Topical tacalcitol treatment for psoriasis

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Multiple studies have shown the benefit of topical tacalcitol treatment for chronic plaque psoriasis. Tacalcitol ointment 4 μg/g is efficacious and well tolerated as both monotherapy and in combination with other treatments such as ultraviolet light therapy. It can be used all over the body including the face and scalp.

Psoriasis is a chronic skin disorder characterized by epidermal proliferation, abnormal keratinization and cutaneous inflammation (Van de Kerkhof, 1995). There are many different treatments for psoriasis including topical dithranol, tar preparations and systemic agents such as methotrexate, cyclosporin, retinoids and ultraviolet light therapy. All these treatments, although effective to a greater or lesser extent in different types of psoriasis, may have disadvantages or sometimes unacceptable side effects.

Although vitamin D_3 had been used for the treatment of psoriasis in the 1930s, the first report that 1α, hydroxyvitamin D_3 could improve psoriasis was in 1985 (Morimoto, 1985). Subsequent interest in topical use of synthetic vitamin D analogues developed to circumvent the calcipotropic effects of systemic agents. Their ease of use, good tolerability, and proven efficacy has established them as the first-line therapy of choice in patients with mild-to-moderate plaque psoriasis (Donaldson and Douglas, 1996).

VITAMIN D3 ANALOGUES

Vitamin D_3 analogues are among the most recent and innovative topical forms of treatment for mild to moderate psoriasis. These analogues work by influencing vitamin D receptors, which have been detected in the keratinocytes of the epidermis, resulting in the normalization of the pathological hyperproliferation of the keratinocytes and promotion of the differentiation of these cells.

To date there are three substances in appropriate formulations which have been approved in some countries for the treatment of psoriasis. These are 1,25 dihydroxyvitamin D_3 (calcitriol), the biological active form of natural vitamin D_3, and the analogues calcipotriol and tacalcitol. This article will provide an overview of the current clinical literature surrounding the use of tacalcitol.

Tacalcitol is chemically very similar to the natural vitamin D_3 metabolite (Van de Kerkhof et al, 1996). Tacalcitol (1α, 24-dihydroxyvitamin D_3) is a synthetic analogue of calcitriol (1α, 25-dihydroxyvitamin D_3) which is the most active metabolite of vitamin D. The affinity of tacalcitol to the vitamin D receptor in human keratinocytes is slightly higher than that of naturally occurring vitamin D. Tacalcitol differs from calcitriol by hydroxylation in the 24 position instead of the 25 position (Baadsgaard et al, 1995) (*Figure 1*).

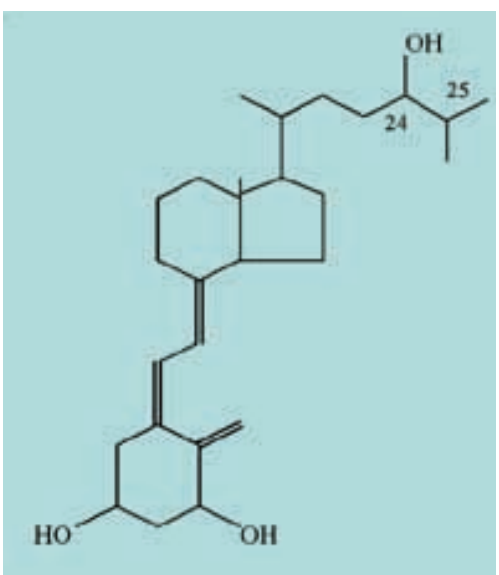

Figure 1. Chemical structure of tacalcitol.

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Tacalcitol binds to specific vitamin D_3 receptors present in the skin and the effect on mRNA gene expression results in reduced keratinocyte proliferation. There is also evidence of tacalcitol's effect upon inflammation and immunological mediators (Peters and Balfour, 1997), which could be an additional reason for the agent's beneficial effect in psoriasis.

EFFICACY

The efficacy of tacalcitol once daily in monotherapy has been demonstrated in several investigations (Scarpa, 1996; Van de Kerkhof et al, 1996; Gollnick and Menke, 1998).

Baadsgaard (1995) reviewed optimal concentrations of tacalcitol for once daily application in a randomized, double blind comparison of seven concentrations of tacalcitol ointment. The maximum healing effect of tacalcitol was obtained with concentrations of 4 μg/g and higher, showing that once daily application achieves maximum efficacy. This can have an important impact on patient compliance and can improve the likelihood of successful treatment outcome.

