

A Critical Appraisal of the PETITE Study Report: Topical Corticosteroids Are Safe and Effective in the Long-term Treatment of Infantile Atopic Dermatitis

It is well known that the presentation format of trial results, or the “frame,” strongly influences understanding, perceptions, and decisions and that the use of spin and selective reporting is a common strategy to achieve favorable conclusions.^{1,2} Most authors of the drug company-sponsored PETITE study have declared conflicts of interest, and we note several respective issues in the published report of this study that make it a good example of “spin.”

REPORTING

The study hypothesis is not clearly stated. The stated primary objective was “to compare the safety of PIM and TCS,” and a secondary objective was “to examine the long-term efficacy of PIM.” A sentence in the Methods section implies that the study should demonstrate equivalence, although neither its design nor reporting meets the requirements for an equivalence trial.³ In particular, neither prespecified comparability margins nor key statistics are provided. The comparator TCS products are not specified, no stratified results for mildly versus medium-potent TCS are reported, and although 64% of the PIM-treated children had to use TCS to control exacerbations, they are not reported separately. It also remains unclear which patients were included in the efficacy analysis, and how missing values were handled.

PRESENTATION AND INTERPRETATION

There was a higher incidence of serious adverse events and serious infections in PIM-treated children, with relative risks of 1.184 (95% confidence interval: 1.003–1.398) and 1.054 (95% confidence interval: 0.855–1.299) outside a 20% equivalence margin that appears justifiable on the basis of

recommendations from regulatory bodies.⁴ The PIM group also experienced significantly more adverse events of bronchitis, infected eczema, impetigo, and nasopharyngitis.

The authors repeatedly emphasize public fears around the potential adverse effects of TCS, but they do not provide the respective data. Instead, in their reply to an e-letter by Santner and McEwan, who called on the authors to report the skin-thinning data, the authors refer to a previous study,⁵ which compared a 4-week continuous use of PIM and betamethasone-17-valerate, a TCS of considerably higher potency to be used over short periods only. They failed to mention some of the benefits of betamethasone, such as the fact that it reduced transepidermal water loss more than PIM and had comparable beneficial effects on stratum corneum hydration, dye penetration, and epidermal differentiation. Both PIM and betamethasone reduced epidermal thickness, with no biologically relevant difference in that study. It is rather inconceivable that clinical assessment of skin thinning was not collected in PETITE, given that it has set out to show some form of “advantage” of PIM over TCS. We call upon the authors to present such data openly rather than divert the reader to older studies with inappropriate comparator TCS. Furthermore, the authors repeatedly state that PIM was steroid-sparing. Patients in the TCS group received more TCS, because they were randomly assigned to TCS. How can the higher number of “steroid days” seriously be sold as a major trial result?

For the above-mentioned reasons, we think that the authors’ conclusions in the PETITE study report are not justified and misleading.

Stephan Weidinger
University Hospital Schleswig-Holstein
E-mail: sweidinger@dermatology.uni-kiel.de

Hansjoerg Baurecht
UKSH Kiel

Jochen Schmitt
Center for Evidenced-Based Healthcare
(TU-Dresden)

Conflict of Interest:

Dr Weidinger has received grants for investigator-initiated trials from and lectured/consulted for Novartis, Biogen, Pfizer, and Galderma.

Dr Schmitt has received grants for investigator-initiated studies from Novartis, Pfizer, Abbott, MSD, Sanofi, and ALK. Hansjoerg Baurecht has no conflicts to disclose.

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Authors’ Response

In response to the points raised by Weidinger and colleagues:

- Our study was not an equivalence/noninferiority trial. The primary objective and statistical analysis were prespecified in the protocol and are reported in the article as stated. Equivalence methods were not used in these analyses. Equivalence was mentioned solely in the context of the sample size calculation, which assessed the length of the 2-sided

95% confidence interval (CI) for the risk differences under various possible incidence rates for test and reference. No formal noninferiority or equivalence margins were defined or planned. A post hoc analysis of the CI for the adverse events (AEs) in Table S3 showed that there are no differences in the incidence of these AEs between treatment groups.

- The PETITE study was open-label and had a “real world” design, which allowed the use of low- to medium-potency TCS according to their label in the respective country. The TCS that were used in each of the 28 countries involved in our study depended on which TCS were locally approved for use in infants.
- Additional subgroup analyses of the PETITE study data are being carried out and will be reported separately.
- No statistical testing of efficacy was planned. The analyses were based on observed values. Patients with a missing evaluation at a visit were not included in the efficacy data summaries. The results were presented for all intent-to-treat patients.
- Skin atrophy was not measured and probably not of major importance in our study, because there was only intermittent use

of low- and medium-potency TCS.

- The analyses of relative risk for serious AEs and serious infections presented by Weidinger et al were not planned in our study. The crude incidences of these events were presented in our article as standard safety-reporting measures. The primary safety analyses were conducted for AEs of primary clinical interest and those with a crude incidence of $\geq 5\%$ in either treatment group as described in our article. This was not an equivalence trial; therefore, no equivalence margins should be applied to any of the analyses. It is also important to point out that infections were recorded as AEs in our study and confirmation of these events by microbial culture was not mandatory.
- Although the incidence density ratio assessed by repeated Poisson regression was higher with pimecrolimus for bronchitis, infected eczema, impetigo, and nasopharyngitis, the crude incidences were only 2% to 4% higher, which we do not consider clinically significant or a convincing reason to favor one atopic dermatitis (AD) treatment over another.
- A noncorticosteroid alternative such as pimecrolimus is needed for the treatment of AD given

concerns that many patients have regarding steroids and their reluctance to use them.^{1,2} The key point that our data show in this regard is that treatment with pimecrolimus minimizes the need for TCS (to a median of 7 days over 5 years) in a “real world” setting.

- We consider the conclusions we have drawn from our study results are appropriate, ie, that both pimecrolimus and TCS are safe for the long-term management of mild-to-moderate AD.

Bardur Sigurgeirsson, MD, PhD
University of Iceland
E-mail: bsig@hudlaeknastodin.is

Thomas Luger, MD
University of Munster

Conflict of Interest:

Dr Sigurgeirsson has been a consultant for Novartis. Dr Luger has collaborated, advised, and lectured for Astellas, Meda, and Novartis.

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Bardur Sigurgeirsson and Thomas Luger

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