Omalizumab for severe atopic dermatitis in 4- to 19-year-olds: the ADAPT RCT

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Scientific summary

The ADAPT RCT

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Scientific summary

Background

Eczema is a chronic inflammatory pruritic skin disorder affecting 10–16% of UK children. It has a significant impact on quality of life (QoL), with economic, psychosocial and mental health implications. In the UK, 1–2% of children experience severe eczema, for whom the impact is felt all the more profoundly.

Patients with severe eczema can be offered systemic immunosuppression. Although potentially effective, there is little published data on the use of systemic immunosuppression in children; these treatments are unlicensed for eczema in children and can be associated with undesirable side effects.

The association between high levels of immunoglobulin E (IgE) and atopy is well established. IgE-bearing cells found in eczema lesions potentially present allergen and trigger inflammation. Furthermore, the T helper 2 (T_h2) pathway drives IgE synthesis, and the blockade of IgE may benefit eczema in the same way as the blockade of T_h2 pathways appears to. Omalizumab (Xolair®, Novartis Pharmaceuticals UK Ltd, Frimley, UK) is an anti-IgE antibody that binds human IgE and interrupts the allergic cascade. It is licensed for patients aged ≥ 6 years for asthma, and safety data suggest that it is well tolerated. It was hypothesised that anti-IgE would reduce IgE levels in children with severe eczema and alleviate their symptoms.

Objectives

The primary objective was to determine whether or not omalizumab improved eczema severity compared with placebo, as assessed by the objective SCORing Atopic Dermatitis (SCORAD) eczema severity score.

The secondary objectives were to (1) evaluate whether or not omalizumab is associated with a change in eczema severity, QoL and coexisting allergic disease using validated questionnaires, (2) assess the impact of omalizumab on the need for topical or other systemic therapies, (3) assess the impact of omalizumab on the rate of eczema exacerbations and infections, (4) assess the impact of omalizumab on allergen reactivity [skin prick tests (SPTs) and IgE levels] and (5) assess the safety of omalizumab in eczema.

Methods

Trial design

This was a randomised, double-blind, parallel-arm, placebo-controlled study to compare anti-IgE (omalizumab) and placebo in severe childhood eczema.

Participants

Participants were recruited from a single centre, with external referrals from participant identification centres.

Inclusion criteria

Participants were eligible if:

- they were aged 4–19 years at enrolment
- they had severe eczema –
    - with an objective SCORAD score of > 40
    - and were unresponsive to optimal topical therapy (potent topical steroids and topical calcineurin inhibitors) or systemic therapy

  - and there was no impression of a lack of compliance
  - and a (Children's) Dermatology Life Quality Index [(C)DLQI] score of ≥ 10
  - and active skin infection had been ruled out and/or adequately treated

- they had a raised specific IgE (SpIgE) level (> 0.35 kUA/l) or SPT result (> 3 mm) in response to at least one food allergen or aeroallergen, and/or
- allergic exposures clinically worsened their eczema
- their total IgE level was > 300 kU/l
- they had clinically proven IgE-mediated allergic disease, including at least one of the following clinically defined conditions –

  - immediate food hypersensitivity
  - allergic rhinoconjunctivitis
  - allergic asthma

- they provided written informed consent, or assent if appropriate.

Exclusion criteria

The exclusion criteria were:

- children and young people and/or families being unable to comply with the injections and clinic visits
- underlying immune compromise, autoimmune disease and immune complex mediated conditions
- malignancy or history of malignancy
- cardiovascular or ischaemic cerebrovascular abnormality
- serious or uncontrolled systemic disease
- pregnancy or lactation
- hypersensitivity or anaphylaxis to anti-IgE injections or its constituents
- patients having an insufficient understanding of trial assessments
- participation in a clinical trial of an investigational medicinal product in the previous 60 days or four half-lives of the relevant medication, in which case entry could be delayed until the appropriate time
- investigator decision.

Randomisation

Participants were allocated 1 : 1 to receive omalizumab or placebo via a secure online randomisation system, using a minimisation procedure with a 10% random element and stratification variables [age (< 10 or ≥ 10 years) and IgE level (≤ 1500 or > 1500 kU/l)].

