Is oral pulsed prednisolone useful in alopecia areata? Critical appraisal of a randomized trial

To the Editor: We read with interest the report of pulsed oral prednisolone in alopecia areata (AA). However, we would contest the basis of the conclusion that this therapy is useful in AA. Points of concern are trial design and methodology, outcome measures, presentation of results and statistical analysis, and consideration of side effects.

The trial conforms to few CONSORT criteria, and contains no sample size or power calculations and little detail about the process and implementation of randomization. Systemic steroids undoubtedly produce short-term regrowth in some patients with severe AA. However, a major issue is whether this is sustained. The authors did include a 3-month follow-up period after cessation of treatment but the number of patients who satisfied the response criteria was given at end of treatment not at the end of study. The outcome measures were ill defined. It is unclear whether the percentages used to classify regrowth refer to increase as a percentage of baseline cover, percentage regrowth of the area of alopecia, or total coverage at final assessment. Further, the authors state that “only moderate to marked regrowth was considered to be significant” (>30% regrowth), but significant to whom? Consider the extreme example of a patient with 0% cover who regrows 31% of the lost area (assuming this is the measure of regrowth used). Then this patient is deemed a success! Relapse was defined as greater than 20% loss and, therefore, our hypothetic patient could lose 20% of this 31% cover, now having 25% cover, and still be regarded as a success. Therefore, response as defined in the study may not be a clinically meaningful response to patients.

Furthermore, there was no inclusion of patients’ assessment of efficacy, the value of the treatment, or effect on quality of life.

The authors report that the “response rate was significantly higher in the drug group (P < .05)” but do not indicate when analysis was performed (treatment end or study end). Analysis should be intention-to-treat not per-protocol as exclusion from analysis of “7 patients lost to follow-up” might introduce unacceptable bias. Re-analyzing the 6-month data by intention-to-treat, including the one placebo responder, there was no significant difference between groups (P = .14). This patient, who unequivocally fulfills the study definition of responder, inexplicably seems to have been omitted from the analysis and from the conclusion of the Abstract.

The demographic details of both groups were similar except for “first episode of AA” (6 patients in the intervention group, 3 in placebo). As first episode of AA is a favorable predictor of response, the study populations are biased toward response in the steroid group, which was not accommodated in the statistical analysis. The authors would appear to have been unaware that randomization may not produce similar patient groups for small numbers.

With such a small study, it is impossible to assess uncommon but potentially serious corticosteroid side effects and, therefore, possible risks, such as glaucoma, aseptic necrosis of the femoral head, and reduced bone density, have not been addressed. In this study, 55% of patients receiving steroid developed side effects. Even if none of these side effects were serious, patients are being asked to choose between one cosmetic problem (AA, albeit with potential psychologic sequelae) and others (steroid acne, weight gain, facial mooning).

Prescribing systemic steroids in AA is a serious therapeutic step, justified only if there is convincing evidence of both meaningful enduring clinical benefit and also low risk of serious side effects. Such evidence is not provided by this article.

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Reply
To the Editor: We are thankful to Sladden and Hutchinson for their interest and critical appraisal of our report on pulse oral prednisolone therapy in alopecia areata (AA).1 We would like to address their concern regarding our report. In response to their concern about sustained hair regrowth, we stress that our objective was to evaluate a commonly used therapeutic modality (pulse oral prednisolone) for AA in a placebo-controlled manner. We definitely have not claimed that oral prednisolone gives a long-lasting hair regrowth; if it did, then the treatment of AA would have been so simple!

According to Hull et al,2 all topical and systemic therapies tried in the treatment of AA have a high failure rate in long-standing cases. They concluded that 60% of patients with extensive patchy alopecia showed a cosmetically worthwhile response to pulse corticosteroids without significant side effects. Our study supports these observations. We have never implied that serious side effects do not occur with pulse corticosteroids. However, wide clinical experience with the use of pulse corticosteroids in treatment of AA and pemphigus at our center clearly suggests that side effects are less frequent compared with those with conventional high-dose daily prednisolone therapy.3-5 Hull et al2 agree that AA is not merely a cosmetic problem, but can have serious psychological effects.

If the lack of an “ideal treatment” prevented physicians from trying new regimens in treatment of such disorders, then medicine would never progress. Ours was an attempt to use a modified regimen of a treatment already in use to achieve cosmetically acceptable hair regrowth without significant side effects.

Although we used an arbitrary limit of more than 30% regrowth of hair as a significant response rate, 25% of the responders had achieved more than 60% regrowth, 75% had between 30% and 60% regrowth, and none of the “hypothesized patients” in our study had a clinical situation such as that illustrated by Sladden and Hutchinson. Response to treatment as significant in the drug group A occurred at the end of active treatment. A total of 7 patients were lost to follow-up because of reasons unrelated to the study. Therefore the statistical interpretation as given by Sladden and Hutchinson appears to be biased. One patient in the placebo group had moderate regrowth of hair at the end of 3 months of follow-up (6 months of study period). The percentage used to quantify regrowth understandably refers to hair regrowth in the lesional area at baseline. Most patients with AA who seek treatment are young or middle-aged with almost a common demographic profile. Patients with long-standing disease are more likely to pursue the treatment option suggested by Hull et al,2 that is, “no treatment.” Quality of life assessment was not in the purview of our study.

We fully acknowledge that systemic steroids are a serious therapeutic decision in the treatment of AA. At the same time, we believe that attempts to design therapies with maximal efficacy and the least side effects in AA should continue. We have emphasized in our report that patients should be informed about possible side effects related to corticosteroid use, expected treatment outcomes, and the need for further studies with large sample sizes to validate our observations.

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