REVIEW ARTICLE

Vitamin D and its Analogs: Dermatologic uses

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ABSTRACT

Vitamin D is of particular interest to dermatologists for two main reasons: it is synthesized in the skin, and is an important treatment option for psoriasis and other skin diseases. It has long been recognized for having a major role in the metabolism of calcium and phosphorus as well as in building and maintaining healthy bones. More recent research has demonstrated the possible effects of vitamin D on other important diseases, including cancer. The physiologically active form of vitamin D is known as calcitriol. Several topical vitamin D_3 analogs (e.g. calcipotriol, tacalcitol and maxacalcitol) are recognised. Psoriasis is the main indication for their use; however they are now being used increasingly in numerous non psoriatic dermatological diseases.

KEYWORDS: Vitamin D, calcipotriol, tacalcitol, maxacalcitol, psoriasis

INTRODUCTION

Vitamin D is a fat-soluble nutrient that human beings obtain from diet, and also synthesize in skin following the exposure to UVB.[1] There are two forms of dietary vitamin D available: Vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Vitamin D_2 and vitamin D_3, whether obtained from diet or synthesized in skin following sunlight exposure, are prohormones and need to be converted in the liver to the major circulating form of vitamin D, 25-hydroxyvitamin D, also called calcidiol. Circulating calcidiol is then converted into calcitriol (1, 25-dihydroxyvitamin D_3), the biologically active form of vitamin D, either in the kidneys or by monocyte-macrophages of the immune system.[2] The physiologically active form of vitamin D mediates its biological effects by binding to the vitamin D receptor (VDR), that is mainly present in the nuclei of different target cells. After binding to the VDR, calcitriol causes a conformational change in the VDR that allows VDR binding to the retinoid X receptor (RXR). The binding of VDR/RXR complex to a specific sequence in the vitamin D-responsive element (VDRE) changes the gene transcription of transport proteins (such as TRPV6 and calbindin) either by increase or decrease. These proteins are involved in absorption of calcium in the intestine.[3]

VDR ligands have been shown to cause stimulation of natural killer cells and enhancement of the phagocytic activity of macrophages. In addition, vitamin D_3 has an effect on adaptive immune system concerning T cell activation and maturation of dendritic cells.[4]

Active vitamin D hormone also increases the production of antimicrobial peptide (AMP) cathelicidin, which is produced in macrophages triggered by bacterial, viral, and fungal infections.[5]

Vitamin D_3 analogs:

Topical vitamin D_3 was approved by U.S. Food and Drug Administration (FDA) for treatment of plaque psoriasis in 1994. Advances in the understanding of its effects have led to its usage in numerous other skin diseases.[6] Several vitamin D analogs (e.g. calcipotriol, tacalcitol and maxacalcitol) are recognised. Their biological effects are mainly due to the hydroxyl groups in the C1 position and in the side-chain.[7]

Topical vitamin D analogues have an antiporolif-

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erative effect, through the inhibition of keratinocytes growth and differentiation and also an anti inflammatory effect. These effects are made through binding with VDR on keratinocytes and T lymphocytes respectively.[8] Calcipotriol and tacalcitol are available in Europe, while calcipotriol is the only used Vitamin D analog in North America. Maxacalcitol is only offered in Japan.[7]

Calcipotriol

Calcipotriol is a synthetic analogue of 1, 25-dihydroxyvitamin D_3. Although they have the same pharmacological properties, calcipotriol is preferred over calcitriol. It is less liable to cause hypocalcaemia because it is rapidly metabolised after topical application.[9] Similar to other vitamin D analogs, it has antiproliferative, anti-inflammatory[10] and immunomodulatory effects.[11] It is commercially available as; Daivonex (in Asia), Dovonex (in USA) and Psorcutum (in Europe), in the form of 50ug/g (0.005%) ointment, cream and solution.

