

Profile of clinical efficacy and safety of topical tacalcitol

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Abstract. Several topical treatments such as ointments, keratolytics, dithranol, tar, corticosteroids and Vitamin D₃ analogues are commonly used in the treatment of mild and/or moderate psoriasis. These treatments can be associated with a variety of local and systemic side effects, as well as to very often unsatisfactory results. The purpose of this critical review of the literature is to evaluate the efficacy and tolerability of the synthesis of new analogues of the Vitamin D₃ Tacalcitol, which is formulated in ointment form at a concentration of 4 µg/g, for the treatment of mild and/or moderate psoriasis (involvement of <20% of the surface of the skin) and to evaluate whether this drug can be used in the treatment of other skin conditions. Based on existing data in the literature, Tacalcitol is an effective drug for the topical treatment of psoriasis and is also able to ensure that the effects last over time, even after treatment has stopped. Tacalcitol is also well tolerated because the onset of side effects, such as local irritation, pruriginous or burning sensations, were reported in only a small percentage of the subjects who were treated. Lastly, the marked regulatory effects it has on the proliferation and differentiation of keratinocytes, as well as on the immunocompetent cells, has led to suggestions that Tacalcitol may be used in other keratinisation disorders and in some hyperproliferative skin diseases. Evaluation of the effective indications to use in these conditions still requires further data confirming its effectiveness, opening the way to wider use of this molecule in dermatology.

Key words: Topical treatment, vitamin D₃ analogues, psoriasis, vitiligo

Introduction

Psoriasis is a chronic, recurrent skin disease which is characterised by erythematous, flaky patches and/or plaques of varying sizes, usually situated at the elbows, the knees, the lumbar-sacral region and on the scalp. Recurrences of psoriasis can be triggered by different factors such as infections, trauma, stress and drugs such as β-Blockers, ACE inhibitors, anti-malarials, lithium and indomethacin (1-3).

Topical treatment of psoriasis is of fundamental importance because it is the elective treatment in localised forms of the disease with a small number of lesions (involving <20% of the surface of the skin), as well as integrating systemic treatment for the serious and diffuse forms. A variety of topical treatments are available, such as emollients, cheratolytics, tar, dithra-

nol, corticosteroids and vitamin D₃ derivatives (Table 1), for the purpose of improving the scaliness, inhibiting the inflammation and influencing the complex immunological reactions that are at the root of the aetiopathogenesis of this disease. The disadvantages of using many of the drugs that are currently available for the topical treatment of mild to moderate psoriasis, are mainly the onset of local and systemic side effects and results that are unsatisfactory at times (4).

The recent introduction of Tacalcitol, a synthetic analogue of vitamin D₃, has provided a further therapeutic possibility. The physiologically active metabolite of vitamin D₃, calcitriol, is involved in the regulation of plasma phosphorus and calcium levels and in the homeostasis of bone tissue. It acts on the skin by modulating growth of the epidermis, keratinisation and the inflammatory response, via the link with a

Table 1. Topical drugs most frequently used in the treatment of mild and/or moderate psoriasis

Category	Name of drug
Corticosteroids	Betamethasone dipropionate – class I Clobetasol - class I Mometasone furoate – class IV Betamethasone valerate - class V Hydrocortisone butyrate - class V Methylprednisolone aceponate – class VII
Acetylenic retinoids	Tazarotene
Coal Tar	Alphosyle
Keratolytics	Salicylic vaseline 5-10% Urea 10-30%
Dithranol	
Vitamin D ₃ derivatives and analogues	Calcipotriol Tacalcitol Calcitriol

specific intercellular receptor (VDR) that belongs to the family of steroid receptors and can be identified in the keratinocytes and fibroblasts in the human dermis (5-6). The use of calcitriol in the topical treatment of psoriasis, a disease that is characterised by an increase in the epidermal cell turnover and by a marked hyperkeratosis, is however limited by the effects on calcium metabolism, or hypercalcinuria, hypercalcaemia, nephrocalcinosis, nephrolithiasis and soft tissue calcinosis.

