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Topical Noncorticosteroid Immunomodulation in the Treatment of Atopic Dermatitis

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Abstract

At present, the first-line drugs for treating atopic dermatitis are topical corticosteroids. They are effective when used short-term; however, long-term use of the corticosteroids is associated with suppressive effects on the connective tissue, seen as skin atrophy or resistance to therapy. Currently, two topical noncorticosteroid immunomodulators tacrolimus (FK506) and pimecrolimus (SDZ ASM 981) are under development, or already on the market in some countries for atopic dermatitis. These two compounds show structural similarity. In T lymphocytes they bind to the same cellular receptor, the FK-binding protein (FKBP) or macrophilin-12. Tacrolimus shows a 3-fold greater affinity to FKBP compared with pimecrolimus. The tacrolimus/pimecrolimus–FKBP complex further binds to calcineurin, an enzyme vital for the early activation of T cells. The consequence of calcineurin binding is a lack of activation of both T helper cell types 1 and 2. Further effects of these compounds have been suggested on other inflammatory cells, such as Langerhans cells and mast cells/basophils. In contrast to corticosteroids, no suppressive effects on connective tissue cells have been observed. Taken together, treatment of inflammation results in healing of the barrier function of the skin. This again results in reduced bioavailability of the drug, as compared with systemic use.

Placebo-controlled studies have shown the efficacy of both tacrolimus (at 0.03 and 0.1%) and pimecrolimus (at 0.6 and 1%). The main adverse event in these studies has been a burning sensation and increased pruritus at the site of application. Typically, these adverse events are observed only during the first days of treatment. Long-term safety studies, of up to one year, have not revealed any new adverse events. So far, long-term use of topical noncorticosteroid compounds has not been associated with signs of immune deficiency. Although there is currently no evidence for clinically relevant, prolonged adverse effects, some of these, such as an increased risk of photocarcinogenesis, need to be monitored. There is evidence from tacrolimus studies that monotherapy results in better long-term results when compared with combination therapy with corticosteroids. Tacrolimus and pimecrolimus could replace topical corticosteroids as the first-line treatment of atopic dermatitis.

Atopic dermatitis is a common disease of unknown etiology. Both genetic and environmental factors play a role in its clinical manifestations. The disease is characterized by itchy, dry skin, a chronically relapsing course, and susceptibility to cutaneous infections.[1,2] The therapies used so far for the treatment of atopic dermatitis include topical corticosteroids as first-line therapy, systemic corticosteroids, natural or artificial ultraviolet (UV) therapies, and immunosuppressive agents such as azathioprine, methotrexate, and cyclosporine as second-line therapy.[3] Of these treatments, efficacy in placebo-controlled trials has only been demonstrated for topical corticosteroids and oral cyclosporine.[4,5] Like other secondary treatments for atopic dermatitis, cyclosporine diminishes, but does not abolish, the need for topical corticosteroid treatment.[6,7] Attempts to develop a topical formulation of cyclosporine with efficacy in atopic dermatitis have failed.[8,9] In contrast, similar formulations of tacrolimus were effective in dinitroclorobenzene-induced atopic dermatitis.[10] Early clinical studies demonstrated the efficacy of tacrolimus ointment in atopic dermatitis.[11,12] Today, the new topical noncorticosteroid immunomodulators, tacrolimus (FK506) and pimecrolimus (SDZ ASM 981) have shown efficacy and an excellent safety profile in clinical studies as topical monotherapy for atopic dermatitis (figure 1).[13-17] Therefore, they are the first potential candidates to supplant topical corticosteroids as the primary treatment of atopic dermatitis.

