A prospective proof of concept study of the efficacy of tacrolimus ointment on uraemic pruritus (UP) in patients on chronic dialysis therapy

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Abstract

Background. Uraemic pruritus (UP) is a serious symptom of chronic dialysis patients and patients with end-stage renal disease. UP causes skin damage, discomfort, sleeping disorders and diminished quality of life. Since UP is considered to be in part an immune-mediated inflammatory process, immunosuppressive drugs like tacrolimus may be beneficial.

Methods. We conducted a prospective study on the effect of 6 weeks treatment with two sequential concentrations of tacrolimus ointment on the severity of UP in chronic dialysis patients and again after 2 weeks wash-out. Twenty-five patients with UP were enrolled in the study; 21 patients completed the study. UP was measured using a validated modified pruritus assessment score and a Visual Analogue Scale (VAS).

Results. The modified pruritus assessment score decreased significantly by 81.8% after 6 weeks treatment from [median score 11 (interquartile range: IQR 6–16) on day 0 to median score 2 (IQR 0–5.25) at week 6: \( P \leq 0.0001 \)]. After 2 weeks wash-out, the median score returned to 72.7% of baseline levels [8 (IQR 2–16)]. Using the VAS score an identical evolution could be demonstrated. Tacrolimus ointment was well tolerated and no serious adverse events were noted. Transient stinging and burning sensation was reported by four patients in the first weeks of the trial, one patient suffered a mild skin rash. No systemic exposure to tacrolimus was detected.

Conclusion. This prospective study has shown that 6 weeks treatment with tacrolimus ointment significantly reduces the severity of UP in chronic dialysis patients and is well tolerated. Randomized placebo-controlled studies are necessary to confirm these encouraging preliminary results.

Keywords: haemodialysis; peritoneal dialysis; tacrolimus ointment; uraemic pruritus

Introduction

Uraemic pruritus (UP) is a frequent and bothersome symptom of patients on chronic dialysis therapy and end-stage renal failure. The incidence of UP has declined over the years thanks to improvements in dialysis efficacy and the use of biocompatible dialysis membranes [1]. While the incidence of UP was estimated to be 85% in the 1970s [2], the current incidence is estimated between 22 [3] and 48% [4]. Still, UP remains a frustrating problem causing serious discomfort and skin damage in affected patients with often complete disturbance of day and night rhythm, sleeping disorders, depression, anxiety and diminished quality of life [4]. Many different therapeutic modalities have been tested with very variable and often only moderate success [5,6].

The pathophysiology of UP is complex and still unknown 'uraemic factors' contribute to its origin [7]. Two favourable hypotheses about the mechanism of UP have been brought forward recently and are supported by preliminary results of therapeutic clinical trials [8]. The first theory involves the opioidergic system (‘the opioid hypothesis’). In this hypothesis UP would be caused by the over-expression of opioid \( \mu \)-receptors in dermal cells and lymphocytes of uraemic patients [9]. Indeed, administration of an oral opiate-receptor antagonist like naltrexone has shown beneficial effects, at least in small uncontrolled studies [10,11]. However, in a subsequent larger trial comprising 23 patients, a significant difference in efficacy could not be demonstrated between 4 weeks of treatment with naltrexone or placebo [3]. Furthermore, in the latter trial 39% of the actively treated patients developed gastrointestinal side effects. More recently, a \( \kappa \)-receptor
agonist (TRK-820) was tested as treatment for UP in two placebo-controlled studies as it was shown that activation of the κ-opioid system is efficient in reducing pruritus in a mouse model [9,12].

In the second hypothesis (‘The immuno-hypothesis’) UP is considered an inflammatory ‘systemic disease’ rather than a local skin disorder. From studies examining the beneficial effects of UVB-exposure on UP, we learned that UVB attenuates the development of Th1 type lymphocytes in favour of the Th2 type [13]. Also, the use of thalidomide, an immunomodulator that suppresses TNF-α production and leads to a Th2 type differentiation with suppression of the IL-2 producing Th1 cells, seems effective in reducing UP [14]. Tacrolimus, a calcineurin inhibitor, also suppresses the differentiation of Th1 lymphocytes and the production of IL-2 [15]. Also, from clinical observations after kidney transplantation, one of the first symptoms to disappear is UP. Anecdotal case reports mention the efficacy of tacrolimus 0.03% ointment in the short-term treatment of UP [16]. However, larger prospective trials are currently missing.

