The topical calcineurin inhibitor pimecrolimus in atopic dermatitis: a safety update

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SUMMARY

Atopic eczema is a chronic inflammatory skin disorder with a relapsing and remitting course. For many decades, topical corticosteroids have been the mainstay therapy for atopic dermatitis. After the introduction of calcineurin-inhibitors as a corticosteroid-free alternative, there were high expectations. After the black box warning from the FDA regarding the potential theoretical risk for developing neoplasia under treatment with calcineurin inhibitors, patients and physicians became uncertain about its safety, regardless of the fact that current scientific data do not support increased concern for risk of malignancy.

Atopic dermatitis is a common chronic inflammatory skin disease with a relapsing and remitting course with pruritus as a leading symptom. The clinical manifestation of eczema usually occurs early in childhood, in infants before the age of 2 years, when over 50% of first eczema symptoms appear. In adults it is less frequent but, nonetheless, in approximately 30% of patients the first manifestation occurs after the age of 18 years (1). In the past decade a steady increase in the prevalence of atopic dermatitis worldwide has been noted, especially in school-age children (10–20%). Many factors are presumed to play a role in the pathogenesis: not only genetic predisposition, an impaired skin barrier, and neuroimmunological and psychological factors, but also environmental stimuli, infections, and other agents may be involved (2). Atopic eczema has a strong impact on the quality of life of patients and their families with consequences for their social and economic situation, and on healthcare system expenses (3).

Wherever possible, the recognition and elimination of triggering and aggravating factors is the main priority in the management of the disease. Continuous patient (or parent) education and appropriate use of emollients and moisturizers to repair the skin barrier and avoid skin dryness is needed for the long-term stabilization of the disease. On the other hand, a strict anti-inflammatory, disease-oriented, and stage-oriented therapy is needed. For more than 50 years, topical cor-

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ticosteroids were the only anti-inflammatory treatment option in atopic eczema. When used properly and carefully advised by a physician, they are an excellent tool and rarely cause adverse events.

Only uncontrolled and long-term application, particularly in sensitive areas like the face or skin folds, may cause side effects such as skin atrophy, striae, perioral dermatitis, or even systemic effects like adrenocorticoid suppression (4). Because atopic eczema is a chronic disease that requires long-term treatment, the introduction of topical calcineurin inhibitors such as pimecrolimus was highly appreciated (5). Therefore, expectations were high that the steroid-free anti-inflammatory therapeutic options using pimecrolimus would be appropriate and safe.

Pimecrolimus: mode of action

Pimecrolimus (Elidel® cream) is a chemical modification of ascomycin produced by S*treptomyces hygroscopicus var. ascomyceticus* and belongs to the immunomodulatory macrolides The mode of action of the topical calcineurin inhibitor (CNI) is more cell-selective than that of corticosteroids. Pimecrolimus blocks the activation of T-cells in affected skin by binding with cytosolic binding protein FKBP-12, a 12 kDa macrophilin, and forming a complex with calcineurin, calmodulin, and calcium, thereby inhibiting the phosphatase activity of calcineurin. The dephosphorylization of the nuclear factor of activated T-cell protein (NF-ATp), a transcription factor necessary for the expression of proinflammatory cytokines such as IL-2, TNF-alpha, IL-4, IL-5, is thus inhibited. Because there is no inhibitory effect on the antigen-presenting cells (APC) (e.g., Langerhans cells) by pimecrolimus, the local immune response is mostly unaffected (6, 7).

Rationale for use

The molecular weight of pimecrolimus, 810 Da, enables penetration and permeation in and through intact skin. It is widely accepted that only substances smaller than 500 Da can penetrate through an intact skin barrier without restriction. In patients with atopic dermatitis, the skin barrier is impaired. Due to the larger size of its molecules, pimecrolimus can penetrate through the stratum corneum and accumulate in the epidermis and dermis, without the tendency to permeate the blood, so practically no systemic absorption takes place (8). Pharmacokinetic investigation reveals that blood serum levels of pimecrolimus in patients (infants, children, and adults) undergoing topical treatment were not detectable or extremely low (< 2ng/ml) in 99.2% of cases, and thus any systemic effect was excluded (9, 10). Furthermore, during treatment with pimecrolimus cream the quality of the skin barrier improves. In addition to the limited systemic absorption of pimecrolimus, it is also more lipophilic than corticosteroids (molecular weight mostly under 500 Da), resulting in a greater affinity for the skin compartment and a lower potential for absorption into systemic circulation (8).

Clinical efficacy and safety in atopic dermatitis

Pimecrolimus 1% cream is approved for: (i) treatment of mild to moderate atopic eczema, (ii) short-term use for acute signs and symptoms; and (iii) intermittent long-term use to avoid the appearance of acute episodes.

