The Role of Topical Vitamin D Modulators in Psoriasis Therapy

Emil A. Tanghetti MD
University of California, Davis Medical Center, Sacramento, CA

ABSTRACT

Psoriasis affects more than 5 million adults in the United States (U.S.), causing significant impairments in quality of life and incurring substantial costs in treatment. The disease is characterized by hyperproliferation and abnormal differentiation of epidermal keratinocytes resulting from a disordered immune response. Topical therapies, such as corticosteroids, are the most common treatment for psoriasis. However, long-term use of more potent topical corticosteroids is associated with potential risk for side effects. Topical vitamin D agents have been developed as a newer therapeutic option for use in place of, or in addition to, topical corticosteroids. These agents act to inhibit keratinocyte proliferation, normalize differentiation and modulate the activity of immune cells with minimal effect on serum calcium hemostasis. Calcipotriene is the most widely used member of this class, and is one of the most frequently prescribed topical agents for psoriasis. Although evidence suggests that it is approximately as effective as low-to-medium potency corticosteroids, it is associated with cutaneous irritation, especially when used in sensitive areas. Calcitriol ointment is a new option for topical therapy and is the only vitamin D_3 ointment available for use in the U.S. and contains the naturally occurring active form of vitamin D_3 that is associated with a relatively low rate of side effects.

INTRODUCTION

Psoriasis is a common and costly dermatologic condition. A recent cross-sectional study reported a prevalence of diagnosed psoriasis of 3.15% in U.S. adults aged 20–59 years.[1] The prevalence of undiagnosed psoriasis in this sample was 0.4% by conservative measures (confirmation by two dermatologists examining photographs of subjects), and 2.28% by less conservative measures (confirmation by at least one of the two evaluators).[1] These values translate to an estimated 5 million U.S. adults with diagnosed psoriasis and 600,000 to 3.6 million more individuals with undiagnosed disease.[1]

The disfiguring, scaling and erythematous plaques that characterize psoriasis can impact patients' quality of life.[2] Psoriasis may affect patients' activities of daily living (ADL), work or school functioning and relationships with friends or partners. A European study reported that disability scores for patients with psoriasis were greatest on questions related to ADL, such as washing and changing clothes, the need for more frequent bathing, sports activities and problems with sleep.[3] Overall, 77% of respondents in this study claimed that psoriasis was a problem in their lives (score of 6–10 on a 10-point scale). It has been reported that the level of disability in psoriasis is comparable to that associated with other major medical diseases. Rapp et al. assessed health-related quality of life in a sample of 317 patients treated for psoriasis using the Short Form-36 Health Survey.[4] Compared to patients with other disease states, scores for physical and mental functioning in patients with psoriasis were among the lowest of all groups (Table 1). Only patients with congestive heart failure had worse scores for physical functioning; only patients with chronic lung disease or depression had worse scores for mental functioning.[4]

The cost of care for patients with psoriasis is also significant. Javitz et al. estimated the direct costs of psoriasis care from analysis of the literature and public and private health care databases.[5] Combined estimates for hospitalization, outpatient physician visits, photochemotherapy, dermatologic prescription medications and over-the-counter medications were $649.6 million per year.[5]

Pathophysiology

Pathologic changes observed in psoriatic skin originally led investigators to hypothesize that psoriasis primarily arose from the dysfunction of epidermal keratinocytes. Characteristics of psoriatic lesions include hyperplasia of the epidermis and growth and dilation of superficial blood vessels. In psoriatic epidermis, the keratinocytes proliferate and mature rapidly, leading to incomplete terminal differentiation. Inappropriate differentiation of these cells leads to limited elaboration of extracellular lipids and poor adhesion of the stratum corneum, resulting in the erythematous scaly plaques typical of psoriasis.[6]

Research over the last few decades reveals psoriasis to be an immune disorder caused by complex interactions between leukocytes, skin cells, and proinflammatory cytokines and chemokines.[6] The immunologic mechanisms of psoriasis are complex and not completely understood; a model of the proposed immunopathogenesis of psoriatic lesions is illustrated in Figure 1.[7] It is believed that abnormal activation of leukocytes leads to the accumulation of T cells and other immune cells in developing psoriatic lesions.