One study undertaken by Van de Kerkhof et al (1996) was a multicentre, double-blind placebo-controlled, randomized trial with centres in the Netherlands and Germany. One hundred and twenty two patients were enrolled into the study, with 60 patients randomized to the application of tacalcitol ointment on the left of the body and placebo ointment to the right of the body and 62 patients applying placebo ointment to the left of the body and tacalcitol ointment to the right of the body. The patients all had chronic, stable plaque-type psoriasis and tacalcitol ointment 4 μg/g (Curatoderm™, Hernmal, Reinbeck, Germany) was used in the study with clinical assessment utilizing the psoriasis area and severity index (PASI) score. Visible improvements in psoriasis were seen after 2 weeks and by the end of 8 weeks treatment, improvement in psoriasis with tacalcitol compared with placebo ointment was significant ($P<0.0001$) (Van de Kerkhof et al, 1996). There was no evidence of hypercalcaemia. Symptoms of local skin irritation were observed in 12.3% of patients, but this was only severe enough to initiate discontinuation of treatment in one patient (Van de Kerkhof et al, 1996).

A study by Scarpa (1996) from Italy compared the efficacy of topical tacalcitol ointment 4 μg/g with 0.1% betamethasone valerate. Seventy six patients were studied in a randomized trial which involved the application of either preparation of symmetrical psoriasis areas on limbs or trunk. Taking into account the erythema, scaliness and thickness of psoriatic plaques, the efficacy of the two preparations were similar.

Farkas et al (1998) was involved in a study at four centres in Hungary. In this trial (a multicentre randomized study), the effectiveness of topical tacalcitol ointment 4 μg/g was compared with topical dithranol, either 1.5% or 3%. As with the other two studies, psoriasis affecting body or limbs was examined, without studying scalps. Application of the different topical preparations over an 8-week period showed a better response to topical tacalcitol, compared with dithranol, 6 weeks after commencement of treatment. The tolerability of the topical tacalcitol was stated as good to very good by 98% of the patients and was significantly better with topical tacalcitol ($P<0.002$) than topical dithranol (Farkas et al, 1998).

In a comparative study between tacalcitol and calcipotriol, once daily topical treatment of stable plaque psoriasis with tacalcitol was compared with twice daily calcipotriol ointment (50 μg/g) in 287 adults in a double-blind, randomized study over an 8-week treatment period (Veien et al, 1997). Both treatments effectively reduced the severity of psoriasis, the mean reduction in sumscore being 4.03 in the tacalcitol group (baseline 7.64) and 5.05 in the calcipotriol group (baseline 7.45). The acceptability of both ointments was excellent and none of the patients had adverse events in terms of disturbances in calcium metabolism. It should be noted that the authors pointed out that the difference in the sumscores may not indicate a clinically relevant difference between the two treatments. Additionally, the authors concluded that:

> **'As a once daily rather than twice daily treatment schedule is likely to increase compliance, tacalcitol is a useful treatment for psoriasis'.**

SCALP PSORIASIS

The effect of tacalcitol ointment on scalp psoriasis was studied by Lüdcke (1998) in a post-marketing surveillance study from Germany. The study, which examined the effectiveness of topical tacalcitol, involved 2 647 patients. For scalp psoriasis, topical treatments with salicylic acid, tar and dithranol preparations, although effective, are not always practical for everyday use. Improvement in scalp psoriasis (erythema, infiltration or scaling) was experienced by 93% of patients in the study. Final assessment of the effectiveness of topical tacalcitol ointment for

scalp psoriasis was judged to be good or very good in 77% of studied individuals.

SAFETY AND TOLERABILITY

The long-term effect of tacalcitol ointment in psoriasis was discussed by Marks (1998). Although a 2 μg/g ointment has been used in Japan, in Europe and elsewhere in the world the use of a 4 μg/g ointment has shown no effect on calcium homeostasis even when used for over a year (Van de Kerkhof et al, 1999). Tacalcitol ointment appears to maintain its effectiveness over more prolonged periods of use and is well tolerated and safe for patients (Marks, 1998; Van de Kerkhof et al, 1999).

This view was supported by work of Van de Kerkhof et al (1999) in a multicentre study from the Netherlands, United Kingdom, Germany, Belgium and Austria. In this study, 197 patients, out of an initial group of 310 patients with active plaque psoriasis using topical tacalcitol 4 μg/g for 3 months, continued with treatment for 15 months. No patient showed any relevant effect on calcium metabolism and there was no evidence that topically applied tacalcitol (up to a maximum of 13 g per day) would influence calcium metabolism in patients with a psoriasis surface area involvement up to 20%. Discontinuation of treatment as a result of skin irritation was only seen in 5.9% of patients, and topical tacalcitol was demonstrated as an efficacious and safe acceptable topical treatment which could be used for the long-term management of psoriasis.

Additionally, Peters and Balfour (1997) reviewed the topical use of tacalcitol for psoriasis and summarized evidence to show that the preparation was an effective and well-tolerated preparation for the treatment of psoriasis.

POST-MARKETING SURVEILLANCE STUDY

Gollnick and Menke (1998) undertook a post-marketing study to assess the effectiveness and safety of topical tacalcitol in 5 205 patients. The mean duration of treatment with tacalcitol was 61 days, but in 47% of patients treatment had lasted for more than 60 days. Tacalcitol as a single agent was used in 53% of patients. However, 23% of patients received concomitant treatment (including topical steroids) and 13% of patients received additional ultraviolet therapy.