In this review, we compare the mode of action of the new

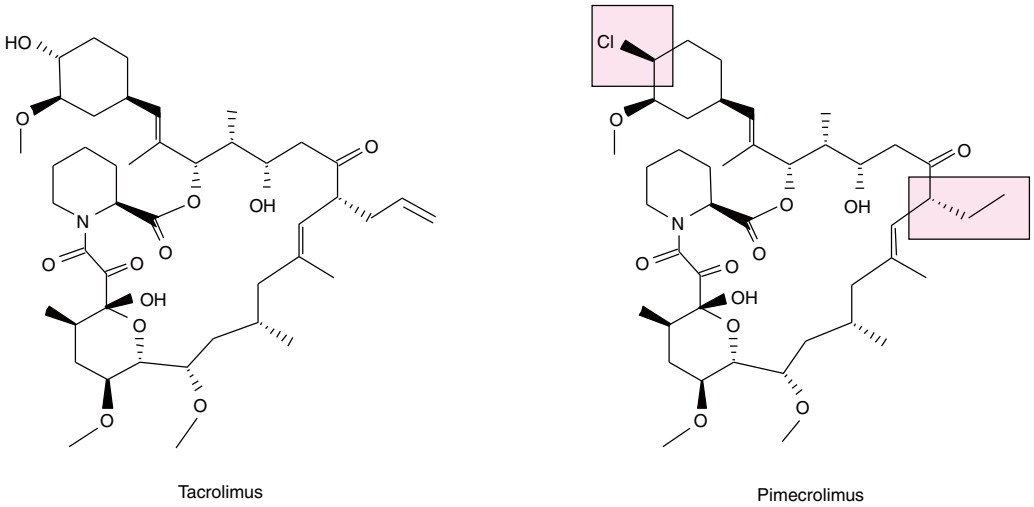

Fig. 1. Molecular structures of tacrolimus and pimecrolimus.

noncorticosteroid immunomodulatory agents, with an emphasis on human studies, and review key clinical studies performed for efficacy and safety with topical tacrolimus and pimecrolimus.

1. How Do Topical Noncorticosteroid Immunomodulators Work in Atopic Dermatitis?

1.1 Altered Immunity in Atopic Dermatitis

Patients with atopic dermatitis show signs of altered immunity in their skin and peripheral blood.[2,18] The skin of most patients with atopic dermatitis is colonized with microbes such as *Staphylococcus aureus* and *Malassezia furfur* (*Pityrosporum ovale/orbiculare*). The incidence of viral infections with herpes simplex, viral warts and molluscum contagiosum is increased. The majority of the patients show diminished delayed-type hypersensitivity reactions to recall antigens of bacterial or fungal origin. Most patients have increased levels of immunoglobulin (Ig) E in both the peripheral blood and the skin. This IgE has specificity to various exogenous environmental antigens, and also sometimes to intrinsic antigens.

1.2 The Role of Exogenous Antigens

The skin in patients with atopic dermatitis differs in several aspects from normal skin (figure 2). The 500 dalton (D) rule has been proposed as a model for the penetration of small molecules. According to this rule, molecules which are larger than 500D cannot penetrate normal epidermis.[19] It should be emphasized that this rule is not universally accepted. Tacrolimus has a molecular size of 822D, and pimecrolimus of 810D; they do not penetrate normal skin. In atopic dermatitis, both the dry skin and visibly inflamed skin show impaired barrier properties, which can be measured as increased transepidermal water loss.[20] Studies using the atopy patch test have demonstrated that large exogenous polypeptides, of the size 15 to 20kD, can penetrate atopic skin and cause an immune reaction of the skin.[21,22] In atopic skin these environmental polypeptides can be bound to CD1a+ antigen-presenting cells of the epidermis, such as Langerhans cells (LC) and inflammatory dendritic epidermal cells (IDEC), which both contain increased densities the high-affinity receptor to immunoglobulin E (FcεRI) on their cell surface.[23] This facilitates the binding of the exogenous environmental polypeptides with the help of free specific immunoglobulin E to the antigen-presenting cells. This 'antigen-focusing' is an especially effective way to present specific antigen to T cells.[24] An additional T cell activation is caused by nonspecific polyclonal T cell activation by superantigens, such as staphylococcal enterotoxins, shown to be common in atopic dermatitis skin[25,26] (figure 3).

