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Systemic immunomodulatory treatments for atopic dermatitis: protocol for a systematic review with network meta-analysis

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ABSTRACT

Introduction: There are numerous new systemic treatments for atopic dermatitis in various stages of development and most are being compared with placebo rather than active comparators. In order to understand the relative efficacy and safety of existing and new treatments for atopic dermatitis, robust mixed comparisons (i.e., direct and indirect) would be beneficial. To address this gap, this protocol describes methods for a systematic review and network meta-analysis of systemic treatments for atopic dermatitis.

Methods and analysis: We will update the search of a previous systematic review, including searches of the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, Latin American and Caribbean Health Science Information database and the Global Resource of EczemA Trials database in addition to clinical trial protocol registries. Title, abstract and full paper screening as well as data extraction will be conducted in duplicate by independent researchers. Primary outcomes include efficacy with regards to clinician-reported signs and patient-reported symptoms and safety with regards to withdrawal from treatment due to adverse events and the occurrence of serious adverse events. Secondary outcomes will include change in quality of life and itch severity. Where possible and appropriate, network meta-analysis will be performed for each outcome using a random-effects model within a Bayesian framework. If appropriate, the review will be transitioned to a living review with continuous updating of the analysis.

Ethics and dissemination: Dissemination in a peer-reviewed scientific journal is planned.

PROSPERO registration number: CRD42018088112.

Keywords: Atopic dermatitis, network meta-analysis, protocol, biologics, therapy

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We will conduct a thorough literature search to identify all relevant trials on the efficacy and safety of systemic treatments for atopic dermatitis, building on a recent Cochrane review that did not incorporate quantitative synthesis.
- The efficacy outcomes of interest represent three important domains, namely change in clinician-reported signs of disease, patient-reported symptoms and patient-reported quality of life.
- Network meta-analysis, if appropriate, will allow comparison of treatments that have not been compared head-to-head.
- Diverse outcome measurement instruments used to assess the three outcome domains may limit our ability to pool results from different studies.
- The study team includes patients, clinicians and methodologists.

INTRODUCTION

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin condition. For most patients, AD is mild and can be managed effectively with over-the-counter emollients and prescription topical therapies including corticosteroids. It is estimated that 7% of children and 2-8% of adults with AD have severe disease.[1 2] For these patients, topical therapies may be unsuccessful or inadequate and treatment with photo- or systemic therapy may be warranted.[3]

For years, systemic therapeutic options were limited to traditional immunosuppressive medications such as cyclosporine, methotrexate, azathioprine, mycophenolate and corticosteroids.[4] More recently, targeted agents have been developed including dupilumab, the first biologic approved for the treatment of moderate-to-severe AD.[5] Many other biologic and small-molecule treatments are currently being tested in clinical trials.[6]

Determining the relative efficacy and safety of the older and newer systemic therapies for AD is challenging. Most randomized controlled trials (RCTs) do not use standardized outcome measures and head-to-head comparison are rare.[4 5 7-13] Therefore, in order for clinicians and patients to understand how established and upcoming therapies compare with regards to efficacy and safety, indirect comparisons must be made. The aim of our study is to conduct a systematic review and network meta-analysis (NMA) to determine the relative efficacy and safety of systemic treatments for AD (Table 1). To date, no NMA has been conducted comparing systemic treatments for AD.

METHODS AND ANALYSIS

This protocol has been written according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidance[14] and has been registered on Prospero (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018088112). The research team consists of AD patients, clinicians and methodologists, all of whom have contributed to the design of this study. The specific research objectives are summarized in Table 1.

Eligibility criteria

All RCTs of immunomodulatory systemic therapies for moderate-to-severe AD will be included in this review, without age and sex restriction. Due to the absence of an established definition of moderate-to-severe AD, RCTs will be eligible when including subjects defined as: "patients with moderate-to-severe AD", "patients with non-adequately controlled AD despite the use of topical anti-inflammatory therapy" or patients with moderate-to-severe AD according to published severity criteria.[15 16] We will summarize the inclusion criteria used for each study. All other study types and disease states will be excluded, including studies on other forms of eczema/dermatitis such as chronic hand dermatitis.

RCTs that compare systemic immunomodulatory therapies for AD with any comparator, including placebo, are eligible. Systemic immunomodulatory therapies include cyclosporine, methotrexate, azathioprine, mycophenolate, corticosteroids interferon-gamma, intravenous immunoglobulin, dupilumab and other novel systemic agents. We will include studies with systemic immunomodulatory therapies as monotherapy or in combination with topical therapies.

Medications used at different dosages will be treated as separately in the primary network meta-analysis. Studies investigating other systemic therapies, such as Chinese herbal remedies, antihistamines, leukotriene antagonists, oral calcineurin inhibitors, vaccinations, phototherapy or antiviral/antibiotic agents will not be considered.

In order to be included, RCTs must report sufficient data on at least one of the primary or secondary outcomes listed in Table 1. Sufficient data include a point estimate and a measure of variance (e.g., standard error, 95% confidence interval) for continuous outcomes and sample size with number of patients experiencing an event for binary outcomes. We will examine these endpoints for short-term (≤16 weeks) and long term (>16 weeks) treatment.

Information sources and search strategy

Our searches will update those of a Cochrane review without quantitative synthesis authored by members of our research team.[17] Electronic searches will be performed in the following databases: Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE via Ovid (from 1946); Embase via Ovid (from 1974); Latin American and Caribbean Health Science Information database (LILACS) (from 1982); the Global Resource of EczemA Trials (GREAT) database. Our search strategies for these databases will be modeled on the Medline strategy originally developed for the previous Cochrane systematic review.[17] Searches will also be performed in the following trials registers: the ISRCTN registry (www.isrctn.com); ClinicalTrials.gov (www.ClinicalTrials.gov); the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au); the World Health Organization International Clinical Trials Registry Platform (ICTRP); the EU Clinical Trials Register (www.clinicaltrialsregister.eu).

We will hand search reference lists of relevant publications that are retrieved as full papers as well as relevant systematic reviews and literature reviews to identify other eligible studies. Experts in the field will be contacted for additional published and unpublished studies.

We will include data from published peer-reviewed journals, conference abstracts, trial registries and product monographs. Only studies published in English will be included, as language restriction has been shown not to bias the results of quantitative syntheses.[18] We anticipate that the language of publication will not be differential with regards to treatment outcomes, and so it is unlikely to bias our results. We will not place any restriction on publication year.

