CASE REPORTS AND LITERATURE REVIEW OF GENITAL PSORIASIS: SUCCESSFUL THERAPY WITH TACROLIMUS

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ABSTRACT

Psoriasis is a chronic, inflammatory skin disease with a high prevalence in the general population. However, though psoriasis may involve all sites of the body, it most frequently involves the genitals. Psoriasis involvement of the genital region can be uncomfortable and embarrassing for both men and women. The psoriatic lesions can cause pain, itching, and burning sensation, furthermore it can determine a significant psychological impact. Patients with recurrent genital lesions experience significantly worse quality of life, sexual dysfunction, and distress. In addition, genital psoriasis (GP) can be difficult to treat, due to the sensitivity of genital skin, and few studies have been published on this topic. This paper aims to summarise the studies reported in the literature, designed to evaluate the efficacy and tolerability of topical tacrolimus on GP. Moreover, we report the cases of two patients presenting with GP who have been treated with tacrolimus.

Keywords: Psoriasis, genital psoriasis, topical therapies, tacrolimus, calcineurin inhibitors, Koebner phenomenon, sexual distress, quality of life.

INTRODUCTION

Genital Psoriasis (GP)

Psoriasis is a common chronic inflammatory skin disease affecting 0.5-4.6% of the world population.[1] The most common form of psoriasis is chronic plaque psoriasis (PP), characterised by well-demarcated plaques with a loosely adherent silvery-white scale. The lesions are typically distributed symmetrically on the scalp, elbows, knees, lumbosacral area, and in the body folds.[2] However, psoriasis may involve all sites of the body, most frequently, the genitals. There are limited epidemiological data on genital involvement in psoriasis. In most cases genital involvement is only a part of generalised PP, often of inverse psoriasis, although it may affect only the genitals in 2-5% of the patients. Recently Meeuwis et al.[3,4] disclosed that frequency of genital involvement was 29-40%; however, in a subsequent study they illustrated that almost 46% of 1,943 patients reported genital lesions (GLs) at some time during the course of their skin disease.

The particular structure of the genital skin, which changes from stratified and keratinised squamous cell epithelium to mucosa, makes the psoriatic lesions (PLs) clinically different to the rest of the body. The skin lesions commonly present in the genital area as thin plaques, well demarcated and erythematous. The typical scales are often absent and when present, are minimal.[4] The diagnosis can be, in most cases, based on the clinical appearance of the lesions. However, vulvar and penile lesions frequently have an atypical appearance; in addition, the particular location sometimes makes it difficult to distinguish psoriasis from sexually transmitted diseases (STDs). When the clinical diagnosis of psoriasis may be difficult, a biopsy should be done.[3]

Psoriasis involvement of the genital region can be uncomfortable and embarrassing for both men and women. The PLs can cause pain, itching, and

burning sensation, furthermore it can determine a significant psychological impact. Patients with recurrent GLs experience significantly worse quality of life (QoL) and more sexual distress, when compared with patients without lesions. The management of GP can be difficult; treatment options for GP are limited and supported by only a small number of reports. The most common topical treatments are corticosteroids, vitamin D analogues, and topical retinoids. However, their use has been limited due to issues of safety and tolerability. The sensitivity and the thinness of the genital skin can increase penetration of topical corticosteroids treatments and the risk of onset of adverse effects (AEs) such as skin atrophy.[5,6] In addition, vitamin D derivatives or topical retinoids may cause skin irritation.[7]

Topical Tacrolimus

Tacrolimus is a macrolide lactone immunosuppressive agent used for prophylaxis of organ rejection after transplantation, and graft-versus-host disease after bone marrow transplantation in patients. Mechanism of tacrolimus involves its binding to immunophilin FK506 binding protein 12, creating a new complex that binds to calcium, calmodulin, and calcineurin, thus inactivating the phosphatase activity of calcineurin. This inhibition prevents signal transduction pathways from occurring, which ultimately halts the transcription of several cytokines, including interleukin-2 (IL-2), IL-3, IL-4, IL-5, IL-8, interferon-γ, and tumour necrosis factor-α.[8] Other actions of tacrolimus include inhibition of histamine release from skin mast cells, impairment of synthesis of prostaglandin D2, downregulation of FCeR1 on Langerhans cells, and inhibition of CD4+ and CD8+ lymphocyte migration.[8,9-14]

