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

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Background

- Plaque psoriasis is a chronic, inflammatory, immune-mediated skin disorder that negatively impacts a patient's quality of life, both physically and psychologically[1,2]
- In individuals with a genetic predisposition, environmental factors (eg physical and psychological stress) may trigger the initiation of psoriasis, beginning with the activation of dendritic cells (Figure 1)[1,3]
- Topical treatments containing corticosteroids and vitamin D analogues target key steps in psoriasis pathogenesis and are essential, well-established first-line treatments for patients with mild-to-moderate psoriasis[4,5]
- Here we discuss recent data showing the anti-inflammatory and immunomodulatory mechanisms underlying the efficacy of fixed-dose combination therapy versus topical steroidal monotherapy, and explore developments in topical drug delivery and the clinical relevance of these data

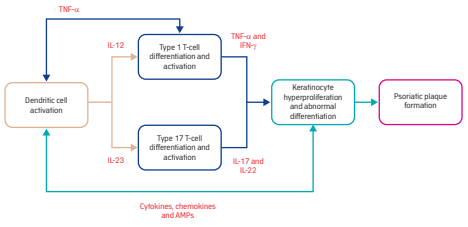

Figure 1. Key steps in the psoriasis pathogenesis loop

Arrows indicate pro-inflammatory mediator release. AMP, antimicrobial peptide; IL, interleukin; IFN, interferon; TNF, tumour necrosis factor

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 underlying inflammation via immunomodulation (rather than immunosuppression), thereby normalizing skin homeostasis, keratinocyte proliferation and differentiation
- Both corticosteroids and vitamin D analogues inhibit pro-inflammatory mediator release (Figure 1) from dendritic cells, Type 1 and 17 (cytotoxic and helper) T-cells, and keratinocytes.[6–9] Vitamin D analogues exert normalizing effects on the hyperproliferation and abnormal differentiation of keratinocytes and also have immunomodulatory effects[6,10]
- Recent preclinical data show that fixed-dose combination treatment provides significantly increased inhibition of pro-inflammatory cytokines compared with monotherapies (Figure 2)[11]
- The effect of fixed-dose combination therapy on cellular targets in psoriasis pathophysiology is summarized in Figure 3a–d

Corticosteroid and vitamin D analogue combination topical treatment may provide long-term management of psoriasis

- Upon clearance of psoriatic plaques and normalization of skin homeostasis, the therapeutic objective shifts to the maintenance of a relapse-free state as psoriatic inflammation tends to recur in previously affected skin locations[12,13]
  - This may be caused by the expression of inflammatory cytokines upon reactivation of immune cells present in the apparently normalized, plaque-free skin after treatment[12,13]
- New data indicate that combination treatment is able to induce regulatory T-cells, as well as counteract the activation and differentiation of cytotoxic T-cells, more effectively than corticosteroids alone (Figure 3e)[11]
  - For example, topical steroid monotherapy can suppress immunomodulatory Type 2 helper T-cells, while combination treatment can prevent this by increasing the release of immunomodulatory cytokines, eg IL-10 (Figure 2)[11]
- Further clinical studies are required to explore the possibility of fixed-dose combination treatment for the long-term management of psoriasis

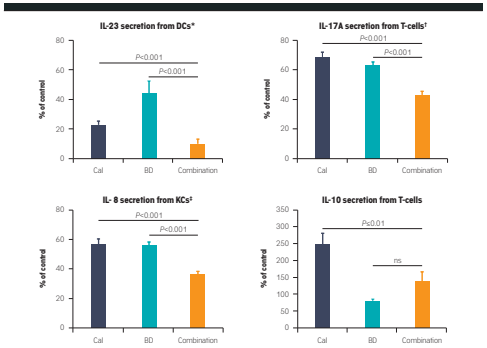

Figure 2. Combination treatment *in vitro* is significantly more effective than monotherapies in inhibiting cytokines released from key cells involved in psoriasis pathogenesis

Levels of pro-inflammatory (IL-23, IL-17A and IL-8) and immunomodulatory (IL-10) cytokines released by DCs, T-cells, and KCs are expressed as percentage of vehicle-treated control (100%).[11] Treatment was applied before DC activation, after (IL-17A) and before (IL-10) Th-cell differentiation, and on stimulated KCs.[11] *Combination treatment also led to TNF-α inhibition (both $P<0.001$); †Similar results were found for the inhibition of IL-22, IL-8, and TNF-α (all $P<0.001$); ‡Similar results were observed for IL-6, IL-17C, and IL-20 (all $P<0.001$). BD, betamethasone dipropionate; Cal, calcipotriol; DC, dendritic cell; IL, interleukin; KC, keratinocyte; ns, not significant; Th, T-helper cell; TNF, tumour necrosis factor