1.3 T Helper Cell Subtypes

The lesional skin of atopic dermatitis contains a large number of T cells which show characteristic cytokine profiles. In a fresh lesion the infiltrate is characterized by cells of the T helper cell type 2 (Th2) cytokine profile, whereas the chronic lesion the T helper cells show a cytokine profile mainly of T helper cell type 1 (Th1).[18] Using a mouse model of atopic dermatitis, Spergel et al.[27] showed that both Th1 and Th2 cytokines are necessary to develop a mature atopic dermatitis lesion. T cells are activated via a calcium-dependent pathway in which calcineurin dephosphorylates the nuclear factor of activated T cell protein (NF-ATp) (for further information see Schreiber and Crabtree[28] and Sigal and Dumont[29]). NF-ATp then migrates to the T cell nucleus, where it leads to the transcription of interleukin (IL)-2 and other cytokines. This early activation leads to secretion of IL-2 receptor and through an autocrine pathway leads to activation and proliferation of T cells which can be selectively inhibited by the topical noncorticosteroid immunomodulating agents.[30,31]

1.4 Effects of Tacrolimus and Pimecrolimus

All studies on antigen-presenting cells have so far been done with tacrolimus only.[23,24] On the inflammatory epidermal and dermal cells in the skin, tacrolimus and corticosteroids seem to have quite opposing effects (figure 2). In Langerhans cells *in vitro*, tacrolimus down-regulates the expression of FcεRI; in contrast, betamethasone up-regulates its expression.[24] The down-regulation of FcεRI by tacrolimus is of potential clinical significance in the therapy of atopic dermatitis. It is currently not known whether the action of tacrolimus on FcεRI depends, as in T cells, on NF-ATp.

Wollenberg et al.[32] showed, in an *in vivo* intervention study with topical tacrolimus, that an increased proportion of CD1a+ cells in the epidermis of atopic dermatitis lesions decreased to normal during clinical improvement with tacrolimus ointment. The CD1a+ population consisted of LC and IDEC. An analysis of the relative proportion of these cell types showed that the decrease in CD1a+ cells was mainly due to a decrease in IDEC. The reduction of CD1a+ cells during treatment with tacrolimus ointment was accompanied by down-regulation of FcεRI expression in both IDEC and LC. The authors concluded that the CD1a+ dendritic cells could represent a target of tacrolimus in therapy for atopic dermatitis.

Tacrolimus and pimecrolimus block the early activation of T cells by binding to the FK506 binding protein (FKBP-12), a 12kD macrophilin.[33,34] The FKBP-12/tacrolimus or pimecrolimus complex inhibits calcineurin and thereby the dephosphorylation of NF-ATp and expression of inflammatory T cell cytokines, such as IL-2, IL-3, IL-4, IL-5, granulocyte-macrophage colony-stimulating factor, interferon (IFN)-γ and tumor necrosis factor (TNF)-α.

In vitro studies have also shown that both tacrolimus and pimecrolimus, through a mechanism that involves binding to the FK506-binding protein, also inhibit the release of inflammatory mediators from mast cells and basophils.[35,36]

1.5 *Staphylococcus aureus* and Atopic Dermatitis

S. aureus is a contributing factor increasing the severity of atopic dermatitis. *S. aureus* is found in more than 90% of atopic dermatitis skin lesions.[18] At our center, in a study of 19 patients, we found that staphylococcal colonization of atopic dermatitis lesions significantly decreased after 1 week, 6 months and 12 months of treatment with 0.1% tacrolimus ointment compared