Topical tacrolimus has been approved by the FDA and European Medicines Agency for the treatment of atopic dermatitis (AD). At 0.03% concentration, it has been approved for use in children aged 2-15 years, while a 0.1% concentration has been approved for use in adults.[8] However, their efficacy has been studied for many off-label indications, including facial and intertriginous psoriasis.[9-12] Tacrolimus is a large lipophilic molecule with molecular weight of 803.5 Da. The cutaneous penetration is lower where the epidermis is thicker, such as PP.[13] Alternatively, tacrolimus absorption is optimal in the sensitive skin areas such as face, neck, flexures, and genital areas without the atrophogenic effect of topical corticosteroid use.[7] This paper aims to summarise the studies reported in the literature designed to evaluate the efficacy and tolerability of topical tacrolimus on GP. Moreover, we will present two case reports in order to demonstrate our experience.

MATERIALS AND METHODS

We used the terms "psoriasis", "genital psoriasis", "tacrolimus", and "topical tacrolimus" when searching for open-label studies, case reports, randomised controlled trials, and small case series in the *Embase*, *PubMed*, and *Cochrane Library* databases. Additional papers were identified using the 'related articles' button in PubMed. Relevant literature published from 2005-2012 was obtained using databases and keywords previously named.

RESULTS

In an open-label, multicentre, non-controlled trial conducted by Rallis et al.,[15] tacrolimus ointment 0.1% was used as the only therapy in six patients with psoriasis on the glans, and one patient with psoriasis on the scrotum. The drug was applied twice daily for 10 days. The severity of erythema, scaling, infiltration, and lesional extent were graded using a 0-3 scale, recalculated every 3 weeks for a total period of 12 weeks. The patients showed a significant improvement within the first 10 days without any drug-related adverse effects (DAEs). However, after the completion of therapy with tacrolimus, all patients had at least one recurrence. In each of these cases, the drug was reapplied for 7 days and led to rapid improvement. The results of the study were very encouraging, however the number of patients is insufficient to evaluate the safety and efficacy of tacrolimus.

Martín Ezquerra et al.[16] enrolled 15 patients (8 male and 7 female) for an open-label clinical trial. 87% of patients had involvement of the face, genitalia, and intertriginous areas. Patients applied 0.1% tacrolimus ointment twice daily for 8 weeks. Efficacy was clinically assessed at baseline (day 1) and days 15, 30, and 60 with the evaluation of erythema, desquamation and infiltration (0-3 scale), reduction of the psoriasis area and severity index (PASI), and reduction of itching. Improvement was seen as early as the 15th day of treatment, and continued throughout the study. The mean PASI score was 12 at baseline, which decreased to 2.2 at the end of the study. Itching also improved

rapidly. However, the calculation of the response to treatment lacks the distinction between facial and flexural areas, and between the different intertriginous areas.

In a randomised, double-blind, single centre study published by Kleyn et al.,[17] 28 psoriatic patients were randomised to apply tacrolimus 0.1% or clobetasone butyrate 0.05% ointment twice daily to all lesions of the face, axillary, submammary, and genital (21 patients) areas for 6 weeks. After this time both groups showed a gradual reduction of the total area affected and improving of erythema, induration, and desquamation, but with no significant difference between the two groups. Subsequently, all the 22 remaining patients (6 withdrew) were given 0.1% tacrolimus to be applied for 12 weeks, but the results were less significant compared to the previous phase of the study. In the tacrolimus group, the AEs reported were burning (n=4), flushing (n=1), and pruritus (n=1) that are similar to the clobetasone group. The researchers concluded that the two drugs have comparable efficacy and side-effect profiles. The lack of information about severity of GP constitutes a shortcoming of the study. In addition, it was not known whether the groups differed significantly in terms of severity of GP, and if so, what the differences were.

Bissonnette et al.[18] treated 12 male patients with GP. Patients received tacrolimus 0.1% ointment twice daily for 8 weeks. Efficacy was assessed by a modification of the PASI scale, adapted for GP (male genital PASI). Severity was also evaluated individually for the glans, shaft of the penis, and scrotum. At week 8, PASI was decreased from a mean score of 15.8 at baseline to 1.2, and 5 patients were completely clear of GLs. Moreover, this improvement was similar for all three areas and tacrolimus treatment was very well tolerated, with only pruritus or burning sensation reported.

Tacrolimus has been used not only in order to induce remission, but also as a maintenance therapy. In a case report presented by Guglielmetti et al.,[19] a 42-year-old female patient with PLs on the vulva and perianal area was initially treated with dapsone until remission. Subsequently, the patient has remained in remission for up 2 years, using only topical therapy with tacrolimus 0.1% and calcipotriol without any AEs reported.