Study records

This systematic review will build upon the results of the previous Cochrane systematic review.[17] The results of updated searches will be uploaded into Abstrackr (http://abstrackr.cebm.brown.edu/) for title and abstract screening.[19] Two independent researchers will screen titles and abstracts of papers, eliminating those deemed irrelevant. A third researcher will resolve discrepancies. Two independent researchers will read each potentially relevant paper in full, selecting papers meeting specific inclusion criteria as above.

Two researchers will independently extract data from each included trial, using the data extraction form from the previous review.[17] The full list of data to be extracted has been previously published. In brief, we will extract general characteristics of the publication, study

date and setting, participant characteristics (age, sex, AD severity), inclusion and exclusion criteria, descriptions of interventions, and outcomes data.

Outcomes

The Harmonizing Outcome Measures for Eczema (HOME) initiative has identified clinician-reported signs, patient-reported symptoms, quality of life and long-term control as core domains for assessment in RCTs for AD.[20] HOME aims to identify individual outcome measures to be used in all RCTs and has selected the Eczema Area Severity Index (EASI) for signs[21] and Patient Oriented Eczema Measure (POEM) for symptoms.[22] No core instruments have been selected for quality of life and long-term control, and long-term control is generally not measured as a separate domain in most RCTs. Unfortunately, most RCTs for AD predate HOME, and as such outcome measures are not standardized across RCTs.[4] Therefore, we will extract data on all measures of signs, symptoms and quality of life.

The two most commonly used measures for clinical signs in AD RCTs are EASI and objective SCORAD (o-SCORAD) and they each have reasonable measurement properties.[23 24] As EASI was selected by HOME as the core outcome for clinical signs, it will be prioritized as the preferred outcome measure in our analysis. Similarly, the POEM scale will be used as the primary measure of AD symptoms. The most prominent symptoms of AD is itch, and separate measurement of change in itch severity will be extracted as a secondary outcome where available. The Dermatology Life Quality Index (DLQI) is the most commonly used instrument for quality of life in RCTs;[25] therefore, despite inadequate evidence for strong measurement properties, it will be prioritized in our analysis.[25]

For each efficacy outcome, we will extract means and standard errors (SEs) for each study arm. Where standard deviations (SD) or confidence intervals are reported, these will be transformed to SEs. Authors of studies that do not report these outcomes as continuous variables or that do not report SD/SE will be contacted for this information. Where SD/SE data are not available, the mean value of known SDs will be imputed from the group of included studies.[26] For each safety outcome, we will extract the sample size of each treatment and the number of patients experiencing the event.

Data synthesis

Where possible, we intend to synthesize study data using NMAs. NMA is an extension of pairwise meta-analysis which simultaneously combines both the direct evidence (i.e., interventions assessed head-to-head) and indirect evidence (i.e., interventions assessed through a common comparator).[27 28] Doing so improves precision of treatment effect estimates and also provides estimates for all pairwise comparisons including those missing from the direct evidence.[28 29]

For each outcome, NMA will be conducted when there are sufficiently similar studies forming a network (i.e., the studies within the set share at least one common treatment). Within each outcome domain (e.g., clinical signs), we plan to analyse each scale (e.g., EASI, o-SCORAD) separately. In a separate analysis, we also plan to combine all scales within an outcome domain using standardized mean differences.

NMA will be performed using a random-effects model within a Bayesian framework using the *gemtc* R package.[30] For continuous outcomes (e.g., change in clinical signs), the NMA model corresponds to a generalized linear model with identity link.[31] For binary outcomes (e.g., adverse events), the NMA model corresponds to a generalized linear model with logit link.[31] We will include random effects on the treatment parameters, which allows each study to have a different but related treatment effect. The between-study variance (heterogeneity) will be assumed to be constant for every treatment comparison. We will use non-informative prior distributions for all model parameters. Convergence of 4 chains will be assessed by the Gelman-Rubin statistic and visual inspection of trace plots.

Two key assumptions of NMA are transitivity and consistency. Transitivity relates to the validity of estimating an unobserved direct comparison through the available indirect evidence. Although transitivity cannot be tested statistically, its plausibility can be conceptually evaluated. The restriction of our analysis to include only studies of moderate-severe AD makes our transitivity assumption plausible. However, this will be evaluated further by examining the distribution of other baseline factors that may influence treatment response, such as concomitant topical therapy, duration of AD, baseline AD severity and age. Consistency extends the assumption of transitivity to "loops" of evidence and relates to the agreement of the direct and indirect estimates. For each analysis, we will empirically assess the consistency of the network by comparing the direct and indirect evidence using a node-splitting approach [32]. This approach estimates the direct and indirect treatment effect estimates separately. Discrepancies between these estimates indicate inconsistency. If there is evidence of inconsistency, only the results of the direct comparisons will be presented.

In addition to summary results presented as an odds ratio or mean with a 95% credible interval, the cumulative rankings of treatments will also be presented. Cumulative ranking probability plots represent the ranking probabilities of the various treatments with a visual estimation of their uncertainty. Rankings will be quantified by the Surface Under the Cumulative Ranking (SUCRA) that express the percentage (0–100%) of efficacy/safety each treatment has compared with an ideal treatment ranked always first without uncertainty [33]. The larger the SUCRA value, the better the rank.

Subgroup and sensitivity analyses

The robustness of the primary efficacy and safety estimates from the NMA will be evaluated by analysing only outcomes with low risk of bias (as defined below). Outcome data on short-term (≤16 weeks) as well as long-term/maintenance (≥16 weeks) treatment will be analysed separately, as well as treatment efficacy & safety in children and adults, if adequate data are available.

Assessment of bias and strength of evidence

Two independent researchers will assess the risk of bias in individual studies using the Cochrane Risk of Bias 2.0 tool.[34] To empirically assess for publication bias, we will compare the results of our trial registry searches with the results from published studies. We will further assess for reporting bias by comparing the outcomes pre-specified in the trial registries with the reported outcomes. We will assess the overall quality of evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.[35]

Updating

A recent study concluded that living network meta-analyses with continuous updating produce strong, timely evidence of comparative effectiveness.[36] The research questions in this systematic review are in line with proposed criteria for continuing a living systematic review, namely (1) the systematic review is a priority for decision making; (2) new information will change decision-making; and (3) there is likely to be, on an ongoing basis, new research relevant to decision making.[37 38] As such, if these criteria are still met at the conclusion of our baseline review and analysis, we will convert the review to a living systematic review with network meta-analysis. Given the number of new systemic medications in development for atopic dermatitis, this is likely to be the case.[6]

Updated searches will be conducted monthly, with relevant studies added to the review. The analysis will be updated every four months at a minimum, but will be updated more frequently if new studies meet any of the following three conditions:

1. Newly identified studies include outcomes data on a new systemic medication not currently included in the network meta-analysis;
2. Newly identified studies include comparisons between medications that have never before been directly compared; or
3. Results of newly identified studies are inconsistent with the results of the most recent network meta-analysis (e.g., if in the most recent network meta-analysis methotrexate is superior at improving symptoms compared with cyclosporine, but in a newly identified clinical trial cyclosporine is found to be superior).

