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CLINICAL REPORT

0.3% Tacrolimus Gel and 0.5% Tacrolimus Cream Show Efficacy in Mild to Moderate Plaque Psoriasis: Results of a Randomized, Open-label, Observer-blinded Study

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The efficacy and safety of 0.3% tacrolimus gel and 0.5% tacrolimus cream compared with calcipotriol ointment were evaluated in adults (*n*=124) with mild to moderate plaque psoriasis. Treatment was twice daily for a maximum of 12 weeks. Clinical efficacy was assessed by the percentage change in the local psoriasis severity index of a target lesion between baseline and week 12. By week 12, the median percentage changes in local psoriasis severity index of the target lesions in the tacrolimus gel, tacrolimus cream and calcipotriol groups were 55.6%, 50.0% and 58.6%, respectively (no statistically significant differences). Clinical improvement was observed after one week and increased throughout the study. Tacrolimus-treated patients experienced more application site skin burning (tacrolimus gel and cream both 31.0% versus 7.5% for calcipotriol; *p*=0.011). Skin burning was mostly mild in intensity and decreased substantially after 1 week of treatment. There were no differences in the nature and incidence of infections and no clinically relevant changes in laboratory values. *Key words: psoriasis; tacrolimus; cream; gel; adults.*

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Psoriasis is a common chronic inflammatory skin disorder that affects 1–3% of the world's population (1). Although the aetiology of psoriasis remains unclear, it appears to be a T-cell-mediated disease that is heavily influenced by genetic and environmental factors (2, 3). Epidermal T cells, activated by a variety of dermal and epidermal cell signals from a site of injury or infection, release cytokines which stimulate keratinocyte hyperproliferation by influencing the expression of keratinocyte surface molecules (4).

Current topical treatments for psoriasis include coal tar, anthralin/dithranol, corticosteroids, calcipotriol, retinoids and ultraviolet light, and although these medications can provide some relief and control of the symptoms, they can be associated with unwanted side effects (5). Therefore there is a need for a new topical treatment that can quickly and effectively improve the clinical signs and symptoms of psoriasis and which can be applied safely for prolonged periods of time.

A new possibility is the calcineurin inhibitor, tacrolimus. Tacrolimus inhibits the transcription and release of interleukin (IL)-2 and other cytokines involved in causing psoriasis such as IL-3, IL-4, IL-5, interferon (IFN)-γ and tumour necrosis factor (TNF)-α (6, 7). Tacrolimus ointment was developed for the treatment of atopic dermatitis, where it has demonstrated significant efficacy in both adults (8, 9) and children (10, 11). However, the penetration of the ointment formulation of tacrolimus was not sufficient in psoriasis patients, and two new tacrolimus preparations in the form of a gel and a cream were developed. Here we present the data from the first European study to compare the efficacy and safety of 0.3% tacrolimus gel and 0.5% tacrolimus cream with 0.005% calcipotriol in the treatment of mild to moderate plaque psoriasis in adults.

MATERIALS AND METHODS

Study design

This was a 14-week, randomized, three-arm, open-label, observer-blinded, parallel group study conducted in 16 centres in 5 European countries. The study was conducted in accordance with the ethical principles described in the Declaration of Helsinki, and the Ethics Committee of each centre reviewed the protocol and granted approval before the start of the study. A screening visit was carried out on day 1 (baseline, treatment allocation) and a target lesion was identified for further evaluation during the study. Assessments were conducted at weeks 1, 2, 4, 8, 12 (end of treatment) and 14 (follow-up visit).

Patients

Following written informed consent from the patient, male and female patients aged 18 years or older who had experienced stable plaque psoriasis for at least 6 months prior to the start of the study were randomized to treatment. The patients were

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required to have a total affected body surface area of ≤10%, and for the clinical assessment, one target lesion located on the trunk or extremities sized between 40 and 200 cm^2 and with a local psoriasis severity index (LPSI) score of ≥5.

Randomization and blinding

The randomization schedule was generated by the study sponsor. Randomization was 1:1:1 and stratified by centre. All patients who entered the treatment period received a consecutive unique patient number. This number was also printed on the sealed box containing the study drug tubes. As this was an open-label, observer-blinded study, the patients were asked not to show their study medication to the investigator. All used, partly used and unused tubes were returned in a sealed box at the end of the study, and the tubes were weighed to calculate medication usage throughout the treatment period.