CASE REPORTS

In our experience of 30 patients (28 males and 2 females) with GP, tacrolimus has been shown to be effective and well tolerated. We present the cases of three patients with GP who were successfully treated with tacrolimus 0.1% ointment.

Case 1

A 40-year-old man with a 6-year history of moderate-to-severe PP was referred to our department in October 2013. The psoriasis involved many areas of the skin, and the lesions were prominent on the elbows, knees, ankles, and the genital area, with a total PASI score of 12. He had been previously treated with topical drugs (corticosteroids, vitamin D analogues, and tar preparations) with limited effectiveness and rapid relapse after interruption.

Complete laboratory tests were performed, including complete blood count, complete liver profile, creatinine, auto-antibodies (antinuclear antibody, extractable nuclear antigen), C-reactive protein, erythrocyte sedimentation rate, etc. Furthermore, the patients were tested for serological markers of hepatitis B virus (HBV), HCV, and HIV infection, and no significant abnormal results were found. Therefore, we decided to start therapy with cyclosporine 300 mg/day (body weight was 72 kg). After 4 weeks of treatment, the patient showed an excellent and rapid improvement with a reduction of the PASI score to 7. After 8 weeks of therapy, the patient showed complete resolution of psoriasis, except for the intertriginous area of the groin, pubic area, gluteal cleft, and perianal area.

We observed several well-defined and erythematous lesions with fine-scale localised scrotal and penile skin; inguinal folds are involved. Well-defined non-scaling plaques were under the prepuce and on the proximal glans, while on the glans, scaling was absent and there were pinpoint bleedings. The diagnosis of cutaneous mycoses was ruled out by direct microscopic examination of potassium hydroxide-treated skin scrapings. Also the diagnosis of infections or eczema was excluded.

The patient experienced discomfort and embarrassment with a profound impact on their QoL and sexual health; he was afraid that his partners could confuse psoriasis with a STD

and the lesions in this area caused irritation and discomfort during sexual intercourse, and burning after intercourse (in the following hours, or days after). The patient reported that he had applied hydrocortisone butyrate 0.1% twice a day without significant clinical changes; therefore, we decided to start treatment with fluticasone propionate 0.05% twice a day for 10 days (consider that the use of more potent corticosteroids is restricted, owing to risk of skin atrophy, as genital skin is susceptible to side-effects) followed by vitamin D analogues once a day for 3 weeks, without any improvement. (Figure 1)

At week 12, after considering the clinical remission of psoriasis with the exception of the genital area, we stopped treatment with cyclosporine and we started therapy with topical tacrolimus 0.1% (informed consent was obtained from the patient and the use of-label of tacrolimus was approved by an independent ethics research committee). The patient was instructed to apply tacrolimus 0.1% ointment twice a day on the affected areas of the penis, including glans, scrotum, pubic and inguinal areas, gluteal cleft, and perianal area, for 4 weeks. After only 2 weeks of treatment, the patient showed an excellent and rapid improvement of erythema and discomfort, including itching, pain, and burning sensation. (Figure 2)

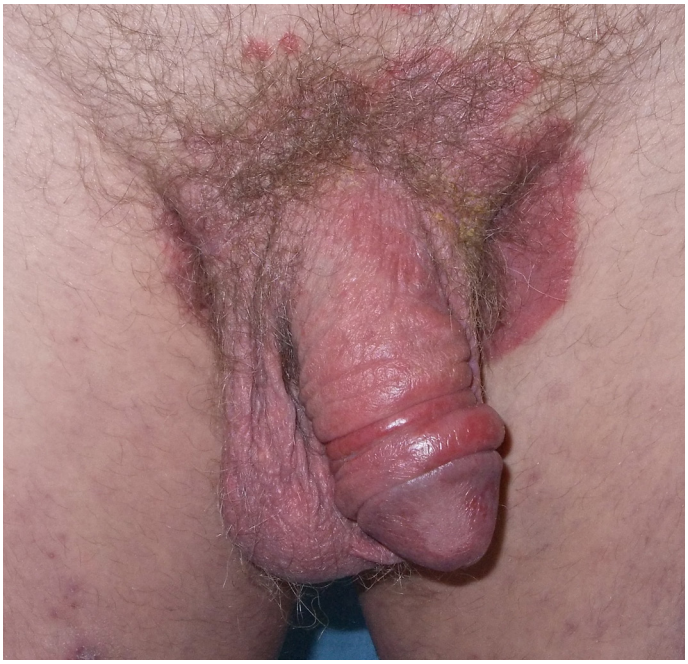

Figure 1: Psoriatic lesions before tacrolimus treatment (Case 1).

