

Topical tacrolimus (FK 506): A new milestone in the management of atopic dermatitis

In 1984, while screening the putative properties of various bacterial extracts, Japanese researchers were able to isolate tacrolimus (FK506), a new substance with immunosuppressive activities, from *Streptomyces tsukubaensis*, a soil microorganism from Mount Tsukuba in Japan. Tacrolimus is a member of the immunosuppressive macrolide family, which includes cyclosporin A, rapamycin, and ascomycin. Since that time, tacrolimus has been introduced successfully as a systemic immunosuppressive drug, mainly in transplantation medicine. In recent years, tremendous progress has been made in the development of a new form of tacrolimus, allowing its use in topical therapy of inflammatory skin diseases. The availability of this new antiinflammatory therapy is the newest milestone since the introduction of topical steroids more than 40 years ago.

MOLECULAR MECHANISM OF ACTION

Immunosuppressive macrolides all have a similar mode of action, which is mediated mainly by specific intracellular ligands, the immunophilins. Among these cytosolic proteins, the 12-kd macrophilin FKBP12 has the highest affinity for tacrolimus. The tacrolimus/FKBP12 complex blocks the calcium-dependent serine/threonine phosphatase calcineurin and thereby the dephosphorylation of the transcription factor NF-AT_p. This results in an inhibition of its translocation to the nucleus and a lack of the transcription of several genes, including mainly cytokines (eg, IL-2, IL-4, or IL-5 in T cells).¹

EFFECTS ON THE SKIN IMMUNE SYSTEM

Alteration of cellular components of the skin immune system by tacrolimus

The so-called skin immune system (SIS), a concept proposed by Bos and Kapsenberg,² is an organ-related immunologic unit that has to fulfill a variety of protective and effector functions because of the interface status of the skin. On the one hand, the SIS comprises cellular elements as keratinocytes or fibroblasts, which provide the "background of the immune reaction" by producing proinflammatory cytokines. On the other hand, leuco-

Abbreviations used

DC: Dendritic cell
LC: Langerhans cell
SIS: Skin immune system

cytes (ie, T lymphocytes, macrophages, mast cells, Langerhans cells [LCs], and other dendritic cells [DCs]) equipped with immune recognition receptors such as T-cell receptor [TCR] and FcR) provide the specificity of the immune reaction. Thus the great variations in the clinical appearance of skin diseases are the product of complex and subtle interactions between these components, and the characteristic lesions of a defined condition (eg, atopic dermatitis) most probably reflect a distinct and unique pattern of immunologic microenvironment on which systemic or topically applied drugs may exert profound alterations. Thus the effect of tacrolimus has been reported on several aspects of skin inflammation. First, tacrolimus significantly and rapidly alters the transcription of the IL-8 receptor gene in human keratinocytes, leading to reduced protein binding of IL-8 to its receptor.³ Similarly, anti-IgE-induced histamine release by human mast cells and basophils is altered by tacrolimus in vitro,⁴ whereas degranulation secondary to activation of protein kinase C by 12-O-tetradecanoylphorbol-13-acetate (TPA) is not affected.

Epidermal LCs are a target of topical tacrolimus therapy

More specifically related to chronic inflammatory skin diseases as atopic dermatitis or allergic contact dermatitis are the putative effects of tacrolimus on antigen-presenting epidermal DCs (ie, LCs and related CD1a+ DCs). Because it has been shown that these cells specifically express large amounts of the high-affinity receptor for IgE (FcεRI) in this disease,⁵ they may represent targets for new drugs as topical immunosuppressive macrolides. Indeed, recent comparative studies designed to explore the effect of tacrolimus and steroids on epidermal LCs and in vitro generated DCs have disclosed a series of interesting properties of the immunosuppressive macrolide (Panhans-Grob B, et al, manuscript submitted). Although freshly isolated LCs express FKBP12, this macrophilin is lost during differentiation of LCs into mature DCs, suggesting that LCs may escape the effect of tacrolimus once they have undergone their maturation

in regional lymph nodes. Most interestingly, tacrolimus inhibited or downregulated the expression of the high-affinity receptor for IgE (FcεRI) and that of the costimulatory molecule CD80 (B7.1), whereas CD86 (B7.2) expression was not affected. Both costimulatory molecules were upregulated by the steroid. Tacrolimus dramatically affected the allostimulatory capacity with a 100 times higher potency than steroids. These *in vitro* results were confirmed in an *in vivo* study monitoring the effect of tacrolimus on the epidermal DCs isolated from lesional skin treated with the compound (Wollenberg et al, manuscript in preparation).