Dermatological uses:

Studies have demonstrated the effectiveness of topical calcipotriol in the treatment of several skin disorders (Table 1). Its potential clinical applications continue to broaden with further knowledge of the mechanism by which vitamin D_3 functions.[6]

Psoriasis

In recent years calcipotriol, has become one of the most widely prescribed treatments for psoriasis. It significantly lowers scores for severity of skin erythema, thickness and scaling. The mechanisms behind the antipsoriatic actions are not completely understood.[12] Calcipotriol binds to the VDR and acts as a heterodimer with the retinoid X receptor (RXR).[13] It induces terminal differentiation, inhibits epidermal proliferation and angiogenesis seen in psoriasis; also induces apoptosis in inflammatory cells and causes a shift from Th1 cytokines to Th2 cytokines.[14,15] It can also modulate the inflammatory process in psoriasis by decreasing the levels of interleukin-1 (IL-1)[16] and IL-6[17] and by reducing the CD45 RO and $CD8^+$ T cells. Moreover, it increases the levels of transforming growth factor-β1 (TGF-β1) and β2, which inhibit the epithelial cell growth.[18] It changes AMP expression in keratinocytes in lesional psoriatic skin. As AMPs act as proinflammatory "alarmins" and play a role in psoriasis pathogenesis, targeting their expression might be beneficial in treatment of this disease.[19]

For the treatment of psoriasis vulgaris, calcipotriol ointment 50 μg/g (no more than 100 g per week) should be applied to affected areas (≤30% of the body surface) twice daily for a recommended period of 4 weeks. After that, it can be applied once daily.[20] Calcipotriol scalp solution 50μg/ml is applied once or twice daily. The dose is slightly less with scalp solution.[21] Because of the risk of facial dermatitis, calcipotriol should not be applied to the face, and patients should wash their hands thoroughly after ointment application to prevent unwanted transfer from hands to face.[22]

Twice-daily calcipotriol is more efficacious than short-contact anthralin[23], tar[24], fluocinonide ointment[25] and is at least as efficacious as betamethasone 17-valerate 0.1% ointment.[26]

Other forms of psoriasis

Although the FDA has approved topical calcipotriol for plaque-type psoriasis, studies have shown calcipotriol to be effective in other forms of psoriasis as well. It has been found to be effective in the treatment of intertriginous and nail psoriasis.[27]

Several case reports have indicated that calcipotriol may be beneficial in the treatment of pustular psoriasis and its variants.[28] Case studies with calcipotriol for the treatment of acrodermatitis continua of Hallopeau, which many consider to be a variant of pustular psoriasis, are promising.[29] In contrast, there was a case report in which a patient with plaque-type psoriasis developed generalized pustular psoriasis after using calcipotriol for 2 weeks.[30]

Table 1 Use of calcipotriol in some dermatological diseases

Disease	Type of study	Effects
Psoriasis Vulgaris	Randomized controlled studies Randomized, double-blind, right/left comparative study.	Calcipotriol is effective as monotherapy Calcipotriol is more efficacious than short-contact anthralin, fluocinonide ointment and as efficacious as betamethasone 17-valerate
Other forms of psoriasis	Uncontrolled and open trial (12) patients with intertriginous psoriasis Double-blind, randomized study (nail psoriasis) Case reports (pustular psoriasis)	Improvement of all patients Improvement of subangual hyperkeratosis Improvement in all patients
Vitiligo	Randomized, double-blind, right/left comparative study. Prospective trial of calcipotrion in conjunction with PUVA	Marked improvement and faster repigmentation compared with placebo Excellent or good response in 6 of 21 patients
Erythema annulare	Case report	Complete disappearance of lesion after 3-months treatment
Lichen amyloidosis	Double blind right-left comparative pilot study	The response to calcipotriol was comparable to betmethasone valerate
Giant viral wart	Case report	Complete disappearance after 2 months of twice calcipotriol daily application.
Acanthosis nigricans	Case report	Slight clinical improvement in roughness and hyperkeratosis
Confluent and reticulated papillomatosis	3 case reports	Improvement in all patients
Ichthyosis	Randomized, double-blind, vehicle controlled, right/left comparative study	Improvement in congenital and sex linked ichthyosis, no improvement in acquired type
Netherton's syndrome	Case report	Significant improvement of erythema and scalling after 2 weeks
Sjogren Larsson Syndrome	Case report	Reduction in symptoms after 2 weeks treatment
Grover's disease	2 case reports	Calcipotriol was effective in both patients
Heriditary epidermolytic palmoplantar keratoderma	Bilaterally paired comparative study with urea	Substantial improvement in favor of the calcipotriol-treated hand
ILVEN	4 case reports (2 children, 2 adults)	Improvement of all patients
Kaposi sarcoma	Case series (8 patients)	4 patients showed no response and 4 showed 50% reduction in size
Keratosis lichenoides chronica	Case report	Marked clinical improvement
Pityriasis rubra pilaris	Case report	Patient with adult PRP showed improvement and patient with juvenile PRP discontinue due to irritation.
Prurigo nodularis	Randomized, prospective, double blind, right/left comparative trial	Calcipotriol was superior to betamethasone in reducing the number and size of nodules.
Morphea	Open-label study (12 patients)	Significant improvement in all patients
Actinic porokeratosis	Case study (3) patients	Improvement in 2 patients only
T-cell lymphoma	Case report (angio-immunoblastic type)	Remission after 2 months of treatment but relapse later on.