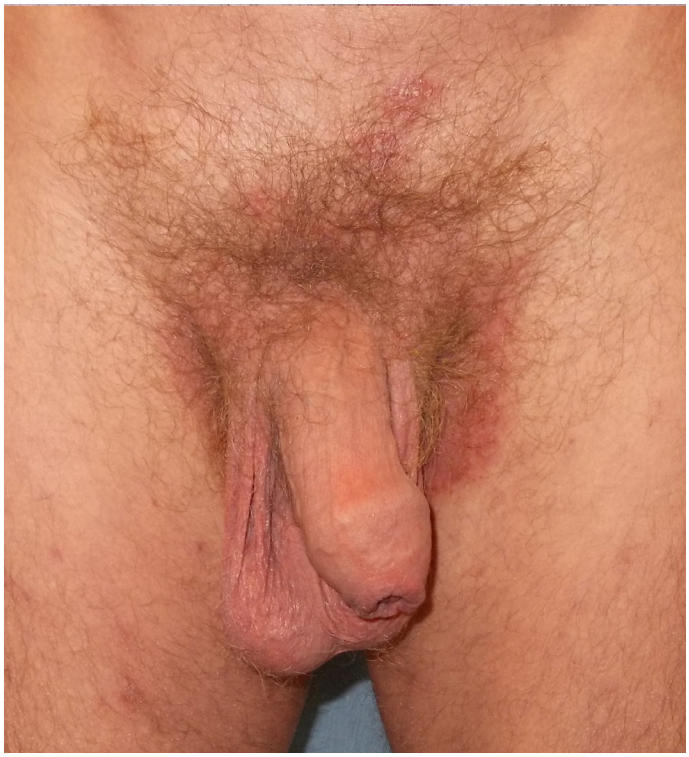

Figure 2: Improvement before tacrolimus treatment (Case 1).

The patient continued to apply tacrolimus ointment once daily. After only 2 weeks the patient showed a clear remission of the GP and treatment was interrupted. No AEs were reported. At a 6 month follow-up visit, after the end of treatment, the patient showed a maintenance of clinical remission.

Case 2

We report the case of a 24-year-old man suffering from plaque-type psoriasis since the age of 6. Various topical therapies (e.g. tar, corticosteroids, vitamin D analogues) and systemic therapies such as cyclosporine and methotrexate were discontinued due to the lack of efficacy. In June 2011, the patient started therapy with ustekinumab 45 mg (body weight was 78 kg) with a rapid improvement of his clinical features, with a visible reduction of erythema and scaling after only 4 weeks, achieving an improvement of his PASI score from baseline exceeding 75% (PASI score of 15 at baseline; PASI score of 3 at week 4). Despite 130 weeks of ustekinumab treatment the patient showed PLs (PASI 3) on genital area, such as glans, shaft of the penis, scrotum, and pubic region. The lesions were well-demarcated, bright erythematous, thin plaques with minimal scaling, and skin appeared to be shiny. (Figure 3)

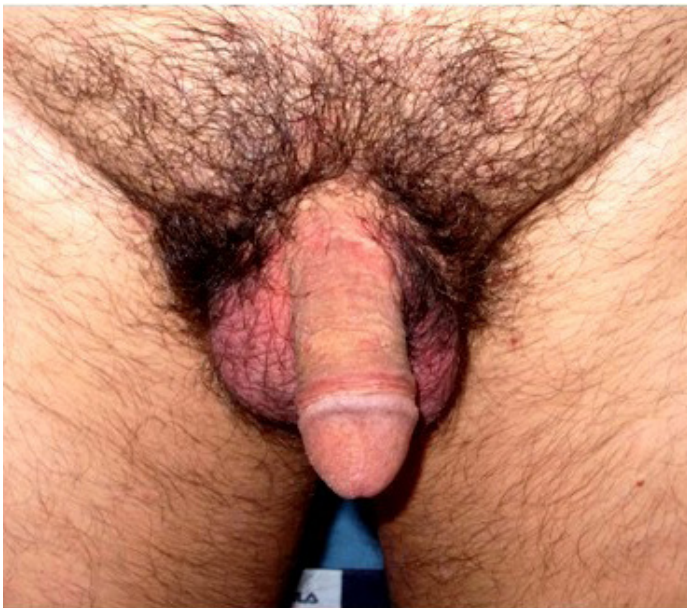

Figure 3: Psoriatic lesions on genital area (Case 2).

