

# Topical Tacrolimus for Psoriasis

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**Abstract:** Tacrolimus ointment is an agent approved for the treatment of atopic dermatitis; however, tacrolimus has been expected also as one of the promising therapeutic strategies for other T-cell mediated inflammatory skin disorders. Recent progress have demonstrated that topical tacrolimus shows beneficial effects for psoriasis depending on sites. In particular, facial, intertriginous, and genital psoriasis respond to topical tacrolimus dramatically in a short period. Further, topical tacrolimus is tolerable also for child psoriasis. Because topical tacrolimus does not induce either skin atrophy or telangiectasia different from corticosteroids, it is recommended to be a first choice. The most proper way of topical tacrolimus therapy at present is to use this ointment intermittently after the remission was once obtained, paying attention to its adverse effects.

## INTRODUCTION

Tacrolimus (FK 506) is a macrolide molecule isolated from the fermentation broth of *Streptomyces tsukubaensis*, which has an immunosuppressive property. Topical tacrolimus is approved for the treatment of atopic dermatitis of adult and also children. A number of studies have shown that topical tacrolimus is effective for a broad spectrum of inflammatory skin disorders. Apart from corticosteroids, topical tacrolimus does not cause either skin atrophy or telangiectasia even by long-term use, which is the major advantage of this drug. One of the possible explanation is that tacrolimus does not affect endothelial cells, keratinocytes and fibroblasts, and thus does not affect collagen synthesis [1, 2] and skin thickness [3]. In this review, I have made a focus on a therapeutic option of topical tacrolimus for psoriasis.

## PHARMACOLOGY OF TACROLIMUS

Tacrolimus is the topical calcineurin inhibitor. Calcineurin is a calcium-binding cytoplasmic protein that is involved in T-cell activation and proliferation. Tacrolimus binds to FK506, and the complex further binds to calcineurin and prevents the dephosphorylation of the nuclear factor of activated T-cells (NFAT), which lead to the blocking of cascade of cytokine gene transcription, such as interleukin-2 (IL-2), IL-4, interferon- $\gamma$  (IFN- $\gamma$ ), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [4]. Other immunomodulatory effects of tacrolimus include the inhibition of mast cell adhesion, the inhibition of the release of the mediators from mast cells and basophils, and the downregulation of the expression of IL-8 receptor [5-7]. Tacrolimus ointment has an inhibitory effect on the function of Langerhans cells [8], and inhibited the *in vitro* T-cell stimulatory effect of antigen presenting dendritic cells [9]. Upon keratinocytes, FK506 upregulated transforming growth factor- $\beta$  (TGF- $\beta$ ) produc-

tion, downregulated inducible nitric oxide synthase (iNOS) production [10], and inhibited TNF- $\alpha$  secretion *via* regulation of NF- $\kappa$ B [11]. Other studies showed that topical tacrolimus therapy reduced the expression of adhesion molecules [12] and some chemokines which recruits eosinophils [13] in the lesional skin of atopic dermatitis.

The possible mechanism of anti-pruritic effect of tacrolimus may be attributed to the reduction of the levels of nerve growth factor, substance P, and neurotrophin-3 in the lesional skin [14, 15].

Additionally, tacrolimus reduces the colonization of *Staphylococcus aureus* in the skin of atopic dermatitis [16, 17], which is considered to result from the improvement of skin inflammation and consequently the repair of barrier function.

## TOPICAL TACROLIMUS THERAPY FOR PSORIASIS

Psoriasis is a chronic inflammatory skin disorder, which is clinically characterized by circumscribed red plaques covered with white scales on the surface. Histological features show proliferation of epidermis with parakeratosis, dilation of superficial blood vessels, polymorphonuclear leukocyte infiltration in the stratum corneum, and perivascular infiltration of mononuclear cells in the upper dermis. A growing body of evidence has shown that immunologic mechanisms are involved, and activated T-cells play a crucial role, *via* an array of proinflammatory cytokines, in the pathogenesis of psoriasis. In psoriasis, activated T-cells predominantly release Th1 cytokines such as IL-2, IFN- $\alpha$  and TNF- $\alpha$ . In particular, TNF- $\alpha$  stimulates keratinocyte proliferation, T-cell and macrophage cytokine production, and expression of adhesion molecules on vascular endothelial cells. In the involved skin of psoriasis, TNF, TNF-receptor1, -receptor2 are upregulated in dermal blood vessels [18]. Biological therapies targeting TNF have been achieved beneficial effects and improved quality of life of patients. TNF is a key regulator of the inflammatory response, and there are a number of TNF-mediated inflammatory diseases [19]. The signaling pathway of TNF might trigger psoriasis. On the other hand, recent advances indicate that psoriasis is a Th17-mediated inflammatory disease [20]. Th17 cells

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**Fig. (1).** Beneficial effect of topical tacrolimus for facial psoriasis. (A) Pre-treatment; (B) after 2 weeks.

