

ORIGINAL ARTICLE

Efficacy of topical tacrolimus for the treatment of persistent pruritus ani in patients with atopic dermatitis

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Background: Pruritus ani (PA) is defined as intense chronic itching affecting perianal skin. **Objective:** We aimed to determine the efficacy of topical tacrolimus treatment in atopic dermatitis (AD) patients who have PA. **Methods:** The study included 32 patients with AD who were suffering PA. Patients were randomized into two groups. In total, 16 patients used 0.03% tacrolimus ointment and 16 patients used vaseline as placebo. All groups applied topical treatments to their perianal area twice daily for 4 weeks. The treatments were then reversed for 4 weeks after a 2 weeks wash out period. **Results:** In total, 32 patients with AD who had refractory anal itching were enrolled in this study. None of the patients had obtained successful results with previous treatments. There was a statistically significant decrease in the recorded EASI, DLQI and itching scores for the tacrolimus group compared to the placebo group at weeks 4 and 6 of treatment ($p < 0.05$). **Conclusion:** Topical tacrolimus treatment was well tolerated and effective in controlling persistent PA in AD patients.

Key words: anal itching, dermatology life quality index, eczema area and severity index, atopic dermatitis, pruritus ani, tacrolimus ointment

Introduction

Pruritus ani (PA) is defined as an intense chronic itching affecting the perianal skin. PA affects 1 – 5% of the general population. In addition, it is four times more common in males than females and is most frequent between the fourth and sixth decades (1,2). Anorectal hemorrhoids and fissures (3), dermatoses of perianal skin (atopic dermatitis (AD), psoriasis, Bowen disease, lichen planus, allergic contact dermatitis), local infections (candidiasis, dermatophyte infections, parasites, condyloma lata), benign and malignant anal tumors, foods (spices, coffee, tea, chocolate) and psychogenic diseases can cause PA (4). Many treatment modalities for perianal pruritus are available, such as topical corticosteroids, topical non-steroid anesthetics and systemic antihistamines (5,6). In addition, anti-pruritic effects of topical calcineurin inhibitors have been reported (7).

In this study, we investigated the efficacy of topical tacrolimus treatment for PA in AD patients.

Patients and methods

In total, 32 AD patients (4 females and 28 males) suffering from persistent anal itching and all of whom had been referred to the Department of Dermatology of Elazığ Education and Research Hospital, were enrolled in this study. The patients were diagnosed in accordance with the Hanifin Rajka classification (8). All patients had suffered symptoms for at least 3 months and prior treatments did not result in stable improvement of anal itching. Detailed anamneses of all patients, including personal and familial atopy histories were taken and physical and dermatological examinations were conducted.

Exclusion criteria

The following are the exclusion criteria for this study

- (1) Patients < 18-years old
- (2) Pregnancy
- (3) Dermatoses in perianal skin including eczema, psoriasis and contact dermatitis
- (4) Positive skin patch test
- (5) Infectious diseases in the perianal skin including tinea infection, parasitosis and herpes infection
- (6) Systemic diseases that can cause perianal itching, including diabetes mellitus, thyroid diseases, cancer and liver diseases
- (7) Patients who had used systemic or topical treatment for anal itching in the past month
- (8) Patients who had previous proctological surgery and had anorectal conditions such as malignant tumors of the anus and rectum, fissures, fecal incontinence or hemorrhoids.

Study plan

After dermatological examination, patients who were enrolled in the trial were subjected to a full blood count, thyroid function test, IgE levels and a skin patch test including the active treatment and placebo in addition to a standard test. Native preparations were performed for fungal investigation. Perianal swabs for bacterial cultures were also taken into account.

Table I. Eczema area and severity index: calculation for patients 8 years of age and older (9).

