

Letter to the Editor

Dear *Cutis*[®]:

There are several points I would like to make in reference to Wolf et al¹ (*Cutis*. 2006;77[suppl 4]: 3-11) and their rosacea trial comparing twice-daily azelaic acid gel 15% with once-daily metronidazole gel 1%. First, referring to an earlier comparison I cowrote on twice-daily azelaic acid gel 15% with twice-daily metronidazole gel 0.75%,² Wolf et al¹ claim that the statistically significant advantage noted for azelaic acid gel 15% with regard to mean percentage decrease in inflammatory lesion count ($P < .001$) “did not meet the requirements for clinical significance set forth in the protocol.” This criticism, first set forth by Czernielewski and Liu³ in a letter to the editor in *Archives of Dermatology*, was countered with a comprehensive reply⁴ that Wolf et al¹ failed to consider. My colleagues and I noted a statement by Senn⁵ in *Statistical Issues in Drug Development*: “The power of a trial is a useful concept when planning a trial but has little relevance to the interpretation of its results.” As my coauthors and I stated, prestudy assumptions determine patient number calculations, but, as in any other trial, the failure to meet prestudy assumptions may change the power but does not invalidate the findings of statistically significant treatment differences, as were found in our study.

Second, I believe that Wolf et al¹ did not meet the primary objective of their study. In the statistics section of their article, their objective was defined as noninferiority of metronidazole gel 1% once daily to azelaic acid gel 15% twice daily after 15 weeks of treatment, using percentage reduction in inflammatory lesion count with a noninferiority margin of 15% for the difference between the 2 treatments. However, in their evaluation of the efficacy data, Wolf et al¹ curiously did not present noninferiority data and did not demonstrate significance for the claimed noninferiority (ie, $P < .05$). In their statistical section, the authors stated that they calculated the 95% confidence interval (CI) of the median difference between treatments. To conclude noninferiority, this CI would have to lie completely above the lower limit of the specified noninferiority margin (ie, -15%), yet the authors did not

present this CI in support of their efficacy claims. Rather, the authors presented the median percentage change from baseline in inflammatory lesion counts (in Figure 1 of their study) separately for each treatment. At first glance, the results might suggest comparable efficacy of both treatments. The median percentage change in inflammatory lesions for metronidazole gel 1% after 15 weeks numerically was only slightly inferior to azelaic acid gel 15%, and the P value for the exploratory analysis did not point to significant differences ($P = .264$).¹ In an appropriate statistical analysis, however, this presentation of the lesion count results would be insufficient to conclude noninferiority. Therefore, the question of noninferiority of metronidazole gel 1% remains unanswered.

Third, I also would like to emphasize that, in our earlier comparison with metronidazole gel 0.75%,² the difference in the mean percentage change in inflammatory lesion count at week 15 (last observation carried forward [LOCF] analysis) (72.7% for azelaic acid gel 15% vs 55.8% for metronidazole gel 0.75%) did exceed the 15% margin emphasized by Wolf et al.¹ I am not aware of clinical data showing superiority of metronidazole gel 1% over metronidazole gel 0.75%, and thus these former findings also might point to potential superiority of azelaic acid gel 15% versus metronidazole gel 1%.²

Finally, our results and those of Wolf et al¹ demonstrate that both azelaic acid gel and metronidazole gel are effective in the treatment of rosacea.^{1,2} Although additional studies might be required for a more precise discrimination between these 2 medications, both nonetheless provide safe and effective treatment options for this chronic and difficult-to-treat condition.

Sincerely,
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Dr. Elewski is a consultant for Intendis, Inc, and has received clinical research support from Galderma Laboratories, LP.

REFERENCES

1. Wolf JE Jr, Kerrouche N, Arsonnaud S. Efficacy and safety of once-daily metronidazole 1% gel compared with twice-daily azelaic acid 15% gel in the treatment of rosacea. *Cutis*. 2006;77(suppl 4): 3-11.
2. Elewski BE, Fleischer AB Jr, Pariser DM. A comparison of 15% azelaic acid gel and 0.75% metronidazole gel in the topical treatment of papulopustular rosacea: results of a randomized trial. *Arch Dermatol*. 2003;139:1444-1450.
3. Czernielewski J, Liu Y. Comparison of 15% azelaic acid gel and 0.75% metronidazole gel for the topical treatment of papulopustular rosacea [letter]. *Arch Dermatol*. 2004;140:1282.
4. Elewski BE, Fleischer AB Jr, Pariser DM. Comparison of 15% azelaic acid gel and 0.75% metronidazole gel for the topical treatment of papulopustular rosacea [comment]. *Arch Dermatol*. 2004;140:1283.
5. Senn S. *Statistical Issues in Drug Development*. New York, NY: John Wiley and Sons; 1997:395.

Author Response

We would like to thank Dr. Elewski for her observation regarding the noninferiority goals in our study comparing metronidazole gel 1% with azelaic acid gel 15%. Her comments offer us the chance to correct any misunderstandings about these data. Indeed, the primary objective of our study was to demonstrate that metronidazole gel 1% is noninferior to azelaic acid gel 15% with respect to reduction in inflammatory lesion counts within a margin of 15% following 15 weeks of treatment. This objective was met in the study.

It was by clerical oversight, rather than failure to meet this objective, that the CI in support of the noninferiority data was not presented in the original article. At end point, patients in the metronidazole group had a median decrease from baseline

in inflammatory lesion count of 77%, compared with 80% for patients in the azelaic acid group in the intent-to-treat population ($P=.264$; 95% CI [-11.6 to 2.3]). Results of the inflammatory lesion count analysis in the per-protocol population also revealed similar median decreases from baseline for both treatment groups (80% vs 85% in the metronidazole and azelaic acid groups, respectively ($P=.188$; 95% CI [-11.2 to 0.7])). We appreciate the opportunity to correct our earlier oversight with these data.

Regarding additional hypothetical arguments posed by Dr. Elewski, we feel that they are not relevant to this article or to this study because they attempt to extrapolate relevance to metronidazole gel 1% from studies that did not include metronidazole gel 1%. This is like comparing apples and oranges.

In conclusion, the findings of our study confirm that metronidazole gel 1% was shown to be noninferior to azelaic acid gel 15%. As Dr. Elewski notes, our study has demonstrated that both azelaic acid gel 15% and metronidazole gel 1% are safe and effective agents for the treatment of rosacea—a welcomed finding clearly stated in our article. It is possible, however, that treatment with once-daily metronidazole gel 1% may improve adherence and may be a more cost-effective way to achieve similar results to the twice-daily azelaic acid gel 15%.

Sincerely,
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Dr. Wolf is an advisory board member, consultant, researcher, and speaker for Galderma Laboratories, LP. The original study was supported by a grant from Galderma Laboratories, LP.