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Vitamin D analogs in the treatment of psoriasis

Where are we standing and where will we be going?

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Vitamin D and analogs exert in the skin and other tissues potent effects on cellular differentiation and proliferation. Moreover, these compounds regulate apoptosis and exert immunomodulatory effects. During the last decades, it has convincingly been shown that vitamin D compounds are effective and safe in the topical treatment of psoriasis, where they nowadays represent a standard therapy. This review summarizes laboratory and clinical investigations related to the treatment of psoriasis with calcitriol or analogs. Additionally, promising concepts for the development of new vitamin D analogs are discussed. As a matter of fact, the final goal to create strong antiproliferative or antiinflammatory acting vitamin D analogs that exert only minor calcemic activity has not been reached until today. New agents that may activate selective vitamin D signalling pathways but may exert only negligible calcemic activity would declare a new era in dermatologic therapy and may also be effective in the topical or systemic treatment of various inflammatory skin diseases including atopic dermatitis and in various cutaneous malignancies, including lymphomas, squamous cell carcinoma or basal cell carcinoma.

The Vitamin D Endocrine System (VDES) in Normal and Psoriatic Human Skin

In humans, vitamin D can be absorbed from the diet or synthesized in the skin from 7-dehydrocholesterol (7-DHC) after exposure to natural (solar) or artificial ultraviolet B (UVB) radiation.[1] At least nine enzymatic reactions are involved in the photochemical cutaneous synthesis of vitamin D, hereunder four photoreversible reactions and one non reversible phototransformation.[1,2] 1,25-Dihydroxyvitamin D ($1,25(OH)_2D$, calcitriol), a seco-steroidal hormone and the biologically active vitamin D metabolite, is synthesized from vitamin D by a well characterized biochemical reaction cascade. In a first step, vitamin D is hydroxylated in the liver in C-25 position by a cytochrome P450 enzyme, the vitamin D-25-hydroxylase (CYP27A1), before it gets hydroxylated a second time in the kidney in C-1 position by another cytochrome P450 enzyme, the 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) to generate the biologically active vitamin D metabolite $1,25(OH)_2D$.[1]

The synthesis of 1,25-dihydroxyvitamin D_3 in the kidney is regulated by a feedback-mechanism of the hormone itself, as well as by parathyroid hormone, calcium and cytokines like Interferon γ (IFNγ) or tumor necrosis factor α (TNFα).[1] In the 1970s it was generally accepted in the scientific community that the kidney was the only source of $1,25(OH)_2D_3$ production. However, during the last decades, in vitro and in vivo investigations (including studies on anephric humans) showed that various cell types including cultured human keratinocytes, monocytes, macrophages osteoblasts, prostate and colon cells, express the enzymatic machinery for the synthesis of $1,25(OH)_2D_3$, i.e., the 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1), and are thus able to synthesize 1,25-dihydroxyvitamin D_3.[1] In keratinocytes, studies could even prove the presence of both 1α-hydroxylase (CYP27B1) and 25-hydroxylase (CYP27A1).[1,3,4] According to these findings,[2,4] the keratinocyte is the only cell type known until today, that has the capacity to synthesize $1,25(OH)_2D_3$ from 7-dehydrocholesterol.

During the last decades, it has been shown that the skin itself is an important target tissue for $1,25(OH)_2D_3$,[5-8] that exerts genomic and non-genomic effects.[9] Non-genomic effects of calcitriol and analogs are mediated by effects on intracellular calcium.[10,11] In keratinocytes and various other cell types, calcitriol rapidly increases free cytosolic calcium levels.[10,11] Genomic effects of $1,25(OH)_2D_3$ are mediated via binding to a nuclear receptor protein, the vitamin D receptor (VDR).[9,12,13] In the skin, VDR is expressed in keratinocytes, fibroblasts, Langerhans cells, sebaceous gland cells, endothelial cells and most cell types related to the skin immune system.[14]

In vitro studies have revealed that $1,25(OH)_2D_3$ is highly effective in inducing terminal differentiation and in inhibiting proliferation of cultured human keratinocytes in a dose-dependent manner (**Table 1**).[5,15,16] Additionally, it acts on many cell types involved in immunologic reactions, including lymphocytes, macrophages and Langerhans cells (**Table 1**).[1,17-21]