CLINICAL EXPERIENCE WITH TOPICAL TACROLIMUS

Topical tacrolimus: The first topically efficient immunosuppressive macrolide

In contrast to cyclosporin A, topically applied tacrolimus penetrated the skin in variable amounts, depending on the concentration and integrity of the treated skin. Therefore beside the oral formulation of tacrolimus, which is now widely used in transplantation medicine and which has been tested successfully on patients with chronic psoriasis,⁶ topical tacrolimus formulations have been developed as a means of delivering therapeutic concentrations to the disease area while minimizing the risk of systemic toxicity. These formulations have been tested in a variety of dermatologic conditions. Thus topical tacrolimus is effective in allergic contact dermatitis as shown in studies performed in animal models and in human subjects as well.⁷ Whether psoriasis vulgaris responds to tacrolimus remains to be verified.

Topical tacrolimus in the management of atopic dermatitis in adults

Most importantly, topical formulations have been used successfully in a series of open trials performed in Japan with patients with atopic dermatitis. These studies already highlighted the therapeutic potential of this immunosuppressive regimen in this particular disease.^{8,9} Recently, a large, placebo-controlled, double-blind, multicenter clinical trial involving over 200 adult patients with atopic dermatitis proved the safety and efficacy of topical tacrolimus in this disease.¹⁰ In this dose-response study 3 different tacrolimus concentrations (0.03%, 0.1%, and 0.3%) were applied for 3 weeks. Thereby a dramatic and highly significant improvement with up to 85% reduction of the clinical score was recorded with all concentrations tested, whereas the systemic absorption was minimal. According to the experience of the investigators with other therapeutic modalities, the efficacy of tacrolimus would be comparable with that of high-potency steroids. A variable burning sensation for a few minutes after application, which disappeared while treatment was continued, was the only adverse effect observed. Most importantly, the itching sensation was dramatically improved within 2 to 4 days. Lesions of trunk extremities and dermatitis lesions on the face both responded, offer-

ing new hope for the treatment of inflammatory lesions in this problematic location on the skin where there is great susceptibility to steroid-induced atrophy and telangiectasia. In fact, the most recent findings from Reitamo et al¹¹ strongly suggest that when compared with steroids under similar conditions, topical tacrolimus applied even under occlusion for several weeks does not alter the collagen synthesis and is devoid of atrophogenic activity.

Topical tacrolimus in the management of atopic dermatitis in children

Because atopic dermatitis occurs most commonly as a chronic skin disease in childhood and topical steroids have been used cautiously because of their well-known side effects, a randomized, vehicle-controlled clinical trial was designed to determine the safety and efficacy of topical tacrolimus in children aged 7 to 16 years. In this issue of *The Journal*, Boguniewicz et al¹² report on the results of this study and show that, as in adults, tacrolimus was proven to act rapidly, to be highly effective (67% to 70% marked-to-excellent improvement) when compared with placebo (38% improvement), and to be safe when used twice a day for a period of 3 weeks. Thus the clinical experience accumulated so far strongly suggests that topical tacrolimus may represent a breakthrough drug in the management of atopic dermatitis.

Topical tacrolimus and UV radiation

Because tacrolimus is an immunosuppressive compound, one of the major concerns would be its safety when used for a long period of time. This issue could be particularly relevant when the skin is exposed to UV radiation, which is known to promote skin cancers as malignant melanoma. However, there is so far no evidence for photocarcinogenic potential in human subjects. Because skin antigen-presenting DCs (eg, LCs or dermal DCs that are responsible for the recognition of tumor cells and their presentation to the SIS) are a target of topical immunosuppression (see above), some alteration of this antitumor activity cannot be excluded. Thus as for any topical immunosuppressant, one should be advised not to apply this new generation of compounds concomitantly with any other therapeutic regimens making use of UV radiation and to avoid extensive sun exposure.

