CONCRETE: Reporting of CONComitant and REscue Topical therapies in Eczema randomized controlled trials evaluating a systemic treatment: a systematic review

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Background

Topical therapies are the first line treatment in atopic dermatitis (syn. atopic eczema or just eczema). These include topicals to induce remission (usually topical corticosteroids and topical calcineurin inhibitors) and emollients (1). Patients with moderate or severe disease that cannot be controlled sufficiently with appropriate topical treatments may require ultraviolet light or a systemic treatment (2). Systemic therapies available for atopic dermatitis (AD) include conventional systemic medications (e.g, methotrexate or ciclosporin), biologics (e.g., dupilumab) and small molecule medications (e.g., inhibitors of Janus Kinase). Large numbers of biologics and small molecules are being studied in many clinicals trials: more than 74 randomized controlled trials (RCTs) have been published since August 2019 and numerous trials are ongoing (3). Active topical therapies are often used in these trials in a variety of ways: (i) topical therapies may be administered intensively before the start of the trial to stabilize the disease (previous topical treatment) (ii) topical therapies are administered during the trial as an add-on therapy/cointervention (concomitant topical treatment); and (iii) topical treatments can be used as a rescue medication (i.e. topical therapies administered in case of insufficient efficacy of the experimental drug, rescue topical treatment) (4). Concomitant and rescue treatments can lead to bias if there are any imbalances between groups, especially if not clearly and fully reported, as they are post randomization data.

Description of the problem or issue

Topical therapies received by patients in AD trials as a concomitant or rescue treatment involve multiple factors (duration of treatment, number of applications, quantities, potency etc) and might influence the interpretation of the trials that evaluate systemic interventions. As such it is crucial that these data should therefore be fully reported to help fully inform trial results.

Why it is important to do this review?

To date, there is limited literature on the reporting of such factors (5) and there is no consensus over how to plan and report the use of topical therapies in eczema trials evaluating a systemic treatment. A systematic review of the current practices for reporting topical therapies in trials of systemic treatments will inform the need to standardize the designing and reporting of concomitant topical therapies.

Research objective

The aim of this study is to investigate how well the use of concomitant and rescue topical therapies is reported in eczema trials.

Study design
A systematic review of published RCTs.

Methods
Searches and study selection
The living systematic review and network meta-analysis (NMA) developed by Drucker AM et al will be used to identify AD trials (6). This NMA included studies with children and adults with moderate-to-severe AD treated for 8 weeks or longer and at least 2 doses of systemic immunomodulatory therapies with any comparator. The living systematic review regularly is updated at http://www.eczematherapies.com/.

Intervention(s), exposure(s)
Systemic immunomodulatory treatments for eczema/AD. Phototherapy will be excluded.

Comparators
Placebo or active comparator.

Types of study to be included
Only published RCTs evaluating systemic treatments in eczema will be included.
RCTs comparing two modes or doses of administration of the same molecule without a placebo or active comparator group will be included. Congress abstracts will be excluded.
Only anti-inflammatory topical therapies will be included in this review, emollients will not be considered.
Ancillary studies will not be considered, only the main publication reporting results for a RCT will be included.

Primary outcome
We will calculate (i) the proportion of RCTs who did not clearly report if concomitant topical therapies were allowed or prohibited in the article and (ii) the proportion of RCTs who did not clearly report if rescue topical therapies were allowed or prohibited in the article.

Secondary outcomes
<u>Concomitant topical therapy</u>
- number of RCTs that planned a concomitant topical therapy (planned, not planned, not reported)
- proportion of RCTs that reported the following items:
    - type of concomitant topical therapy Y/N
    - potency of topical treatment if applicable Y/N
    - duration of treatment allowed Y/N
    - number of applications per day allowed Y/N
    - quantities permitted (e.g., fingertip unit, number of tubes or grams)
    - differences in treatments use between the 2 arms Y/N
    - quantities applied Y/N
    - how amount of treatment was measured Y/N
- whether the main trial analyses were adjusted for concomitant topical therapies

<u>Rescue topical therapy</u>
- number of studies that allowed a rescue topical therapy (allowed, prohibited or not reported)
- proportion of RCTs that reported the following items:
    - type of rescue topical therapy Y/N
    - potency of topical treatment if applicable Y/N
    - duration of treatment allowed Y/N

- number of applications per day allowed Y/N
- quantities permitted (e.g., fingertip unit, number of tubes or grams)
- decision to use rescue treatment Y/N
- differences in treatments use between the 2 arms Y/N
- quantities applied Y/N
- how amount of treatment was measured Y/N

- whether the rescue topical therapies were handled in the analysis

- To estimate the evolution over time in the proportion of RCTs that did not provide any information on the use of rescue and concomitant topical therapies

Data extraction
This will be conducted by two reviewers independently using a piloted structured data extraction form developed to collect the relevant information from the selected articles (using the software Airtable®). Differences will be resolved by a third reviewer.
Before the start of the study, the two reviewers will evaluate a set of 10 papers and will resolve any differences in extraction and ensure interpretation of the data extraction tool is the same for all reviewers. Extraction tool may be modified at this stage.
Data will be extracted from the included article and/or its supplementary files for the reporting data.