Activated T cells secrete a variety of proinflammatory cytokines, including interferon γ (IFN-γ), interleukin-2 (IL-2) and tumor necrosis factor α (TNF-α).[8] This cytokine milieu probably leads to keratinocyte hyperplasia through initiation of a programmed injury-repair response.[6] Each of the many steps and intermediaries in this process represents potential targets for therapy.

Topical Treatments: The Foundation of Therapy

Topical agents are the most commonly used therapy for psoriasis. A recent study of U.S. dermatologists reported that 86% of all patients with psoriasis receive topical therapy.[9] This option was not reserved for patients with mild disease; 47% of patients with moderate psoriasis and 37% with severe psoriasis were also treated with topical agents. This study also reported that a large proportion of patients had disease that was inadequately controlled by their current therapy; psoriasis in 39% of patients with severe, 26% with moderate and 15% with mild disease was inadequately controlled. These data highlight the chronic nature of psoriasis and the need for continued development of new therapies, improved approaches to current therapy and better patient education.

Corticosteroids remain the most commonly used class of topical therapy. Pearce et al., in an analysis of the National Ambulatory Medical Care Survey from 1990 to 2001, found that topical corticosteroids were listed in 77% of patient visits, compared to 28% for noncorticosteroidal therapies.[10] Over the 12-year study period, the most commonly listed individual agent was clobetasol propionate (7.6% of drug mentions). Starting in 1994, however, the synthetic vitamin D agent calcipotriene, which was introduced that year, became the single-most listed medication. Prescribing patterns differed between dermatologists and non-dermatologists, with non-dermatologists relying more heavily on topical corticosteroids (Table 2).

Although topical corticosteroids can produce rapid improvement in symptoms, long-term use is complicated by the potential for a range of adverse effects.[11] Local cutaneous effects of corticosteroids include atrophy of the dermis and epidermis,

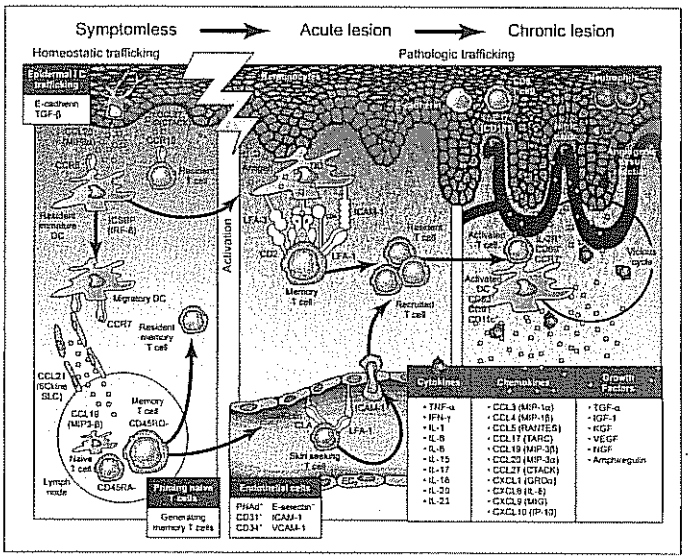

FIGURE 1. The left panel illustrates the normal interplay of Langerhans cells, resident dendritic cells, and T cells between skin and lymph nodes. The acute psoriatic lesion (middle panel) forms following a stimulus that leads to activation of T cells and dendritic cells. Cytokines secreted by these cells trigger the hyperproliferation and altered differentiation of keratinocytes via programmed pathways. A loop of continued activation of immune cells and keratinocytes sustain the chronic psoriatic lesion (right panel).[7] Adapted from: Nickoloff BJ, Nestle FO. Recent insights into the immunopathogenesis of psoriasis provide new therapeutic opportunities. *J Clin Invest.* 2004;113(12):1664-1675.

TABLE 1.