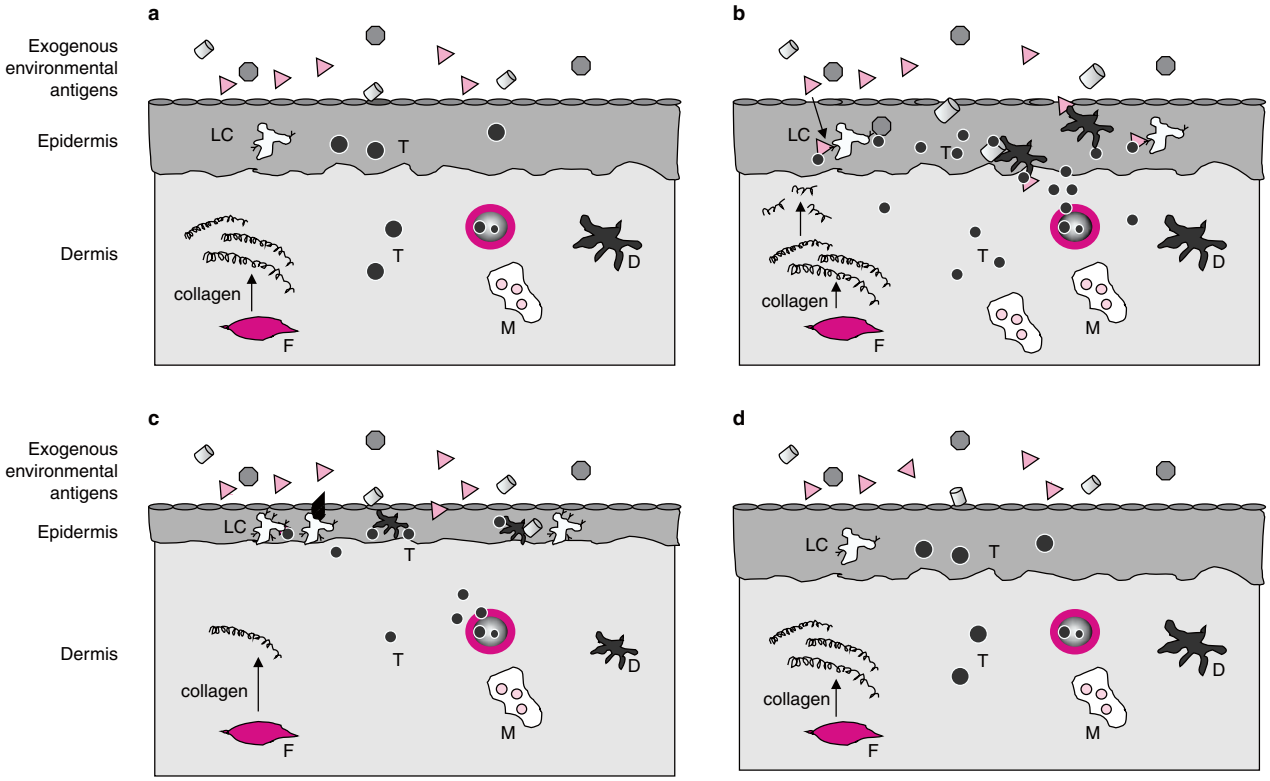

Fig. 2. The skin in atopic dermatitis: (**a**) normal skin; (**b**) skin in atopic dermatitis (inflammation); (**c**) skin in atopic dermatitis (treated with corticosteroids); and (**d**) skin in atopic dermatitis [treated with tacrolimus (pimecrolimus?)]. **D** = dendritic cell (for example inflammatory epidermal dendritic cell); **F** = fibroblast; **LC** = Langerhans cells; **M** = monocyte/macrophage; **T** = T cell.

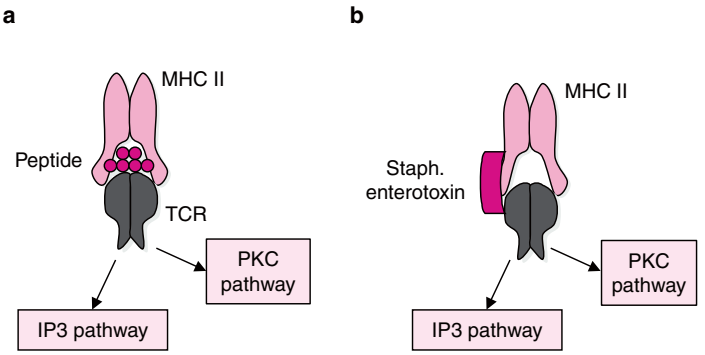

Fig. 3. Specific T cell activation through the major histocompatibility complex II (MHC II)/T cell receptor (TCR) signal by (**a**) antigens processed by antigen presenting cells; and (**b**) non-specific activation by staphylococcal superantigens. Both activate the same pathways leading to the activation of T cells via inositol-3-phosphate (IP3)/calcineurin pathway and protein kinase C (PKC) pathway. These pathways are inhibited by tacrolimus. **Staph.** = *Staphylococcus* spp.