However, whereas the synthetic analogues of vitamin D₃, particularly Tacalcitol, have the same effectiveness in the regulation of cell proliferation and differentiation, it does not interfere with the phosphocalcine homeostasis (7-8).

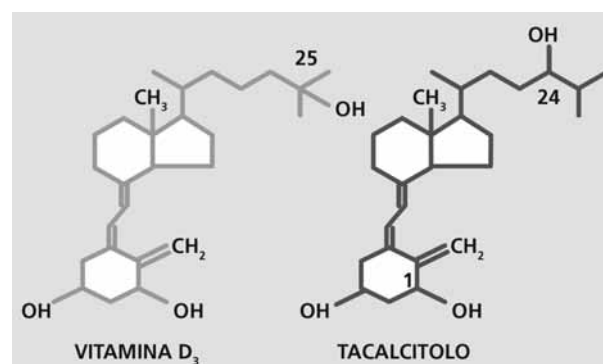
The only structural difference between Tacalcitol and calcitriol is the hydroxylation in position 24 instead of position 25 (Figure 1). Apart from the above-mentioned structural characteristics, Tacalcitol has several biological properties in common with vitamin D₃.

Tacalcitol's affinity for bonding with murine epidermal receptors (VDR) has been shown to be the same as that of calcitriol, whereas in a culture of human keratinocytes, Tacalcitol shows a greater affinity for bonding with the VDR than calcitriol has, inhibiting proliferation and inducing differentiation of the keratinocytes. The influence of Tacalcitol on the phospho-

calcine metabolism is however markedly lower compared with that of vitamin D₃ (9-10).

It has also been demonstrated that single or repeated applications of Tacalcitol leads to systemic absorption through the skin affected by psoriasis of a quantity of the drug less than 0.1% of the dose applied: pharmacokinetic parameters cannot be evaluated from these quantities. Studies conducted in vivo have shown that Tacalcitol bonds completely to the plasma proteins and that its metabolites are excreted mainly through the urine and faeces (11).

Tacalcitol has been formulated in Europe as an ointment with a concentration of 4 µg/g and dosage instructions give a single daily application for a maxi-

**Figure 1.** Structure of vitamin D₃ and Tacalcitol

imum length of treatment that is even longer than 8 consecutive weeks (12). Numerous short and long term clinical trials which have involved a large number of patients for varying periods of time have confirmed the efficacy of Tacalcitol as first-line monotherapy in the topical treatment of psoriasis (13).

Clinical studies: evaluation of efficacy and tolerability

The efficacy of Tacalcitol ointment in the treatment of vulgar psoriasis has been demonstrated by many clinical trials.

In 1996, Van de Kerkhof and collaborators reported the results of a multicentre, double blind study conducted on 122 patients with a mild and moderate degree of psoriasis, between Tacalcitol ointment at a concentration of 4 µg/g and a placebo, applied once a day for 8 weeks. The thickness of the plaques, the desquamation and the erythema were evaluated at each check-up. Therapeutic efficacy was classified as I) complete resolution of lesions II) Excellent response (75-99%) and III) good response (improvement to 50-74% of the lesions). With Tacalcitol, the improvement in the clinical parameters was shown to be significantly greater compared with that observed with the placebo, even after the first few weeks of treatment. Furthermore, this improvement was evident for the whole of the treatment period. Suspension of the treatment was only made necessary in 12.3% of cases due to the side effects that were observed during the period of treatment, which consisted of local irritations such as pruritus, a burning sensation and erythema. No systemic side-effects were reported or any changes to the haematochemical parameters (14).

In another long term multicentre study conducted by Van de Kerkhof in 1997, Tacalcitol was evaluated in 58 patients with plaque psoriasis. The patients were treated for a period of time that varied from 12 to 62 weeks using tacalcitol ointment 4 µg/g. A considerable improvement in the erythema, the desquamation and the inflammatory infiltrate was noted after only 4 weeks.