Vitiligo

Calcipotriol has recently been shown to cause repigmentation in vitiligo when used as a monotherapy or in combination with PUVA (psoralen + ultraviolet A). Several studies reported a secondary hyperpigmentation effect when calcipotriol is combined with PUVA or NB-UVB therapy in psoriasis.[31] Furthermore, vitamin D and its chemically engineered analogs are thought to control multiple intracellular pathways concerning melanin synthesis and melanocyte survival. All these findings encouraged clinicians to study the effects of vitamin D analogs in treatment of vitiligo, thus opening new era in treatment of depigmentation. It is better to use calcipotriol after UVA exposure because calcipotriol concentration can be significantly decreased when used before UVA exposure by about 2% to 75%.[32]

Combination treatment with corticosteroids in vitiligo was found to be significantly superior to either treatment given alone. First, a rapid response is obtained. Second, combination treatment results in a better stability of the repigmentation obtained. Third, combination treatment also seems to decrease the incidence of the local adverse effects of topical corticosteroids when used alone.[33]

The exact mode of action of calcipotriol in vitiligo is not yet known. Topical calcipotriol has been known to express vitamin D_3 receptors in skin (keratinocytes) and it was suggested that vitamin D_3 is involved in the regulation of melanin synthesis by melanocytes. This may be a possible mode of action of calcipotriol.[34] The mechanism by which vitamin D can regulate melanin synthesis may be through either regulation of melanocyte proliferation and function or modulation of T lymphocytes activity and synthesis of some cytokines e.g. TNF-α and IFN-γ.[35]

Furthermore, vitamin D is known to have antioxidant properties and regulatory function of the ROS. This could be another possible mechanism of action by the protection of vitiliginous skin from ROS that are excessively produced in vitiligo. Moreover, calcipotriol may be effective treatment of vitiligo through the modification of the defective calcium homeostasis in melanocytes and keratinocytes.[36]

Erythema annulare centrifugum (EAC)

Calcipotriol is thought to be efficacious in treatment of EAC as it inhibits keratinocyte hyperproliferation, regulates epidermal differentiation, suppresses cutaneous inflammation which are the main processes that contribute to the development of EAC.[37]

Lichen amyloidosis

In their pilot study, Koo *et, al*, suggested that twice-daily application of calcipotriol ointment was as effective as betamethasone 17-valerate ointment in treatment of lichen amyloidosis. As in psoriasis, calcipotriol inhibits the epidermal hyperproliferation and hyperkeratosis and this results in reduction in roughness and hyperpigmentation of skin lesions. However, the magnitude of reduction is usually too small to be apparent clinically. The authors suggested that betamethasone 17-valerate ointment remains of choice in treatment of lichen amyloidosis as it is less expensive and non irritant in contrast to calcipotriol.[38]

Giant viral wart

Topical vitamin D_3 derivatives have shown effectiveness for HPV-related diseases[39] using an occlusive dressing, and also for recalcitrant warts

in immunocompromised patients.[40] Labandeira *et, al*[41] reported a patient with a giant viral wart that healed after simple application of calcipotriol cream, without recurrence during 6 years of follow-up. The efficacy of vitamin D_3 derivatives for treating warts may be through their biologic actions including regulation of epidermal cell proliferation and differentiation and modulation of cytokine production. [41]

Acanthosis nigricans

No randomized controlled studies are available concerning the use of calcipotriol in treatment of acanthosis nigricans. There is a report of a 60-year-old man who had a history of transitional cell carcinoma of the bladder and developed acanthosis nigricans in the hands, forearms, groin, neck and axillae. After twice-daily application of calcipotriol cream for 3 months, the patient showed improved clinical response with reduction in papillomatosis and hyperkeratosis of the treated sites.[42] Lee *et, al*., recently suggested that calcipotriol is also a simple, cheap and good agent for treatment of hyperkeratosis of the nipple associated with acanthosis nigricans.[43]