Physiological and Pharmacological Actions of Vitamin D Analogs in Normal and Psoriatic Human Skin

Modulation of proliferation and differentiation in keratinocytes. Many in vitro and in vivo studies demonstrate

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Table 1. Selection of laboratory investigations demonstrating biological effects of $1,25(OH)_2D_3$ and analogs on skin and immune cells

Effect	Study type	Reference
At relatively low concentration ($<10^{-8}$ M), calcitriol promotes proliferation of keratinocytes; in contrast at higher concentrations ($\geq 10^{-8}$ M), keratinocyte proliferation is inhibited.	In vitro experiments	5, 15, 16, 22
Topical treatment with calcitriol or analogs (calcipotriol) exerts antiproliferative and differentiation-inducing effects in epidermal keratinocytes of lesional psoriatic skin.	Immunohisto-chemical in situ analysis of psoriatic skin	7, 8
In dendritic cells, calcitriol suppresses expression of MHC II molecules and of costimulatory molecules including CD40, CD80 and CD86. Production of IL-10 is stimulated and production of IL-12 is inhibited, leading to a suppression of T-cell activation.	In vitro experiments	17, 25
Vitamin D analogs suppress IgE-production and IgE-mediated cutaneous reactions.	In vitro experiments	28
Calcitriol induces the expression of the CCR-10 receptor on the surface of T-cells, which leads to a migration of these T-cells towards CCL-27-expressing epidermal keratinocytes.	In vitro experiments	20
Physiological concentrations of 1,25-dihydroxyvitamin D_3 generate in keratinocytes apoptosis-resistance against ceramides, ultraviolet radiation and tumor necrosis factor α (TNFα). In contrast, pharmacological concentrations of 1,25-dihydroxyvitamin D_3 ($\geq 10^{-6}$ M) induce apoptosis.	In vitro experiments	30, 31

dose-dependent effects of vitamin D analogs on cell proliferation and differentiation. At lower concentrations ($<10^{-8}$ M), $1,25(OH)_2D_3$ promotes proliferation of keratinocytes in vitro, at higher pharmacological doses ($\geq 10^{-8}$ M) keratinocyte proliferation is inhibited.[5,15,16] In psoriatic skin, immunohistochemical and biochemical analyses have demonstrated antiproliferative and pro-differentiating effects in epidermal keratinocytes along with treatment with $1,25(OH)_2D_3$ or analogs in vivo.[7,8] It has been shown that the immunohistochemical staining pattern for various markers of epidermal proliferation [e.g., proliferating cell nuclear antigen (PCNA), Ki-67-antigen] and differentiation (e.g., involucrin, transglutaminase K, filaggrin, cytokeratin 10) changes in lesional psoriatic skin along with topical treatment with $1,25(OH)_2D_3$ or analogs almost completely to the staining pattern characteristic for nonlesional psoriatic or normal skin.[7,8] Although the mechanisms that mediate the antiproliferative and pro-differentiating effects of vitamin D analogs on keratinocytes are not completely understood, it is well known that these effects are at least in part genomic and mediated via VDR. It has been demonstrated that keratinocytes from vitamin D receptor-deficient mice do not respond in vitro to the antiproliferative effects of vitamin D analogs.[22] It has been reported that $1,25(OH)_2D_3$ (10^{-8} m) suppresses the proliferation rate of wild-type keratinocytes maintained in low calcium (68 ± 3.6% of control), while in contrast, no modulation of proliferation is observed in keratinocytes from VDR null mice.[22]

At present, the molecular mechanisms by which vitamin D analogs regulate epidermal proliferation and differentiation are not completely understood. Major candidates for calcitriol target genes that may mediate $1,25(OH)_2D_3$-induced terminal differentiation in keratinocytes are components of the hedgehog signalling pathway and distinct cell cycle associated proteins (i.e., INK4 family), including p21/WAF-1.[23,24]