Interventions

The dosage and frequency of treatment with omalizumab were determined by manufacturer's dosing tables. The placebo doses were matched. Because of historical changes to the dosing tables, the maximum dose was higher than in previous eczema studies. The dose in the manufacturer's tables that was closest to the child's weight and IgE levels was used. When participant total IgE levels were above the dosing limit of 1500 kU/l, they received the maximum dose for their weight. Participants received treatment for 24 weeks and were seen every 2 or 4 weeks in accordance with their dosing schedule. They were followed up for a further 24 weeks.

Primary outcome

The primary outcome was objective SCORAD score at 24 weeks.

Blinding

Participants, caregivers and staff responsible for the outcome assessments were blinded to treatment allocation.

Results

Recruitment took place between 20 November 2014 and 6 October 2016. A total of 63 participants were randomised; one participant was not eligible and was withdrawn before any study drug was administered. The results of the remaining 62 participants were analysed (omalizumab, $n = 30$; placebo, $n = 32$). Trial assessments were completed by 31 August 2017.

The mean age of the participants was 10.3 years, 52% were male and the median baseline total IgE level was 8373 kU/l. The mean eczema severity at baseline, as measured by the objective SCORAD was 54.9; the mean total SCORAD score (sum of the objective and subjective SCORAD scores) was 69.3 and the mean Eczema Area and Severity Index (EASI) score was 44.5. Baseline characteristics were generally well balanced across treatment arms, including baseline use of potent topical steroids.

Four participants withdrew from treatment in the placebo arm and one participant was withdrawn by investigators from the omalizumab arm. Adherence to treatment by all other participants was 100%. Follow-up rates were 96.8% at 24 weeks and 98.4% at 48 weeks.

Primary outcome

Omalizumab improved objective SCORAD scores compared with placebo at 24 weeks.

The unadjusted mean objective SCORAD score improved by –12.4 {55.5 [standard deviation (SD) 9.5] at baseline and 43.1 [SD 12.5] at the end of treatment [week 24]} in the omalizumab arm and by –5.1 [54.3 (SD 7.7) at baseline and 49.2 (SD 11.3) at 24 weeks] in the placebo arm. After adjustment for baseline objective SCORAD score, age and IgE level using a linear mixed model, the estimated mean treatment arm difference was –6.9 [95% confidence interval (CI) –12.2 to –1.5; $p = 0.013$] at 24 weeks in favour of omalizumab. The prespecified minimum clinically important difference (MCID) was 8.5. Although the average treatment effect was smaller than the trial team aimed to detect, as the MCID is contained well within the 95% CI, an important average clinical benefit cannot be ruled out. The treatment effect was marginally reduced in sensitivity analysis adjusting for use of alternative systemic therapy (AST) (i.e. systemic immunosuppression), oral prednisolone and potent topical steroid use; however, overall, the results were consistent with the primary analysis, identifying a significant treatment effect. The causal effect among compliers (participants who completed > 50% of treatment injections) was also consistent with the primary outcome (causal effect –7.09, 95% CI –12.9 to –1.31; $p = 0.016$). A post hoc analysis identified a greater treatment effect in participants with lower baseline IgE levels (adjusted treatment effect for median baseline IgE level of 8373 kU/l was –7.9, 95% CI –13.7 to –2.2; $p = 0.007$).

To assess if the benefits of treatment persisted beyond the treatment period, an exploratory analysis using an extended linear mixed model was conducted on objective SCORAD scores at 48 weeks (24 weeks post treatment). The point estimate was, on average, in favour of omalizumab with the 95% CI extended to include no difference or favouring placebo at 48 weeks (adjusted mean difference for the week 48 objective SCORAD was –2.8, 95% CI –8.6 to 3.0; $p = 0.346$).