Body region	EASI Score
Head/Neck (H)	$(E + I + Ex + L) \times \text{Area} \times 0.1$
Upper limbs (UL)	$(E + I + Ex + L) \times \text{Area} \times 0.2$
Trunk (T)	$(E + I + Ex + L) \times \text{Area} \times 0.3$
Lower limbs (LL)	$(E + I + Ex + L) \times \text{Area} \times 0.4$

EASI = Sum of the four body region scores above.

The patients were randomized into two groups. In total, 16 patients were treated with topical 0.03% tacrolimus ointment twice daily for 4 weeks, and 16 patients were treated with pure vaseline twice daily for 4 weeks as a placebo. At the end of the 4-week period, the patients were re-examined. After a 2-week washout period, the treatments were reversed for 4 weeks. Side effects, such as skin burning, of treatment with tacrolimus ointment were evaluated. After the treatment was completed, the patients were followed-up for 8 weeks to assess any relapse. At the beginning of the study period, instructions regarding perianal hygiene were given to the patients.

Evaluation of treatment efficacy

Patients were evaluated by the same physician at the first visit and at weeks 4, 6, 10, 14 and 18. Perianal skin was evaluated using the Eczema Area and Severity Index (EASI) score (9) at the initiation of treatment and at weeks 4, 6 and 10 (Table I).

The percentage of the area involved for each of the four body regions was assigned a proportional score from 0 to 6 during the analysis: 0 = no eruption; $1 \leq 10\%$; $2 \leq 10 - 29\%$; $3 \leq 30 - 49\%$; $4 \leq 50 - 69\%$; $5 \leq 70 - 89\%$; and $6 \geq 90 - 100\%$. Each of the four body regions was assessed separately for the key signs of erythema, induration/papulation/edema, excoriations and lichenification. The average degree of severity of each sign in each of the four body regions was assigned a score of 0 – 3 (none, mild, moderate and severe) (9). In this index, the buttocks and feet were counted as part of the lower extremities.

In our study, the perianal region was counted as part of the lower extremities. The percentage of area score was $1 (\leq 10\%)$. The average degree of severity of each sign ($E + I + Ex + L$) was calculated for each patient and the total EASI score was calculated.

In addition, before and after treatment, the patients were requested to score their perianal itching in the range 0 – 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe). Another parameter used was the dermatology life quality index (DLQI) (10) and its Turkish version (11). We used the DLQI score at the initiation of the treatment and at weeks 4, 6 and 10.

The primary aim was a reduction in itch. The secondary aims were clinical improvement of the perianal skin using the EASI score and improvement in the quality of life as assessed by the DLQI questionnaire.

Statistical analyses

The Statistical Package for Social Sciences (SPSS) for Windows (version 18.0) was used for data analysis. Quantitative data were expressed as the mean $\pm$ standard deviations and qualitative data were expressed as numbers (%). The independent two samples *t*-test, the χ^2 test and Fisher's exact test were used to compare the groups.

Results

In total, 32 patients with AD suffering from refractory anal itching were enrolled in this study. Sixteen patients were treated with topical 0.03% tacrolimus ointment, and 16 patients were treated with pure vaseline as a placebo treatment. In the tacrolimus group,

the ages of the patients ranged from 18 to 56 years with a mean of 38.12 ± 11.1 years. In the placebo group, the ages of the patients ranged from 24 to 66 with a mean of 37.11 ± 10.3 years. Disease duration in the tacrolimus group was 8.00 ± 7.84 years and 3.93 ± 4.17 years in the placebo group. No statistically significant differences between the groups in terms of age, gender and disease duration were identified ($p > 0.05$). There were no statistically significant differences between the groups in EASI, DLQI and itching scores before treatment ($p > 0.05$). There was a statistically significantly lower finding in the EASI, the DLQI and the itching scores for the tacrolimus group compared to the placebo group at weeks 4 and 6 of treatment ($p < 0.05$; Table II). In addition, the patients were evaluated regarding side effects. Skin burning was reported in four patients (12.5%) in the tacrolimus group. In addition, the patients were followed-up for 8 weeks after completion of the treatments. When the rates of relapse were investigated, relapse was detected in 13 patients in the tacrolimus group (81.25%) and 11 in the placebo group (68.75%).

