Editorial:

Topical Macrolide Immunomodulators for Therapy of Atopic Dermatitis

Nidhal Abdul-Muhaimen *PhD*,**Ahmad Hachem muhana** *MSc*

Introduction

To date, tacrolimus (FK 506) and the ascomycin derivative pimecrolimus (SDZ ASM 981) are the most studied topical macrolide immunomodulators. Both of these drugs have a high specificity for inhibiting the expression of inflammatory T-cell cytokines and have shown promising results in the treatment of atopic dermatitis (AD) when applied topically [(1)].

Topical calcineurin inhibitors

Tacrolimus is a topical formulation of the immunomodulatory agent FK 506 and is available as a 0.03% and 0.1% ointment. Originally used for atopic dermatitis, tacrolimus modulates immune-cell function by inhibiting calcineurin-dependent dephosphorylation- activation of specific nuclear factors and therefore preventing transcription of proinflammatory cytokines [(2)].

Improved therapy for atopic dermatitis

Once AD has been diagnosed, two therapeutic strategies can be used to address the pathophysiologic abnormalities found in these patients: the first strategy is the traditional mainstay of topical treatment of atopic dermatitis is steroid ointments [(3)].

Potent topical steroids have a high intial success rate in clearing an eczematous rash, but the effects tend to diminish later on, a phenomenon known as tachyphylaxis.

Dept. Medical Microbiology, College of Medicine, Al-Nahrain University.
Adress Correspondence to: Dr Nidhal Abdul-Muhaimen

Long term use of these medications is associated with many potential risks, especially in infants and children, and stronger steroids are more likely to produce adverse local and systemic effects. Skin atrophy, telengectasia, stria, secondary infection, acneiform eruption, hypopigmentation, purpura, poor wound healing can result from long-term application of topical steroids, particularly when used on face, groin, and intertriginous areas of the body [(4)].

Clinically significant suppression of the hypothalamic-pituitary-adrenal axis also can result from the long term treatment of topical steroids, especially in an infant, whose body surface is large compared with his or her weight. When long-term treatment of AD is required, the adverse effects of steroids make them an unsatisfactory treatment. In addition, Colonization and infection with *Staphylococcus aureus* contributes to the severity of AD and reduce corticosteroids sensitivity. These observations suggest a role for antibiotic/corticosteroid combination or topical macrolide immunosuppressive ointment such as tacrolimus ointment in the treatment of AD. Finally, a number of patients with AD may not response appropriately to their topical steroid due to complication by superinfection with S. aureus [(5)].

The new immunomodulators tacrolimus and pimecrolimus represent a safer class of drugs that alter the local immune response in a more targeted fashion than do older steroids

[6]. These drugs suppress cytokine gene transcription by inhibiting calcineurin, resulting in fewer activated T cells in the skin. Both have proven to be safe and effective in adult and pediatric populations. Systemic absorption is generally not significant with either of these agents. Patients experience less burning if eczematous patches are treated initially with a corticosteroid with transition to calcineurin inhibitors after partial clearing. Improvements tend to be steady, with progressively smaller areas requiring treatment [7]. These agents are particularly useful on the eyelids and face, in cases of refractory dermatitis, in areas prone to steroid atrophy (thus they particuraly useful for the treatment of areas such as the face and intertriginous regions).

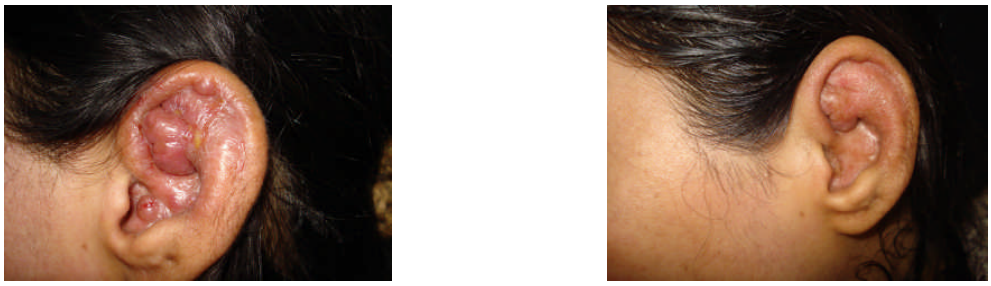

Figure 1: A 29-year-old patient who was insensitive to topical corticosteroid therapy quickly responded to O.l% tacrolimus ointment. (Left) Before treatment with 0.1% tacrolimus;(right) 10days after application of 0.1% tacroJimus. Histology from biopsy taken prior to treatment revealed an eczema; immunohistochemical reactivity,*positive*

IMMUNE MODULATION OR IMMUNE SUPPRESSION?

The difference between immune modulation and immune suppression is subtle. In AD there is an immune pathology in which skin lesions have infiltrates of inflammatory immune cells (i.e., T cells, macrophages, basophils, eosinophils). In this instance, application of a drug that blocks the activation of these cells at the site of the lesion reverses the immune pathology and thus can be considered to modify the local immune response. On the other hand, systemic immune suppression with such drugs as tacrolimus (Prograf®) and cyclosporin (Neoral®) was developed to suppress a normal immune response to the nonself antigens of an allograft. In doing so, it also suppresses normal immune responses to infectious agents and decreases immune surveillance in the protection against cancer.

Tacrolimus ointment and pimecrolimus cream are considered to be immune modulators because they target a specific immune pathology and because their action seems to be limited to the site of the immune pathology [8].

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