Immunomodulatory effects of $1,25(OH)_2D_3$ and analogs in human skin. Many cell types involved in immunologic reactions (e.g., monocytes, T-and B-lymphocytes, Langerhans cells) do not only express VDR, but moreover possess the enzymatic machinery [25-hydroxyvitamin D-1α-hydroxylase (CYP27B1)] for the local synthesis of $1,25(OH)_2D_3$.[1] This local synthesis of $1,25(OH)_2D_3$ in immune cells is considered to be of high importance for regulation and control of various immune responses. Today, it is known that $1,25(OH)_2D_3$ inhibits activation of T-cells and induces the generation of $CD25^+/CD4^+$ regulatory T-cells.[1,25] In dendritic cells, $1,25(OH)_2D_3$ inhibits maturation and induces a phenotype that promotes tolerance and inhibits immunity after stimulation with antigens (**Table 1**).[1,17,20,25] It also suppresses the expression of MHC II molecules and of costimulatory molecules including CD40, CD80 and CD86 in dentritic cells.[1,17,20,25] In these cells, production of IL-10 is stimulated and production of IL-12 inhibited, leading to suppression of T-cell activation.[1,17,20,25]

Impressive effects of vitamin D compounds were reported in animal models of and in diseases that are related with the function of T-cells or dendritic cells (experimentally induced allergic encephalomyelitis, collagen-induced arthritis, autoimmune thyreoiditis, diabetes mellitus type I, graft-versus-host reaction).[1] Furthermore, recent studies show that vitamin D deficiency may promote the pathogenesis of many autoimmune diseases like diabetes mellitus type I and that a sufficient vitamin D serum concentration may reduce the incidence of those diseases.[1] At present, a connection between vitamin D and pathogenesis of atopic dermatitis (AD) is discussed. Epidemiologic studies have indicated that patients with atopic dermatitis have a lower vitamin D intake as compared to controls.[26] More recently, a correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in children was reported.[27] In that study, mean serum levels of 25-hydroxyvitamin D were significantly higher ($p < 0.05$) in patients with mild disease.[27] The authors concluded that vitamin D deficiency may be related to the severity of AD and advocate the need for studies evaluating the use of vitamin D as a potential treatment in patients with this disease.[27] In line with these findings, it has been previously demonstrated that vitamin D analogs suppress in vitro IgE-production and IgE-mediated cutaneous reactions (**Table 1**).[28] These immunomodulatory effects identify vitamin D analogs, most likely new vitamin D analogs with more selective immunomodulatory activity, as promising new drugs for the prevention and therapy of inflammatory skin diseases including psoriasis, atopic dermatitis and allergic contact dermatitis.

New insights from the last years demonstrate that calcitriol induces the expression of the CCR-10 receptor on the surface of T-cells, which leads to a migration of these T-cells towards

CCL-27-expressing epidermal keratinocytes (**Table 1**).[20] This UVB-induced and vitamin D mediated T-cell mobilization from the blood vessels of the dermis into the epidermis characterizes another immunomodulatory effect of vitamin D compounds: an on-demand rising of the T-cell answer in the epidermis.[20] The clinical relevance of this function of vitamin D compounds is not totally clarified until now and remains subject of further studies.

In recent years, it was also shown that the vitamin D endocrine system is a potent regulator of the innate immune response.[1,18,19,29] Constant exposure to a wide variety of different microbial pathogens represents a major challenge for human skin.[29] Antimicrobial peptides (AMPs) are important mediators of cutaneous innate immunity, they protect primarily against microbial infections.[29] Cathelicidins were among the first AMPs identified in human skin and recent evidence indicates that they exert a dual role in innate immune defense:[29] At first, they are able to kill pathogens directly due to their antimicrobial activity.[29] Second, these peptides initiate a potent host response to infection causing cytokine release, inflammation and a cellular response.[29] Disturbed cathelicidin expression and function has been reported in several common inflammatory skin diseases, including psoriasis where cathelicidin peptide converts inert self-DNA and self-RNA into an autoimmune stimulus.[29] In atopic dermatitis reduced levels of cathelicidin facilitating microbial superinfections have been discussed.[29] Additionally, abnormally processed cathelicidin peptides were shown to promote inflammation and a vascular response in rosacea.[29] Until recently, the precise molecular mechanisms underlying cathelicidin regulation were unknown.[29] Recently, the vitamin D_3 pathway was identified as the major regulator of cathelicidin expression in human skin and other tissues.[29] It was demonstrated that the human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly upregulated in myeloid cells by 1,25-dihydroxyvitamin D_3.[1,18,19] These mechanisms are of high importance for the defense against infectious diseases, including tuberculosis. More recently, it was also shown that T-cell cytokines differentially control human monocyte antimicrobial responses by regulating vitamin D metabolism.[21] Consequently, therapies targeting vitamin D_3 signaling may provide new approaches for infectious and inflammatory skin diseases by modulating both innate and adaptive immune functions.[29]