We therefore conducted a prospective, proof-of-concept, single-centre study to evaluate the efficacy of sequential use of tacrolimus ointment 0.1% followed by 0.03% on the severity and incidence of UP in patients on chronic dialysis therapy.

Subjects and methods

Study design

This was a prospective single-centre study using two sequential concentrations of tacrolimus ointment (0.1 and 0.03%) in consecutive order for two active treatment periods of each 3 weeks. After a total of 6 weeks uninterrupted active treatment, 2 weeks of wash-out were considered before patients were finally re-evaluated.

Study endpoints

The primary endpoint of the study was the change in baseline UP score as assessed by the UP assessment questionnaires after 6 weeks of consecutive treatment with two different concentrations (0.1 and 0.03%) of tacrolimus ointment. Secondary endpoints comprised the occurrence of study drug-related clinical adverse events and side effects and safety endpoints assessed by laboratory tests. The evolution of the UP score after a 2-week treatment-free wash-out period was also evaluated.

Study population

Between July and August 2003 all patients on chronic haemodialysis therapy (n = 131) and chronic peritoneal dialysis treatment (n = 49) in permanent follow-up in our hospital were questioned about the occurrence of pruritus. From all patients that confirmed to suffer from UP and met the inclusion and exclusion criteria (n = 27), 25 accepted to enrol in the study. Two patients who were eligible refused to participate in the trial. Four additional patients with UP failed to meet the inclusion and exclusion criteria. All participants gave their written informed consent and the study was approved by the Ethics Committee.

Inclusion and exclusion criteria

All chronic haemodialysis or peritoneal dialysis patients suffering from UP and above the age of 18 years were eligible for the study. Participants had to give their written informed consent before commencement of the study. Exclusion criteria were specific pruritus treatments currently employed or in the last 3 months. In these treatments were included phototherapy (UVB), capsaicin/lidocain, acupuncture, cholestyramine, opioid agonists/antagonists, serotonin antagonists, corticosteroids, thalidomide, nicergoline, immunosuppressive drugs and any other experimental or investigational drug. Patients with proven skin disorders associated with pruritus (e.g. eczema, atopic dermatitis) were excluded as well as patients with a known allergy for tacrolimus ointment or macrolides. Patients with cognitive impairment who failed to comprehend the study and/or the pruritus questionnaire (see below) were excluded as were patients known to have a history of non-compliance.

Tacrolimus ointment use

During the first 3 weeks of the active treatment period, enrolled patients were treated with tacrolimus ointment in a concentration of 0.1%. All patients received one tube containing 30 g and were instructed to apply the ointment twice daily on all affected skin surfaces in a thin layer. They received the information contained in the package insert of Protopic® on method of application, precautions, side effects and contraindications in a separate patient information brochure especially developed for study purposes. After 3 weeks all patients were switched to tacrolimus ointment at a concentration of 0.03% (one tube of 30 g) for another 3 weeks of active treatment. Patients had to return their unfinished ointment tubes at the end of each active treatment period.

Evaluation of UP

Patients answered identical pruritus questionnaires on six different time points during the study. The first questionnaire was answered on day 0 of the study before treatment was started. Consecutive questionnaires were completed on weeks 1, 3, 4 and on week 6 at the end of the active treatment period. The last questionnaire was answered after a 2-week wash-out period (week 8). The questionnaire consisted of a combination of UP scoring systems:

(i) Modified pruritis assessment score as described by Pauli-Magnus et al. [3].

(a) Severity of pruritus. A slight itching sensation without necessity of scratching received 1 point, with necessity to scratch but without excoriations 2 points, scratching accompanied by excoriations 4 points and pruritus causing in addition total restlessness received 5 points.

(b) Distribution of pruritus. Itching at less than two locations received 1 point, more than two locations 2 points and generalized itching 3 points. The score of
severity and distribution of pruritus was recorded and multiplied separately for the morning and the afternoon so that a maximum of 30 points could be achieved.

(c) Sleep disturbance. Each episode of waking up because of itching received 2 points (maximum of 10 points) and each scratching episode leading to excoriations during the night received 1 point (maximum 5 points). The score of sleep disturbance and the severity-distribution score was added to assess the final score with a maximum of 45 points.

