

NOTES & COMMENTS

Combination of topical anthralin and calcipotriene in alopecia areata: A discussion of the mechanisms of action

To the Editor: The study by Krueger et al¹ presented the combination of anthralin and calcipotriene in the treatment of alopecia areata (AA), and the result was impressive. It may provide us with an alternative approach to tackle treatment-resistant AA when conventional treatments fail. However, the rationale of combination treatment and the underlying mechanisms are interesting and worth further discussion.

The authors mentioned the possible mechanisms of calcipotriene in AA, which may be related to irritant dermatitis or allergic contact dermatitis. Although topical vitamin D analogues do cause irritant dermatitis, the reported percentage of skin irritation is only 10% to 15% according to the product label.² Besides, it is commonly believed that topical calcipotriene-induced allergic contact dermatitis is rare considering the widespread usage of the drugs.³ Although the data from psoriatic subjects may not be accurately extrapolated to other populations, a study of calcipotriol patch tests in healthy volunteers may provide us with some information.⁴ The results showed that score 1/2 (doubtful reaction) is common on day 2 in all groups including vehicle control, so this reaction type may not be a reliable indicator. Score 1 reaction was present in slightly more than 10% of the subjects who received 50 µg/mL concentration on day 2. On day 3, less than 5% of this group showed score 1 or score 2 reactions. That is to say, the percentage of irritation after patch testing using the calcipotriol solution is not much different from that in psoriatic subjects (10% to 15%). Although the methods of application (patch test vs topical) and preparations (50 µg/mL solution vs 50 µg/g cream) were different, the study results may be useful to estimate the irritation potential of calcipotriol in subjects with normal skin turnover. Therefore, the rationale to use topical vitamin D analogues as a method to “bolster the resultant dermatitis” is not convincing given the less than 15% chance to elicit this irritant effect. Whether the reported case had

irritant or allergic reaction to calcipotriene was not known, as combination treatment with anthralin was used, and no patch test result of calcipotriene was provided. The idea of combining 2 contact sensitizers, which included diphenylcyclopropenone (DPCP) and anthralin, as a contact immunotherapy regimen was tried by some researchers, but the results were conflicting and may increase the severity of adverse effects.⁵ The more commonly postulated mechanisms of vitamin D analogues in the treatment of AA are related to its immunomodulatory effects, such as enhancement of regulatory T cells, inhibition of CD8⁺ T-cell activation, and mitigated interferon-γ-induced loss of immune privilege of the hair bulb.⁶ However, the mechanisms of anthralin or DPCP in the management of AA are not fully understood. Some evidence shows that DPCP treatment is associated with altered peribulbar CD4⁺/CD8⁺ ratio and inflammatory cytokine profiles.⁵ Whether combining topical calcipotriene and anthralin exerts a synergistic effect remains to be studied. The reason for the potential synergy might be explained with the effects of the anti-inflammatory cytokine interleukin (IL)-10. Evidence showed that anthralin stimulated the production of IL-10 in a rat model of AA⁷ and upregulated IL-10 receptors on a human keratinocyte cell line.⁸ As mentioned earlier, calcipotriol induces regulatory T cells, and regulatory T cells are known to produce IL-10. In addition, some experiments revealed that calcipotriol enhanced IL-10 secretion in human psoriatic skin⁹ and also increased IL-10 receptor gene expression in human epidermal cells.¹⁰ Combining these 2 agents might further increase the activity of IL-10, thus mitigating the effects of other proinflammatory cytokines in AA lesions.

In addition, the authors stated that “calcipotriene causes allergic contact dermatitis, likely via thymic stromal lymphopoietin (TSLP), which adds an additional mechanism of immunomodulation.” This hypothesis is also intriguing, and further discussion is necessary. Evidence showed that the expression of TSLP may be differently affected by topical calcipotriol in different species. TSLP was increased in keratinocytes after topical calcipotriol in a mouse model, but another study showed that a similar effect was not observed in normal human or monkey skin.¹¹ On the other hand, topical calcipotriol was shown to induce the expression of TSLP in human psoriatic skin

lesions.¹² Whether TSLP is inducible by calcipotriol in AA is still unknown. However, even if AA lesions show increased production of TSLP after topical calcipotriol, whether TSLP poses a positive or negative effect is still uncertain. A genetic study of AA lesions found increased expression of T helper cell (Th)2, Th1, IL-23, and IL-9/Th9 pathway genes, including the *TSLP* gene.¹³ Therefore, the complex pathophysiology of AA may not be fully explained by the theory of Th1/Th2 balance. The authors of the previous case report developed a combination regimen that may potentially be valuable in treatment-resistant AA, and further research is needed to delineate the possible mechanisms of action.

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