Innovation in topical therapy for psoriasis with corticosteroid and vitamin D analogue combination

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Background
- Psoriasis plagues a chronic, inflammatory immune-mediated skin disorder that negatively impacts patients’ quality of life both physically and psychologically.
- In individuals with a genetic predisposition, environmental factors (e.g., physical and psychological stress) may trigger the induction of psoriasis, beginning with the activation of dendritic cells. (Page 1) 1
- Topical treatments containing corticosteroids and vitamin D analogues target key sites in psoriasis pathogenesis and are essential well-established first-line treatments for patients with mild-to-moderate disease. (Page 1) 2
- Here we discuss recent data showing the anti-inflammatory and immunomodulatory mechanisms underlying the efficacy of fixed-dose combination therapy versus fasciculated monotherapy, and explore developments in topical drug delivery and the clinical relevance of these data.

Corticosteroid and vitamin D analogue combination treatment addresses therapeutic goals, resulting in increased effectiveness versus monotherapy
- The treatment goal is to clear the psoriatic plaques by inhibiting the inflammatory skin microenvironment (rather than immunosuppression), thereby normalizing skin homeostasis, keratinocyte proliferation and differentiation.
- Both corticosteroids and vitamin D analogues inhibit pro-inflammatory mediator release. (Page 1) (Page 1) 3
- Corticosteroids and vitamin D analogues exhibit additive effects in vitro. (Page 1) (Page 1) 4
- Recent preclinical data show that fixed-dose combination treatment provides significantly increased inhibition of pro-inflammatory cytokines compared with monotherapy. (Page 1) (Page 1) 5
- The effect of fixed-dose combination therapy on cellular targets in psoriasis pathophysiology is summarized in Figure 3a and 3c. (Page 1) (Page 1) 6

Combination therapy attenuates side effects associated with their individual monotherapies
- Long-term cumulative use of topical corticosteroids and vitamin D analogue monotherapy is associated with increased risk of skin atrophy and perioral dermal infarction respectively. (Page 1) (Page 1) 7
- Recent studies in cultured skin models demonstrated that the addition of Calorates early signs of betamethasone-induced skin atrophy by modulating key epidermal markers. (Page 1) (Page 1) 8
- A 12-week clinical study demonstrated that daily treatment with Calorates/Angel significantly reduced the overall number of adverse events – particularly clearing/drying effects, whereas the use of Calorates/Angel with Calorates/Angel – compared with vitamin D analogue monotherapy (Calorates/Angel 50mg/g) (Page 1) (Page 1) 9

Corticosteroid and vitamin D analogue combination topical treatment may provide long-term management of psoriasis
- Upon elimination of psoriatic plaques and normalization of skin homeostasis, the therapeutic objective shifts to the maintenance of antimicrobial free sites as psoriasis inflammatory tends to recur in previously affected skin locations. (Page 1) (Page 1) 10
- This may be achieved by the expression of inflammatory cytokines upon reactivation of immune cells present in the apparently normal-skin after treatment (Page 1) (Page 1) 11
- New data indicate that combination treatment is able to reduce induction 34-fold, as well as counteract the activation of pro-inflammatory of cytokines 35-fold, more effectively than corticosteroids alone (Page 1) (Page 1) 12
- For example, topical corticosteroids alone can suppress immunomodulatory Type II helper T-cells, while combination treatment can prevent this by inhibiting the release of immunomodulatory cytokines. (Page 1) (Page 1) 13
- Further clinical studies are required to explore the possibility of fixed-dose combination treatment for the long-term management of psoriasis.

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Conclusions
- Overall, fixed-dose combination of corticosteroid and vitamin D analogue has demonstrated superior efficacy over monotherapies in both preclinical and clinical studies, as well as in daily practice.
- The rationale for fixed-dose combination therapy is further supported by minimized adverse events usually associated with corticosteroid and vitamin D analogue monotherapy, such as skin atrophy and perioral skin irritation, respectively.
- Sequential delivery of active ingredients in combination formulations or in aerosol foam has shown improved clinical responses and quality of life, while providing patients with more therapeutic options (such as the 100g tube).
- A randomized clinical trial with Calorates/Angel foam has recently been initiated to examine the long-term management of plaque psoriasis (PS3033, NCT02989942).

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References