The improvement in the clinical parameters under investigation persisted for the whole duration of the study. Moreover, 57% of patients judged the treat-

ment with Tacalcitol as being good or very good (15).

However, another study conducted in 1996 by Scarpa compared the clinical efficacy of Tacalcitol ointment (4 µg/g) with Betametazone Valerate ointment 0.1%, applied once a day in 63 patients over a period of 6 weeks. No significant differences were observed between Tacalcitol and the Betametazone Valerate 0.1% in reducing the thickness of the plaques, although the steroid showed a more marked effect on the desquamation and the erythema.

However, it was observed that relapses occurred more rapidly in the patients treated with Betametazone Valerate, even during the first month after suspension of the treatment (16).

The efficacy of Tacalcitol was therefore found to be comparable to that of topical corticosteroids and also to that of calcipotriol, with a lower percentage of relapses and side effects and greater cosmetic acceptability compared with commonly used topical treatments (17).

Association with UVB

Preliminary studies have examined the association of Tacalcitol ointment with phototherapy using UVB rays, with the aim of improving efficacy and tolerability. Twenty two patients with a mild and/or moderate degree of psoriasis were included in an open study which compared the association of Tacalcitol ointment with narrow band UVB phototherapy (NB UVB) and NB UVB phototherapy on its own. The treatment outline gave a single application of Tacalcitol in the evening whereas the NB UVB was administered 3 times a week according to a classic phototherapy protocol. The results highlighted the usefulness of this association because the lesions healed sooner, meaning that the total dose of UVB was reduced. Lastly, the association showed excellent tolerability with no phototoxic side effects (18).

Other possible uses

Tacalcitol ointment has been approved in Europe for the treatment of a mild and/or moderate degree of

psoriasis, but different authors have recently proposed that this molecule should be used in the treatment of other dermatological conditions, due to its proven capacity for influencing inflammatory processes of the skin, epidermal proliferation and differentiation of keratinocytes (19).

Tacalcitol, phototherapy and vitiligo

Vitiligo is a skin pigmentation disorder which is characterised by achromatic areas of varying morphology. It is genetic in about one third of cases and has an autoimmune pathogenetic component.

The association between phototherapy and Tacalcitol in the treatment of vitiligo was proposed following evidence that subjects with psoriasis who were treated with a combined therapy that required the topical application of phototherapy with psoralene and UVA (PUVA) developed a hyperpigmentation in the treated areas (20). After this, Katyama and collaborators proposed an open study in 2003 conducted on 15 patients, using a treatment that associated Tacalcitol and exposure to solar radiation. Most of the patients included in the study had not responded to traditional therapies for vitiligo. Each patient was instructed to expose themselves to solar radiation for 30 minutes before topical application of Tacalcitol ointment. 40% of the patients reported a clinical response that varied from good to excellent. Parallel experiments *in vitro* showed that Tacalcitol associated with solar radiation can induce the expression of messenger RNA for the *c-kit* gene by the melanocytes. In subjects with vitiligo, this expression is inhibited in the perilesional melanocytes. These data suggest therefore that the therapeutic association of Tacalcitol ointment and phototherapy could potentially represent a further therapeutic option for treating subjects with vitiligo (21).

Topical treatment with Tacalcitol ointment is also associated with NB UVB phototherapy in vitiligo, in order to increase efficacy.

In 2001 Leone and collaborators presented the preliminary results of an open study conducted in single blind on 32 patients with vitiligo (22).

