High placebo rates in clinical trials: Is the problem scoring systems or drug efficacy?

To the Editor: When clinical studies report high placebo rates of success, reviewers tend to blame study design (eg, use of allowed other therapies), investigator bias, scoring systems—or all 3. There is, however, an additional and sometimes alternative explanation: the intervention being tested just doesn't work that well. When the effect of a treatment is relatively small, then by necessity, the bar for success cannot be very high. When that bar is low, placebo variation can appear to be high because of the underlying nature of the disease and investigator uncertainty. The history of psoriasis trials highlights exactly this point. When drugs of modest effectiveness were tested using the PASI50 (a 50% reduction in Psoriasis Area and Severity Index) as a benchmark for success, placebo rates ran around 15% to 27%, and medication efficacy was approximately 50% to 65%.[1] There were many articles and complaints about the PASI as a scoring system at that time. However, when the next generation of more effective medications was tested and the PASI 75 could be used, there was substantially more separation between treatment and placebo, with placebo rates routinely running less than 10%. In this new era of PASI 90 and PASI 100, placebo rates are de minimus—and the trials are essentially unblinded because the improvement is so complete and rapid. The same transformation will happen in hidradenitis suppurativa. Despite the burst of publications and research creating new scoring systems and concerns about the high placebo rates in some recent trials,[2] the work by Frew et al[3] suggests that alternative scoring systems do not solve the problem of detecting a difference; they just measure it differently. Scoring systems definitely matter; the first infliximab study of hidradenitis suppurativa failed to meet its primary endpoint.[4] However, we have a scoring system now that is demonstrated to work—the Hidradenitis Suppurativa Clinical Response (HiSCR), which can easily be adapted to higher levels of efficacy, moving from 50% to 75%. We should be patient before we overdesign a new generation of scoring systems—and let the efficacy of the new medications we have under study catch up with us first.

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REFERENCES

1. Krueger GG, Papp KA, Stough DB, et al. A randomized, double-blind, placebo-controlled phase III study evaluating efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. *J Am Acad Dermatol*. 2002;47(6):821-833.
2. Amir Ali A, Seng EK, Alavi A, Lowes MA. Exploring changes in placebo treatment arms in hidradenitis suppurativa randomized clinical trials: a systematic review. *J Am Acad Dermatol*. 2020;82(1):45-53.
3. Frew JW, Jiang CS, Singh N, et al. Clinical response rates, placebo response rates, and significantly associated covariates are dependent on choice of outcome measure in hidradenitis suppurativa: a post hoc analysis of PIONEER 1 and 2 individual patient data. *J Am Acad Dermatol*. 2020;82(5):1150-1157.
4. Grant A, Gonzalez T, Montgomery MO, Cardenas V, Kerdel FA. Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. *J Am Acad Dermatol*. 2010;62(2):205-217.

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