Treatment

Patients applied either 0.3% tacrolimus gel, 0.5% tacrolimus cream or 0.005% calcipotriol ointment twice daily to all affected body areas. There was to be an interval of 10–14 h between applications. After clearance (defined as no scaling, thickening or redness of the skin), the lesions were to be treated for 7 additional days. The maximum treatment period was 12 weeks.

Prohibited therapies during the study included intranasal or inhaled corticosteroids (>2 mg prednisolone equivalent/day), systemic and topical corticosteroids, light treatments, antipsoriatics (tazarotene, tar, topical retinoids, psoralens, salicylic acid, anthralin), immunosuppressive drugs, chemotherapy agents, systemically administered drugs with the potential to alter tacrolimus concentrations (inhibitors/inducers of cytochrome P450 3A4 isoenzyme, e.g. clotrimazole, barbiturates), drugs that can exacerbate psoriasis (lithium salts, betaadrenergic blocking agents, antimalarials) and other medicated topical agents. Over the counter or prescribed non-steroidal anti-inflammatory drugs for arthritis or other inflammatory conditions were permitted as were non-medicated emollients, sunscreens on body areas untreated with study drug, and systemic anti-infective therapies.

Assessments

The foremost treatment comparison was between 0.3% tacrolimus gel and 0.5% tacrolimus cream. The main assessment of clinical efficacy was the percentage change between day 1 (baseline) and week 12 (end of treatment) in LPSI of the target lesion. LPSI was selected because the evaluation of a local target lesion was considered to be a more sensitive measurement of treatment efficacy. The LPSI of the target lesion was calculated by summing the severity ratings for erythema, induration and scaling using the scoring system from the psoriasis area severity index (PASI) (12) and the score ranged from 0 to a maximum of 12.

Additional clinical assessments included the change in LPSI of the target lesion over time, the change in total affected body surface area over time, the physician's and patient's assessment of clinical response, and the cosmetic acceptability of each treatment.

Safety assessments during the study included the monitoring of adverse events and vital signs as well as the clinical laboratory evaluations (sodium, potassium, calcium, chloride, magnesium, serum glutamic oxaloacetic transaminase (SGOT, AST), serum glutamic pyruvic transaminase (SGPT, ALT), alkaline phosphatase, lactate dehydrogenase (LDH), gamma glutamyl transferase (GGT), glucose, creatinine, urea, total and direct bilirubin; haematology profile: haematocrit, haemoglobin, thrombocytes, erythrocytes, leucocytes). An adverse event was defined as any untoward occurrence in a patient during the study, regardless of whether it was related to the study treatment.

Statistical analyses

The planned sample size of 120 patients was based on feasibility (number of sites and length of time for recruitment) and the fact that this was a pilot study. Power calculations revealed that if the difference in mean percentage change of LPSI assessment was equal to 15 (assumed SD=23.6), a power of 80% would be achieved with 40 patients per treatment group.

The statistical analysis was based on the intent-to-treat population (full analysis set) which was defined as all randomized patients who received at least one application of study medication. The comparison of 0.3% tacrolimus gel versus 0.5% tacrolimus cream was analysed using the Wilcoxon rank-sum test. The additional efficacy assessments were also analysed by Wilcoxon rank-sum test or Cochran-Mantel-Haenszel test as appropriate, while Fisher's exact test was used to compare the incidence of adverse events between treatment groups.

RESULTS

Patient demographics and baseline characteristics

In total, 124 patients comprised the intent-to-treat population: 42 patients each in the 0.3% tacrolimus gel and 0.5% tacrolimus cream treatment groups and 40 patients in the calcipotriol treatment group (Table I). The treatment groups were comparable with respect to demographics, mean duration of psoriasis, mean duration of current stable disease, and mean affected body surface area.

Patient disposition

More patients in the tacrolimus gel and calcipotriol treatment groups completed the 12-week treatment period (34 patients, 81.0% and 35 patients, 87.5%, respectively) compared with the tacrolimus cream group (30 patients, 71.4%). Seven patients (16.7%) and 10 patients (23.8%) in the tacrolimus gel and tacrolimus cream groups, respectively, discontinued the study prematurely for reasons other than complete clearance compared with 3 patients (7.5%) in the calcipotriol group. There were no major differences among the treatment groups in the reasons for discontinuation; adverse events were the main reason in the tacrolimus gel (three patients, 7.1%) and calcipotriol (three patients, 7.5%) treatment groups. In the tacrolimus cream group, two patients (4.8%) withdrew from the study because of an adverse event while two further patients were withdrawn because of lack of efficacy.