Numerous international controlled clinical studies prove the efficacy and safety of pimecrolimus. Just a few days (2–4) after initiation of treatment, there is significant improvement of atopic dermatitis (11). In patients treated with pimecrolimus cream, the number of flares and the amount of topical steroids used were significantly reduced (12). An extensive study and clinical research program evaluated over 40,000 patients treated with pimecrolimus in various age groups, also comprising infants under the age of 2 (13). An extremely large number of patients used it during the postmarketing phase (14).

FDA warning

On February 2005 the pediatric advisory committee of US Food and Drug Administration (FDA) recommended a black box warning for the pimecrolimus cream (Elidel®) and the tacrolimus ointment (Protopic®), justifying their concerns regarding potential safety risks (15). These were mainly directed against extensive off-label use, especially in infants under the age of 2, and uncontrolled continuous long-term application, and were not primarily focused on the few reports of lymphoma. The warning regarding the potential risk of cancer was based on 20 case reports of lymphoma and 10 cases of skin neoplasm worldwide in patients treated with tacrolimus and/or pimecrolimus (16). Like all such reports, the majority of these were single cases reported spontaneously without an exact verification of the causal relation between CNI and carcinomas, and none of them resulted from any systematic scientific analysis proving an increased cancer risk (16, 17).

Despite the absence of a verified causal relationship for an increased risk of neoplasms, the FDA issued a warning on the potential risk of neoplasms following the topical application of CNIs. Opinion leaders and experts worldwide disagreed with and even strongly criticized the FDA decision, demanding withdrawal of the warning (18–20). However, the FDA did not decide to modify essentially its original decision on pimecrolimus (15).

Increased cancer risk: scientific background or misinterpretation?

Modern drugs such as pimecrolimus must undergo intensive preclinical research to exclude any potential risk before they are approved for use in humans. Animal models are valuable tools to evaluate the safety concerns. The importance of findings in animal models and in vitro studies should not be overestimated; they have limits in interpretation and are not objective without taking into consideration the specific application in humans. The first step to show any systemic effect should be to prove that a topically applied calcineurin inhibitor permeates and enters the blood circulation (21, 22). In an animal experiment, increased blood levels of pimecrolimus were measured after topical application of an alcoholic solution of pimecrolimus. In this model there was an increased risk for developing tumors (23). Considering the fact that the drug levels measured in this experiments were 60-fold higher than the highest dosage ever measured after topical application in humans, this suggests that any risk exists almost exclusively only in theory (13, 16, 17, 21). Furthermore, in 99.2% of samples taken from patients topically treated with 1% pimecrolimus the serum levels were below the limit of detection or < 2ng/ml (9, 10).

Upon analyzing the details of the reported lymphomas, it is noteworthy that they differ clinically and histologically from commonly observed cases. Thus, there is reason to suspect that these patients may never have had atopic dermatitis, but were treated for a pre-existing condition mimicking eczema (19).

Another argument for misinterpreting the risk is that the reported cancer rate in patients under treatment with topical pimecrolimus is much lower than the expected incidence of cancer in the normal population: The lymphoma ratio is 22:100,000, the ratio of non-melanoma skin neoplasm is 533:100,000, and the malignant melanoma ratio is 14:100,000 (15). Considering these data, there is no evidence that the incidence is increased in the population treated with topical calcineurin inhibitors; in fact, the rate is lower than expected. This is a very interesting finding in view of the *per se* increased rate of neoplasm in patients with atopic dermatitis (lymphoma 2 times higher and non-melanotic skin cancer 1.5 times higher compared to the normal population) (24, 25).

There is no doubt that initial enthusiasm in using topical calcineurin inhibitors is partially replaced by more cautious guidelines in atopic dermatitis patients with a need for anti-inflammatory therapy. The contentious points made by the FDA cannot be solved by discussions and statements. Long-term observational safety studies are underway to evaluate the risk for cancer. They should prove and critically evaluate the efficacy and safety (14). The current data do not support increased concern for development of malignancies. There is no doubt that topical calcineurin inhibitors such as pimecrolimus should be prescribed by physicians experienced in treating atopic dermatitis. Physicians and patients (and parents of underage patients) must be educated about the correct use of the medication in order to avoid drug side effects. Patients should be advised to use a conventional sun protection product while being treated with topical CNIs.

Both topical CNIs as well as topical corticosteroids are essential tools for the treatment of atopic eczema. Particularly for the treatment of sensitive skin areas such as the face and the intertriginous areas, pimecrolimus should be considered the treatment of choice. Effective treatment of atopic eczema requires multimodal therapeutic concepts with respect to the different stages of the disease: moisturizing emollients, strategies to avoid the itch-scratch cycle, and symptomatic anti-inflammatory treatment accompanied by efforts to eliminate or avoid any possible trigger factors.

Treating atopic dermatitis with new topical CNIs such as pimecrolimus reduces the amount of topical steroids needed and reduces the number of flare-ups. However, there should be no tendency to replace topical corticosteroids because the two treatments complement one another.

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A U T H O R S ' A D D R E S S E S

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