Discussion

PA has several causes and has been divided into subtypes including idiopathic and secondary PA. Idiopathic PA is diagnosed in cases in which no etiology can be found and accounts for 25 – 75% of PA cases. Secondary PA is diagnosed when an underlying cause can be found; once the cause has been treated, the PA can usually be easily treated (12). The main symptom of PA is the intolerable impulse to scratch the perianal area and pruritus, which occurs especially after a bowel movement and at bedtime (13). The presence of atopy may be relevant since many patients with AD experience disproportionate pruritus compared to patients without atopy (14).

For the PA patients, life style modification should initially be suggested. The perianal area should be maintained dry and clean. Patients should be educated to clean the perianal area with water after defecation and to avoid severe rubbing. In addition, perianal skin should be dried with a hair dryer or gently tapped with cotton swabs (2). The use of warm water and low water pressure is important to avoid irritation of the anus (15). In addition, patients must avoid underwear that cannot absorb sweat well, preferably loose cotton underwear (2,16).

Many treatment modalities for PA are available. If a specific cause of perianal pruritus is identified, appropriate treatment such as antifungals and anthelmintics should be given. For idiopathic PA, topical corticosteroids are widely used (5). Al-ghnaniem et al.

Table II. The initial findings of tacrolimus and placebo groups and recovery rates of patients at weeks of 4, 6 and 10.

		Tacrolimus	Placebo	<i>p</i>
Initial	EASI score*	1.70 ± 0.45	1.80 ± 0.56	0.584
	Itching score*	3.75 ± 0.44	3.81 ± 0.40	0.681
	DLQI score*	9.00 ± 5.00	9.68 ± 3.36	0.652
4th week	EASI score*	0.72 ± 0.41	1.67 ± 0.64	0.001
	Itching score*	1.68 ± 1.30	3.62 ± 1.02	0.001
	DLQI score*	2.6 ± 2.41	8.62 ± 3.53	0.001
6th week	EASI score*	1.02 ± 0.54	1.72 ± 0.61	0.002
	Itching score*	2.43 ± 1.41	3.93 ± 0.25	0.001
	DLQI score*	5.25 ± 5.19	9.56 ± 3.18	0.008
10th week	EASI score*	2.22 ± 3.71	0.92 ± 0.71	0.180
	Itching score*	3.12 ± 1.45	1.43 ± 1.41	0.002
	DLQI score*	7.18 ± 5.34	3.56 ± 4.22	0.042
18th week	Positive relapse (%)	13 (81.25),	11 (68.75)	0.685
	Negative relapse (%)	3 (18.75)	5 (31.25)	

*Mean $\pm$ SD.



Figure 1. Perianal area with induration, papulation, edema, hyperpigmentation and lichenification before the topical tacrolimus treatment.

(17) reported that the application of 1% hydrocortisone for the treatment of PA was effective in 68% of the patients compared to the placebo group. However, Öztaş et al. (4) compared the effectiveness of perianal cleansing and topical corticosteroid (mometasone furoate) and did not find a statistically significant difference between the two treatments. Topical corticosteroids, especially if used for a long time, can cause atrophy, bacterial and fungal infections, allergic contact dermatitis, telengectasia, purpura and scar formation (18).

Another treatment for PA is topical capsaicin. Lysy et al. (19) reported that 0.006% topical capsaicin ointment in the treatment of PA was statistically significant compared with placebo. Capsaicin causes a mild perianal burning sensation.

Itch is caused by irritation to the end of unmyelinated C-fibers located at the epidermal-dermal junction. Histamine is the main mediator of pruritus, but other compounds such as serotonin, prostoglandins, endogenous opioids and neuropeptides also play a role (20). This situation is especially important in AD patients, because pruritus in AD is due to the presence of many inflammatory pruritogenic factors other than histamine (21–23).