All the patients showed symmetrical lesions. The Study compared the clinical efficacy of Tacalcitol

ointment in association with NB UVB versus phototherapy with NB UVB. The protocol gave instructions for a single daily application of Tacalcitol ointment on lesions on one hemilateral of the body (left or right at random) and the administration of NB UVB on both hemilaterals 3 times a week for an overall duration of 6 months. The results highlighted a greater percentage of repigmentation in the lesions treated with the associated therapy compared with those treated only with NB UVB. Furthermore, the first signs of repigmentation were observed after less than 5 weeks of treatment in the lesions treated with Tacalcitol ointment and NB UVB; however, in the lesions treated with NB UVB as monotherapy, the first signs of repigmentation were observed after 7 weeks. Therefore at the end of the study it was demonstrated that Tacalcitol ointment associated with NB UVB was able to determine a quicker and more consistent clinical improvement of the lesions compared with NB UVB phototherapy alone. The results of this study are very promising; however, this data must be confirmed through clinical trials that include a greater number of patients, in order to clarify Tacalcitol's exact mechanism of action with regard to vitiligo.

Tacalcitol and verruciform epidermodysplasia

Verruciform epidermodysplasia is a chronic skin condition, caused by some serotypes of Human Papilloma Virus (HPV), which affects individuals who are genetically predisposed (recessive autosomic transmission), to a marked potential for neoplastic degeneration (Bowen's Disease, spinal and basal cell carcinoma). In a study conducted in 2002, Hayashi and collaborators reported the case of a 69 year old female patient with localised Verruciform epidermodysplasia which had been successfully treated with Tacalcitol. Due to the onset of significant side effects, the patient's treatment with retinoids *per os* (etretinate 10 mg/day), was suspended and the patient was then treated with daily applications of Tacalcitol ointment for 6 months. This treatment resulted in a remarkable improvement in the erythema, the hyperkeratosis and the thickness of the plaques. Furthermore, no new lesions were found during the entire period of treatment with Tacalcitol (24).

Tacalcitol and Grover's Disease

Grover's Disease is a pruriginous dermatitis which generally affects male subjects and is localised mainly on the trunk. The diffuse, papulous and papulo-vesicular lesions are grouped together. The histopathological characteristic of the lesions is the presence of acantolysis.

In 2001 Hayashi reported the case of a female patient, 31 years old, with Grover's Disease and treated with Tacalcitol twice a day. A partial remission of the skin lesions was observed during the first week of treatment with Tacalcitol and there was complete remission after a month of treatment.

Although numerous cases of spontaneous remission of Grover's Disease have been reported, the sudden disappearance of the lesions after treatment with Tacalcitol suggests that this drug has a possible role in the remission of the clinical symptoms.

Conclusions

The exact molecular mechanisms responsible for the pathogenesis of psoriasis are as yet unknown, although both genetic and immunologic events seem to be involved. The importance of hereditary factors has been suggested by epidemiological studies and then confirmed by the recent localisation of the genes that are probably responsible for susceptibility to the development of psoriasis in chromosomes 17q, 6p and 8q (25).

Psoriasis is characterised histologically by epidermal hyperplasia, absence of the granulosa layer and parakeratosis. Furthermore, a lengthening of the papillae can be seen in the dermis as well as dilated and tortuous capillaries and an inflammatory infiltrate made up of lymphocytes, macrophages, neutrophils and mast cells. Lastly, a histological pathognomonic aspect is the discovery of Munro-Sabouraud microabscesses.

It has not yet been established which is the "target" cell for the primary defect in psoriatic skin but the keratinocytes, fibroblasts and endothelial cells are probable candidates. Three theories have been put forward to explain the immunological mechanisms at

the basis of the aetiopathogenesis of psoriasis: direct activation of the keratinocytes due to physical or chemical stimuli with consequent stimulation of the T lymphocytes, the activation of the T lymphocytes mediated by the presentation of antigens and/or super antigens by the antigen presenting cells (Figure 2) with a consequent release of cytokines, which are responsible for the stimulation of the keratinocytes and lastly, an autoreactivity mechanism that is accompanied by a persistent stimulation of the T lymphocytes (26).