Patient and public involvement

Our research team includes atopic dermatitis patients, one of whom represents the Dutch Association for People with Atopic Dermatitis (VMCE), a patient advocacy group. They have contributed to the development of this protocol including the selection of outcomes of importance to patients. They will continue to contribute to the study going forward, ensuring that our results are presented in a way that is meaningful to patient decision making.

ETHICS AND DISSEMINATION

There is no primary data collection involved in this study, and so research ethics approval is not required.

In this systematic review and network meta-analysis, we will provide the first comprehensive quantitative synthesis of systemic treatments for AD. We plan to disseminate our results through publication in a peer-reviewed scientific journal. We will report our results following the framework laid out in the PRISMA extension for NMA.[39] Ideally, in the future, new treatments for AD will be assessed against existing treatments in head-to-head RCTs. In the absence of those comparisons, our robust statistical approaches will provide comparative efficacy and safety data to aid decision making for clinicians and patients.

Table 1. Specific objectives (Participants, Interventions, Comparators, Outcomes, Design).

Participants	Patients (children and adults) with moderate-to-severe atopic dermatitis
Interventions	Systemic immunomodulatory agents, including: • Cyclosporine • Methotrexate • Azathioprine • Mycophenolate • Corticosteroids • Dupilumab • Nemolizumab • Lebrikizumab • Ustekinumab • Fezakizumab • Baricitinib • Apremilast • Interferon • Intravenous immunoglobulin • Others, including new agents whose first trials are published between publication of this protocol and our final literature search
Comparators	Any, including placebo
Outcomes	*Primary outcomes - Efficacy* 1. Change in investigator-reported clinical signs (e.g., EASI, o-SCORAD) 2. Change in patient-reported symptoms (e.g., POEM) *Primary outcomes - Safety* 3. Withdrawal from systemic treatment due to adverse events 4. Occurrence of serious adverse events *Secondary outcomes* 5. Change in health-related quality of life (e.g., DLQI) 6. Change in itch severity
Design	Randomized controlled trials

DLQI, Dermatology Life Quality Index; EASI, Eczema Area Severity Index; o-SCORAD, objective SCORAD; POEM, Patient Oriented Eczema Measure

AUTHOR CONTRIBUTIONS

Dr. Drucker contributed to study design and drafted the protocol manuscript.

Dr. Flohr contributed to study design, drafted the PROSPERO protocol and provided critical revisions on the manuscript.

All other authors contributed to study design and provided critical revisions on the manuscript.

Drs. Spuls, Küster, Schmitt and Flohr are authors on a previous Cochrane systematic review on this topic.

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COMPETING INTERESTS STATEMENT

Aaron M Drucker: Departmental research funding from Sanofi and Regeneron and consultancy for Sanofi, RTI Health Solutions and Eczema Society of Canada as well as Astellas Canada, Prime Inc, Spire Learning and the Eczema Society of Canada.

Phyllis I Spuls: Principal investigator (PI) Methotrexate versus Azathioprine for severe Atopic Dermatitis (MAcAD) trial, PI of the Dutch national systemic therapy atopic eczema registry (TREAT NL) for adults and children. PS has served as a consultant to AbbVie, Anacor, Leo Pharma, Novartis and Sanofi, has received independent research grants (>4 years ago) from Leo Pharma and Schering-Plough, and has been involved in performing clinical trials with pharmaceutical industries that manufacture drugs used for the treatment of atopic dermatitis.

Jochen Schmitt: Department research funding from Sanofi, Pfizer, ALK, Novartis, and MSD. PI of the German national AE registry (TREAT Germany).

Carsten Flohr: Chief Investigator (CI) of the TREatment of severe Atopic eczema in children Trial (TREAT), a UK National Institute of Health Research funded multi-centre study comparing methotrexate and Ciclosporin (www.treat-trial.org.uk). CI of the UK national systemic therapy atopic eczema registry (A*STAR) for adults and children. Consultancy for Sanofi/Regeneron.

All other team members have no conflict of interest to declare.

REFERENCES

1. Silverberg JI, Simpson EL. Associations of childhood eczema severity: a US population-based study. *Dermatitis : contact, atopic, occupational, drug* 2014;25(3):107-14. doi: 10.1097/DER.0000000000000034

2. Barbarot S, Auziere S, Gadkari A, et al. Epidemiology of atopic dermatitis in adults: results from an international survey. *Allergy* 2018 doi: 10.1111/all.13401

3. Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *Journal of the American Academy of Dermatology* 2014;71(2):327-49. doi: 10.1016/j.jaad.2014.03.030

4. Roekevisch E, Spuls PI, Kuester D, et al. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. *The Journal of allergy and clinical immunology* 2014;133(2):429-38. doi: 10.1016/j.jaci.2013.07.049

5. Beck LA, Thaci D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *The New England journal of medicine* 2014;371(2):130-9. doi: 10.1056/NEJMoa1314768

6. Paller AS, Kabashima K, Bieber T. Therapeutic pipeline for atopic dermatitis: End of the drought? *The Journal of allergy and clinical immunology* 2017;140(3):633-43. doi: 10.1016/j.jaci.2017.07.006

7. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet* 2017;389(10086):2287-303. doi: 10.1016/S0140-6736(17)31191-1

8. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *The New England journal of medicine* 2016 doi: 10.1056/NEJMoa1610020

9. Thaci D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet* 2015 doi: 10.1016/S0140-6736(15)00388-8

10. Goujon C, Viguier M, Staumont-Salle D, et al. Methotrexate Versus Cyclosporine in Adults with Moderate-to-Severe Atopic Dermatitis: A Phase III Randomized Noninferiority Trial. *J Allergy Clin Immunol Pract* 2017 doi: 10.1016/j.jaip.2017.07.007

11. Schram ME, Roekevisch E, Leeflang MM, et al. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. *The Journal of allergy and clinical immunology* 2011;128(2):353-9. doi: 10.1016/j.jaci.2011.03.024

12. Guttman-Yassky E, Brunner PM, Neumann AU, et al. Efficacy and safety of fezakinumab (an anti-IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments - A randomized, double-blind, phase 2a trial. *Journal of the American Academy of Dermatology* 2018 doi: 10.1016/j.jaad.2018.01.016

13. Guttman-Yassky E, Silverberg JI, Nemoto O, et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. *Journal of the American Academy of Dermatology* 2018 doi: 10.1016/j.jaad.2018.01.018

14. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *Bmj* 2015;349:g7647. doi: 10.1136/bmj.g7647

15. Chopra R, Vakharia PP, Sacotte R, et al. Severity strata for EASI, mEASI, oSCORAD, SCORAD, ADSI and BSA in adolescents and adults with atopic dermatitis. *The British journal of dermatology* 2017 doi: 10.1111/bjd.15641

16. Leshem YA, Hajar T, Hanifin JM, et al. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. *The British journal of dermatology* 2015;172(5):1353-7. doi: 10.1111/bjd.13662

17. Küster D, Spuls PI, Flohr C, et al. Effects of systemic immunosuppressive therapies for moderate-to-severe eczema in children and adults. *Cochrane Database of Systematic Reviews* 2015(11) doi: 10.1002/14651858.CD011939

18. Morrison A, Polisena J, Husereau D, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *Int J Technol Assess Health Care* 2012;28(2):138-44. doi: 10.1017/S0266462312000086

19. Rathbone J, Hoffmann T, Glasziou P. Faster title and abstract screening? Evaluating Abstrackr, a semi-automated online screening program for systematic reviewers. *Syst Rev* 2015;4:80. doi: 10.1186/s13643-015-0067-6

20. Schmitt J, Apfelbacher C, Spuls PI, et al. The Harmonizing Outcome Measures for Eczema (HOME) roadmap: a methodological framework to develop core sets of outcome measurements in dermatology. *The Journal of investigative dermatology* 2015;135(1):24-30. doi: 10.1038/jid.2014.320

21. Schmitt J, Spuls PI, Thomas KS, et al. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *The Journal of allergy and clinical immunology* 2014;134(4):800-7. doi: 10.1016/j.jaci.2014.07.043

22. Spuls PI, Gerbens LAA, Simpson E, et al. Patient-Oriented Eczema Measure (POEM), a core instrument to measure symptoms in clinical trials: a Harmonising Outcome Measures for Eczema (HOME) statement. *The British journal of dermatology* 2017;176(4):979-84. doi: 10.1111/bjd.15179

23. Rehal B, Armstrong AW. Health outcome measures in atopic dermatitis: a systematic review of trends in disease severity and quality-of-life instruments 1985-2010. *PloS one* 2011;6(4):e17520. doi: 10.1371/journal.pone.0017520

24. Schmitt J, Langan S, Deckert S, et al. Assessment of clinical signs of atopic dermatitis: a systematic review and recommendation. *The Journal of allergy and clinical immunology* 2013;132(6):1337-47. doi: 10.1016/j.jaci.2013.07.008

25. Heinl D, Chalmers J, Nankervis H, et al. Eczema Trials: Quality of Life Instruments Used and Their Relation to Patient-reported Outcomes. A Systematic Review. *Acta Derm Venereol* 2016;96(5):596-601. doi: 10.2340/00015555-2322

26. Furukawa TA, Barbui C, Cipriani A, et al. Imputing missing standard deviations in meta-analyses can provide accurate results. *Journal of clinical epidemiology* 2006;59(1):7-10. doi: 10.1016/j.jclinepi.2005.06.006

27. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005;331(7521):897-900. doi: 10.1136/bmj.331.7521.897 [published Online First: 2005/10/15]

28. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;23(20):3105-24. doi: 10.1002/sim.1875

29. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012;3(2):80-97. doi: 10.1002/jrsm.1037 [published Online First: 2012/06/01]

30. Network Meta-Analysis Using Bayesian Methods. R package [program]. 0.8-2 version, 2016.

31. Dias S, Welton NJ, Sutton AJ, et al. A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. London2014.

32. Dias S, Welton NJ, Caldwell DM, et al. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010;29(7-8):932-44. doi: 10.1002/sim.3767 [published Online First: 2010/03/10]

33. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64(2):163-71. doi: 10.1016/j.jclinepi.2010.03.016

34. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 2011;343:d5928. doi: 10.1136/bmj.d5928

35. Higgins J. Green S. Cochrane handbook for systematic reviews of interventions version 5.1. 0. The Cochrane Collaboration, 2011, 2013.

36. Nikolakopoulou A, Mavridis D, Furukawa TA, et al. Living network meta-analysis compared with pairwise meta-analysis in comparative effectiveness research: empirical study. *Bmj* 2018;360:k585. doi: 10.1136/bmj.k585

37. Elliott JH, Synnot A, Turner T, et al. Living systematic review: 1. Introduction-the why, what, when, and how. *Journal of clinical epidemiology* 2017 doi: 10.1016/j.jclinepi.2017.08.010

38. Synnot A, Turner T, Elliott J. Cochrane Living Systematic Reviews. Interim guidance for pilots., 2017.

39. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162(11):777-84. doi: 10.7326/M14-2385

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	✓ 1a	Identify the report as a protocol of a systematic review
Update	N/A 1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	✓ 2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	✓ 3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Email addresses for all authors provided in online submission
Contributions	✓ 3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	N/A 4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	✓ 5a	Indicate sources of financial or other support for the review
Sponsor	N/A 5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	✓ 5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	✓ 6	Describe the rationale for the review in the context of what is already known
Objectives	✓ 7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	✓ 8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	✓ 9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	✓ 10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated Reference given to recent Cochrane review
Study records:		
Data management	✓ 11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

	Selection process	✓ 11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
	Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items		12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization		13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies		14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis		15a	Describe criteria under which study data will be quantitatively synthesised
	✓	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	✓	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	✓	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	✓	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	✓	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Systemic immunomodulatory treatments for atopic dermatitis: protocol for a systematic review with network meta-analysis

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Systemic immunomodulatory treatments for atopic dermatitis: protocol for a systematic review with network meta-analysis

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ABSTRACT

Introduction: There are numerous new systemic treatments for atopic dermatitis in various stages of development and most are being compared with placebo rather than active comparators. In order to understand the relative efficacy and safety of existing and new treatments for atopic dermatitis, robust mixed comparisons (i.e., direct and indirect) would be beneficial. To address this gap, this protocol describes methods for a systematic review and network meta-analysis of systemic treatments for atopic dermatitis.

Methods and analysis: We will update the search of a previous systematic review, including searches of the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, Latin American and Caribbean Health Science Information database and the Global Resource of EczemA Trials database in addition to clinical trial protocol registries. Title, abstract and full paper screening as well as data extraction will be conducted in duplicate by independent researchers. Primary outcomes include efficacy with regards to clinician-reported signs and patient-reported symptoms and safety with regards to withdrawal from treatment due to adverse events and the occurrence of serious adverse events. Secondary outcomes will include change in quality of life and itch severity. Where possible and appropriate, network meta-analysis will be performed for each outcome using a random-effects model within a Bayesian framework. If appropriate, the review will be transitioned to a living review with continuous updating of the analysis.