with baseline.[37] These decreases followed clinical improvement. Tacrolimus has no inhibitory effect on bacteria *in vitro*, including *S. aureus*;[38] thus decreases in colonization probably reflect improvement of skin barrier function. Studies have shown that the colonization of atopic dermatitis skin with superantigen-producing *S. aureus* contributes to the severity of atopic skin disease.[39-41] Superantigen-mediated activation of T cells are resistant to corticosteroids, which may, in part, account for the increased clinical severity.[25] Hauk and Leung[26] showed that tacrolimus specifically blocks *S. aureus* superantigen-induced T cell proliferation in peripheral blood mononuclear cells of patients with atopic dermatitis and healthy volunteers, compared with dexamethasone. Antigen-processing by LC seems not to be involved in this process. Interestingly, it was recently shown that NF-ATp controls superantigen-induced shock.[42] This is important, as the inhibitory effect of tacrolimus on T cells is mediated through the same pathway, the calcineurin-mediated dephosphorylation of NF-ATp. The fact that this path is independent of the glucocorticoid receptor could account for the positive therapeutic response observed with tacrolimus ointment in patients with atopic dermatitis who are clinically insensitive to topical corticosteroid therapy.

1.6 The Dermis and Noncorticosteroid Immunomodulation

Compared with healthy dermis, the dermis of patients with moderate to severe atopic dermatitis shows decreased amounts of collagens type I and III (H. Kyllönen et al., unpublished observations), the two collagens which form over 70% dry weight of the skin (figure 2). Currently, it is not clear whether these reduced amounts are solely due to decreased synthesis after corticosteroid therapy[43] or UV-phototherapy,[44] or whether inflammation in atopic dermatitis increases degradation of collagen. The reduced collagen synthesis can be seen in extreme cases as visual atrophy. While it is clear that this atrophy is to a large part due to inhibitory effects of external corticosteroids on collagen synthesis, other intrinsic factors have to be considered. Many studies have shown important inhibitory or stimulatory effects of inflammatory cytokines on collagen or proteases causing collagen breakdown.[45-48] A study has shown that either type I or III collagen can serve as a reservoir of inflammatory cytokines, such as IL-2.[49] In addition, a recent study has suggested that the presence of type I collagen causes direction of early maturation of Th cells towards Th1, rather than Th2.[50] Taken together, at the present it is not clear how much of the reduced collagen synthesis is due to corticosteroids and how much due to inflammation. In future this question may be answered using noncorticosteroid monotherapy.

Until now, most studies attributing the effect of corticosteroids on the dermis and collagen synthesis, have either used healthy individuals or the corticosteroid effect has been measured by ultrasound. The ultrasound does not seem a reliable method for detecting inflamed skin, because even if total control of the disease is achieved residual inflammation will make the skin appear thicker than without inflammation. Short-term treatment with tacrolimus under occlusion did not have any effect on the collagen synthesis of treated skin in healthy individuals and patients with atopic dermatitis. Betamethasone, in contrast, reduced type I collagen synthesis to 20% and that of type III collagen to 30% of baseline value.[51] Betamethasone, but not tacrolimus, also reduced skin thickness both in controls and patients with atopic dermatitis. Pimecrolimus was studied under nonoccluded condition in healthy individuals for 28 days.[52] No effect on skin thickness was seen. However, the true clinical situation is long-term treatment. We have noticed a more than 2-fold increase in collagen synthesis in patients previously treated with corticosteroids after 1 year of tacrolimus treatment (H. Kyllönen et al., unpublished observations), suggesting that a repair is possible after prolonged corticosteroid treatment.

2. Clinical Efficacy

2.1 Efficacy Compared With Placebo

Several placebo-controlled studies with tacrolimus[13,14,20,53] and pimecrolimus[16,17,54,55] have shown significant efficacy of these compounds as compared with vehicle treatment. In the first randomized, double-blind study with tacrolimus ointment in patients with moderate to severe atopic dermatitis, performed as a multi-center study in Europe, ointments containing 0.03% (n = 54), 0.1% (n = 54), and 0.3% tacrolimus (n = 51), or a vehicle control (n = 54) were applied twice daily in 13 to 60-year-old patients.[13] Treatment duration was 3 weeks, and the treatment area was less than 10% of body surface area (not more than 1000cm^2). Efficacy was measured with a combined score for er-

ythema, edema and pruritus. The median decrease in clinical score was significantly greater than vehicle control for all the tacrolimus concentrations used. There was no significant difference among the three concentrations. A similar double-blind, multicenter study was performed in the US in 180 children aged 7 to 16 years old.[14] Results of this 3-week study was similar to the European study with all tacrolimus ointments (0.03, 0.1 and 0.3%) being significantly more effective than vehicle treatment.