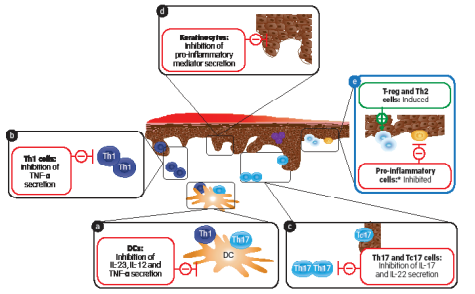

Figure 3. Summary of the complementary and additive actions of corticosteroid and vitamin D analogue combination treatment on cellular targets in the pathophysiology of psoriasis

Panels (a) to (d) represent therapeutic targets for inhibiting the pro-inflammatory environment. Panel (e) corresponds to the possible key targets for long-term maintenance therapy. Plus and minus signs indicate induction and inhibition, respectively. *Resting and naive DCs and T-cells. DC, dendritic cell; IL, interleukin; Tc, cytotoxic T-cell; Th, T-helper cell; TNF, tumour necrosis factor; T-reg, regulatory T-cell

Clinical benefits of corticosteroid and vitamin D analogue fixed-dose combination treatment

- Corticosteroids and vitamin D analogues are directed at different targets in psoriasis pathogenesis. Their complementary and additive effects observed in preclinical data have translated into clinically effective fixed-dose combination therapies, as supported by randomized, double-blind, controlled clinical studies[14,15]
- For example, fixed-dose combination calcipotriol (Cal)/betamethasone dipropionate (BD) aerosol foam was significantly more efficacious in improving mean modified Psoriasis Area and Severity Index (mPASI; excluding the head, which was not treated) score than the individual active ingredients after 4 weeks ($P<0.001$ versus both Cal foam and BD foam)[14]

Combination therapy attenuates side effects associated with their individual monotherapies

- Long-term continuous use of topical corticosteroids and vitamin D analogue monotherapy is associated with increased risk of skin atrophy and perilesional skin irritation, respectively (Table 1)[5,9,16]
  - Recent studies in cultured skin cells demonstrated that the addition of Cal reduces early signs of betamethasone-induced skin atrophy by modulating key extracellular matrix components[17]
  - A 52-week clinical study demonstrated that daily treatment with Cal/BD ointment significantly reduced the overall number of adverse events – particularly burning, itching, and erythema of skin – compared with vitamin D analogue monotherapy (Cal ointment, 50 µg/g)[18]

Table 1. Summary of the effects of corticosteroids and vitamin D analogues in skin atrophy[17,19,20]

Mechanism	Effect of corticosteroids	Effect of vitamin D analogues	Overall clinical effect of combination treatment
Lipid synthesis	↓	↑	Prevents skin barrier and water loss impairment caused by corticosteroids
AMPs, eg LL-37	↓	↑	
KC proliferation	↓	=	Attenuates epidermal thinning by corticosteroid-induced reduction of epidermal cells
Change in tissue modelling and structure: • Hyaluronic acid • Matrix metalloproteinases	↓	↑	Limits epidermal thinning from corticosteroid-induced loss of cellular volume
Collagen synthesis and turnover	↓	↑	Reduces dermal thinning caused by corticosteroid-induced decrease in matrix network
Glycosamine synthesis	↓	↑	Increases water-binding capacity of the skin, decreasing corticosteroid-induced dermal thinning
Elastic fibre synthesis	↓	↑	Attenuates reduced skin flexibility/ elasticity observed in topical steroidal monotherapy

Downward arrow indicates down-regulation, upward arrow indicates up-regulation, equal sign indicates no effect. The data presented here are based on non-inflamed skin. AMP, antimicrobial peptide; KC, keratinocyte

Challenges of drug delivery in topical formulations

- Poor penetration of active ingredients into the skin can result in low, or lack of, clinical efficacy
- The rate-limiting step for most topical treatments is the concentration of active ingredients dissolved in the vehicle
- One potential method of enhancing the rate of skin penetration is to increase the concentration of active ingredients dissolved in the applied product beyond the normal solubility limit, ie create a supersaturated solution
- A recent study with Cal/BD aerosol foam demonstrated that a stable supersaturated environment was created and maintained for clinically relevant time periods (at least 26 hours in the laboratory setting)[21]
  - This state was created after rapid evaporation of the propellants during application and may explain the observed increase in bioavailability of Cal/BD aerosol foam versus Cal/BD ointment[21]

An innovative drug delivery formulation results in improved efficacy

- A number of studies have demonstrated the superior efficacy of Cal/BD aerosol foam compared with traditional formulations such as ointments, gels, and lotions (Table 2)[15,22–24]
- The increased efficacy of Cal/BD aerosol foam is also associated with a similar safety profile, as demonstrated in a pooled safety analysis comparing fixed-dose combination Cal/BD aerosol foam with BD foam, Cal foam, Cal/BD ointment, and vehicles (foam and ointment)[25]