Comparison of Short Form-36 Scores Between Healthy Adults and Patients With Psoriasis and Other Chronic Health Conditions*

	Physical Component Summary Score		Mental Component Summary Score	
	Mean (SD)	Rank*	Mean (SD)	Rank*
Psoriasis	41.17 (14.21)	10	45.69 (11.37)	9
Healthy adults	55.26 (5.10)	1	53.43 (6.33)	1
Dermatitis	46.88 (11.49)	2	46.16 (12.06)	8
Arthritis	43.15 (11.62)	6	48.81 (11.11)	7
Cancer	45.12 (11.60)	3	48.82 (11.07)	6
Chronic lung disease	42.31 (14.08)	8	44.47 (12.28)	10
Hypertension	44.31 (10.76)	5	52.22 (9.28)	2
Myocardial infarction	42.64 (10.02)	7	51.67 (8.19)	4
Congestive heart failure	34.50 (12.08)	11	50.43 (11.13)	5
Type 2 diabetes	41.52 (11.27)	9	51.90 (9.55)	3
Depression	44.96 (12.05)	4	34.84 (12.17)	11

*Higher rank indicates better functioning
Adapted with permission from: Rapp SR, Feldman SR, Exum ML, Fleischer AB Jr, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol.* 1999;41:401-407.

striae, telangiectases and other conditions. These effects are more common with long-term use, more potent corticosteroid formulations or when corticosteroids are used on such areas as the face and intertriginous zones.[11,12] Systemic effects, including suppression of the hypothalamic-pituitary-adrenal axis, are uncommon but may occur with more potent topical corticosteroids, particularly if used over a large surface area for a prolonged time.[11,12] Tachyphylaxis may also develop with repeated use of topical corticosteroids, limiting their effectiveness.[11,12]The potential risks associated with topical corticosteroids may lead some patients to be fearful of and non-compliant with corticosteroid therapy. In a questionnaire-based study of 200 patients with atopic eczema, 72.5% of patients said that they were concerned about using topical corticosteroids; nearly one quarter said that they were non-compliant with treatment because of their concern.[13] The authors suggested that this degree of concern was disproportionate to the actual risks associated with topical corticosteroids. Other investigators have reported high rates of non-compliance with all topical psoriasis treatments. One study reported a 73% rate of non-compliance; in this study, compliance was slightly higher with vitamin D analogs (57%) compared to corticosteroids (50%).[14] Of equal concern is the large number of patients who are inappropriately using topical steroids on a chronic basis. They see some efficacy and are largely unaware of the chronic side effect of atrophy especially when used on facial or groin areas. In some situations these topical steroids are used as emollients since most prescription plans encourage the use of generic topical steroid ointments. Constant vigilance and education of the patient by the treating physician is necessary to prevent topical steroid overuse.

Nevertheless, the long-term use of topical corticosteroids may be limited by real or perceived potential for adverse effects. Options to minimize the side effects of corticosteroid therapy and maximize efficacy include the use of alternative agents and combination or sequential therapy using agents with different mechanisms of action. Non-corticosteroidal topical agents available for use in psoriasis include synthetic vitamin D products, anthralin and tar-based formulations, the retinoid tazarotene, salicylic acid, and 5-fluorouracil, among others. Aside from the synthetic vitamin D agents, non-corticosteroidal agents are used infrequently for the treatment of patients with psoriasis. In the study by Pearce et al., for example, tazarotene, salicylic acid, and coal tar each represented only 5% of non-corticosteroid prescriptions by dermatologists, compared to 42% for calcipotriene. There were no non-corticosteroids among the top five listed medications prescribed by non-dermatologists.[10]

TABLE 2.

Frequency of Psoriasis Therapies Prescribed by Dermatologists and Non-Dermatologists (1990-2001)[10]

	Dermatologists	Non-dermatologists
Topical steroid only	5996 (58.7%)	1611 (76%)
Topical non-steroid only	830 (8.1%)	67 (3.2%)
Combination topical	1783 (17.4%)	24 (1.2%)
Systemic only	818 (8.0%)	252 (11.9%)
Combination topical/ Systemic	794 (7.8%)	164 (7.7%)

In thousands and proportion of visits.
Adapted with permission from: Pearce DJ, Stealey KH, Balkrishnan R, Fleischer AB Jr, Feldman SR. Psoriasis treatment in the United States at the end of the 20th century. *Int J Dermatol.* 2006;45:370-374.