Secondary outcomes

Omalizumab improved eczema severity (total SCORAD and Eczema Area and Severity Index scores) compared with placebo

The mean total SCORAD score changed by –16.4 and –8.2 and the EASI changed by –12.7 and –5.1 within the omalizumab and placebo arms, respectively, in favour of omalizumab. Significant between-arm differences were seen for secondary measures of eczema severity. The treatment effect at week 24 was –8.3 (95% CI –15.1 to –1.1; $p = 0.024$) (MCID 8.7) for the total combined objective and subjective SCORAD (total SCORAD) and –6.7 (95% CI –13.2 to –0.1; $p = 0.046$) (MCID 6.6) for the EASI, in favour of omalizumab.

The difference between the two arms persisted to a lesser extent until 48 weeks, which was 24 weeks after treatment had been discontinued.

The treatment effect was, on average, in favour of omalizumab for patient-reported symptoms measured using the Patient-Oriented Eczema Measure (POEM), but the 95% CI included no difference or favouring placebo (treatment effect –1.1, 95% CI –4.6 to 2.4; $p = 0.527$) (MCID 3.4). A post hoc analysis identified a significant interaction between age and the week 24 POEM score. A larger significant treatment effect on POEM score was observed for children aged < 10 years (treatment effect –5.2, 95% CI –10.0 to –0.5; $p = 0.031$) than for those aged ≥ 10 years (treatment effect 2.8, 95% CI –1.8 to 7.4; $p = 0.230$). It was anecdotally observed that caregivers filled out questionnaires for younger children, whereas older children completed the questionnaires themselves, which may explain these results.

Potent topical steroid use was reduced in the omalizumab-treated arm

The median number of days of potent topical steroid use over the 24-week treatment period was 48% higher in the placebo arm than in the omalizumab arm. Of a total of 168 days (24 weeks), the median number of days of potent topical steroid use was 109 [interquartile range (IQR) 34–164 days] in the omalizumab arm and 161 (IQR 82–171 days) in the placebo arm ($p = 0.067$). The average percentage of body surface area (BSA) over which potent topical steroids were used per participant in the placebo arm was double that per participant in the omalizumab arm [omalizumab median 15.5% (IQR 9.9–46.3%) vs. placebo median 31.3% (IQR 14.0–55.0%)]. The median weight of potent topical steroids used was 76% higher in the placebo arm (102 g) than in the omalizumab arm (58 g) at week 24.

This effect persisted to 48 weeks. The median number of days of topical steroid use remained higher in the placebo arm by this time point; of a total of 336 days (48 weeks), the median number of days of use was 188 in the omalizumab arm (IQR 49–299 days) and 291 in the placebo arm (IQR 111–336 days). Over 48 weeks, participants in the omalizumab arm used potent topical steroids over a median of 18.25% of their BSA, compared with 31.5% of participants' BSAs in the placebo arm. The median total weight used over 48 weeks was higher in the placebo arm (144 g) than in the omalizumab arm (82 g).

Omalizumab-treated participants had a reduced treatment burden

There were fewer treatment failures requiring rescue therapy with oral corticosteroids and less systemic immunosuppression initiation in the omalizumab arm, but the numbers were small. The overall treatment burden, defined as protocol-defined treatment failure or requirement for AST, was one participant in the omalizumab arm (3.3%) and five participants in the placebo arm (16.1%). Of these, one participant experienced treatment failure and required oral steroids in the omalizumab arm, compared with three participants in the placebo arm (3.3% vs. 9.7%). Five participants started AST with systemic immunosuppression within 30 weeks of their baseline visit: one in the omalizumab arm (whose study medication was withdrawn by investigators after their week 4 visit) and four in the placebo arm (3.3% vs. 12.9%).

Omalizumab improved quality of life [(Children's) Dermatology Life Quality Index and the Paediatric Allergic Disease Quality of Life Questionnaire] compared with placebo

At week 24, the QoL scores favoured omalizumab for the (C)DLQI. The treatment effect was –3.5 (95% CI –6.4 to –0.5; $p = 0.022$) (MCID 3.3 for the DLQI), with a 50% reduction in the omalizumab arm, from 17.0 (SD 5.6) at baseline to 8.5 (SD 5.9) at week 24.