Ethics and dissemination: Dissemination in a peer-reviewed scientific journal is planned.

PROSPERO registration number: CRD42018088112.

Keywords: Atopic dermatitis, network meta-analysis, protocol, biologics, therapy

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We will conduct a thorough literature search to identify all relevant trials on the efficacy and safety of systemic treatments for atopic dermatitis, building on a recent Cochrane review that did not incorporate quantitative synthesis.
- The efficacy outcomes of interest represent three important domains, namely change in clinician-reported signs of disease, patient-reported symptoms and patient-reported quality of life.
- Network meta-analysis, if appropriate, will allow comparison of treatments that have not been compared head-to-head.
- Diverse outcome measurement instruments used to assess the three outcome domains and other differences in trial design may limit our ability to pool results from different studies.
- The study team includes patients, clinicians and methodologists.

INTRODUCTION

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin condition. For most patients, AD is mild and can be managed effectively with over-the-counter emollients and prescription topical therapies including corticosteroids. It is estimated that 7% of children and 2-8% of adults with AD have severe disease.[1 2] For these patients, topical therapies may be unsuccessful or inadequate and treatment with photo- or systemic therapy may be warranted.[3]

For years, systemic therapeutic options were limited to traditional immunosuppressive medications such as cyclosporine, methotrexate, azathioprine, mycophenolate and corticosteroids.[4] More recently, targeted agents have been developed including dupilumab, the first biologic approved for the treatment of moderate-to-severe AD.[5] Many other biologic and small-molecule treatments are currently being tested in clinical trials.[6]

Determining the relative efficacy and safety of the older and newer systemic therapies for AD is challenging. Most randomized controlled trials (RCTs) do not use standardized outcome measures and head-to-head comparison are rare.[4 5 7-13] Therefore, in order for clinicians and patients to understand how established and upcoming therapies compare with regards to efficacy and safety, indirect comparisons must be made. The aim of our study is to conduct a systematic review and network meta-analysis (NMA) to determine the relative efficacy and safety of systemic treatments for AD (Table 1). To date, no NMA has been conducted comparing systemic treatments for AD.

METHODS AND ANALYSIS

This protocol has been written according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidance[14] and has been registered on Prospero (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018088112). The research team consists of AD patients, clinicians and methodologists, all of whom have contributed to the design of this study. The specific research objectives are summarized in Table 1.

Eligibility criteria

All RCTs of immunomodulatory systemic therapies for moderate-to-severe AD will be included in this review, without age and sex restriction. Due to the absence of an established definition of moderate-to-severe AD, RCTs will be eligible when including subjects defined as: "patients with moderate-to-severe AD", "patients with non-adequately controlled AD despite the use of topical anti-inflammatory therapy" or patients with moderate-to-severe AD according to published severity criteria.[15 16] We will summarize the inclusion criteria used for each study. All other study types and disease states will be excluded, including studies on other forms of eczema/dermatitis such as chronic hand dermatitis.

RCTs that compare systemic immunomodulatory therapies for AD with any comparator, including placebo, are eligible. Systemic immunomodulatory therapies include cyclosporine, methotrexate, azathioprine, mycophenolate, corticosteroids interferon-gamma, intravenous immunoglobulin, dupilumab and other novel systemic agents. We will include studies with systemic immunomodulatory therapies as monotherapy or in combination with topical therapies.

Medications used at different dosages will be treated as separately in the primary network meta-analysis. Studies investigating other systemic therapies, such as Chinese herbal remedies, antihistamines, leukotriene antagonists, oral calcineurin inhibitors, vaccinations, phototherapy or antiviral/antibiotic agents will not be considered.

In order to be included, RCTs must report sufficient data on at least one of the primary or secondary outcomes listed in Table 1. Sufficient data include a point estimate and a measure of variance (e.g., standard error, 95% confidence interval) for continuous outcomes and sample size with number of patients experiencing an event for binary outcomes. We will examine these endpoints for short-term (≤16 weeks) and long term (>16 weeks) treatment.

Information sources and search strategy

Our searches will update those of a Cochrane review without quantitative synthesis authored by members of our research team.[17] Electronic searches will be performed in the following databases: Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE via Ovid (from 1946); Embase via Ovid (from 1974); Latin American and Caribbean Health Science Information database (LILACS) (from 1982); the Global Resource of EczemA Trials (GREAT) database. Our search strategies for these databases will be modeled on the Medline strategy originally developed for the previous Cochrane systematic review.[17] Searches will also be performed in the following trials registers: the ISRCTN registry (www.isrctn.com); ClinicalTrials.gov (www.ClinicalTrials.gov); the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au); the World Health Organization International Clinical Trials Registry Platform (ICTRP); the EU Clinical Trials Register (www.clinicaltrialsregister.eu).

We will hand search reference lists of relevant publications that are retrieved as full papers as well as relevant systematic reviews and literature reviews to identify other eligible studies. Experts in the field will be contacted for additional published and unpublished studies.

We will include data from published peer-reviewed journals, conference abstracts, trial registries and product monographs. Only studies published in English will be included, as language restriction has been shown not to bias the results of quantitative syntheses.[18] We anticipate that the language of publication will not be differential with regards to treatment outcomes, and so it is unlikely to bias our results. We will not place any restriction on publication year.

Study records

This systematic review will build upon the results of the previous Cochrane systematic review.[17] The results of updated searches will be uploaded into Abstrackr (http://abstrackr.cebm.brown.edu/) for title and abstract screening.[19] Two independent researchers will screen titles and abstracts of papers, eliminating those deemed irrelevant. A third researcher will resolve discrepancies. Two independent researchers will read each potentially relevant paper in full, selecting papers meeting specific inclusion criteria as above.

Two researchers will independently extract data from each included trial, using the data extraction form from the previous review.[17] The full list of data to be extracted has been previously published. In brief, we will extract general characteristics of the publication, study date and setting, participant characteristics (age, sex, AD severity), inclusion and exclusion

criteria, descriptions of interventions, and outcomes data. To our knowledge, trial reports of systemic therapy for AD have not included individual patient-level data. As such, data will be extracted at the trial arm level, rather than the individual patient level. If, in the future, individual patient data becomes more readily available for relevant trials, incorporating such individual patient data could improve the precision of the NMA.[20]

Outcomes

The Harmonizing Outcome Measures for Eczema (HOME) initiative has identified clinician-reported signs, patient-reported symptoms, quality of life and long-term control as core domains for assessment in RCTs for AD.[21] HOME aims to identify individual outcome measures to be used in all RCTs and has selected the Eczema Area Severity Index (EASI) for signs[22] and Patient Oriented Eczema Measure (POEM) for symptoms.[23] No core instruments have been selected for quality of life and long-term control, and long-term control is generally not measured as a separate domain in most RCTs. Unfortunately, most RCTs for AD predate HOME, and as such outcome measures are not standardized across RCTs.[4] Therefore, we will extract data on all measures of signs, symptoms and quality of life.

