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.

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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.

REFERENCES

1. Boutron I, Dutton S, Ravaud P, Altman DG. Reporting and interpretation of randomized controlled trials with statistically nonsignificant results for primary outcomes. *JAMA*. 2010;303(20):2058–2064
2. Dwan K, Altman DG, Arnaiz JA, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PLoS One*. 2008;3(8):e3081
3. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA*. 2012;308(24):2594–2604
4. Food and Drug Administration; Center for Drug Evaluation and Research; Center for Biologics Evaluation and Research. Draft guidance: guidance for industry non-inferiority clinical trials. Available at: www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf. Assessed May 20, 2015
5. Jensen JM, Pfeiffer S, Witt M, et al. Different effects of pimecrolimus and betamethasone on the skin barrier in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2009; 123(5):1124–1133

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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

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