The treatment effect also favoured omalizumab for the Paediatric Allergic Disease Quality of Life Questionnaire (PADQLQ) (treatment effect –0.5, 95% CI –0.9 to 0.0; $p = 0.050$) (MCID 0.33).

There was a persistence of an effect to 48 weeks in both (C)DLQI and PADQLQ scores, 24 weeks after treatment stopped.

Baseline skin prick test and response to omalizumab

The average number of positive SPTs per participant at week 24 was 44% lower in the omalizumab arm, compared with the placebo arm [incidence rate ratio (IRR) 0.56, 95% CI 0.40 to 0.78; $p = 0.001$].

Disease burden of infected eczema and eczema exacerbations

There were similar numbers of infective eczema and eczema exacerbation episodes in both arms. Five participants (17%) in the omalizumab arm and six participants (19%) in the placebo arm experienced one infected eczema exacerbation episode. One participant (3%) in the omalizumab arm and two participants (6%) in the placebo arm experienced two infected eczema episodes.

Five participants (17%) had one eczema exacerbation in the omalizumab arm and four participants (13%) had one eczema exacerbation in the placebo arm. Two further participants (6%) in the placebo arm each had two eczema exacerbations.

Adverse events

The rate of non-serious respiratory adverse events was higher in the placebo arm, with 26 events in 15 participants (50%) in the omalizumab arm and 63 events in 25 participants (78%) in the placebo arm, corresponding to an IRR of 0.69 (95% CI 0.49 to 0.96). The number of participants with at least one non-serious dermatological adverse event was higher in the placebo arm: 31 participants (97%) on placebo and 23 participants (77%) on omalizumab experienced at least one event.

The number of serious adverse events was matched between the arms, with a total of seven events occurring in six participants in both arms. There was one serious potential adverse reaction of anaphylaxis in the omalizumab arm during the treatment phase, in a participant who had a pre-existing history of idiopathic anaphylaxis. This participant had two further anaphylaxis events after treatment discontinuation. Therefore caution should be exercised when prescribing omalizumab in female patients with a previous history of anaphylaxis to other triggers, particularly during the initial treatment phase. These patients have recently been identified in the literature as having a higher risk of anaphylaxis to omalizumab treatment.

Conclusions

To our knowledge, this is the largest randomised, double-blind, placebo-controlled trial of omalizumab in eczema to date, and is the first to demonstrate a positive clinical outcome. The Atopic Dermatitis Anti-IgE Paediatric Trial (ADAPT) specifically targeted a paediatric atopic population. Treatment with omalizumab appears to improve eczema severity and QoL in children with severe eczema, in spite of the highly elevated IgE levels (the median baseline total IgE level was 120 times the upper limit of the normal range of total IgE level and 5.6 times higher than the maximum dose omalizumab is designed for) and reduced use of potent topical steroids. To our knowledge, the doses of omalizumab used in this study, in line with manufacturer's guidelines, were the highest used in any study of eczema. The data suggest that children with lower baseline total IgE levels achieved a better clinical response.

The clinically important improvements in QoL included a 50% reduction in the (C)DLQI. There was a reduction in the treatment burden with less rescue therapy with oral steroids and less need for systemic immunosuppression.

The results were consistent across the range of primary and secondary outcome measures and robust to a range of sensitivity analyses; however, the precision of the treatment estimates was limited by the small sample size. Retention in the study was high, with 98.4% of participants providing 48-week data despite the frequent study visits for treatment and assessment.

When treatment was discontinued at 24 weeks, the point estimates of treatment effect suggest a continued benefit to 48 weeks, albeit to a lesser extent than the benefit up to 24 weeks. However, this observation is

limited by the small sample size and further research on the optimal duration of treatment and duration of benefit is needed. There was some evidence that omalizumab may improve other systemic allergic disease. Further research is needed to understand the full potential of omalizumab.

Trial registration

This trial is registered as ISRCTN15090567, EudraCT 2010-020841-29 and ClinicalTrials.gov NCT02300701.

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