Three placebo-controlled studies comparing tacrolimus 0.03, 0.1% and vehicle with a 12-week duration have been performed in the US.[53,54,56] The total number of patients in these three studies was over 900. Tacrolimus was significantly more effective than placebo in all studies. No significant difference was observed between the two tacrolimus concentrations studied. In all five studies treatment efficacy compared to baseline was clearly over 50%.[13,14,53,54,56] Pimecrolimus cream was compared to vehicle in a proof-of-concept study in a single-center study performed in Amsterdam.[16] The size of the lesion was 1 to 2% of total body area. Pimecrolimus cream 1% was applied once or twice daily. Pimecrolimus was significantly more effective than vehicle treatment, whereas twice daily application was significantly more effective than once daily.

In a randomized, double-blind multicenter three-week study with 260 adult patients, pimecrolimus cream (0.05, 0.2, 0.6 and 1%) were compared with vehicle and betamethasone valerate cream.[17] With the exception of the lowest concentration of pimecrolimus, all other concentrations were more effective than vehicle treatment. There was a dose-dependent increase of efficacy with increasing concentration of pimecrolimus. The average improvement with 1% pimecrolimus was slightly under 50% (46.7%). When treatment efficacy was compared to clinical severity of disease, treatment results were better in patients with mild disease compared to those with moderate disease.Two independent 6-week, randomized, multicenter trials studying a total of 403 patients with mild to moderate atopic dermatitis compared treatment with 1% pimecrolimus cream or vehicle cream.[57] Significant improvement in clinical score relative to vehicle treatment was observed with pimecrolimus treatment. The overall improvement was comparable to the adult study of 3 weeks.[17]

2.2 Efficacy Compared With Corticosteroids

Short-term studies of 3 weeks duration have compared tacrolimus with hydrocortisone acetate in children,[58] tacrolimus with hydrocortisone butyrate in adults,[59] and pimecrolimus with betamethasone valerate.[17] Tacrolimus 0.03 and 0.1% was compared to 1% hydrocortisone acetate treatment in 2 to 15-year-old children with moderate to severe atopic dermatitis in a 3 week randomized, double-blind study.[58] Treatment was restricted to 60% of total body surface. Both tacrolimus concentrations were significantly more effective than hydrocortisone acetate, with tacrolimus 0.1% being significantly more effective than 0.03%, a finding not seen in US studies.[53,54,56] In adult patients with moderate to severe atopic dermatitis, tacrolimus 0.03 and 0.1% twice daily was compared to 0.1% hydrocortisone butyrate, a midpotent to potent topical corticosteroid.[59] Tacrolimus 0.1% showed similar efficacy as hydrocortisone butyrate, and both these ointments were significantly more effective than 0.03% tacrolimus ointment.

Comparisons of pimecrolimus cream (0.05, 0.2, 0.6 and 1%) to betamethasone valerate cream in 260 adult patients with mainly moderate atopic dermatitis showed that betamethasone valerate was significantly more effective than pimecrolimus at all concentrations studied (0.05 to 1%).[17]

Full reports of long-term comparative studies are not available. One such study, of pimecrolimus compared with triamcinolone acetate cream is available as an abstract and showed similar efficacy of both treatments for those patients who completed the study.[60] Over 50% of the patients on pimecrolimus did not complete the study, which raises questions about an intent-to-treat analysis as it would seem likely that patients with more severe disease might have a less effective treatment result.[18,60,61]

We believe that the true test of these compounds will be in long-term use, as this is a chronic disease that tends to need long-term treatment. Although topical corticosteroids are often used long-term for the treatment of atopic dermatitis they are only approved for short-term use. Therefore, there is practically no data available on whether we should use them until all symptoms have vanished or sparingly to have best efficacy, while avoiding adverse effects. The ongoing long-term comparative study of tacrolimus/corticosteroid should shed light on this question.