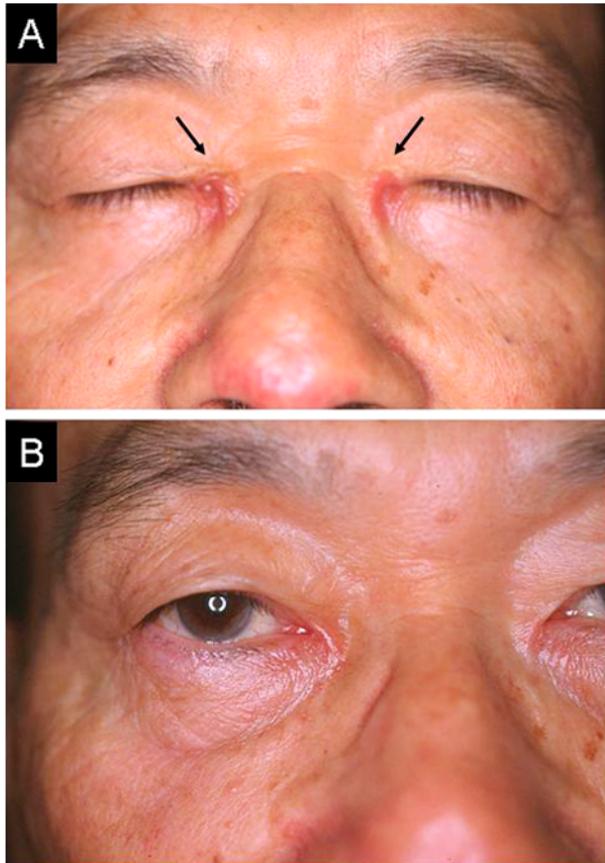
produce IL-17, which promotes neutrophil migration [21]. Also, Th17 cells secrete IL-6, IL-21, IL-22, TNF- $\alpha$ , and IFN- $\gamma$ . IL-23 promotes the expression of IL-17, and upregulates IL-22. IL-22 has effects on keratinocyte proliferation and differentiation. Thus, the IL-23/IL-17 inflammatory pathway is central to the pathogenesis of psoriasis [22].

The efficacy of topical tacrolimus ointment for chronic psoriasis plaques is controversial [23-25], because the absorption of this drug is interfered by the thick scales of psoriasis. Previous studies showed that no significant difference was found in the effect between topical tacrolimus ointment and placebo, although 0.3% topical tacrolimus was applied only once daily in a pilot study [23]. By contrast, with the improvement of the disadvantage of absorption of this drug by occlusion method every 2-3 days, application of 0.3% tacrolimus ointment resulted in a significant reduction in erythema, infiltration, superficial blood flow, and epidermal thickness, compared with the control vehicle [24]. Another method of increasing the penetration of tacrolimus is to use combined with 6% salicylic acid gel, which is reported to be effective for plaque-type psoriasis [26]. Tacrolimus moderately effected on epidermal proliferation, and reduced several T-cell subsets infiltrated in the lesional psoriatic skin, but these effects were significantly induced by calcipotriol [27].

On the other hand, we for the first time reported that topical tacrolimus shows dramatical effect for facial psoriatic lesions [28]. Since then, several reports demonstrated that topical tacrolimus is highly effective for facial and intertriginous psoriasis [29-32]. In an open-label trial, 0.1% tacrolimus ointment was applied twice daily for 8 weeks for the facial or intertriginous areas in 21 patients with psoriasis [29]. A total of 81% (17 of 21 patients) showed complete clearance at day 57. Our open-labeled, uncontrolled trial also showed similar effects, and an improvement in erythema, infiltration and desquamation of the facial psoriasis was obtained by 4-weeks' 0.1% tacrolimus ointment

without occlusion [30]. A complete clearance was noted in 10 patients (47.6%). In a randomized, double-blinded, controlled, multicenter study, 167 patients were treated with tacrolimus for 8 weeks [31]. As early as day 8, more patients had experienced clearance or excellent improvement, and at the end of the 8-week treatment period, 65.2% of the tacrolimus ointment group were clear or almost clear, with a significant predominance compared with control group. On the other hand, topical tacrolimus is effective for not only mild but also severe facial plaque psoriasis, although in a single case report [33]. Additionally, tacrolimus is tolerably effective for intertriginous and genital psoriasis [29, 34-36]. Tacrolimus was significantly more effective for facial and genitofemoral areas of psoriasis, compared with calcitriol ointment [37]. Taken together, topical tacrolimus is successfully used for facial and intertriginous psoriasis [38], even in pediatric patients [39, 40]. Facial psoriasis lesions are usually not covered by thick scales, and thus the penetration is not blocked, which may in part explain the efficacy of topical tacrolimus. A representative photographs before and after topical tacrolimus therapy are shown in Fig. (1). Tacrolimus is tolerably effective even for the sites close to the eye (Fig. 2). In the majority of cases, facial psoriasis improved as early as 1 week; however, relapse is frequently seen. Therefore, it is recommended to use tacrolimus ointment intermittently thereafter.