Synthetic Topical Vitamin D Agents

Synthetic topical vitamin D agents have become an important option in psoriasis therapy. The therapeutic use of vitamin D for patients with psoriasis dates to the 1930s, when it was used as an oral agent, assuming that vitamin D was the metabolite that acted to clear psoriasis lesions after exposure to sunlight.[15] Since that time, extensive research has contributed to our understanding of the role of vitamin D in skin and the development of new agents for the treatment of psoriasis.

The Biology of Vitamin D and the Skin

Investigators have demonstrated that the hormonally active compound 1α,25-dihydroxyvitamin D_3 (calcitriol) affects cellular functions in a wide range of tissues. Specific actions with relevance to psoriasis include inhibition of skin cell growth and modulation of immune response.[16,17] Calcitriol may exert autocrine and paracrine effects in the epidermis, acting through the vitamin D receptor (VDR) on keratinocytes and other cells.[18]The VDR binds to and activates transcription of vitamin D responsive genes. A wide range of genes are regulated by calcitriol, including many that influence growth, differentiation and inflammation in keratinocytes.[18]

Epidermal keratinocytes contain all the biochemical pathways necessary to produce calcitriol. In the presence of ultraviolet light (UV), the precursor 7-dehydrocholesterol is converted to previtamin D_3, which undergoes thermal isomerization to vitamin D_3 (Figure 2). Subsequent hydroxylations within the keratinocytes produce calcitriol.[16,18] Experimental findings suggest that conversion of vitamin D_3 to calcitriol in skin cells may contribute to normalization of keratinocyte hyperproliferation.[18] Calcitriol has also been shown to have immunomodulatory effects on monocytes, macrophages, T cells and dendritic cells.[18]These findings and others support the vitamin D pathway as a target for psoriasis therapy.

Vitamin D Agents in Psoriasis

Several vitamin D agents have been developed for use in psoriasis. In the U.S., calcipotriene and calcitriol have been approved for use in psoriasis. A third vitamin D agent, tacalcitol, is available in Europe. These agents represent an additional therapeutic option for the treatment of psoriasis; they may be used as alternatives to or in combination with topical corticosteroid therapy to maximize efficacy and/or minimize side effects of long-term treatment.

Calcipotriene, a synthetic analog of vitamin D, is one of the most commonly prescribed medications for the treatment of psoriasis.[10] The most prominent side effect of calcipotriene is a relatively high incidence of skin irritation, particularly when applied to the face or intertriginous areas; up to 20% of patients develop irritation at those sites.[12] Clinical studies suggest that the combination of this agent with topical corticosteroids results in greater efficacy and less frequent skin irritation than does monotherapy. A recent randomized, double-blind trial compared the combination of calcipotriene plus betamethasone dipropionate to monotherapy with either agent in 1,417 patients with scalp psoriasis.[19] After eight weeks of treatment, the proportion of patients with "absence of disease" or "very mild disease" was significantly higher in the combination therapy group (68.4%) compared to the betamethasone (61%, $P<0.0079$) or calcipotriene (43.4%, $P<0.0001$) monotherapy groups. Side effects were lower in the betamethasone dipropionate and combination groups than in the calcipotriene only group. Calcipotriene has also been combined with phototherapy. One small study (n=11) reported that, compared to placebo, the addition of calcipotriene to UVA phototherapy led to more rapid clearance of plaques and a 26.5% reduction in the dose of UVA required.[20] Because calcipotriene is inactivated by UVA, the agent must be applied after phototherapy sessions.[12]