2.3 Safety

Burning sensation of the skin was the only adverse event that showed a higher incidence with tacrolimus ointment or pimecrolimus cream, compared with the vehicle control in short-term studies.[13,14,16,17] In long-term studies skin burning, erythema and pruritus were common, but tended to occur only during the first few days of treatment.[15,56,62] Burning and also erythema of the face were aggravated by alcohol uptake in some patients. The cause of burning is not known, and it is unclear whether any treatment, e.g. antihistamines, could be useful in the prevention of it. Using timed suction blisters of the skin, we have observed that there is an early release of some neuropeptides which could be responsible for these symptoms (Reitamo S et al., unpublished observations). Uncontrolled safety studies of 1 year duration did not show any safety concerns.[15,56,62] Bacterial colonization with *S. aureus* was reduced to a great extent and there were no other apparent signs of immune suppression. Using historical comparisons there was no apparent increase in herpes simplex infection.[15,63] Also, there was no decrease in recall antigen reactions[15] and the number of pigment nevi had not increased (Reitamo S et al., unpublished observations). Long-term compar-

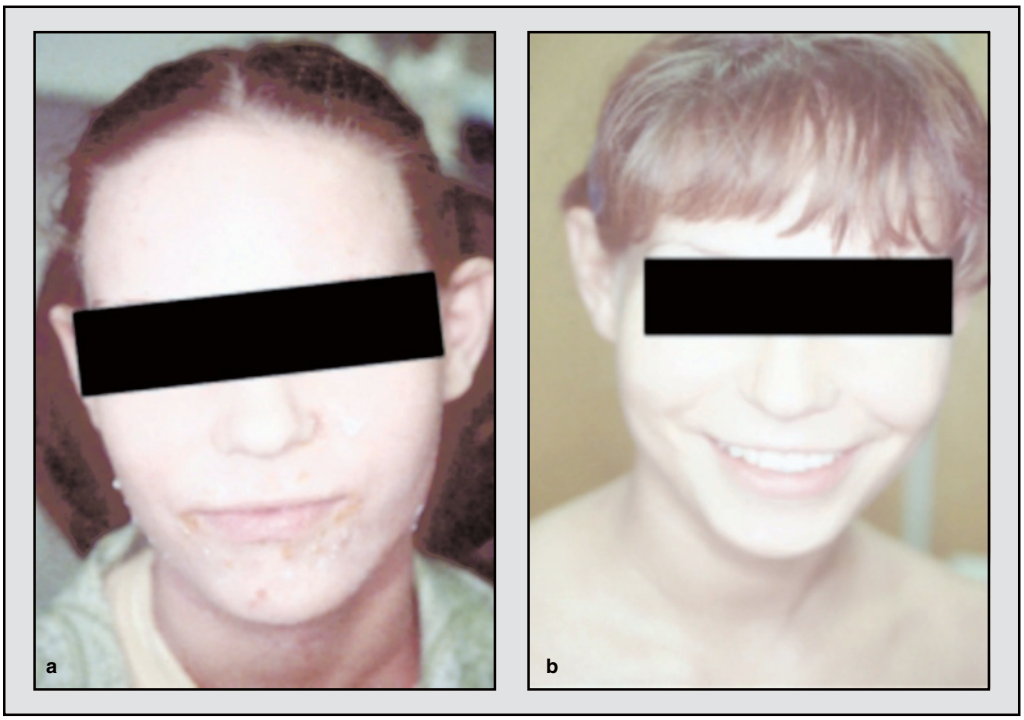

Fig. 4. An 18-year-old patient with severe atopic dermatitis not responsive to corticosteroids: (**a**) before treatment with tacrolimus ointment; and (**b**) after 3 years of tacrolimus ointment monotherapy.

ative studies for tacrolimus are ongoing. So far, however, the main outcome seems to be that these compounds have a good safety profile and can therefore be used long-term.[15,56,62] During long-term studies with tacrolimus, some of our patients experienced several months in which no treatment was necessary (Reitamo S et al., unpublished observations). It would be of interest to assess this prospectively. Long periods of clearance, in which treatment would be unnecessary, would be a great advantage over conventional corticosteroid treatment.