Regulation of apoptosis. It has been demonstrated that physiological concentrations of 1,25-dihydroxyvitamin D_3 in keratinocyte cultures do not induce apoptosis but generate an apoptosis-resistance against ceramides, ultraviolet radiation and tumor necrosis factor α (TNFα) (**Table 1**).[30,31] Those antiapoptotic/cytoprotective effects of $1,25(OH)_2D_3$ are obviously linked to the production of sphingosine-1-phosphate. This hypothesis has been proven by the fact that the antiapoptotic effect of 1,25-dihydroxyvitamin D_3 can be completely suppressed by addition of the sphingosine kinase-inhibitor N,N-dimethylsphingosine.[30,31] In contrast, pharmacological concentrations of 1,25-dihydroxyvitamin D_3 ($\geq 10^{-6}$ M) do induce apoptosis. Dose-dependent differential effects have been also observed in the regulation of keratinocyte growth, where, as mentioned above, relatively low concentrations of 1,25-dihydroxyvitamin D_3 (around 10^{-11} M) stimulate cell proliferation, whereas higher concentrations of 1,25-dihydroxyvitamin D_3 have a dose-dependent antiproliferative effect.[5,15,16]

Biological effects of $1,25(OH)_2D$ and analogs in psoriatic skin. The precise mechanisms underlying the therapeutic effectiveness of vitamin D analogs in psoriasis are still not completely understood. Modulation of various markers of epidermal proliferation [proliferating cell nuclear antigen (PCNA) and Ki-67 antigen] and differentiation (involucrin, transglutaminase K, filaggrin, cytokeratins 10, 16) was shown in situ in lesional psoriatic skin after topical application of vitamin D analogs (**Table 1**).[7,8] Interestingly, the effects of topical treatment with vitamin D analogs on dermal inflammation are less pronounced (CD-antigens, cytokines, HLA-DR etc.,) as compared to effects on epidermal proliferation or differentiation.[7,8] This could possibly be explained by the fact that the bioavailability of topically applied vitamin D compounds in the dermal compartment may be markedly reduced as compared to the epidermal compartment.[7,8]

In lesional psoriatic skin, the clinical improvement correlates with an increase of VDR mRNA in $1,25(OH)_2D_3$ treated skin.[32] However, not all patients with psoriasis respond to treatment with vitamin D analogs: "responders" can be discriminated from "non-responders" by an increase in VDR mRNA in treated skin areas.[32]

From studies analyzing VDR expression and genotype in psoriasis,[33-40] some report a correlation between VDR expression or individual VDR genotypes and the skin eruptions of psoriasis, as well as with responsiveness to treatment with vitamin D analogs.[35] While no differences in VDR genotype between controls and psoriasis patients were reported at the BsmI site, some analyses reported significant difference in terms of ApaI SNP[35] and FokI SNP.[36] According to Colin et al. the FokI polymorphism is associated with the response to calcipotriol. Under conditions of vitamin D deficiency/insufficiency, this finding might have clinical implications. Other studies have shown that distinct vitamin D receptor genotypes are not associated with clinical response to calcipotriol.[37]

Data concerning serum levels of $1,25(OH)_2D$ or 25(OH) D in psoriatic patients are also conflicting. Some studies report reduced levels of $1,25(OH)_2D$ in patients with manifest psoriasis.[41] Additionally, the coincidence of pustular psoriasis with hypocalcemia[42] and the exacerbation of psoriasis along with chloroquin therapy [thereby reducing $1,25(OH)_2D$ levels via inhibition of 1α-(OH)ase (CYP27B1)] are well known.[43]

Clinical Use of Calcitriol and Analogs in Psoriasis

In 1985, MacLaughlin et al. reported that psoriatic fibroblasts were partially resistant to the antiproliferative effects of $1,25(OH)_2D_3$.[44] This laboratory finding prompted them to speculate that calcitriol may be effective in the treatment of the hyperproliferative skin disease psoriasis.