Confluent and reticulated papillomatosis

Confluent and reticulated papillomatosis (CRP) consists of flat, brown papules localized primarily to the intermammary and interscapular regions. There are many reports[44-46] describing the efficacy of calcipotriol ointment in CRP. Calcipotriol was applied twice daily for 3-4 weeks. The etiology of this disease is unknown; however, the response to calcipotriol appears to support the theory that it is a disorder of keratinisation.[6]

Ichthyosis

Congenital ichthyosis is a group of disorders of keratinisation characterized by hyperproliferation. Controlled studies have demonstrated the therapeutic benefit of calcipotriol in congenital ichthyoses.[28]

The recognition of the modulatory effect of vitamin D_3 on epidermal differentiation and proliferation has created interest in its potential use in diseases with defects in cornification. In a randomized, double-blind, vehicle-controlled, right/left comparative study, the efficacy of calcipotriol in certain disorders of keratinization was determined. The multicenter investigation included patients with ichthyosis vulgaris, congenital ichthyoses (epidermolytic hyperkeratosis, lamellar ichthyosis, ichthyosis linearis circumflexa, and congenital ichthyosiform erythroderma), X-linked ichthyosis, hereditary palmoplantar keratoderma, keratosis pilaris, and Darier's disease.[47]

There was statistically significant improvement in those patients with congenital ichthyoses and those with X-linked ichthyosis. Although ichthyosis vulgaris was responsive, it was not statistically significant. Keratosis pilaris and palmoplantar keratoderma appeared to be unresponsive. None of the patients developed hypercalcaemia. Therefore; it appears that vitamin D_3 may be advantageous in treatment of certain disorders of keratinization.[48]

Netherton's syndrome

Topical calcipotriol ointment was well-tolerated and effective in the treatment of NS in a 9-year-old boy with twice daily application of topical 0.05% calcipotriol ointment. Skin lesions showed significant reduction of erythema and scaling after two weeks of the treatment, and a total remission was obtained one week later.[49]

Sjogren Larsson syndrome

It is a rare, autosomal recessive inherited disorder. Lucker *et, al*[50] studied the effect of twice daily application of calcipotriol ointment for 12 weeks in 2 patients with Sjogren Larsson syndrome. They suggested that calcipotriol might be a considered for the treatment of ichthyosis present in Sjogren-Larsson syndrome.

Grover's disease

Grover's disease (transient acantholytic dermatosis) is characterized histologically by the presence of acantholytic cells in epidermis. There are some reports that showed a successful treatment of Grover's disease with calcipotriol.[51] The mode of action of vitamin D_3 in Grover's disease is still unknown.[52]

Heriditary Epidermolytic Palmoplantar Keratoderma

Lucker *et, al*[53] described an adult male patient suffering from hereditary palmoplantar keratoderma. This patient was treated with calcipotriol ointment on one side of the body and urea 40mg/g twice daily on the other side for 3 months. At the end of the study, calcipotriol-treated side showed more improvement of skin lesions.[53]

Inflammatory linear verrucous epidermal nevus (ILVEN)

Several investigators have reported the efficacy of calcipotriol in the treatment of inflammatory linear verrucous epidermal nevus.[54] In one report, a 5-year-old boy with inflammatory linear verrucous epidermal nevus on the right side of his trunk and lower extremity applied the medication twice daily. During a 12-week period, there was flattening of the lesions and a reduction in pruritus. Laboratory results did not reveal hypercalcaemia.[54] There have also been reports of successful treatment of ILVEN in adults.[55,56] The advantageous results raise the question of whether inflammatory linear verrucous epidermal nevus is a linear variant of psoriasis.[6]

Kaposi sarcoma (KS)

KS is a multisystem vascular neoplasia that occurs predominantly in men who are in some degree of immunocomprossion. Vitamin D_3 receptors were shown to be expressed at high levels in KS cells. Calcipotriol was reported to cause reduction of KS lesions in 50% of patients treated with twice daily application of calcipotriol ointment for about 4 weeks.[57]

Keratosis lichenoides chronica

Keratosis lichenoides chronica, considered to be a rare variant of lichen planus, may be responsive to topical calcipotriol. Case studies of the use of calcipotriol for this rare dermatosis are promising.[58, 59] In one report of a 53-year-old patient, once-daily application of calcipotriol for 4 months proved to be efficacious. The mechanism of action of calcipotriol is not clear. It is believed; however that it causes the suppression of lymphocytes proliferation by decreasing IL-1 and IL-8 and the induction of terminal differentiation and inhibition of proliferation of keratinocytes.[58]

Pityriasis rubra pilaris (PRP)

Because of the clinical and histologic similarities between psoriasis and PRP, it would be logical to conclude that calcipotriol would be useful in PRP.[6] Case reports have indicated the potential use of calcipotriol in the treatment of PRP. In two patients with classic juvenile PRP and one patient

with atypical adult-onset pityriasis rubra pilaris, the application of calcipotriol ointment resulted in clinical improvement. One patient with classic juvenile PRP discontinued treatment because of irritation caused by the drug.[60] Controlled studies are required to determine the therapeutic role of calcipotriol.