(ii) Visual Analogue Scale (VAS). Using a VAS, patients were instructed to estimate the intensity of their pruritus with at the lower end a ‘zero’ score indicating no itching and at the higher end a ‘10 score’ representing unbearable pruritus.

(iii) Current anti-pruritic therapy. Patients were asked if they were taking any specific medication for pruritus and allowed by the study protocol (see exclusion criteria).

(iv) Sleeping medication. Patients were asked if they were using any sleeping medication because of pruritus.

(v) Quality-of-life. Patients were asked if pruritus caused anxiety and nervousness and/or depression.

(vi) Dialysis effect. Patients were asked if, in their opinion, dialysis treatment had any effect on pruritus. If indeed they stated that there was an effect, it was asked if dialysis therapy improved or worsened pruritus.

(vii) Area of pruritus. Patients were asked to mark the body surface areas where the pruritus usually occurred using a body diagram originally employed for clinical assessment of severity of burns using ‘the rule of nines’ (9%) [17].

(viii) Side-effects. Patients were asked if they experienced any new symptoms, complaints or side effects since using tacrolimus ointment or if any existing conditions had worsened since the start of active treatment.

Laboratory assessments

Biochemical laboratory tests were performed at the start of the active treatment period (day 0) and again at the end of the active treatment period (week 6). These tests included: plasma calcium, phosphorus, magnesium concentrations; urea and creatinine, liver function tests, ferritin levels, C-reactive protein, haemoglobin levels, parathyroid hormone, 25-OH-vitamin D and tacrolimus blood concentration (only at week 6). The latter were measured using a microparticulate immunoassay (IMx II, Abbott Laboratories) with a lower detection limit of 2 ng/ml.

Dialysis efficacy

The efficacy of dialysis therapy was assessed by calculated Kt/V according to Daugirdas [18] and per cent urea reduction rate (URR%) on two occasions: the first time before the start of active treatment and the second time after 6 weeks of tacrolimus ointment therapy. Dialysis modality and membrane type remained unchanged throughout the study period in all patients.

Safety and concomitant medication

During the study (including the wash-out period) adverse events were noted in the Case Report Form (CRF) and all concomitant drugs were checked. The specific side effects related to the use of tacrolimus ointment were double-checked as part of the evaluation questionnaire (see above).

Statistical analysis

Distribution for continuous data was evaluated (Kolmogorov–Smirnov and Shapiro–Wilk) and consequently parametric tests and non-parametric tests were applied when appropriate. Data are expressed as mean ± standard deviation (SD) or median with interquartile (1st to 3rd) range (IQR) when appropriate. Non-parametric tests were used for dichotomous, ordinal and categorical variables (SAS 8.02 software). A paired t-test or ANOVA for repeated measurements (normal distribution) and repeated measures analysis of variance on ranks (non-parametric) were applied when appropriate. Continuous clinical variables were evaluated using univariate linear regression analysis. A P-value < 0.05 was considered statistically significant.

Results

Patient demographics

A total of 27 patients (i.e., 15% of the total chronic dialysis population in follow-up in our centre) suffering from UP were eligible for enrolment in the study. Two patients (7.4%) declined to participate in the trial after reading the patient information brochure. Of the 25 patients that started the study, 21 (84%) completed the study. Four patients withdrew from the study; one patient withdrew her consent after 1 week because of side effects (severe ‘stinging’ after applying tacrolimus ointment); the second patient withdrew from the study after 1 week because of lack of efficacy and the remaining two patients were excluded from the trial after 3 weeks by the investigators because they did not comprehend the purpose of the UP questionnaire. Two (9.5%) patients were using an anti-histamine (cetirizine) for UP. The demographic characteristics of the remaining 21 patients that completed the study are summarized in Table 1.

Efficacy assessment

The characteristics of UP assessed by a self-reporting questionnaire are summarized in Table 2. Most patients reported the anterior chest and abdomen (18%), the back (26%) and limbs (33%) as the most frequently affected body areas. Five patients were taking sleeping medication in order to alleviate nocturnal UP at the start of the study. All of them could discontinue these drugs after 6 weeks of active treatment. (The number of patients on sleeping medication prior to and after 6 weeks of active treatment significantly differed statistically, \( P = 0.02 \)) The number of patients that reported nervousness as a result of UP at the beginning of the trial significantly decreased after 6 weeks active therapy \( (P = 0.001) \). In 85.7% of patients, dialysis did not influence the clinical course of UP. The modified
pruritus assessment score but not the VAS score was associated with the time on dialysis therapy ($r^2 = 0.48$, $P = 0.003$). Neither the VAS score nor the modified UP assessment score were associated with dialysis efficacy ($Kt/V$ and PRU), serum phosphorus concentration or parathyroid hormone (PTH) levels.