The two most commonly used measures for clinical signs in AD RCTs are EASI and objective SCORAD (o-SCORAD) and they each have reasonable measurement properties.[24 25] As EASI was selected by HOME as the core outcome for clinical signs, it will be prioritized as the preferred outcome measure in our analysis. Similarly, the POEM scale will be used as the primary measure of AD symptoms. The most prominent symptoms of AD is itch, and separate measurement of change in itch severity will be extracted as a secondary outcome where

available. The Dermatology Life Quality Index (DLQI) is the most commonly used instrument for quality of life in RCTs;[26] therefore, despite inadequate evidence for strong measurement properties, it will be prioritized in our analysis.[26]

For each efficacy outcome, we will extract means and standard errors (SEs) for each study arm. Where standard deviations (SD) or confidence intervals are reported, these will be transformed to SEs. Authors of studies that do not report these outcomes as continuous variables or that do not report SD/SE will be contacted for this information. Where SD/SE data are not available, the mean value of known SDs will be imputed from the group of included studies.[27]

The two included safety outcomes are withdrawal from treatment due to adverse events (tolerability) and the occurrence of serious adverse events. For these outcomes we will rely on reporting of these terms in the trial publications. Where adverse event rates in those specific categories are not given in the report, we will contact the authors for that data. For each safety outcome, we will extract the sample size of each treatment and the number of patients experiencing the event.

Data synthesis

Where possible, we intend to synthesize study data using NMAs. NMA is an extension of pairwise meta-analysis which simultaneously combines both the direct evidence (i.e., interventions assessed head-to-head) and indirect evidence (i.e., interventions assessed through a common comparator).[28 29] Doing so improves precision of treatment effect estimates and also

provides estimates for all pairwise comparisons including those missing from the direct evidence.[29 30]

For each outcome, NMA will be conducted when there are sufficiently similar studies forming a network (i.e., the studies within the set share at least one common treatment). Within each outcome domain (e.g., clinical signs), we plan to analyse each scale (e.g., EASI, o-SCORAD) separately. In a separate analysis, we also plan to combine all scales within an outcome domain using standardized mean differences.

NMA will be performed using a random-effects model within a Bayesian framework using the *gemtc* R package.[31] For continuous outcomes (e.g., change in clinical signs), the NMA model corresponds to a generalized linear model with identity link.[32] For binary outcomes (e.g., adverse events), the NMA model corresponds to a generalized linear model with logit link.[32] We will include random effects on the treatment parameters, which allows each study to have a different but related treatment effect. The between-study variance (heterogeneity) will be assumed to be constant for every treatment comparison. We will use non-informative prior distributions for all model parameters. Convergence of 4 chains will be assessed by the Gelman-Rubin statistic and visual inspection of trace plots.

Two key assumptions of NMA are transitivity and consistency. Transitivity relates to the validity of estimating an unobserved direct comparison through the available indirect evidence. Although transitivity cannot be tested statistically, its plausibility can be conceptually evaluated. The restriction of our analysis to include only studies of moderate-severe AD makes our transitivity

assumption plausible. However, this will be evaluated further by examining the distribution of other baseline factors that may influence treatment response, such as concomitant topical therapy, duration of AD, baseline AD severity and age. Consistency extends the assumption of transitivity to "loops" of evidence and relates to the agreement of the direct and indirect estimates. For each analysis, we will empirically assess the consistency of the network by comparing the direct and indirect evidence using a node-splitting approach.[33] This approach estimates the direct and indirect treatment effect estimates separately. Discrepancies between these estimates indicate inconsistency. If there is evidence of inconsistency, only the results of the direct comparisons will be presented.

In addition to summary results presented as an odds ratio or mean with a 95% credible interval, the cumulative rankings of treatments will also be presented. Cumulative ranking probability plots represent the ranking probabilities of the various treatments with a visual estimation of their uncertainty. Rankings will be quantified by the Surface Under the Cumulative Ranking (SUCRA) that express the percentage (0–100%) of efficacy/safety each treatment has compared with an ideal treatment ranked always first without uncertainty [34]. The larger the SUCRA value, the better the rank.

Subgroup and sensitivity analyses

The robustness of the primary efficacy and safety estimates from the NMA will be evaluated by analysing only outcomes with low risk of bias (as defined below). Subgroup analyses will also be conducted for children and adults. Outcome data on short-term (≤16 weeks) as well as long-term/maintenance (>16 weeks) treatment will be analysed separately. We chose this cut off as

most trials of systemic treatments for AD are 12-16 weeks in length. While the HOME group has included long-term control as a core outcome domain for clinical trials, we will most likely not be able to assess true long-term control in our analysis, as this is unfortunately rarely assessed in clinical trials.[21]

Assessment of bias and strength of evidence

Two independent researchers will assess the risk of bias in individual studies using the Cochrane Risk of Bias 2.0 tool.[35] To empirically assess for publication bias, we will compare the results of our trial registry searches with the results from published studies. We will further assess for reporting bias by comparing the outcomes pre-specified in the trial registries with the reported outcomes. We will assess the overall quality of evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.[36]

Updating

A recent study concluded that living network meta-analyses with continuous updating produce strong, timely evidence of comparative effectiveness.[37] The research questions in this systematic review are in line with proposed criteria for continuing a living systematic review, namely (1) the systematic review is a priority for decision making; (2) new information will change decision-making; and (3) there is likely to be, on an ongoing basis, new research relevant to decision making.[38 39] As such, if these criteria are still met at the conclusion of our baseline review and analysis, we will convert the review to a living systematic review with network meta-analysis. Given the number of new systemic medications in development for atopic dermatitis, this is likely to be the case.[6]

Updated searches will be conducted monthly, with relevant studies added to the review. The analysis will be updated every four months at a minimum, but will be updated more frequently if new studies meet any of the following three conditions:

1. Newly identified studies include outcomes data on a new systemic medication not currently included in the network meta-analysis;
2. Newly identified studies include comparisons between medications that have never before been directly compared; or
3. Results of newly identified studies are inconsistent with the results of the most recent network meta-analysis (e.g., if in the most recent network meta-analysis methotrexate is superior at improving symptoms compared with cyclosporine, but in a newly identified clinical trial cyclosporine is found to be superior).