Prurigo nodularis

Prurigo nodularis is characterized by epidermal proliferation and pruritic nodules on the distal extremities.[28] Vitamin D_3 analogues may be advantageous in the management of prurigo nodularis. Both tacalcitol and calcipotriol appear to be effective therapy for prurigo nodularis.[61,62] In a randomized, prospective, double blind, right/left comparative trial, calcipotriol ointment was found to be superior to betamethasone ointment in reducing the number and size of nodules.[62] Calcipotriol may be more effective treatment than steroid therapy, with the former clearing the prurigo nodules more rapidly. Furthermore, calcipotriol doesn't have the same cutaneous and systemic adverse effects associated with chronic steroid therapy. The mechanism of action of calcipotriol in the treatment of prurigo nodularis is not yet certain.[62]

Morphea

Morphea is a localized form of scleroderma. It is characterized by increased deposition of dermal collagen and increased T cell activation with elevation of serum IL-2 receptor level.[28] Calcitriol was previously tried with some success in patients with systemic scleroderma.[63] This gave the idea of using topical vitamin D analogs in treatment of morphea. Cunningham *et, al*[64] found calcipotriol ointment to be effective in treatment of skin lesions of morphea when applied twice daily under occlusion.

The mechanism of action of calcipotriol in the treatment of morphea is unknown; however, immunomodulatory function of calcipotriol may play a role. The inhibition of IL-2 and other mediators of activated T cells by calcipotriol may contribute to its therapeutic benefit in morphea.[63] In addition calcipotriol has significant effect on cultured fibroblasts resulting in inhibition of cell proliferation which may be another mechanism of action.[63]

Disseminated Superficial Actinic Porokeratosis

In one report, 3 patients with disseminated superficial actinic porokeratosis were treated with topical calcipotriol ointment daily. Improvement varied between 50% and 70% and was maintained for 2 to 6 months in 2 patients.[65]

T-cell lymphoma

One report described the treatment of T-cell lymphoma with topical calcipotriol.[66] A patient with high-grade angioimmunoblastic T-cell lymphoma entered remission with treatment, but relapsed later on. Vitamin D_3 and related compounds exert an antitumour effect by suppressing the production of growth promoting lymphokines, such as IL-2 by activating T lymphocytes and IL-1 by monocytes thereby inhibiting T-cell proliferation.[66] They also exert direct inhibitory effect on immunoglobulin synthesis by activated B lymphocytes and indirectly by inhibition of T-helper cells. These effects may be mediated through VDR.[28]

Miscellaneous dermatoses

Topical calcipotriol has been found to be effective in some dermatological diseases such as extragenital lichen sclerosus[67], seberrheic dermati-

tis[68], Darier's disease[69], Flegel's disease[70], peeling skin syndrome[71], oral leukoplakia[72] and cutaneous metastatic breast cancer.[73]

Side effects

Overall, vitamin D analogues are tolerated well; the most common adverse effect reported in literature is a mild irritant contact dermatitis.[74] In more severe cases, erythema and scaling are present. The face is particularly sensitive to calcipotriol. Facial irritation may be seen not only after local application, but also after transfer of calcipotriol ointment applied elsewhere. Facial irritation can almost always be avoided if the face is not treated, and if the patients are instructed to wash hands after applying the ointment.[75,76] In a patch-test study, calcipotriol was confirmed to be a weak irritant. Unfortunately, it is not possible to predict which patients will become irritated by calcipotriol. Hypercalcaemia has also been reported, but this appears inconsequential in treatment doses.[77]

Safety

The effect on calcium and bone metabolism is the main concern in adjusting the dose of calcipotriol. In different short-term and long-term clinical trials, there was no change in serum calcium levels when the patients were treated with 100 g or 120 g calcipotriol ointment per week. Only one patient showed elevation of serum calcium after application of very high doses of calcipotriol ointment (approximately 400 g during 10 days) that is, about 3 times the amount permitted for use of calcipotriol. There is another report of a patient who had a moderate degree of renal impairment and developed hypercalcaemia with excessive use of calcipotriol ointment.[78]