Ointment usage

The median daily study drug usage was 4.04 g, 4.85 g and 4.77 g for the tacrolimus gel, tacrolimus cream and calcipotriol treatment groups, respectively.

Table I. *Patient demographics and baseline characteristics – number of patients (%)*

Parameter	0.3% tacrolimus gel (n = 42)	0.5% tacrolimus cream (n = 42)	0.005% calcipotriol (n = 40)
Age (years)			
Mean (SD)	45.4 (15.3)	48.3 (15.0)	50.9 (14.1)
Min–Max	18–76	25–82	18–74
Sex			
Male	26 (61.9)	33 (78.6)	26 (65.0)
Female	16 (38.1)	9 (21.4)	14 (35.0)
Ethnic group			
Caucasian	41 (97.6)	39 (92.9)	39 (97.5)
Oriental	1 (2.4)	3 (7.1)	1 (2.5)
Duration of psoriasis (years)			
Mean (SD)	14.1 (12.2)	20.5 (15.3)	22.3 (14.0)
Min–Max	0.7–55.3	1.3–69.3	2.4–51.3
Duration of current stable disease (months)			
Mean (SD)	40.5 (60.1)	49.3 (84.5)	35.9 (46.5)
Min–Max	6.3–336.5	6.3–466.9	6.3–215.1
% BSA affected at baseline			
Mean (SD)	6.2 (2.4)	6.7 (2.1)	6.0 (2.2)
Min–Max	1–10	2–10	3–10
LPSI at baseline			
Mean (SD)	7.0 (1.6)	7.1 (1.8)	7.5 (1.6)
Min–Max	5–12	4–12	5–11
PASI at baseline			
Mean (SD)	6.8 (3.8)	7.5 (4.3)	6.9 (3.0)
Min–Max	1.4–21.8	1.7–19.5	1.4–14.0

Intent-to-treat population. BSA, body surface area; LPSI, local psoriasis severity index; PASI, psoriasis area severity index.

Efficacy

Main efficacy assessment. The median percentage change in the LPSI of the target lesion between baseline and week 12 was slightly lower in the tacrolimus gel and tacrolimus cream treatment groups (55.6% and 50%, respectively) compared with the calcipotriol group (58.6%). There were no statistically significant differences among treatment groups.

Additional efficacy assessments. Clinical improvement in the median percentage change in LPSI of the target lesion was observed in all three treatment groups after one week of treatment, and continued to increase during the study with improvement being swiftest and greatest in the patients applying calcipotriol (Fig. 1). The patients in the tacrolimus treatment groups experienced a greater decrease in total affected body surface area during the treatment period compared with the calcipotriol-treated patients. The median percentage change in total affected body surface area between baseline and week 12 was 40%, 37.5% and 21.1% for the tacrolimus gel, cream and calcipotriol groups, respectively.

With respect to the physician's assessment of response at the target lesion, 44.4%, 45.2% and 48.6% of the patients in the tacrolimus gel, tacrolimus cream and calcipotriol groups received a rating of 'much better' at week 12 (Fig. 2). Altogether 47.2%, 51.6% and 51.4% of patients in the respective treatment groups rated their psoriasis as 'much better'.

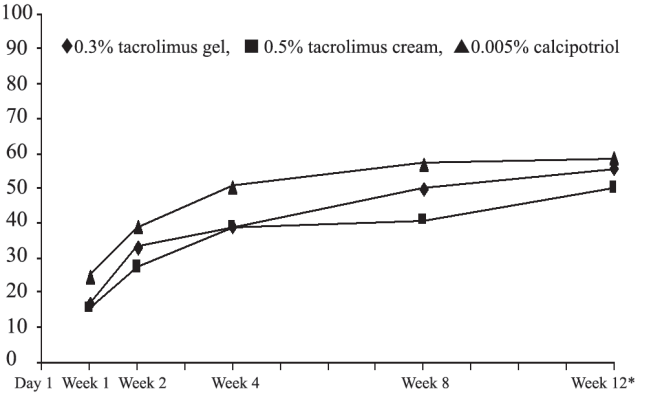

Fig. 1. Median percentage change from baseline over time in local psoriasis severity index (LPSI) of the target lesion, intent-to-treat population.
*= End of treatment