Topical tacrolimus is a corticosteroid-free immunomodulator developed for the treatment of AD (24). Tacrolimus induces calcineurin inhibition that interrupts cytokine gene expression and leads to the down regulation of T-cell activity. In addition, calcineurin inhibitors may influence nerve fiber function directly



Figure 2. Perianal area at fourth week of the topical tacrolimus treatment.

by binding to a receptor on small unmyelinated sensory nerve fibers (25).

The development of topical calcineurin inhibitors has resulted in a significant improvement in the treatment of AD (26). In addition to inhibiting calcineurin activity and suppressing cytokine production by T cells, tacrolimus targets other processes, including reducing cell-surface expression of receptors and co-stimulatory molecules on epidermal antigen-presenting cells (27,28) and blocking the release of inflammatory mediators from mast cells and basophils (29). The efficacy and safety of tacrolimus ointment for AD has been demonstrated in large, multicenter studies (30,31) and it has been shown to be well tolerated. Skin burning is the most common side effect, but is typically transient, lasting 15 – 20 min, and occurring during the first few days of treatment (30). Therefore, tacrolimus provides the efficacy of topical corticosteroids without the associated side effects (32).

In this study, we investigated the efficacy of 0.03% tacrolimus ointment in AD patients with anal itching. Few studies have assessed topical tacrolimus treatment for perianal diseases. Schaubert et al. (33) reported that 0.1% topical tacrolimus therapy is effective, safe and well tolerated in the treatment of perianal eczema. In addition, Suys (34) evaluated topical tacrolimus treatment in resistant idiopathic PA patients. They demonstrated a significant reduction in symptoms in 68% of the patients after 2 weeks of treatment. However, no information regarding relapse was provided in either of these studies.

We report here a significant improvement in EASI, DLQI and itching scores of the patients after 4 weeks of treatment with tacrolimus ointment. There was a significant reduction in symptoms in 80% of the patients, according to the EASI score, in the tacrolimus group. This proportion was 6.66% in the placebo group. Especially, there was a rapid reduction in perianal erythema in a few days. However, induration/papulation/edema, excoriations and lichenification in perianal area dissolved more slowly. In the tacrolimus group, EASI scores decreased at the fourth week of the therapy and this situation continued for few weeks after the washout period. Therefore, we showed that the efficacy of tacrolimus treatment continued for few weeks after the end of therapy.

In addition, 75% of the patients showed a significant improvement in quality of life. This proportion was 7.6% in the placebo group. The main symptom that affects the quality of life was anal itching in our patients; a significant reduction was found in 56.25% of the patients in the tacrolimus group compared to 6.25% in the placebo group. The persistent anal itching was affecting the quality of life by intense and painful pruritus. Because of the pruritus, most of the patients were feeling embarrassed and this situation was affecting social or leisure activities. In this study, we showed that the anal itching dissolved rapidly in tacrolimus group in a few days and also the dermatological life quality scores decreased.

In addition, when we compared weeks 4 and 10, a rapid response to tacrolimus treatment was identified in the placebo group. All of the scores decreased after the washout period with the usage of tacrolimus treatment in the placebo group. However, the relapse ratio was high in both groups. Relapse ratio was 81.25% in tacrolimus group and 68.75% in placebo group at week 18. We think that this situation is related to the usage of placebo treatment after the washout period in the tacrolimus group.

Conclusion

In conclusion, our data suggest that topical tacrolimus treatment is effective in AD patients who have refractory anal itching.

However, the relapse of anal pruritus in patients is a significant problem, as the treatment would have to be used for long periods to control anal itching. Despite this, we believe topical tacrolimus is a safe treatment for prolonged PA. Patients exhibited a rapid reduction in symptoms and no significant side effects such as skin atrophy, telengectasia, purpura and scar formation, which typically occur during topical corticosteroid treatment of long duration, were identified.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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