Patient and public involvement

Our research team includes atopic dermatitis patients, one of whom represents the Dutch Association for People with Atopic Dermatitis (VMCE), a patient advocacy group. They have contributed to the development of this protocol including the selection of outcomes of importance to patients. They will continue to contribute to the study going forward, ensuring that our results are presented in a way that is meaningful to patient decision making.

ETHICS AND DISSEMINATION

There is no primary data collection involved in this study, and so research ethics approval is not required.

We plan to disseminate our results through publication in a peer-reviewed scientific journal. We will report our results following the framework laid out in the PRISMA extension for NMA.[40]

SUMMARY

In this systematic review and network meta-analysis, we will provide the first comprehensive quantitative synthesis of systemic treatments for AD. As new systemic treatments are developed and tested clinically, with some eventually obtaining clinical approval, it will be essential to compare new and established treatments in rigorous manor. Ideally, new treatments for AD will be assessed against existing treatments in head-to-head RCTs. However, this is unlikely to be the case. Using psoriasis as an example, most new systemic agents are only compared with placebo, rather than an active comparator. Recent NMAs for psoriasis have provided a solution, giving patients, clinicians and other stakeholders a means of comparing relevant therapeutic options.[41 42] NMA does have limitations in the setting of systemic therapies for AD, particularly differences in clinical trial design across included studies. Nevertheless, in the absence of head-to-head trial comparisons, the NMA approach provides comparative efficacy and safety data to aid decision making by clinicians and patients.

Table 1. Specific objectives (Participants, Interventions, Comparators, Outcomes, Design).

Participants	Patients (children and adults) with moderate-to-severe atopic dermatitis
Interventions	Systemic immunomodulatory agents, including: • Cyclosporine • Methotrexate • Azathioprine • Mycophenolate • Corticosteroids • Dupilumab • Nemolizumab • Lebrikizumab • Ustekinumab • Fezakinumab • Baricitinib • Apremilast • Interferon • Intravenous immunoglobulin • Others, including new agents whose first trials are published between publication of this protocol and our final literature search
Comparators	Any, including placebo
Outcomes	*Primary outcomes - Efficacy* 1. Change in investigator-reported clinical signs (e.g., EASI, o-SCORAD) 2. Change in patient-reported symptoms (e.g., POEM) *Primary outcomes - Safety* 3. Withdrawal from systemic treatment due to adverse events 4. Occurrence of serious adverse events *Secondary outcomes* 5. Change in health-related quality of life (e.g., DLQI) 6. Change in itch severity
Design	Randomized controlled trials

DLQI, Dermatology Life Quality Index; EASI, Eczema Area Severity Index; o-SCORAD, objective SCORAD; POEM, Patient Oriented Eczema Measure

AUTHOR CONTRIBUTIONS

Dr. Drucker contributed to study design and drafted the protocol manuscript.

Dr. Flohr contributed to study design, drafted the PROSPERO protocol and provided critical revisions on the manuscript.

Dr. Ellis, Dr. Jabbar-Lopez, Dr. Yiu, Mr. Arents, Mr. Burton, Dr. Spuls, Dr. Küster and Dr. Schmitt contributed to study design and provided critical revisions on the manuscript.

Drs. Spuls, Küster, Schmitt and Flohr are authors on a previous Cochrane systematic review on this topic.

As this is a protocol paper, the research has not yet been conducted and no data has been acquired or interpreted.

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS STATEMENT

Aaron M Drucker: Departmental research funding from Sanofi and Regeneron and consultancy for Sanofi, RTI Health Solutions and Eczema Society of Canada as well as Astellas Canada, Prime Inc, Spire Learning and the Eczema Society of Canada.

Phyllis I Spuls: Principal investigator (PI) Methotrexate versus Azathioprine for severe Atopic Dermatitis (MAcAD) trial, PI of the Dutch national systemic therapy atopic eczema registry (TREAT NL) for adults and children. PS has served as a consultant to AbbVie, Anacor, Leo Pharma, Novartis and Sanofi, has received independent research grants (>4 years ago) from Leo

Pharma and Schering-Plough, and has been involved in performing clinical trials with pharmaceutical industries that manufacture drugs used for the treatment of atopic dermatitis.

Jochen Schmitt: Department research funding from Sanofi, Pfizer, ALK, Novartis, and MSD. PI of the German national AE registry (TREAT Germany).

Carsten Flohr: Chief Investigator (CI) of the TREatment of severe Atopic eczema in children Trial (TREAT), a UK National Institute of Health Research funded multi-centre study comparing methotrexate and Ciclosporin (www.treat-trial.org.uk). CI of the UK national systemic therapy atopic eczema registry (A*STAR) for adults and children. Consultancy for Sanofi/Regeneron.

All other team members have no conflict of interest to declare.

REFERENCES

1. Silverberg JI, Simpson EL. Associations of childhood eczema severity: a US population-based study. *Dermatitis : contact, atopic, occupational, drug* 2014;25(3):107-14. doi: 10.1097/DER.0000000000000034

2. Barbarot S, Auziere S, Gadkari A, et al. Epidemiology of atopic dermatitis in adults: results from an international survey. *Allergy* 2018 doi: 10.1111/all.13401

3. Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *Journal of the American Academy of Dermatology* 2014;71(2):327-49. doi: 10.1016/j.jaad.2014.03.030

4. Roekevisch E, Spuls PI, Kuester D, et al. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. *The Journal of allergy and clinical immunology* 2014;133(2):429-38. doi: 10.1016/j.jaci.2013.07.049

5. Beck LA, Thaci D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *The New England journal of medicine* 2014;371(2):130-9. doi: 10.1056/NEJMoa1314768

6. Paller AS, Kabashima K, Bieber T. Therapeutic pipeline for atopic dermatitis: End of the drought? *The Journal of allergy and clinical immunology* 2017;140(3):633-43. doi: 10.1016/j.jaci.2017.07.006

7. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet* 2017;389(10086):2287-303. doi: 10.1016/S0140-6736(17)31191-1

8. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *The New England journal of medicine* 2016 doi: 10.1056/NEJMoa1610020

9. Thaci D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet* 2015 doi: 10.1016/S0140-6736(15)00388-8

10. Goujon C, Viguier M, Staumont-Salle D, et al. Methotrexate Versus Cyclosporine in Adults with Moderate-to-Severe Atopic Dermatitis: A Phase III Randomized Noninferiority Trial. *J Allergy Clin Immunol Pract* 2017 doi: 10.1016/j.jaip.2017.07.007