Cosmetic acceptability of the medication. Most patients in all three treatment groups found the odour of the study medications to be acceptable. However, significantly more patients applying calcipotriol were dissatisfied with regard to staining of clothes caused by the ointment (25.7% versus 2.8% for tacrolimus gel; Cochran-Mantel-Haenszel test p=0.0035 and versus 6.5% for tacrolimus cream; p=0.025) and greasiness of the formulation (20% versus 0.0% for tacrolimus cream; Cochran-Mantel-Haenszel test p=0.0094 and versus 5.6% for tacrolimus gel; p=NS).

Safety

Twenty-six patients (61.9%) in the tacrolimus gel group, 28 patients (66.7%) in the tacrolimus cream group and 27 patients (67.5%) in the calcipotriol experienced adverse events during the study. Of these, 19 patients (45.2%), 24 patients (57.1%) and 13 patients (32.5%) in the respective treatment groups had causally related adverse events, most of which occurred at the site of treatment application and were mild to moderate in intensity. Application site skin burning was the most frequent adverse event reported by the patients applying tacrolimus gel and tacrolimus cream (both 31.0% versus 7.5% in the calcipotriol group; Fisher's exact test, p<0.011, Table II) followed by application site pruritus (tacrolimus gel 9.5% and tacrolimus cream 16.7%, versus 7.5% in the calcipotriol group; p=NS). Most cases of skin burning and pruritus were mild in intensity and decreased greatly in prevalence after the first week of treatment as the clinical condition of skin improved.

Skin burning, exacerbation of psoriasis and skin ir-

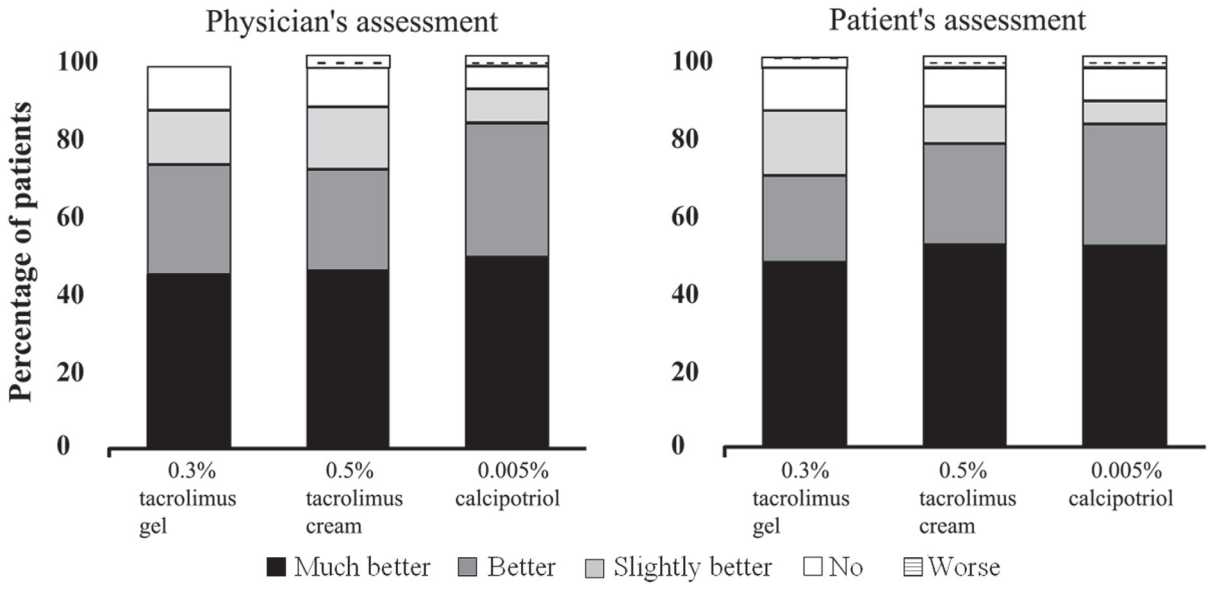

Fig. 2. Physician's and patient's assessment of resonse at the target lesion at week 12 (end of treatment).

ritation led to the withdrawal of three patients in the tacrolimus gel group while in the tacrolimus cream group, skin burning and a brain neoplasm (unlikely relationship to treatment) led to treatment discontinuation in two patients. In the calcipotriol group, exacerbation of psoriasis in one patient and two cases of skin irritation led to withdrawal from the study. There were three serious adverse events reported in two patients during the study; none of the events were related to the study medication.