Laboratory profiles during several long-term studies have been unremarkable.[15,56,62] Drug concentrations in the blood have been shown to decrease a few days after starting therapy for both tacrolimus and pimecrolimus.[13,64] During long-term treatment about 75% of the patients did not show detectable blood concentrations of tacrolimus.[15] The only exception has been children with Netherton syndrome, an autosomal recessive disease characterized by congenital erythroderma, who despite a good treatment results showed high tacrolimus trough blood concentrations.[65] Blood concentrations from pimecrolimus long-term studies have not yet been reported. In a short-term study they have been low.[64]

There has been no evidence of an increased risk of any type of infection compared with historical data from the literature. In terms of mode of action, topical tacrolimus and pimecrolimus may decrease immune surveillance of treated skin, and thus, over a period of many years, increase the risk of basal cell or squamous cell carcinoma. Thus, patients receiving therapy with a topical immunomodulator should be educated on adequate measures of sun protection, and an important aim of post-marketing research should be long-term safety.

3. Why Should Patients Be Treated with Monotherapy?

We have experience from many patients who have used cyclosporine, together with topical corticosteroids, who have significantly improved after switching to tacrolimus monotherapy (Reitamo S et al., unpublished observations). This suggests that tacrolimus monotherapy can greatly improve the treatment of severe atopic dermatitis (figure 4). When tacrolimus is used as long-term treatment in a clinical research project which emphasizes treatment of all atopic dermatitis until the skin is totally cleared and pruritus as resolved, an improvement in patients with moderate to severe atopic dermatitis of at least 90% can be expected in half of the patients.[15] These findings need to be reperated in a controlled study. Total use of tacrolimus ointment decreased with time, and some patients also had treatment-free periods of several weeks. After 12 months of monotherapy several patients showed normalization of the transepidermal water loss and they had no pruritus. In patients with at least 90% improvement, we have observed also a decrease in serum and skin immunoglobulin

E levels (Reitamo S et al., unpublished observations). This improvement of the skin, apparently to normal, after long-term tacrolimus treatment raises questions of whether all skin symptoms in atopic dermatitis are actually of a secondary nature, with a primary disorder in the bone marrow cells. This would mean that the disease would need redefining since pruritic dry skin has been the central prerequisite for the diagnosis of atopic dermatitis.

Sugiura et al.[66] showed recently that by treating only the face with tacrolimus, and the rest of the body with corticosteroids, there was, after an initial response, quite poor long-term results. These results were dependent on the severity of dermatitis, with treatment results inversely related to severity of dermatitis.[66] We can confirm these findings from several patients treated outside clinical trials.

Most of the patients undergoing pimecrolimus treatment in clinical trials had either mild or moderate disease, although a few had severe atopic dermatitis. From the available study in adults it can be concluded that approximately half of such patients will respond to pimecrolimus monotherapy.[17] The treatment results with pimecrolimus in pediatric studies seem better.[54,55] However, these studies used vehicle as control therapy and corticosteroids were allowed as rescue therapy. Therefore, the results cannot be directly compared with those from the adult studies.

4. Status of Marketing Approvals

For atopic dermatitis, tacrolimus ointment 0.1% has been on the market in Japan for treatment of adults since 1999 and in the US and Canada since 2001 as 0.03 and 0.1% ointment for adults and 0.03% ointment for children. A marketing authorization application for tacrolimus ointment 0.03 and 0.1%, has been approved by the European Agency for the Evaluation of Medicinal Products (the drug is now available in many European countries). Pimecrolimus cream 1% is being developed for atopic dermatitis. In the US, pimecrolimus cream 1% was approved in 2001. In Europe it should be available in Denmark in 2002.

5. Conclusions

The main advantage of topical noncorticosteroid immunomodulatory agents is that they do not cause skin atrophy and therefore do not prevent healing of the skin. Tacrolimus and pimecrolimus have a similar structure and mode of action, but comparison of three 3-week clinical studies using the same efficacy parameters and corticosteroid comparators, although no direct comparison, suggest that tacrolimus is more effective.[17,58,59] To avoid any possible risks associated with the use of these two treatments, detailed knowledge of drug blood concentrations in comparison with clinical outcome needs to be obtained. It seems likely that the group of patients who would benefit least from treatment would be those with severe and wide-spread disease who experience poor efficacy, so that any risks do not outweigh the benefits. The clinical data collected so far indicates that there is no increased risk of skin cancer, infection or other undesirable immunosuppressive effects.

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