Table 2. Summary of studies comparing Cal/BD aerosol foam with Cal/BD gel or ointment

Design	Duration	N	Comparator(s)	Outcomes
Phase IIa, exploratory, single centre, intra-individual comparison[15]	4 weeks	24	Cal/BD foam vs Cal/BD ointment vs BD foam vs foam vehicle (all n=24)	TCS decrease: −6.00 vs −5.25 (Cal/BD ointment; $P=0.038$) vs −4.96 (BD foam; $P=0.005$)
Phase II, randomized, multicentre[22]	4 weeks	376	Cal/BD foam (n=141) vs Cal/BD ointment (n=135) vs foam (n=49) and ointment (n=51) vehicle	Treatment success rates: 54.6% vs 43.0% (Cal/BD ointment; $P=0.025$) mPASI mean difference: −0.6 vs Cal/BD ointment ($P=0.005$)
Phase III, randomized, parallel group (PSOABLE)[23]	12 weeks	463	Cal/BD foam (n=185) vs Cal/BD gel (n=188) vs foam (n=47) and gel (n=43) vehicles	Treatment success rates: 38% vs 22% (Cal/BD gel; $P<0.0001$) mPASI mean difference: −0.6 vs Cal/BD gel ($P=0.028$)
Phase III, randomized, parallel group (PSO-ABLE, HRQoL analysis)[24]	12 weeks	463	Cal/BD foam (n=185) vs Cal/BD gel (n=188)	DLQI scores of 0/1: 40.5% vs 44.1% (Cal/BD gel; $P=0.003$); EQ-5D utility index: 0.09 vs 0.03 (Cal/BD gel; $P<0.001$)

All studies were investigator blinded. BD, betamethasone dipropionate; Cal, calcipotriol; DLQI, Dermatology Life Quality Index; EQ-5D, EuroQoL-5D-5L-PSO; HRQoL, health-related quality of life; mPASI, modified Psoriasis Area and Severity Index (excluding head, which was not measured); TCS, total clinical score (sum of erythema, scaling, and plaque thickness)

Conclusions

- **Overall, fixed-dose combination of corticosteroids 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 treatment is further supported by minimized adverse events usually associated with corticosteroid and vitamin D analogue monotherapy, such as skin atrophy and perilesional skin irritation, respectively**
- **Improved delivery of active ingredients via innovative formulations, eg aerosol foam, has shown improved clinical response and quality of life, while providing patients with more therapeutic options suited to their lifestyle**
- **A randomized clinical trial with Cal/BD aerosol foam has recently been initiated to examine the long-term management of plaque psoriasis (PSOLONG; NCT02899962)**

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References

1. Nestle FO *et al. N Engl J Med* 2009;361:496–509
2. Hrehorow E *et al. Acta Derm Venereol* 2012;92:67–72
3. Kim J & Krueger JG. *Dermatol Clin* 2015;33:13–23
4. Laws PM & Young HS. *Expert Opin Pharmacother* 2010;11:1999–2009
5. Menter A *et al. J Am Acad Dermatol* 2009;60:643–59
6. Bikle DD. *J Nutr* 1995;125:1709S–14S
7. Lange K *et al. Skin Pharmacol Appl Skin Physiol* 2000;13:93–103
8. Norris DA. *J Am Acad Dermatol* 2005;53:S13–25
9. Segaert S & Rapke M. *J Drugs Dermatol* 2013;12:e129–37
10. Gottlieb A. *Psoriasis Forum* 2015;21:35–41
11. Lovato P *et al. J Dermatol Sci* 2016;81:153–64
12. Clark RA. *J Invest Dermatol* 2011;131:283–5
13. Suarez-Farinas M *et al. J Invest Dermatol* 2011;131:391–400
14. Lebwohl M *et al. J Clin Aesthet Dermatol* 2016;9:34–41
15. Queille-Roussel C *et al. Clin Drug Investig* 2015;35:239–45
16. Scott LJ *et al. Am J Clin Dermatol* 2001;2:95–120
17. Norsgaard H *et al. Arch Dermatol Res* 2014;306:719–29
18. Kragballe K *et al. Br J Dermatol* 2006;154:1155–60
19. Schoepe S *et al. Exp Dermatol* 2006;15:406–20
20. Jensen JD *et al. Arch Dermatol* 2011;147:95–8
21. Lind M *et al. Dermatol Ther (Heidelb)* 2016;6:413–25
22. Koo J *et al. J Dermatolog Treat* 2016;27:120–7
23. Paul C *et al. J Am Acad Dermatol* 2016;74:AB260 (abst P37.12)
24. Paul C *et al. J Eur Acad Dermatol Venereol* 2017;31:119–26
25. Menter A *et al. Skinmed* 2017;15:119–24