Oral manifestations are rare in psoriasis [41]. A geographic tongue with marked fissuring is frequently associated with pustular psoriasis; however, the incidence of oral manifestations is considered to be less than 2% of patients with psoriasis vulgaris. In most of the reported cases, the clinical course of the oral lesions parallel with that of cutaneous lesions, and oral psoriasis exclusively presenting oral involvement is extremely rare [42, 43]. Oral psoriasis is clinically classified into two groups; well-defined, silvery or grayish white lesions and a diffuse erythema of the mucosa. Lip lesions respond well to topical tacrolimus ointment [44].



**Fig. (2).** Topical tacrolimus is tolerably effective even for sites close to the eye (arrow). (A) Pre-treatment; (B) after 1 week.

Additionally, topical tacrolimus is shown to be effective for pustular psoriasis, with [45] or without [46] oral immunosuppressive therapy.

#### THERAPEUTIC OPTIONS FOR OTHER INFLAMMATORY SKIN DISORDERS

Topical application of tacrolimus has been shown to be effective in the treatment of several inflammatory skin disorders other than atopic dermatitis and psoriasis [47, 48]. Tacrolimus inhibits calcineurin, which consequently suppresses activation and differentiation of T-cells as well as other proinflammatory cytokines. Thus, a number of therapeutic usefulness of topical tacrolimus in particular for T-cell mediated skin diseases, such as eczema, seborrheic dermatitis, pyoderma gangrenosum, lichen planus, lichen sclerosus, vitiligo, alopecia areata, and so on [49]. Additionally, topical tacrolimus is occasionally effective for other disorders which are not always T cells play a central role in the pathogenesis, suggesting that tacrolimus may possess various pharmacological mode of action.

From the viewpoint of site of application, tacrolimus is dramatically effective for membranous lesions, such as orogenital areas. It is well-known, and there are a number of reports that topical tacrolimus is effective for oral [50, 51] and vulvovaginal [52, 53] lichen planus. Lichen sclerosus on the mucous sites (lip, vulvar) are also reported to be suc-



**Fig. (3).** Prominent scaly erythema on the upper lids induced by 0.1% tacrolimus eye drops.

cessfully treated with 0.3% tacrolimus ointment [54-57]. Of interest, comedos in the genital areas complicated by lichen sclerosus were also improved [56]. Additionally, another report have shown that topical tacrolimus is effective for perianal ulcerating Crohn's disease [58]. These results suggest the site-specific effectiveness for topical tacrolimus therapy.

#### ADVERSE EFFECTS OF TOPICAL TACROLIMUS THERAPY

The most common adverse effects of topical tacrolimus therapy are sensation of the skin burning, pruritus, flu-like symptoms, skin erythema, and headache. In most of the cases, tacrolimus is tolerable for facial use. Herpes simplex infection is occasionally seen on the face during topical tacrolimus therapy. Other less common symptoms include eczema herpeticum, molluscum contagiosum, and warts. As described before, topical tacrolimus is effective especially for facial psoriasis; however, deep fungal infection is rarely reported [59]. Tacrolimus rarely induces allergic contact dermatitis [60]. Patch test shows delayed reaction. Fig. (3) shows a peri-ocular scaly erythema during preclinical trial with FK506 eye drops (0.1%) for severe catarrhal conjunctivitis, which was suspicious of allergic contact dermatitis. Also, topical tacrolimus is effective for rosacea, whereas a rosacea-like granulomatous eruption appeared during tacrolimus use [61, 62], thus attention should be paid. Although there may be a risk of lymphoma related to topical tacrolimus in animal studies, there are so far no reports of malignancy occurrence during topical tacrolimus use in healthy individuals.

#### CONCLUSION

Topical tacrolimus is a promising tool which is expected as a useful and safe therapeutic option for psoriasis, especially on the facial, intertriginous and genital areas. Because patients worry about the outlook of facial psoriasis, tacrolimus may help to release the stress and improve their quality of life. Further studies which prove the efficacy and safety of tacrolimus ointment for psoriasis will be necessary.

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