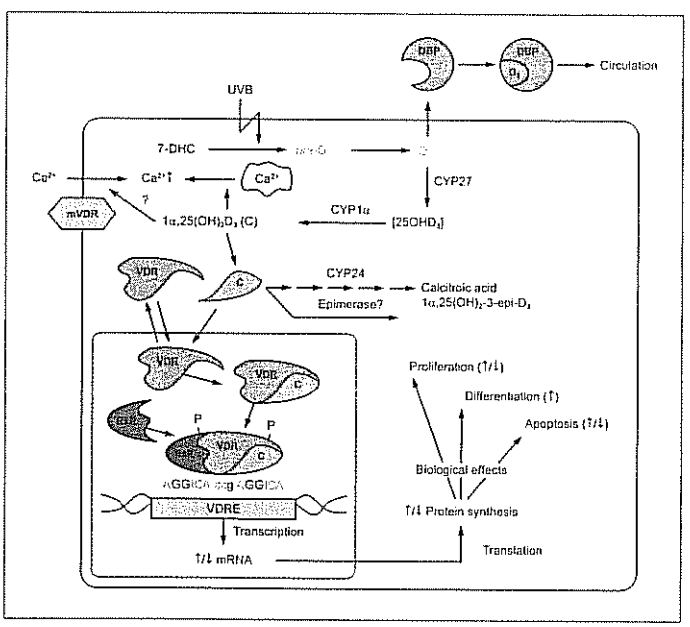

FIGURE 2. Epidermal keratinocytes contain all the necessary machinery to produce calcitriol from its initial precursor, 7-DHC. Following exposure to UVB, 7-DHC is converted to previtamin D_3. Subsequent hydroxylations produce the hormonally active metabolite calcitriol ($1\alpha,25(OH)_2D_3$), which inhibits the proliferation and alters the differentiation of keratinocytes.[23] Adapted with permission from: Lehmann B et al. *Exp Dermatol.* 2004;13(suppl 4):11-15

Tacalcitol is a synthetic vitamin D agent approved in Europe for the treatment of psoriasis. A systematic review of topical agents reported that tacalcitol was associated with the lowest rate of adverse events among non-corticosteroids (4.8% of patients).[21] However, the results of a double-blind, head-to-head comparison in 287 patients suggests that tacalcitol may be less effective than calcipotriene; mean reductions in severity score were 4.03 in the tacalcitol group and 5.05 in the calcipotriene group, a statistically significant difference.[22]

Calcitriol is a new option for topical therapy and is the only vitamin D_3 ointment approved for use in the U.S. for the treatment of psoriasis. Like tacalcitol, it has been associated with a low rate of adverse events such as irritation.[21] Unlike tacalcitol or calcipotriene, calcitriol is the naturally occurring active form of vitamin D_3. This unique agent provides a new option for the long-term management of psoriasis. In the accompanying articles, the efficacy, safety, and optimal use of calcitriol for the treatment of psoriasis are described in detail.

CONCLUSION

Psoriasis is a common and chronic dermatologic condition that is associated with significant impairment of quality of life. The pathophysiology of psoriasis is characterized by keratinocyte hyperproliferation, abnormal differentiation and a disordered immune response. Topical agents are the cornerstone of therapy, and corticosteroids are the most commonly used class of topical treatment. However, adverse effects can limit the long-term use of topical corticosteroids. The class of vitamin D agents interferes with the pathophysiology of psoriasis by inhibiting keratinocyte proliferation and modulating the activity of immune cells while minimizing the other metabolic effects of vitamin D. Calcitriol, a naturally occurring active form of vitamin D_3, is a new option for the topical treatment of psoriasis.

ACKNOWLEDGEMENTS

Writing and Editorial assistance provided by Joshua F. Kilbridge, medical writer, and Medisys Health Communications. Funding was provided by Galderma Laboratories, L.P.

DISCLOSURES

Dr. Tanghetti is a consultant, speaker and investigator for Allgeran, Stiefel and Obagi. He is also a speaker and investigator for Galderma.

REFERENCES

1. Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: Results from NHANES 2003-2004. *J Am Acad Dermatol.* 2009;60(2):218-224.
2. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol.* 2008;58(5):826-850.

