacitinib 30 mg (adult second-line combination therapy).

The key drivers of cost effectiveness were week-16 response probabilities and conditional discontinuation probabilities (used to inform the week-52 response and annual discontinuation), which are as expected, as these are the key effectiveness estimates in the model. In particular, the NMA for week-16 response was associated with substantial uncertainty, especially for abrocitinib, due to small numbers informing the network.

Key scenarios that had a substantial impact on the cost-effectiveness results were reducing the time horizon in the adult analyses to 5 years and 18 years of age for the adolescent analyses, as well as using data from TA534 and an alternative NMA where censoring for rescue therapy was included.

The EAG cautions the interpretation of the cost-effectiveness results presented in the MTA report as they are based on list prices for abrocitinib, baricitinib, dupilumab, tralokinumab and upadacitinib, but all have confidential patient access scheme (PAS) in place.

Conclusions

The population which is most likely to be important for decision-making is the adult second-line systemic treatment subgroup, in particular, the combination treatment analyses, as all three new drugs have a proposed position in this part of the treatment pathway. Furthermore, clinical experts advising the EAG considered combination therapy is more widely using in clinical practice in England. For this population, composite outcome data were available for each new treatment under consideration, as well as for one of the relevant comparators, dupilumab (which is approved for use by NICE at this step in the treatment pathway). Baricitinib, in combination with topical corticosteroid (TCS), is also a relevant comparator in the adult second-line systemic treatment population. However, composite outcome data for baricitinib were not made available to the EAG for inclusion in the clinical effectiveness analysis. Instead, the EAG obtained EASI 75 data for baricitinib and included this in the adult second-line systemic combination treatment NMA. As such, a scenario looking at the cost effectiveness of each of the three new drugs compared with baricitinib was explored to support decision-making.

As the adult first-line systemic treatment and adolescent populations are also relevant for decision-making, the EAG was able to produce base-case cost-effectiveness results for the new drugs using the EASI 75 outcome, as the composite outcome was unavailable. However, RCT data for CsA were not available for the comparison with upadacitinib in the first-line setting, but observational data were identified that could be used in the NMA. Though the EAG notes that even though observational data for CsA are the best available evidence, it is associated with the bias inherent in observational studies and the results should be interpreted with caution. Additionally, for the adult first-line systemic treatment population, outcome data were only available for combination therapy, but the EAG's clinical experts considered it to be more relevant for clinical practice. Thus, the EAG considered missing monotherapy data are unlikely to be critical for decision-making for the adult first-line systemic treatment subgroup.

Analyses of the adolescent population were limited to assessing monotherapy, as combination data for dupilumab were unavailable to inform the NMA. Thus, the adolescent monotherapy analyses may potentially underestimate the relative effectiveness of the treatments when used in combination with TCS in clinical practice, as combination treatment results typically demonstrate higher treatment effectiveness.

The summary of product characteristics for both abrocitinib and upadacitinib takes into consideration circumstances, where moving to the lower or higher dose of each drug may be beneficial and this is likely to happen in clinical practice. However, analyses exploring increasing or decreasing dose for abrocitinib and upadacitinib were not possible as efficacy data based on titrating dose are unavailable. Nonetheless, the EAG considers that clinical and cost-effectiveness results for abrocitinib and upadacitinib by low and high dose are useful to facilitate consideration of the impact of dose titration for each drug.

The robustness of the clinical and cost-effectiveness analyses is limited by the use of post hoc subgroups; while the use of subgroups increases the comparability and applicability of the analyses, it introduces bias and uncertainty to the results generated by the NMAs. In particular, the sample size of the second-line systemic therapy subgroup in the abrocitinib trials was very small as the majority of patients in the abrocitinib trials were eligible for first-line rather than second-line systemic therapy.

This research assesses the clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib as alternative therapies for treating moderate-to-severe AD compared to standard practice with systemic immunosuppressants. At the different steps in the treatment pathway assessed, new options were identified that represent a cost-effective use of scarce NHS resources.

Study registration

This study is registered as PROSPERO CRD42021266219.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Evidence Synthesis programme (NIHR award reference: 135138) and is published in full in *Health Technology Assessment*; Vol. 28, No. 4. See the NIHR Funding and Awards website for further award information.

Health Technology Assessment

HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.6

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The research reported in this issue of the journal was commissioned and funded by the Evidence Synthesis Programme on behalf of NICE as project number NIHR135138. The contractual start date was in August 2021. The draft report began editorial review in February 2022 and was accepted for publication in February 2023. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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