Different clinical studies and research have demonstrated that Tacalcitol can influence the principal pathogenetic factors of psoriasis by inducing normalisation of keratinocyte differentiation, performing an anti-proliferative action and finally modulating the inflammatory response (27).

On a molecular level, Tacalcitol acts by inhibiting the expression of messenger RNA for the *c-fos* and *c-myc* genes. These genes code for the nuclear *DNA-binding proteins* that are implicated in cellular proliferation (28). Furthermore, the expression of cytokeratin 16 and involucrin, which are absent in normal skin but are increased in the psoriatic lesions, shows a marked reduction after the application of Tacalcitol ointment at the concentration of 4 µg/g. After the application of Tacalcitol, it is also possible to observe the normalisation of the synthesis of filaggrin, which is present in the corneal layer of the normal epidermis but absent in the psoriatic epidermis (29).

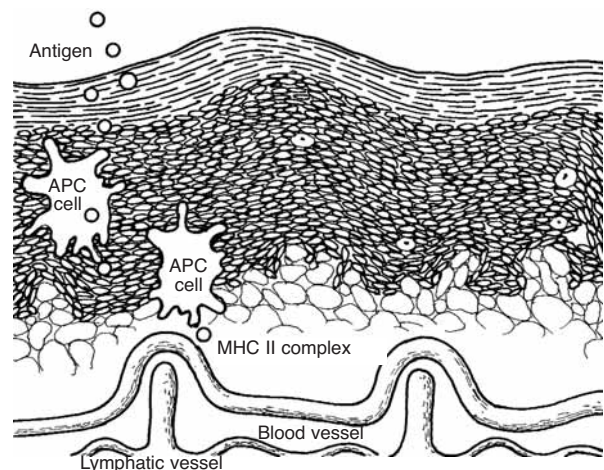


Figure 2. Activation of the antigen presenting cells (APC)

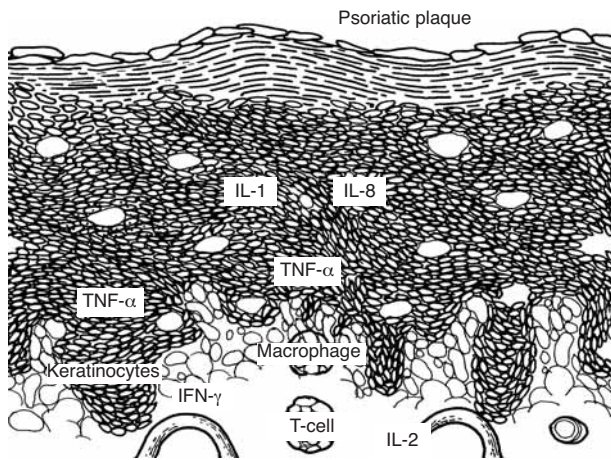


Figure 3. Overexpression of TNF- α and formation of the psoriatic plaque

Tacalcitol inhibits the production of IL 8 induced by the Tumor Necrosis Factor (TNF) by the fibroblasts in the dermis, as well as the production of IL-8 induced by the IL-1 in the mononucleate haematic cells (Figure 3). Experimental studies have shown that Tacalcitol also inhibits, in a dose-dependent manner, the production of IL-3 induced by IL-1 by the endothelial cells in the dermal microcirculation (30).

In conclusion, the capacity of Tacalcitol to inhibit keratinocyte proliferation, while at the same time encouraging differentiation, the capacity to modulate some mediators in the inflammatory process and the immune system of the skin, were the rationale for conducting several clinical trials. Based on the results of these clinical trials, it has been shown that Tacalcitol, used in the treatment of mild/moderate psoriasis, can induce a rapid improvement or the complete resolution of the psoriatic lesions, with beneficial effects that continue even after treatment has stopped. The advantage of the single daily application improves patient compliance and the low systemic absorption rate means that the drug is safe, with a very low risk of systemic side effects (31).

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