Figure 4: A rapid improvement of genital lesions after 2 weeks of tacrolimus treatment (Case 2).

The patient referred that often genital skin folds are susceptible to maceration or fissuring, probably due to the combination of moisture, warmth, and friction (Koebner phenomenon) associated with marked itching and burning sensation in the affected area. He often had irritation and discomfort during sexual intercourse, and experienced erectile difficulties when his penile skin contained cracks or blood. We decided to employ tacrolimus ointment 0.1% to the affected genital area (informed consent was obtained from the patient, and the use of-label of tacrolimus was approved by an independent ethics research committee) twice daily for 2 weeks, then once a day for 2 weeks. The patient experienced a rapid improvement of GLs after only 2 weeks, without any AEs or side-effects. We interrupted association with tacrolimus 0.1% after 4 weeks (Figure 4) and, actually, the patient has been undergoing treatment with ustekinumab 45 mg for 3 years without any relapse of psoriasis in the genital area (PASI score 0).

Case 3

A 22-year-old man presented with chronic PP since the age of 12. He had been previously treated with topical steroid ointment with little effect. Examination revealed erythematous, hyperkeratotic patches, and plaques involving elbows, knees, and the genital area, with a total PASI score of 8. Having obtained informed consent, a skin biopsy was also performed to obtain a histological confirmation of the diagnosis of psoriasis. Indeed microscopic examination revealed the presence of regular epidermal hyperplasia, parakeratosis with intracorneal microabscesses, minimal spongiosis, and a mild perivascular inflammatory infiltrate around papillary ectatic and convoluted vessels, features consistent with psoriasis.

The patient was instructed to apply tacrolimus 0.1% ointment twice a day on the affected areas of the penis and scrotum, for 2 weeks, then once a day for 2 weeks (informed consent was obtained from the patient and the use of-label of tacrolimus was approved by an independent ethics research committee). Topical calcipotriene was applied once a day on the other skin areas for 4 weeks. After 4 weeks, the patient showed a clear remission of the PLs including genital area, with a PASI score of 0, and tacrolimus treatment was interrupted. No AEs were reported.

DISCUSSION

Sexual dysfunction and distress are particularly high when genital skin is affected. In addition the GP can be difficult to treat due to the sensitivity of genital skin[3,4] and few studies have been published on this topic. In the last years, topical immunomodulators have been introduced that allow safer treatment of psoriasis on the face and genital skin. Topical tacrolimus is a calcineurin inhibitor, approved for treatment of AD. Recent clinical trials and case series showed an impressive

efficacy in treating facial and flexural psoriasis, where the application of potent corticosteroids carries the risk of significant AEs, due to the sensitivity of the skin.[9-12]

Long term use of corticosteroids may lead to skin atrophy, telangiectasia, striae, dyspigmentation, rebound dermatitis and contact allergy, and in rare cases, hypothalamic–pituitary–adrenal axis suppression, growth retardation, and Cushing's syndrome.[20] Tacrolimus do not cause such AEs; instead they can lead to reactions at the application site, such as transient skin burning, itching, or skin infections.[21] In addition, in 2005 the FDA issued a boxed warning for topical calcineurin inhibitors, regarding a possible risk of lymphomas and skin cancers linked to these drugs. However, these concerns are not supported by current data.[22] According to these data, the open studies on GP treated with tacrolimus 0.1% ointment, reported in this review, have shown good efficacy and excellent safety profiles, without DAEs.[15-18]

In addition, our clinical results confirmed that tacrolimus ointments are able to improve GP severity, as testified by the significant reduction of the erythema and discomfort, including itching, pain, and burning sensation in all patients treated. Regarding the safety profile, tacrolimus appear to be safe, since only mild side-effects including itching and burning sensation may occur, and they do not show the typical long term side-effects of steroids, although no extensive studies so far have confirmed their safety in long-term treatment.

All results demonstrate that tacrolimus ointment may be a new, safe option for the treatment of GP. It would be useful to increase the number of patients in future studies to confirm the safety profile of the drug. Also, further double-blind studies comparing topical tacrolimus and conventional therapies would be informative. Furthermore, as shown, the recurrence of GLs after treatment is frequent and the reported studies do not allow establishment of the dosage for maintenance therapy.

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