Treatment with Calcineurin Inhibitors of Oral Lichen Planus. An Attempt to Clarify the Issue.

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(95% CI: 0.94-1.47)). Again, severity of AD was a significant risk factor and highly potent topical steroids were associated with an increased risk of lymphoma [12].

As severity of a topic dermatitis, and therefore its extent, have been found to be a significant risk factor, crucial is the amount of the drug absorbed through the skin or through mucosae.

Absorption through the skin

Passeron et al. found in 14 patients with ELP that the blood concentrations of pimecrolimus were always above the threshold (mean value, 2.84 ng/mL; extreme values, 0-6.19 ng/mL) [13]. Yan et al. found, in Netherton syndrome, that pimecrolimus blood levels ranged from 0.625 to 7.08 ng/ml, in any case being much lower than expected even when applied to 50% of total body surface area [14]. According to Mc Caughey et al. in 9/10 of ELP subjects treated with pimecrolimus, the levels were consistently low. In another article, pimecrolimus blood levels were detected in 5/10 subjects and all stayed below 4 ng/mL [15]. In another article, Tacrolimus 0.1% was applied in 50 patients with ELP up to 39 months and its mean blood levels were low and even decreased with duration of therapy from 2.7 microg/l (week 1) to 0.5 microg/l (week 32) [16].

Animal studies revealed, however, that the concentration of tacrolimus in the lymph node draining the treated skin area is equal to that found in the lymph nodes of animals treated with oral tacrolimus, even though the serum concentration of tacrolimus was low [17].

To evaluate better the relevance of those concentrations, one should keep in mind that the trough levels of tacrolimus administered orally have even calculated to be fairly consistent at 7.9-18 ng·h/mL without variations with age or sex [18] and that, at such levels, lymphoma, non-melanoma skin cancers and melanomas have been consistently reported, related to the level of immunosuppression.

The inhibition of immune competent cells, which normally prevent malignancies to develop, is considered to be the main mechanism of tumorigenesis promotion. In particular, a reduction of the CD4/CD8 ratio has been found in the lymph nodes of mice treated with tacrolimus [19]. Even this issue is controversial, however. In fact, it has been shown that patients treated in such a way displays a normal immune response to vaccination [20], develop an adequate delayed hypersensitivity reaction as demonstrated by cases of contact dermatitis [21], and have an infection rate within the expected range given the predisposition of the patient with atopic dermatitis to cutaneous infections [11].

If systemic carcinogenicity of topical tacrolimus is still dubious, more evidence favors the local carcinogenicity.

Local carcinogenicity

The local carcinogenic potential of long-term topical tacrolimus application has been claimed. However, up to 2005, only 10 cases of skin tumors mostly affecting the area where the drug had been applied had been reported, consisting of squamous cell carcinoma, cutaneous sarcoma and malignant melanoma [22].

In fact, tacrolimus has also a direct carcinogenic potential promoting the transformation of initiated cells. Tacrolimus is used in ELP essentially for its capacity to augment apoptosis in T-cells, which are the main effectors in ELP, but tacrolimus inhibits apoptosis in non-lymphoid cells as well [22]. Tacrolimus leads to Erk activation in the mucosal epithelium and inhibits the induction of p53, both being important cancer signaling pathways. Bax, which is a proapoptotic member of the Bcl-2 family and its transcription is directly regulated by p53, is reduced in epithelial cells of tacrolimus treated mucosa and even in carcinoma cells. Lastly, tacrolimus-binding protein FKBP 38 blocks apoptosis, binds to Bcl-2 and targets Bcl-2 to the mitochondria [23].

Lichen planus

ELP refers to the oral localization of a chronic disease, named lichen planus that usually affects the skin. Mucosal lesions may be atrophic or erosive and may involve the oral mucosa and the vulva and the penis as well. Lichen planus is an autoimmune disease in which CD4 and CD8 lymphocytes attack the keratinocytes of the basal layer of the epidermis and tend to destroy them. Interleukins IL-6 and IL-8 are released into the circulation and their blood level parallels the severity of the disorder as well as the efficacy of the treatment [24]. The erosion is caused by the particular aggressiveness of CD8 cells which destroy the entire epidermis. Ulcerations may also occur, depending on additional factors like trauma or infections.

Long standing erosion can result in squamous cell carcinoma. Cofactors may be tobacco smoking, alcoholism, coinfection with oncogenic types of human papilloma virus and HCV, and immunesuppression [25]. The possibility of immune suppression raises the issue whether a patient with ELP could be treated with topical tacrolimus. The problem is a difficult one, especially after the FDA warning. Blood levels should be diriment for the systemic carcinogenicity. From the oral mucosa the blood concentration of pimecrolimus absorbed is said to be 2.84 ng/mL as an average; extreme values ranging between 0-6 and 19 ng/mL) [13], quite close to 20 ng/ml, which is regarded as relatively safe for patients using oral tacrolimus after a kidney transplantation [26].

As for the local carcinogenicity, the problem could be resolved on the basis of the evaluation of the two levels of risk. Pty