Topical Tacrolimus for Atopic Dermatitis: Euphoria and Vigilance

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Today, there is ample scientific evidence for the clinical effectiveness, safety and patient comfort of tacrolimus ointment in the treatment of moderate to severe atopic dermatitis. Recent, well-documented reports on double-blind, vehicle-controlled, randomized clinical studies encompass data from 419 adults [1] and 235 children [2] who were successfully treated with 0.1 and 0.03% tacrolimus ointment for up to 3 months. Concerning long-term treatment, two open studies have observed 316 adults [3] and 255 children [4] who were treated with 0.1% tacrolimus ointment for up to 1 year. Transient local burning and pruritus, occurring in every second patient, were the principal adverse effects, and there is apparently little risk of skin infections. This bright picture is endorsed by a significantly positive health-related quality of life assessment in 900 children and adults [5].

Tacrolimus ointment has not yet been released in most countries. For use in daily practice, a topical formulation is easily prepared from available FK-506 capsules on a prescription basis [6]. Most of the existing evidence on the treatment of atopic dermatitis with tacrolimus ointment stems from the particular clinical settings that are inherent in double-blind, randomized study protocols, not always representative of real-life conditions. One example is the steroid washout phase required by these studies prior to patient enrollment. Complete abstinence from any topical treatment throughout the resulting rebound phase is itself part of a rational treatment strategy for chronic atopic facial dermatitis. With the tacrolimus option at hand, management of this therapeutic cul-de-sac of the corticosteroid treatment era should be reversed [7],

and therapeutic abstinence is likely to become obsolete in daily practice.

However, this realistic perspective raises questions that have not been answered by the clinical trials. Kawasaki and coworkers, reporting in this issue of *Dermatology* [8], show that topical tacrolimus treatment of steroid-aggravated facial atopic dermatitis is effective without a washout, and not associated with a rebound phenomenon. Remarkably, the authors have excluded patients with severe dermatitis from their study, as the use of topical tacrolimus on erosive lesions is officially prohibited in Japan, where the ointment is already marketed (Protopic). Erosive dermatitis increases the systemic absorption of the FK-506 molecule and is more prone to secondary bacterial or viral infection. Clinically infected atopic dermatitis also excluded patients from participation in the clinical trials. Early herpes simplex infection is much more difficult to spot amidst erosive, excoriated lesions. Is the above-mentioned assessment of the risk of infectious complications associated with tacrolimus ointment really representative of field conditions? Have a second look!

The two recent vehicle-controlled clinical studies report 22 (3.4%) cases of herpes simplex infection during treatment with tacrolimus ointment, of which 3 presented as eczema herpeticum [1, 2]. In the two open long-term studies, 31 (5.4%) cases of herpes simplex infection were observed, of which 7 presented as eczema herpeticum [3, 4]. Taken together, every fifth herpes simplex infection diagnosed in these trials during tacrolimus treatment presented as an eczema herpeticum; in the vehicle-controlled

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trial with children alone [2], every third case of herpes simplex infection had disseminated during the treatment! Within the trials, herpes dissemination occurred exclusively in association with tacrolimus treatment; 5 (0.75%) cases of herpes simplex infection were reported from the vehicle-treated groups. The overall incidence of herpes simplex infections reported in these trials (58/1,553; 3.75%) is not unusual for a population with moderate to severe atopic dermatitis; the rate of conversion from herpes simplex infection to eczema herpeticum within the treated study collective is certainly not a 'quantité négligeable'!

The risk of acute infectious complications during treatment with tacrolimus ointment is not a major problem if the prescribing dermatologist as well as the treated patient

are informed, and rational precautions are respected. However, atopic dermatitis is a benign disease, and the uncertainty regarding the consequences of a long-term local immunosuppression, especially on sun-exposed skin sites, endows our specialty with a responsibility as challenging as the therapeutic perspectives. Therefore, vigilance is more appropriate than euphoria, at times when immunomodulation of atopic dermatitis with the **Tsukuba macrolide immunosuppressor** becomes clinical routine. The acquisition of the necessary clinical expertise relies on a continuous effort to adapt clinical guidelines, based on careful documentation and communication of whatever is not yet evidence based in treating atopic dermatitis with topical tacrolimus: it's time for 'tacro surveillance'!

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