Another line of investigation was the result of a clinical observation. In 1985, Morimoto and Kumahara reported that an osteoporosis patient, who was treated orally with $1α-(OH)D_3$, had a remission of psoriatic skin lesions.[45] They demonstrated in

Table 2. Selection of clinical trials demonstrating safety and efficacy of $1,25(OH)_2D_3$ and analogs in the treatment of psoriasis

Effect	Study type	Reference
Treatment of psoriasis patients with calcipotriol ointment and cream reduces mean PASI (Psoriasis Area and Severity Index) scores by 55–72% and 49–50%, respectively after a treatment for 6–8 weeks.	Clinical trial	49, 55
Twice-daily application of calcipotriol cream is significantly more effective than once-daily application of calcipotriol cream in terms of the mean percentage reduction in PASI from baseline (48.3% vs. 40.6%, p = 0.006)	Randomized, double-blind, controlled trial	49, 55
Twice daily application of calcitriol 3 microg/g ointment in patients with mild to moderate chronic plaque-type psoriasis is non-inferior to calcipotriol 50 microg/g ointment for global improvement. Calcitriol applied twice daily over a 12-week treatment period demonstrated similar efficacy as compared to calcipotriol, while showing a significantly better safety profile.	Investigator-masked, randomized, multicenter trial	54
Maxacalcitol 25 μg/g has been reported as more effective than once-daily calcipotriol (50 μg/g).[51] The most common adverse event observed in psoriasis patients treated with maxacalcitol (6–50 μg/g maxacalcitol ointment), was a burning sensation in treated skin lesions. In three out of four patients developing this side effect in one study, symptoms were severe enough to recommend discontinuation of the treatment.	Clinical trial	51
Oral calcitriol is effective and safe in the treatment of psoriasis	Long-term follow-up study	46, 71
Calcipotriol solution is effective in the topical treatment of scalp psoriasis	Double-blind, randomized multicentric study	67–69

a follow up study that almost 80% of 17 patients with psoriasis who were treated orally with 1α-$(OH)D_3$ at a dose of 1.0 μg/day for up to 6 months showed clinically significant improvement.[46]

In the last years, numerous studies have reported that various vitamin D analogs, including calcitriol, calcipotriol, tacalcitol, hexafluoro-1,25-dihydroxyvitamin D_3 and maxacalcitol are effective and safe in the topical treatment of psoriasis (**Table 2**).[47-55]

Calcipotriol/calcitriol. Applied twice daily in amounts of up to 100 grams of ointment (50 μg calcipotriol/g ointment) per week, calcipotriol was shown to be slightly more effective in the topical treatment of psoriasis than betamethasone 17-valerate.[55] A mild dermatitis on the face has been reported as side effect in about 10% of patients treated with calcipotriol (50 μg/g) and was not reported after topical treatment with calcitriol.

Maxacalcitol. In one study, maxacalcitol 25 μg/g has been reported as more effective than once-daily calcipotriol (50 μg/g) (**Table 2**).[51] Allergic contact dermatitis to vitamin D analogs is very rare.[57-59] The most common adverse event observed in psoriasis patients treated with maxacalcitol (6–50 μg/g maxacalcitol ointment), was a burning sensation in treated skin lesions.[51] In three out of four patients developing this side effect in one study, symptoms were severe enough to recommend discontinuation of the treatment.[51]

Tacalcitol. Efficacy and safety of treatment with tacalcitol (4 μg/g and 20 μg/g) has been shown as well.[53,54,60] In one study, topical treatment with tacalcitol was generally well tolerated and there were no serious or unexpected adverse events reported. However, discontinuation of the treatment as a result of skin irritation was seen in 5.9% of the patients.[54] The greatest incidence of cutaneous side-effects occurred during initial treatment and decreased markedly as the treatment was well-tolerated with continued use.[54]