UP measured by the modified pruritus assessment score (Figure 1) was significantly reduced by 81.8% after 6 weeks of treatment with tacrolimus ointment. The median score decreased from 11 (IQR 6–16) on day 0 to 2 (IQR 0–5.25) at week 6 ($P < 0.0001$). After a 2-week wash-out, the median score returned to 72.7% of baseline levels (8, IQR 2–16). Using the VAS score an identical evolution could be demonstrated (Figure 2): median VAS score decreased significantly by 42.9% between day 0 [7 (IQR 6–8)] and week 6 [4 (IQR

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**Fig. 1.** Evaluation of the severity of uremic pruritus by the modified pruritus assessment score after 6 weeks of active treatment with tacrolimus ointment and after two weeks wash-out ($n = 21$). *$P < 0.01$: statistically significant difference in median score between week 6 and baseline (day 0, $P < 0.0001$) and after wash-out (week 8, $P = 0.002$).
P = 0.0002) and returned to 85.7% of the baseline score after 2 weeks wash-out (n = 21). Horizontal lines indicate the mean VAS score at different time points while vertical lines indicate standard deviation. *P < 0.05: statistically significant difference in score between week 6 and baseline (day 0, P = 0.0002) and after wash-out (week 8, P = 0.04).

**Safety assessment**

Laboratory biochemical tests, dialysis efficacy and blood pressure at the start and the end of the active treatment period are compared in Table 3. The PTH level increased significantly during the active treatment period from a median 82.6 ng/l (IQR 48.8–124) at baseline to 105.5 ng/l (IQR 63.4–169.1) (P = 0.007). At the same time the concentration of 25-OH-hydroxy vitamin D decreased from 40.4±22.8 mg/l on day 0 to 33.3±16 mg/l at week 6 (P = 0.04). There were no other significant differences between parameters on the two assessment time points. In none of the patients was tacrolimus detected in the blood at the end of 6 weeks active treatment (< 2 ng/ml) as measured by immunoassay.

Clinical adverse events that occurred during the trial and were reported in the CRF were: acute pancreatitis (one), decubitus ulcer (one), acute peritonitis (one), periarteritis of the shoulder (one), fungal oesophagitis (one), transplantectomy (one), hypotension (one) and infection of a renal cyst in a patient with adult polycystic kidney disease (one). None of these events were considered as related to the study drug.

Specific drug-related adverse events were reported by the patients in the questionnaire and double-checked by
the investigators. After 1 week of active treatment five patients had reported side-effects from the ointment: four patients mentioned a transient tingling of the skin immediately after application while the remaining patient noticed a slight red skin rash. After 3 weeks, one patient still reported a tingling sensation and another sensed a burning skin irritation immediately after using the study drug. One patient described a short-lasting increase in pruritus the first 15 min following skin application (on weeks 4 and 6). At week 6, one patient still suffered from tingling of the skin immediately after applying the ointment.