Table II. *Most common* adverse events and infections regardless of relationship to study drug – [No. of patients (%)]*

Parameter	0.3% tacrolimus gel (n = 42)	0.5% tacrolimus cream (n = 42)	0.005% calcipotriol (n = 40)
Total	26 (61.9)	28 (66.7)	27 (67.5)
Application site			
burning	13 (31.0)	13 (31.0)	3 (7.5)
pruritus	4 (9.5)	7 (16.7)	3 (7.5)
warmth	4 (9.5)	1 (2.4)	0 (0.0)
erythema	0 (0.0)	0 (0.0)	3 (7.5)
dryness	0 (0.0)	2 (4.8)	0 (0.0)
photosensitivity	0 (0.0)	2 (4.8)	0 (0.0)
Oedema, peripheral	0 (0.0)	1 (2.4)	2 (5.0)
Influenza	2 (4.8)	1 (2.4)	0 (0.0)
Laryngitis	1 (2.4)	0 (0.0)	2 (5.0)
Nasopharyngitis	3 (7.1)	3 (7.1)	3 (7.5)
Pruritus	1 (2.4)	0 (0.0)	2 (5.0)
Seborrhoeic dermatitis	1 (2.4)	0 (0.0)	2 (5.0)
Skin burning sensation	1 (2.4)	3 (7.1)	2 (5.0)
Headache	0 (0.0)	3 (7.1)	6 (15.0)
Flushing	1 (2.4)	4 (9.5)	0 (0.0)
Hypertension	2 (4.8)	0 (0.0)	1 (2.5)
Arthralgia	0 (0.0)	0 (0.0)	2 (5.0)

Intent-to-treat population.
*At least 4% of patients in any treatment group.

There were no differences among the three treatment groups in the nature and incidence of infections. There were no clinically relevant changes in laboratory values or vital signs throughout the study in any of the patients and no differences among treatment groups.

DISCUSSION

This is the first study to describe the efficacy and safety of the novel tacrolimus formulations, 0.3% tacrolimus gel and 0.5% tacrolimus cream, compared with 0.005% calcipotriol ointment in the treatment of mild to moderate plaque psoriasis in adult patients. The study results showed that after 12 weeks of treatment the clinical efficacy of the 0.3% tacrolimus gel was comparable to that of calcipotriol. The efficacy of the 0.5% tacrolimus cream formulation was slightly lower compared with calcipotriol and tacrolimus gel. The calcipotriol-treated patients had the fastest improvement, although by week 12, there was little difference between the calcipotriol and tacrolimus gel treatment groups. This may suggest that a longer treatment period may be necessary to achieve optimal efficacy with tacrolimus.

The higher incidence of causally related adverse events observed in the patients applying the tacrolimus formulations can be attributed to the higher incidence of skin burning; otherwise there were no differences among treatment groups in the incidence of drug-related adverse events. Transient skin burning at the site of application is a common adverse effect associated with tacrolimus ointment (8–11) and this appears to be true for the tacrolimus gel and cream formulations. Skin burning normally lasts around 10 min (11) and for most patients in this study, discomfort was not sufficient to warrant discontinuation of treatment, and the preva-

lence of skin burning decreased greatly as the clinical condition of the skin improved.

A potential weakness of the study was the possibility of observer bias. The patients were asked not to show their study medication to the investigator or discuss the type of topical treatment used, but it is possible that the patients may have unwittingly given some clue to the investigator. In addition, the higher incidence of skin burning observed in the patients applying the tacrolimus formulations may also have indicated to the investigator which study treatment had been randomized.

In conclusion, in this study setting, the two novel tacrolimus formulations demonstrated efficacy comparable with that of calcipotriol ointment, and 0.3% tacrolimus gel and 0.5% tacrolimus cream are possible therapeutic options for the treatment of mild to moderate plaque psoriasis in adults.

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