For each identified trial, the following data that will be extracted are described in Appendix 1.

Risk of bias assessment
We will not perform a risk of bias of individual studies as we are interested in the methodology of the studies included rather than making conclusions from the outcomes of these studies.

Strategy for data synthesis
A narrative synthesis will be conducted to describe and summarize the information from the included studies. Continuous descriptive data will be expressed with mean (standard deviation) or median (interquartile range), depending on normality, while categorical data will be presented with number (%).
Multivariate logistic regression modelling will be performed to analyse associations between publications with no provided clear information on rescue topical therapies / concomitant topical therapies and other factors including: funding, country, year of publication, impact factor of the journal, number of patients randomized, how primary outcome was blinded (patient and/or investigator), journal's guidelines for trial registration and journal's policy on adhering to CONSORT guidelines.

Anticipated start date
24/07/2023

Anticipated completion date
01/10/2023

Planned dissemination
The study results will be presented at scientific conferences and published in a peer reviewed journal. This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PRISMA 2020) (7). If we demonstrate that concomitant and rescue topical therapies are poorly reported in eczema trials, the development of international consensus for reporting topical treatments in RCTs could be proposed.

References

1. Wollenberg A, Kinberger M, Arents B, et al. European guideline (EuroGuiDerm) on atopic eczema - part II: non-systemic treatments and treatment recommendations for special AE patient populations. J Eur Acad Dermatol Venereol. 2022;36:1904-1926.
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3. Sawangjit R, Dilokthornsakul P, Lloyd-Lavery A, Lai NM, Dellavalle R, Chaiyakunapruk N. Systemic treatments for eczema: a network meta-analysis. Cochrane Database Syst Rev. 2020;9:CD013206.
4. Gossec L, Landewé RB, Maillefert JF, Dougados M; OMERACT 7 Special Interest Group. Concomitant therapies as an outcome measure. Part 1: Drugs. J Rheumatol. 2005;32:2447-8.
5. Chis Ster AM, Cornelius V, Cro S. Current approaches to handling rescue medication in asthma and eczema randomized controlled trials are inadequate: a systematic review. J Clin Epidemiol. 2020;125:148-157.
6. Drucker AM, Morra DE, Prieto-Merino D, et al. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. JAMA Dermatol. 2022;158:523-532.
7. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

Appendix 1
Extraction form

A. GENERAL CHARACTERISTICS

A1. Title	*(text)*
A2. First author	*(text)*
A3. Year of publication	*(text)*
A4. Journal of publication	*(text)*
A5. Country of the corresponding author	*(text)*
A6. Funding	Public/Private/Both/Not reported
A7. Number of patients randomized	*(text)*
A8. How primary outcome was blinded (patient and/or investigator)	Patient/Investigator/Both/Neither

B. JOURNAL'S CHARACTERISTICS

B1. IF of the journal [2022, Journal Citation Reports]	*(text)*
B2. Journal's guidelines require trial registration	Yes/No/Not specified
B3. Journal's policy on adhering to CONSORT guidelines	Yes/No/Not specified

C. CONCOMITANT TOPICAL THERAPIES

C1. Clearly report if concomitant topical therapies were allowed or prohibited	Yes/No/Unsure
C2. Planned concomitant topical therapies	Planned/Not planned/Not reported
C3. Reported type of concomitant topical therapy *(e.g., topical corticosteroids, topical calcineurin inhibitors)*	Yes/No
C4. Potency of topical treatment if applicable	Yes/No/Not applicable
C5. Duration of treatment allowed	Yes/No
C6. Number of applications per day allowed	Yes/No
C7. Quantities permitted *(e.g. finger tip unit, number of tubes or grams)*	Yes/No
C8. Concomitant topical therapies summarised by group	Yes/No
C9. If C8=yes, how concomitant topical therapies were summarised	*(text)*
C10. Whether the groups were tested for imbalances	Yes/No

D. RESCUE TOPICAL THERAPIES

D1. Clearly report if rescue topical therapies were allowed or prohibited	Yes/No/Unsure
D2. Planned rescue topical therapies	Planned/Not planned/Not reported
D3. Reported type of rescue topical therapy *(e.g., topical corticosteroids, topical calcineurin inhibitors)*	Yes/No

D4. Potency of topical treatment if applicable	Yes/No/Not applicable
D5. Duration of treatment allowed	Yes/No
D6. Number of applications per day allowed	Yes/No
D7. Quantities permitted *(e.g. finger tip unit, number of tubes or grams)*	Yes/No
D8. Decision to use rescue treatment	Yes/No/Unclear ("at investigation discretion")
D9. Rescue topical therapies summarised by group	Yes/No
D10. If D9=yes, how rescue topical therapies were summarised	*(text)*
D11. Whether the groups were tested for imbalances	Yes/No

E. STATISTICAL ANALYSIS

E1. Analysis population for primary analysis	ITT / per protocol / other / unclear
E2. Use of concomitant treatment adjusted for analysis	Yes/No/NA
E3. If E2=yes, adjustment for	Primary analysis Sensitivity analysis
E4. If E2=yes, method of adjustment	*(text) / Not reported*
E5. Use of rescue treatment was accounted for analysis	Yes/No/NA
E6. If E5=yes, how	*(text) / Not reported*