Discussion

We have demonstrated for the first time in a prospective, open-label, proof-of-concept study that 6 weeks treatment with tacrolimus ointment (Protopic 0.1 and 0.03%) results in a significant reduction of UP score in chronic dialysis patients. This study confirms previous anecdotal cases reporting on the beneficial effects of local treatment with tacrolimus ointment on UP [16]. Of course, a prospective placebo-controlled trial would be necessary to confirm a causal relationship between tacrolimus and reduction of UP symptoms. The fact that 2 weeks after discontinuation of the study drug, the UP score returned to baseline values indicates that the use of tacrolimus ointment was, to some extent, responsible for these favourable findings. However, it does not completely rule out a placebo effect. It is well known that emollients are also effective in reducing the severity of UP, especially in patients with xerosis related to uraemia [19]. Therefore, a potential hydration (placebo) effect of the ointment containing tacrolimus warrants a controlled study. Another point of discussion is what degree of severity of pruritus is considered as clinically relevant. We, like others [3,20], did not define a minimum VAS or modified pruritus assessment score for patients to participate in the present study because we wanted to evaluate the effect of tacrolimus ointment on different degrees of pruritus. However, the fact that 71.4% of patients suffered from skin excoriations as a result of UP, the mean VAS score before the start of the study was 6.71 (range 4–10) and that 76.2% of patients had failed previous therapy for UP (including UVB therapy, glucocorticosteroids, serotonin agonists and capsaicin), indirectly indicates that pruritus was clinically relevant in the present study population. That in the present study not only the VAS was used but also the more extensive and validated modified pruritus assessment score for uraemic patients, as described by Pauli-Magnus et al. [3], strengthens our findings. Less objective evaluation methods on the impact of UP on the patient’s daily behaviour, like the use of sleeping medication and pruritus-induced nervousness [4], also improved with the use of tacrolimus in this study. The type of dialysis treatment did not influence the results of this study. Taking into account the small absolute numbers, both for haemodialysis and peritoneal dialysis patients, treatment with tacrolimus ointment resulted in a statistically significant improvement of both pruritus scores (data not shown). Because biocompatible dialysis membranes have been reported advantageous for correction of UP [8], all patients in the present study were treated with biocompatible (polysulfone) membranes. However, the small and heterogeneous study population cautions against drawing definite conclusions from the present findings. The clinical beneficial effect of tacrolimus ointment on UP in the present trial at least warrants further investigation and comparison with other agents such as μ-opioid receptor antagonists [3,10,11], κ-opioid receptor agonists [9,12] and 5-HT3-receptor antagonists [20], especially when taking into account the side-effect profiles of the latter drugs. The use of tacrolimus ointment was well tolerated in the present trial and no serious drug-related adverse events were noted. Apart from the transient stinging and burning sensation reported by 19% of the study patients in the first weeks of the trial, only one patient suffered a mild skin rash while an initial increase in pruritus after application of the ointment was noticed in another patient. All of these known side effects are identified in the package insert of Protopic®. None of the clinical adverse events occurring during the active treatment period could be attributed to the use of tacrolimus ointment. Infectious complications might have been the result of systemic exposure to the drug but tacrolimus blood levels were undetectable in all patients (by immunoassay), making the latter reasoning unlikely, more so because primary skin infections were also lacking.

The financial implications of tacrolimus ointment therapy are important as the drug is currently not reimbursed for this indication. In order to reduce costs, patients were switched to the 0.03% concentration after 3 weeks of treatment—analogous to the regimen used in atopid dermatitis (see package insert Protopic)—and without any loss of beneficial effect (data not shown). An estimation of the individual costs was hampered by a large inter-individual variability in dosage used, ranging from 4 to 29 g (mean 15.7 g) in 3 weeks. Based on weighting of the returned unfinished tubes, it was estimated that 30 g (one tube) of tacrolimus ointment was used every 6 weeks; resulting in an annual cost of €410 for the 0.1% and €370 for the 0.03% concentration. However, although very substantial, this cost has to be weighted against the financial burden of alternative local and systemic anti-pruritic treatment, which had failed previously for the majority (76.2%) of patients.

The exact reason why PTH levels increased and 25-OH-vitamin D concentrations decreased significantly after 6 weeks treatment with tacrolimus ointment is not clear. Changes in drug maintenance therapy (phosphate binders, vitamin D3 supplements) were ruled out, as were changes in dialysis prescription or calcium-phosphorus product (see Tables 1 and 3). A direct causal relationship between local application of tacrolimus and alterations in vitamin D metabolism seems less likely as there is no evidence that tacrolimus...
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Ointment would interfere with the non-enzymatic synthesis of cholecalciferol under influence of ultraviolet light. The modified pruritus assessment score correlated with time on dialysis in the present study but not with PTH concentration and this is in accordance with other reports [21].

In conclusion, as demonstrated in this single-centre proof-of-concept study, 6 weeks treatment with tacrolimus ointment significantly reduces the severity of UP in chronic dialysis patients and is well tolerated.

Large, randomized placebo-controlled studies are necessary to confirm these encouraging preliminary results. Tacrolimus ointment could therefore become a valuable agent for treating this cumbersome uraemic symptom in chronic dialysis patients.

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