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Facial Flush Reaction after Alcohol Ingestion during Topical Pimecrolimus and Tacrolimus Treatment

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Key Words

Vitiligo • Alcohol intolerance • Topical calcineurin inhibitors • Pimecrolimus cream • Tacrolimus ointment

Pimecrolimus and tacrolimus, topical calcineurin inhibitors, are approved for the treatment of atopic dermatitis and have recently been introduced for the treatment of vitiligo lesions offering the advantage to be used for a prolonged time avoiding the side effects related to the long-term use of topical steroids. Although no signs of atrophy, telangiectasia or tachyphylaxis have been described with their use, the topical treatment with tacrolimus and pimecrolimus can produce transient adverse events, generally of mild to moderate severity, such as burning, feeling of warmth, smarting, pain, soreness and rosaceiform dermatitis at the site of application [1–4].

Recently in the literature several cases of an asymptomatic red flushing of the face after a moderate alcohol ingestion in tacrolimus-treated patients have been described [1, 5]. We report the case of an erythematous flushing of the face after a small alcohol ingestion in 7 patients during the treatment of their facial vitiligo with topical calcineurin inhibitors.

Twenty-five patients suffering from a chronic-stable localized vitiligo were instructed to apply the calcineurin inhibitors to the lesions of the face twice daily for 24 weeks; 13 patients were treated with pimecrolimus 1% cream and 12 with tacrolimus 0.1% ointment. In 2 (15%) pimecrolimus-treated patients (44-year-old female and 27-year-old male) and in 5 (42%) tacrolimus-treated patients (1 male and 4 females, aged between 23 and 54 years), the appearance of a facial flush reaction was observed after the inges-

tion of small quantities of beer or wine. The patients reported the sudden onset of an itching-burning sensation quickly followed by flushing. The facial reaction occurred within 5 and 10 min after the alcohol ingestion and between 2 and 4 weeks after the start of the treatment. The erythema was confined not only to the treated facial areas, but it also extended to the healthy skin, and its total extension varied among the patients. No other systemic symptoms or signs were recorded during the development of the flush reaction. The facial flushing disappeared after 20–30 min from its beginning. After the end of the treatment, the flush reaction of the face did not reappear even after alcohol intake. None of the patients had experienced such symptoms before, had ever noted intolerance to topical products containing ethanol or was suffering from rosacea.

The association between a flush reaction of the face and alcohol consumption has already been described, occurring in 6–7% of the topical-tacrolimus-treated patients [1, 5]; to our knowledge, no similar associations for pimecrolimus-treated patients have been observed up to date. Furthermore, alcohol intolerance has usually been reported in patients with atopic dermatitis. This is the first report in patients with vitiligo. The exact pathophysiological mechanism is still unknown, but 3 hypotheses can be formulated. Either ethanol or calcineurin inhibitors have been shown to induce the release of neuropeptides, and probably their combination could lead to an extreme vasodilatation [6]. The second hypothesis is linked to the aldehyde-dehydrogenase-inhibiting function of the calcineurin inhibitors in the areas where they are applied; in this way, the subsequent accumulation of acetaldehyde could lead to vasodilatation following alcohol consumption as described for disulfiram-treated patients after alcohol ingestion [7]. The third hypothesis is linked to a possible interaction of the two drugs on the calcineurin-calmodulin-calcium complex where both alcohol and tacrolimus/pimecrolimus are known to act [8]. Moreover, an abundant presence of *Demodex* mites has been observed in patients with flares of rosacea occurring during topical tacrolimus and pimecrolimus treatment [2, 9].

It is possible that the treatments with calcineurin inhibitors lead to an incipient rosacea with flares that appear after alcohol consumption. Despite its difficult pathogenesis and the absence of predictive factors, the flush reaction of the face should be recognized as a new side effect of the treatment with topical calcineurin inhibitors, both pimecrolimus and tacrolimus, independently from the skin disease.

References

- 1 Reitamo S, Wollenberg A, Schöpf E, et al: Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. The European Tacrolimus Ointment Study Group. *Arch Dermatol* 2000;136:999–1006.
- 2 Lübke J, Stucky L, Saurat JH: Rosaceiform dermatitis with follicular *Demodex* after treatment of facial atopic dermatitis with 1% pimecrolimus cream. *Dermatology* 2003;207:204–205.
- 3 Langley RG, Luger TA, Cork MJ, et al: An update on the safety and tolerability of pimecrolimus cream 1%: evidence from clinical trials and post-marketing surveillance. *Dermatology* 2007;215(suppl 1):27–44.
- 4 Jacobi A, Braeutigam M, Mahler V, et al: Pimecrolimus 1% cream in the treatment of facial psoriasis: a 16-week open-label study. *Dermatology* 2008;216:133–136.
- 5 Milingou M, Antille C, Sorg O, Saurat JH, Lübke J: Alcohol intolerance and facial flushing in patients treated with topical tacrolimus. *Arch Dermatol* 2004;140:1542–1544.
- 6 Trevisani M, Smart D, Gunthorpe MJ, et al: Ethanol elicits and potentiates nociceptor responses via the vanilloid receptor-1. *Nat Neurosci* 2002;5:546–551.
- 7 Morales-Molina JA, Mateu-de Antonio J, Grau S, Ferrández O: Alcohol ingestion and topical tacrolimus: a disulfiram-like interaction? *Ann Pharmacother* 2005;39:772–773.
- 8 Ohashi I, Pohorecki R, Morita K, Stemmer PM: Alcohols increase calmodulin affinity for Ca^{2+} and decrease target affinity for calmodulin. *Biochim Biophys Acta* 2004;1691:161–167.
- 9 Antille C, Saurat JH, Lübke J: Induction of rosaceiform dermatitis during treatment of facial inflammatory dermatoses with tacrolimus ointment. *Arch Dermatol* 2004;140:457–460.

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