Thus, it is suggested that treatment with calcipotriol ointment is safe when used in adequate amounts (up to 100 g per week). When the patients are in need to be treated with greater amounts of ointment, it is advisable to monitor serum parathyroid hormone levels (PTH). Any decrease in serum PTH can adequately indicate a change in calcium homeostasis, in contrast to estimation of serum calcium which is not sensitive enough to changes occurring in calcium metabolism.[79]

Calcipotriol as well as the other vitamin D analogues are not teratogenic when used during pregnancy. Calcipotriol treatment should be stopped, if pregnancy occurs but there is no need to terminate pregnancy. There is also no exact data concerning the excretion of calcipotriol in milk or its use during lactation.[79]

Contraindications

Calcipotriol is contraindicated for use in patients suffering from hypercalcemia, hypercalciuria, urolithiasis, parathyroid disease, photosensitivity; pregnant and lactating females; and also patients who concomitantly use vitamin D or calcium or any other drug that affects calcium metabolism.[80]

Tacalcitol

Tacalcitol [1, 24(OH) D] is another synthetic vitamin D analogue developed for topical use in psoriasis. The analogue 1, 24$(OH)_2$ D is equipotent with 1,25$(OH)_2$ D, in its affinity for the VDR and in its capacity to inhibit keratinocyte proliferation and to stimulate keratinocyte Differentiation in vitro. Also, tacalcitol is as effective as 1, 25$(OH)_2$ D in increasing cytosolic calcium levels in cultured keratinocytes.[81]

Although tacalcitol may be advantageous over 1, 25$(OH)_2$ D, for clinical use, it is much less selective than calcipotriol in its effects on calcium

metabolism. Tacalcitol ointment 2pg/g and 4pg/g was reported to improve psoriasis in an open-label study. In a subsequent controlled study, in which patients applied tacalcitol ointment twice daily to a single lesion for 4 weeks, a concentration of 2pg/g was superior to 1pg/g and as effective as 4pg/g. In another dose finding study, tacalcitol ointment was applied once daily to $2cm^2$ areas of lesional psoriasis for 4 weeks. When different body regions were treated with tacalcitol ointment 2 pg/g, the treatment was more effective on the face than on other skin areas.[79]

There is limited knowledge about the efficacy of tacalcitol compared with topical antipsoriatic agents. Apparently treatment with tacalcitol ointment 2pg/g twice daily is as effective as hydrocortisone-butyrate, but slightly less effective than betamethasone 17-valerate. Used at a low concentration (2pg/g), tacalcitol ointment is well tolerated, and skin irritation is uncommon.[82]

Regarding safety, hypercalcaemia was not observed in 2 studies that included 210 patients. However, there is no information on the amount of tacalcitol ointment used by these patients. In a smaller study that included 12 patients, an average cumulative dose of 340pg (approximately 42 g of tacalcitol ointment 2pg/per week) did not increase serum calcium levels. There is no information available on the more sensitive markers of calcium metabolism (24-hour calcium excretion and serum PTH) during tacalcitol therapy.[83]

Maxacalcitol

Maxacalcitol (22-oxacalcitriol), a vitamin D_3 analogue, is widely used for the treatment of psoriasis in Japan.[84] It has an excellent safety profile. However, for some patients whose skin lesions do not respond well to topical vitamin D_3 treatment alone, we need to consider a combination therapy to get the maximum improvement with the minimum adverse effect.[85]

Although it is an effective treatment for psoriasis vulgaris, systemic calcium homeostasis might be affected at the upper limits of the maximal recommended doses (10 g/day). Calcipotriol has advantages over maxacalcitol to combine with narrow band UVB in treatment of psoriasis regarding the narrow-band UVB-accumulated treatment dose and improvement rate of psoriasis area and severity index (PASI) scores.[86] Vitamin D_3 analogues, tacalcitol, calcipotriol, and maxacalcitol, suppress keratinocyte proliferation and induce differentiation with similar potency.[87]

CONCLUSION

Vitamin D analogs are effective in treatment of dermatoses characterized by hyperproliferation and impaired terminal cell differentiation by an immunologic mechanism and regulation of intracellular calcium concentration. Multiple studies have demonstrated the exciting potential uses of topical vitamin D_3 analogs in different skin diseases in addition to plaque-type psoriasis. Further research into the mode of action of vitamin D_3 could create new indications for the topical vitamin D_3 analogues.

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