Concerning specific local-safety parameters of various vitamin D analogs including cumulative irritancy, cutaneous contact sensitization, photoallergic contact sensitization and phototoxicity the results of four separate studies were analyzed.[61] In that study, calcitriol (3 μg/g) ointment was classified as non-irritant compared to calcipotriol, tacalcitol and white petrolatum (control), petrolatum and tacalcitol were slightly irritant and calcipotriol was moderately irritant.[61] Using standard photoallergenicity testing methodology, no skin reactions of photoallergic nature were found.[61]

Combined topical treatment with calcipotriol ointment (50 μg/g) and betamethasone ointment was shown to cause less skin irritation and to be slightly more effective than calcipotriol used twice daily.[62]

It is a fact that patients with psoriasis may need intermittent treatment for their whole lives. It is now acepted that vitamin D analogs are effective and safe for the topical treatment of skin areas that are usually difficult to treat and that respond slowly.[63] They do not exhibit tachyphylaxis and topical treatment can be continued indefinitely. Additionally, they are effective in the treatment of psoriatic skin lesions in children and in HIV-patients.[64-66]

Treatment of face and flexures. In general, the use of calcipotriol ointment on face and flexures is not recommended due to irritancy. Nevertheless, most patients tolerate calcitriol or analogs on these sites. Calcitriol ointment (3 μg of calcitriol per gram of petrolatum) was found to be better tolerated and more effective than calcipotriol ointment (50 μg of calcipotriol per gram of petrolatum) in the treatment of psoriasis in sensitive areas.[63]

Treatment of scalp psoriasis. Calcipotriol solution has been shown to be effective in the topical treatment of scalp psoriasis (**Table 2**, reviewed in refs. 67–69), including a double-blind, randomized multicenter study.[67] 49 patients were treated twice a day over four weeks.[67] 60% of patients on calcipotriol showed clearance or marked improvement vs. 17% in the placebo group. No side effects were reported.

Treatment of nail psoriasis. Nails in general respond slowly and are very difficult to treat. Although it has been reported that calcipotriol ointment is effective in the treatment of nail psoriasis, there has been no consistently effective treatment for psoriatic nails up to now.[70]

Oral treatment with vitamin D and analogs. The efficacy and safety of oral calcitriol (**Table 2**) as a potential treatment of

psoriasis was demonstrated in a long-term follow-up study.[71] Of the 85 patients receiving oral calcitriol for 36 months, 88.0% had some improvement in their disease, while 26.5%, 26.3% and 25.3% had complete, moderate and slight improvement in their disease, respectively. To avoid its effects on enhancing dietary calcium absorption, it is very important to provide calcitriol at night time. Perez et al.[71] showed that as a result of this dosing technique along with maintaining a calcium intake of no more than 1 g/day, calcitriol doses of 2 μg to 4 μg/night are nicely tolerated by psoriatic patients.

Combination of vitamin D analogs with other therapies. Kragballe and coworkers reported that efficacy of topical calcipotriol treatment in psoriasis can be ameliorated by simultaneous ultraviolet-B phototherapy.[72] This therapeutic efficacy of UV-B in psoriasis may be at least in part due to an increased cutaneous vitamin D synthesis. Vitamin D analogs can be topically applied at any time up to two hours before or immediately after UV-radiation. The combination of topical treatment with vitamin D analogs and UV-radiation does not alter the tolerability or safety of therapy.[72,73]

Results of a controlled, right/left study have demonstrated that pretreatment of psoriasis with tacalcitol increases the responsiveness to 311-nm UV-B[74] and that tacalcitol ointment (4 μg/g) and 0.1% tazarotene gel are both comparably effective in improving the therapeutic result of PUVA (psoralen plus UV-A) therapy in patients with chronic plaque-type psoriasis.[75,76] Adverse reactions occurred more often with 0.1% tazarotene than with tacalcitol but were generally mild and completely reversible upon using a lower concentration of 0.05% tazarotene.[75] It has been concluded that both agents, besides accelerating the treatment response, might also help to reduce possible long-term hazards of PUVA treatment by virtue of their UV-A dose-sparing effect. A case report previously described two patients treated with a combination treatment of calcipotriol and bath psoralens and UV-A who developed hyperpigmentation at the lesional sites where calcipotriol ointment was applied.[77]