3. Dubertret L, Mrowietz U, Ranki A, et al. European patient perspectives on the impact of psoriasis: The EUROPSO patient membership survey. *Br J Dermatol. 2006*;155(4):729-736.
4. Rapp SR, Feldman SR, Exum ML, et al. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol.* 1999;41(3 Pt 1):401-407.
5. Javitz HS, Ward MM, Farber E, et al. The direct cost of care for psoriasis and psoriatic arthritis in the United States. *J Am Acad Dermatol.* 2002;46(6):850-860.
6. Krueger JG, Bowcock A. Psoriasis pathophysiology: Current concepts of pathogenesis. *Ann Rheum Dis.* 2005;64 Suppl 2:ii30-ii36.
7. Nickoloff BJ, Nestle FO. Recent insights into the immunopathogenesis of psoriasis provide new therapeutic opportunities. *J Clin Invest.* 2004;113(12):1664-1675.
8. Traub M, Marshall K. Psoriasis—Pathophysiology, conventional, and alternative approaches to treatment. *Altern Med Rev.* 2007;12(4):319-330.
9. Patel V, Horn EJ, Lobosco SJ, et al. Psoriasis treatment patterns: Results of a cross-sectional survey of dermatologists. *J Am Acad Dermatol.* 2008;58(6):964-969.
10. Pearce DJ, Stealey KH, Balkrishnan R, et al. Psoriasis treatment in the United States at the end of the 20th century. *Int J Dermatol.* 2006;45(4):370-374.
11. Del Rosso J, Friedlander SF. Corticosteroids: Options in the era of steroid-sparing therapy. *J Am Acad Dermatol.* 2005;53(1 Suppl 1):S50-S58.
12. Lebwohl M, Ali S. Treatment of psoriasis. Part 1. Topical therapy and phototherapy. *J Am Acad Dermatol.* 2001;45(4):487-498.
13. Charman CR, Morris AD, Williams HC. Topical corticosteroid phobia in patients with atopic eczema. *Br J Dermatol.* 2000;142(5):931-936.
14. Fouéré S, Adjadj L, Pawin H. How patients experience psoriasis: Results from a European survey. *J Eur Acad Dermatol Venereol.* 2005;19 Suppl 3:2-6.
15. Nagpal S, Lu J, Boehm MF. Vitamin D analogs: Mechanism of action and therapeutic applications. *Curr Med Chem.* 2001;8(13):1661-1679.
16. Holick MF, Smith E, Pincus S. Skin as the site of vitamin D synthesis and target tissue for 1,25-dihydroxyvitamin D_3. Use of calcitriol (1,25-dihydroxyvitamin D_3) for treatment of psoriasis. *Arch Dermatol.* 1987;123(12):1677-1683a.
17. Manolagas SC, Provvedini DM, Tsoukas CD. Interactions of 1,25-dihydroxyvitamin D_3 and the immune system. *Mol Cell Endocrinol.* 1985;43(2-3):113-122.
18. Lehmann B. Role of the vitamin D_3 pathway in healthy and diseased skin—Facts, contradictions and hypotheses. *Exp Dermatol.* 2009;18(2):97-108.
19. van de Kerkhof PC, Hoffmann V, Anstey A, et al. A new scalp formulation of calcipotriol plus betamethasone dipropionate compared with each of its active ingredients in the same vehicle for the treatment of scalp psoriasis: A randomized, double-blind, controlled trial. *Br J Dermatol.* 2009;160(1):170-176.
20. Speight EL, Farr PM. Calcipotriol improves the response of psoriasis to PUVA. *Br J Dermatol.* 1994;130(1):79-82.
21. Bruner CR, Feldman SR, Ventrapragada M, Fleischer AB Jr. A systematic review of adverse effects associated with topical treatments for psoriasis. *Dermatol Online J.* 2003;9(1):2.
22. Veien NK, Bjerke JR, Rossmann-Ringdahl I, Jakobsen HB. Once daily treatment of psoriasis with tacalcitol compared with twice daily treatment with calcipotriol. A double-blind trial. *Br J Dermatol.* 1997;137(4):581-586.
23. Lehmann B, Querings K, Reichrath J. Vitamin D and skin: New aspects for dermatology. *Exp Dermatol.* 2004;13 Suppl 4:11-15.

ADDRESS FOR CORRESPONDENCE

Emil A. Tanghetti, MD
University of California, Davis Medical Center
5601 J Street
Sacramento, CA 95819
E-mail:.....et@dermatologyandlasersurgery.com