FUTURE PERSPECTIVES OF TOPICAL TACROLIMUS

Topical tacrolimus: A new therapy that still requires more clinical experience

Although the design of the clinical trials performed so far used an application frequency of twice a day, some recent pharmacologic data suggest that an application once a day or even once every other day may be sufficient to maintain a low but efficient tissue level of the compound. One may even speculate that once to twice a week may be sufficient to control this chronic

disease under optimal safety conditions. Thus as was the case for topical steroids many years ago, physicians still have to learn to optimize use of this new generation of compounds.

Topical tacrolimus: A self-regulatory therapy?

Some observations during the clinical trial have suggested that tacrolimus ointment may display some interesting characteristics that may be of relevance for efficacy and safety. Indeed, it is well accepted that compounds greater than approximately 500 d hardly penetrate the epidermis of normal skin. This is in contrast to inflamed skin and especially atopic dermatitis, which, due to increased permeability, allows the penetration of molecules of higher molecular weight, including tacrolimus (823 d). Thus once the inflammation (and the permeability) decreases under the activity of topical tacrolimus, the compound will penetrate the skin less when the lesions have improved, thereby limiting the putative side effects of this particular regimen. The fact that the burning sensation rapidly decreases with the improvement of the skin lesions supports this assumption. Thus because of its rapid onset of action and its molecular weight, this compound may have some unexpected self-regulatory activities that could be beneficial for its safety.

CONCLUSION

Clinical experience and in vivo studies have confirmed that although it is highly efficient in atopic dermatitis, topical tacrolimus ointment is devoid of many side effects of the topical steroids (eg, epidermal atrophy, striae-distensae, or telangiectasia). Topical tacrolimus therefore doubtlessly represents the first new topical antiinflammatory therapy for atopic dermatitis since the introduction of topical steroids more than 40 years ago. Moreover, this new treatment may also represent a new

therapeutic option for a series of other chronic dermatologic diseases (eg, alopecia areata, lupus erythematoses, and lichen planus).

Thomas Bieber, MD, PhD
Department of Dermatology
Friedrich-Wilhelms University
Bonn, Germany

REFERENCES

1. Schreiber SL, Crabtree GR. The mechanism of action of cyclosporin A and FK506. *Immunol Today* 1992;13:136-42.
2. Bos JD, Kapsenberg ML. The skin immune system: progress in cutaneous biology. *Immunol Today* 1993;14:75-8.
3. Schulz BS, Michel G, Wagner S, et al. Increased expression of epidermal IL-8 receptor in psoriasis: downregulation by FK-506 in vitro. *J Immunol* 1993;151:4399-406.
4. de Paulis A, Stellato C, Cirillo R, et al. Anti-inflammatory effect of FK-506 on human skin mast cells. *J Invest Dermatol* 1992;99:723-8.
5. Bieber T. FcεRI expressing antigen presenting cells: new players in the atopic game. *Immunol Today* 1997;18:311-3.
6. The European FK 506 Multicentre Psoriasis Study Group. Systemic Tacrolimus (FK 506) is effective for the treatment of psoriasis in a double-blind, placebo-controlled study. *Arch Dermatol* 1996;132:419-23.
7. Lauerma AI, Maibach HI, Granlund H, et al. Inhibition of contact allergy reactions by topical FK506. *Lancet* 1992;340:8818.
8. Nakagawa H, Etoh T, Ishibashi Y, et al. Tacrolimus ointment for atopic dermatitis. *Lancet* 1994;344:8926.
9. Aoyama H, Tabata N, Tanaka M, Uesugi Y, Tagami H. Successful treatment of resistant facial lesions of atopic dermatitis with 0.1% FK506 ointment. *Br J Dermatol* 1995;133:494-6.
10. Ruzicka T, Bieber T, Schopf E, et al. A short-term trial of tacrolimus ointment for atopic dermatitis. European Tacrolimus Multicenter Atopic Dermatitis Study Group. *N Engl J Med* 1997;337:816-21.
11. Reitamo S, Rissanen J, Remitz A, et al. Tacrolimus ointment does not affect collagen synthesis: results of a single-center randomized trial. *J Invest Dermatol* 1998. In press.
12. Boguniewicz M, Fielder VC, Raimer S, Lawrence ID, Leung DYM, Hanifin JM. A randomized vehicle controlled trial of tacrolimus ointment for treatment of atopic dermatitis in children. *J Allergy Clin Immunol* 1998;102:635-42.