REVIEW

Strategies used for measuring long-term control in atopic dermatitis trials: A systematic review

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Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease. There are no standardized methods for capturing long-term control of AD.

Objective: We sought to identify how long-term control has been captured in published randomized controlled trials (RCTs). Results will initiate consensus discussions on how best to measure long-term control in the core outcome set for AD.

Methods: We conducted a systematic review of RCTs of AD treatments published between 2000 and 2013, with a follow-up period of 3 months or longer, at least 1 outcome measure recorded at 3 or more time points, full article available, and published in English.

Results: In all, 101 of 353 RCTs were eligible. Methods to capture long-term control included: repeated measurement of AD outcomes (92 RCTs; 91%), use of AD medication (29 RCTs; 28.7%), and AD flares/remissions (26 RCTs; 25.7%). Repeated measurements of AD outcomes were typically collected 3 to 5 times during a trial, but analysis methods often failed to make best use of the data. Time to first flare was most commonly used for trials including flare data (21/52). Medication use was recorded based on quantity, potency, and frequency of application.

Limitations: We included RCT data only.

Conclusion: This review illustrates the difficulties in measuring long-term control, and points to the need for improved harmonization of outcomes. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.05.043.)

Key words: atopic dermatitis; atopic eczema; flares; long-term control; outcome measures; randomized controlled trials; systematic review.

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Atopic dermatitis (AD) (atopic eczema) is a highly prevalent, itchy, inflammatory skin condition that affects children and adults. As with other chronic inflammatory diseases, AD severity tends to wax and wane over time, with periods of relative remission, interspersed with periods of increased disease activity or "flare."[1] AD treatments aim to reduce disease intensity, minimize the number of flares, and increase the duration of remissions. The ability to measure long-term control of AD over time is an important outcome when evaluating effectiveness of treatments, as this reflects patients' experiences of living with the condition, and long-term control has been identified as a core outcome to be included in future AD clinical trials.[2]

CAPSULE SUMMARY

- There is no consensus over how best to measure long-term control of atopic dermatitis in clinical trials.
- To date, repeated measurement of eczema severity, assessment of flares, and use of atopic dermatitis medications have all been used.
- Consensus agreement of core outcome sets for atopic dermatitis will improve evidence-based practice.

To date, there is little consensus over how best to capture long-term control in AD. Two systematic reviews have demonstrated the variability in AD flare definitions used in published studies,[3,4] and have highlighted the methodological challenges in capturing AD flares. Other approaches to capture long-term control include measurement of anti-inflammatory medication use over time, or the repeated measurement of AD severity and other health outcomes.

The Harmonizing Outcome Measures for Eczema (HOME) initiative (www.homeforeczema.org) identified long-term control as 1 of 4 key domains to measure in all clinical trials in AD. The current systematic review has been conducted to inform the HOME initiative's consensus discussions on how long-term control has been captured in previously published randomized controlled trials (RCTs). It represents stage 1 on the HOME Roadmap,[5] namely to identify available outcome instruments for capturing the domain of interest.

METHODS

This systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations.[6] The protocol was agreed to before starting the review, and registered online (October 6, 2014) (http://nottingham.ac.uk/research/groups/cebd/documents/researchdocs/ltc-protocol-final.pdf).

Eligibility criteria and search strategy

We searched for RCTs with at least a 3-month follow-up period[7] that included adults or children with AD, and were published between January 1, 2000, and March 12, 2013. This period was chosen as, before 2000, most AE trials were of relatively short duration.[8] Eligible studies were identified using the Global Resource of Eczema Trials (GREAT) database (www.greatdatabase.org.uk). This freely available online database contains records of RCTs for AD treatments found within MEDLINE, EMBASE, CINAHL, AMED, LILACS, the Cochrane Library, and the Skin Group Specialized Register databases.

The search strategy used to identify RCTs in the GREAT database and validation of the GREAT database have been published elsewhere.[9] Observational studies were not included in this review because of time and resource limitations.

Study selection and data extraction

Inclusion criteria were predefined. Studies were included if the duration of patient follow-up was 3 months or longer, and a clinician- or patient-reported outcome measure was recorded at 3 or more time points. We excluded studies published in abstract form only, that did not include clinical outcomes (eg, studies only containing data pertaining to biomarkers or skin barrier function tests), and not published in English. Titles of studies were retrieved and the full text was then obtained and screened against the inclusion criteria by 2 authors (N. K. R. and S. B.). Responses were compared and discrepancies resolved by consensus (N. K. R. and S. B.).

Studies that met the inclusion criteria were divided between author pairs, who independently extracted data using a standardized data extraction form. Details were extracted for: (1) trial attributes (size of trial, age of participants); (2) repeated measurement of clinician- or patient-reported AD outcomes over time; (3) use of AD medication—defined as any treatment used to control AD symptoms other than the randomly allocated intervention; and (4) AD flares/relapse—defined as a decline in condition (worsening of symptoms) that met 1 of the recommended descriptions of flare,[3] regardless of whether "flare," "relapse," or "remission" was specifically used within the text. For all long-term control outcomes, details of how the outcomes were recorded, analyzed, and presented in the article were recorded. Data extraction forms