Efficacy and safety

Tacalcitol monotherapy and combined therapy both showed efficacious results (Gollnick and Menke, 1998). Patients treated with tacalcitol treatment alone experienced an average reduction in sumscore (erythema, infiltration, scaling) by 57%. Monotherapy was judged to be good or very good in 72% of patients, whereas combined therapy was assessed to be good or very good in up to 73% of patients, with tolerability to treatment being good or very good in 94% of patients, even when applied to the face, scalp and other sensitive areas. Particularly good results were achieved when patients who had just experienced their first onset of psoriasis were treated with tacalcitol, suggesting that this agent should be considered the therapy of choice in newly presenting patients.

Combination therapy

Assessment of tacalcitol efficacy in combination with other proven therapies, including cortico-steroids, urea, emollients or ultraviolet therapy, was stated by the investigators to be 'very good' or 'good' in 68–73% of cases (Gollnick and Menke, 1998). The study also demonstrated that tacalcitol combination therapy was well-accepted in daily practice and the requirement of only once daily application of tacalcitol could also help minimize the complexity of the treatment regimen with ultraviolet B. The combination of tacalcitol with other treatments did not appear to increase the incidence of side effects (Gollnick and Menke, 1998).

Compliance

The study showed that once daily application with tacalcitol took just 12 minutes a day which, for the majority of patients, represented a time saving of up to half an hour daily compared to conventional therapies (Gollnick and Menke, 1998). This, alongside the good tolerability profile, may help to explain the finding that compliance with tacalcitol 4 μg/g was judged by the supervising specialists to be 'good' or 'very good' in 91% of patients (Gollnick and Menke, 1998).

TACALCITOL AND ULTRAVIOLET B THERAPY

Kokelj et al (1996) studied the effects of topical tacalcitol in conjunction with ultraviolet B therapy. It had been noted by other workers that tacalcitol could be used effectively in conjunction with psoralen and ultraviolet A (PUVA) therapy, but this study showed that the addition of tacalcitol once a day to ultraviolet B phototherapy could increase the antipsoriatic effective of ultraviolet B and produce a significant ultraviolet B sparing effect. Twenty two patients

with mild psoriasis receiving 3 times weekly ultraviolet B (300–310 nm) were studied and no patient showed superior results with treatment from ultraviolet B alone. The average time to clearance was 36 days with combination therapy using topical tacalcitol with ultraviolet B, compared with a longer 53 days for ultraviolet B alone. Topical tacalcitol is well tolerated and effective when combined with systemic agents used for the treatment of psoriasis (Gollnick and Menke, 1998).

DISCUSSION

Psoriasis is a common skin disorder and, until recently, dithranol and tar preparations were the main topical treatment. Skin irritancy and staining, together with the inconvenience of tar therapy, have meant the therapies are less suitable for outpatient use, and patients with moderate or severe psoriasis may require a systemic therapy. The development of vitamin D analogues has improved the topical treatment of psoriasis, with ease of use a major contribution for patients.

The topical vitamin D analogue tacalcitol has been shown in multiple studies to be effective for the topical management of mild to moderate psoriasis and can be used effectively once daily. This, combined with its good tolerability profile, appears to have a positive impact on compliance in both combination and monotherapy. Topical tacalcitol appears to have no significant effect on calcium metabolism in patients, is well tolerated and safety studies have not indicated any problems with its routine use in psoriasis patients for up to 12 months.

As well as being used in monotherapy in psoriasis, topical tacalcitol can be used in conjunction with other topical therapies (e.g. topical steroids) and can be used in conjunction with ultraviolet therapy — either PUVA or ultraviolet B. Furthermore, the concomitant use of tacalcitol with ultraviolet therapy appears to increase the antipsoriatic effect in patients, and also reduces ultraviolet B requirements in patients. Tacalcitol can be used as first-line treatment for psoriasis and is suitable for use all over the body including the scalp. It need only be used once daily, saving patient time and encouraging patient compliance, which is a key consideration for therapeutic success. Tacalcitol, used topically, is a useful, safe and effective treatment for patients with psoriasis. It is particularly convenient for outpatient use, but can also be used effectively on inpatients with the disease. HM

Conflict of interest: Professor Harrison is a member of the Crookes Advisory Board.

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KEY POINTS

- Topical tacalcitol is a vitamin D_3 analogue which has been shown in multiple studies to be effective for the topical management of mild to moderate psoriasis.
- Topical tacalcitol has good patient acceptability and can be used all over the body including the face and scalp.
- Topical tacalcitol has a low incidence of side effects.
- Topical tacalcitol is efficacious in conjunction with other topical agents and has shown benefit when used in conjunction with ultraviolet therapy, and could reduce the ultraviolet B dosage.
- Long-term use of topical tacalcitol has shown no significant effect on calcium metabolism and is well tolerated and safe for patients.
- The once daily application of topical tacalcitol is sufficient for achieving maximum efficacy. This minimizes the complexity of the therapy when combined with other antipsoriatic treatments and improves the likelihood of patient compliance.