The efficacy of topical treatment with vitamin D analogs in psoriasis can also be increased by combination with other therapies: tumor necrosis factor α (TNFα)-inhibitors, methotrexate (MTX), low dose oral cyclosporine (2 mg/kg/day), oral acitretin, topical dithranol, topical steroids.[78-83] It has been shown for example that the combination of calcipotriol and MTX is safe and well tolerated and resulted in lower cumulative dosages of MTX compared with MTX and vehicle.[81]

As an outlook in the future, it can be assumed that the number of different vitamin D compounds, that will be used for the topical treatment of psoriasis, will continue to increase. Moreover, these compounds will be available in different formulations and in combination with corticosteroids and other agents.

Perspectives for the Evaluation of New Vitamin D Analogs with Less Calcemic Activity

For supraphysiological doses may be needed to reach clinical improvement, the use of vitamin D analogs in dermatology was considered decades ago to be limited since serious side effects, mainly on calcium metabolism, might occur. Consequently, it has been in recent years a major goal to synthesize new vitamin D compounds with strong immunosuppressive, antiproliferative and/or differentiating effects but only marginal effects on calcium metabolism. Although this major goal has still not been reached, clinical and laboratory findings during the last decades have now resulted in promising concepts.

A major break-through for the topical treatment with vitamin D analogs was the development of calcipotriol (calcipotriene, MC 903). Calcipotriol has similar VDR binding properties as compared to calcitriol, but has low affinity for the vitamin D binding protein (DBP). These properties result in strong effects in the target tissue skin and reduced unwanted systemic effects, when topically applied for the treatment of skin diseases. Consequently, calcipotriol is very effective and safe in the topical treatment of psoriasis.[49,62,63] In vivo studies in rats showed that effects of calcipotriol on calcium metabolism are 100–200x lower as compared to calcitriol, while in vitro effects on proliferation and differentiation on human keratinocytes are comparable.[84,85] Serum half-life in rats was shown to be 4 min after treatment with calcipotriol in contrast to 15 min after treatment with calcitriol.[84,85] The rapid degradation of calcipotriol after systemic administration has limited its oral use but made it an ideal drug for topical use.

Other promising approaches are: (1) The creation of new synthetic compounds that are metabolized in the skin and therefore exert only little systemic side effects. Vitamin D analogs, obtained by a combination of the 20-methyl modification with biologically interesting artificial side chain subunits or 2β-substituted calcitriols are promising candidates.[85-87] (2) Enhancing the local concentration of calcitriol in the skin without generating systemic side effects via inhibiting the cutaneous activity of vitamin D metabolizing enzymes, i.e., various hydroxylases [catabolic D_3-OHases, i.e., 24-hydroxylase (CYP24A1)] that are present in the skin and mediate the catabolism of calcitriol.[88,89] A well characterized inhibitor of CYP24A1 in the skin is ketoconazole.[88,89] It is a promising concept to enhance the concentration of endogeneous calcitriol locally in the skin by the topical application of these compounds without generating systemic side effects. (3) The synthesis of new vitamin D analogs that activate different vitamin D signaling pathways and may induce strong effects on cell proliferation and differentiation in the target tissues skin or immune system, but only marginal effects on calcium metabolism via different affinities for the various homo- or heterodimers of VDR and nuclear cofactors including RXRα.[90,91]

Conclusions

Vitamin D and its analogs exert in the skin and in other tissues various effects on cellular differentiation, proliferation, regulate apoptosis and act on the immune system. During the last decades, it has convincingly been shown that vitamin D compounds are effective and safe in the topical treatment of psoriasis, where they nowadays represent a standard therapy. However, the final goal to create strong antiproliferative or antiinflammatory acting vitamin D analogs that exert only minor calcemic activity has not been reached until today. These new agents that may activate selective

vitamin D signaling pathways but may exert only negligible calcemic activity would declare a new era in dermatologic therapy and may also be effective in the topical or systemic treatment of various inflammatory skin diseases including atopic dermatitis and in various cutaneous malignancies, including lymphomas, squamous cell carcinoma or basal cell carcinoma.

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