11. Schram ME, Roekevisch E, Leeflang MM, et al. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. *The Journal of allergy and clinical immunology* 2011;128(2):353-9. doi: 10.1016/j.jaci.2011.03.024

12. Guttman-Yassky E, Brunner PM, Neumann AU, et al. Efficacy and safety of fezakinumab (an anti-IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments - A randomized, double-blind, phase 2a trial. *Journal of the American Academy of Dermatology* 2018 doi: 10.1016/j.jaad.2018.01.016

13. Guttman-Yassky E, Silverberg JI, Nemoto O, et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. *Journal of the American Academy of Dermatology* 2018 doi: 10.1016/j.jaad.2018.01.018

14. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *Bmj* 2015;349:g7647. doi: 10.1136/bmj.g7647

15. Chopra R, Vakharia PP, Sacotte R, et al. Severity strata for EASI, mEASI, oSCORAD, SCORAD, ADSI and BSA in adolescents and adults with atopic dermatitis. *The British journal of dermatology* 2017 doi: 10.1111/bjd.15641

16. Leshem YA, Hajar T, Hanifin JM, et al. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. *The British journal of dermatology* 2015;172(5):1353-7. doi: 10.1111/bjd.13662

17. Küster D, Spuls PI, Flohr C, et al. Effects of systemic immunosuppressive therapies for moderate-to-severe eczema in children and adults. *Cochrane Database of Systematic Reviews* 2015(11) doi: 10.1002/14651858.CD011939

18. Morrison A, Polisena J, Husereau D, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *Int J Technol Assess Health Care* 2012;28(2):138-44. doi: 10.1017/S0266462312000086

19. Rathbone J, Hoffmann T, Glasziou P. Faster title and abstract screening? Evaluating Abstrackr, a semi-automated online screening program for systematic reviewers. *Syst Rev* 2015;4:80. doi: 10.1186/s13643-015-0067-6

20. Leahy J, O'Leary A, Afdhal N, et al. The Impact of Individual Patient Data in a Network Meta Analysis: An investigation into parameter estimation and model selection. *Res Synth Methods* 2018 doi: 10.1002/jrsm.1305

21. Schmitt J, Apfelbacher C, Spuls PI, et al. The Harmonizing Outcome Measures for Eczema (HOME) roadmap: a methodological framework to develop core sets of outcome

measurements in dermatology. *The Journal of investigative dermatology* 2015;135(1):24-30. doi: 10.1038/jid.2014.320

22. Schmitt J, Spuls PI, Thomas KS, et al. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *The Journal of allergy and clinical immunology* 2014;134(4):800-7. doi: 10.1016/j.jaci.2014.07.043
23. Spuls PI, Gerbens LAA, Simpson E, et al. Patient-Oriented Eczema Measure (POEM), a core instrument to measure symptoms in clinical trials: a Harmonising Outcome Measures for Eczema (HOME) statement. *The British journal of dermatology* 2017;176(4):979-84. doi: 10.1111/bjd.15179
24. Rehal B, Armstrong AW. Health outcome measures in atopic dermatitis: a systematic review of trends in disease severity and quality-of-life instruments 1985-2010. *PloS one* 2011;6(4):e17520. doi: 10.1371/journal.pone.0017520
25. Schmitt J, Langan S, Deckert S, et al. Assessment of clinical signs of atopic dermatitis: a systematic review and recommendation. *The Journal of allergy and clinical immunology* 2013;132(6):1337-47. doi: 10.1016/j.jaci.2013.07.008
26. Heinl D, Chalmers J, Nankervis H, et al. Eczema Trials: Quality of Life Instruments Used and Their Relation to Patient-reported Outcomes. A Systematic Review. *Acta Derm Venereol* 2016;96(5):596-601. doi: 10.2340/00015555-2322
27. Furukawa TA, Barbui C, Cipriani A, et al. Imputing missing standard deviations in meta-analyses can provide accurate results. *Journal of clinical epidemiology* 2006;59(1):7-10. doi: 10.1016/j.jclinepi.2005.06.006

28. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005;331(7521):897-900. doi: 10.1136/bmj.331.7521.897 [published Online First: 2005/10/15]

29. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;23(20):3105-24. doi: 10.1002/sim.1875

30. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012;3(2):80-97. doi: 10.1002/jrsm.1037 [published Online First: 2012/06/01]

31. Network Meta-Analysis Using Bayesian Methods. R package [program]. 0.8-2 version, 2016.

32. Dias S, Welton NJ, Sutton AJ, et al. A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. London2014.

33. Dias S, Welton NJ, Caldwell DM, et al. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010;29(7-8):932-44. doi: 10.1002/sim.3767 [published Online First: 2010/03/10]

34. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64(2):163-71. doi: 10.1016/j.jclinepi.2010.03.016

35. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 2011;343:d5928. doi: 10.1136/bmj.d5928

36. Higgins J. Green S. Cochrane handbook for systematic reviews of interventions version 5.1. 0. The Cochrane Collaboration, 2011, 2013.

37. Nikolakopoulou A, Mavridis D, Furukawa TA, et al. Living network meta-analysis compared with pairwise meta-analysis in comparative effectiveness research: empirical study. *Bmj* 2018;360:k585. doi: 10.1136/bmj.k585

38. Elliott JH, Synnot A, Turner T, et al. Living systematic review: 1. Introduction-the why, what, when, and how. *Journal of clinical epidemiology* 2017 doi: 10.1016/j.jclinepi.2017.08.010

39. Synnot A, Turner T, Elliott J. Cochrane Living Systematic Reviews. Interim guidance for pilots., 2017.

40. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162(11):777-84. doi: 10.7326/M14-2385

41. Sbidian E, Chaimani A, Garcia-Doval I, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev* 2017;12:CD011535. doi: 10.1002/14651858.CD011535.pub2

42. Jabbar-Lopez ZK, Yiu ZZN, Ward V, et al. Quantitative Evaluation of Biologic Therapy Options for Psoriasis: A Systematic Review and Network Meta-Analysis. *The Journal of investigative dermatology* 2017;137(8):1646-54. doi: 10.1016/j.jid.2017.04.009

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	✓ 1a	Identify the report as a protocol of a systematic review
Update	N/A 1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	✓ 2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	✓ 3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Email addresses for all authors provided in online submission
Contributions	✓ 3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	N/A 4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	✓ 5a	Indicate sources of financial or other support for the review
Sponsor	N/A 5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	✓ 5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	✓ 6	Describe the rationale for the review in the context of what is already known
Objectives	✓ 7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	✓ 8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	✓ 9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	✓ 10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated Reference given to recent Cochrane review
Study records:		
Data management	✓ 11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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