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Chair and Department of Dermatology, Medical University of Lublin

MAŁGORZATA MICHALSKA, EMILIA CHADAJ,
AGNIESZKA KRAKOWSKA, DOROTA KRASOWSKA

New macrolactam immunomodulators in the topical treatment of inflammatory dermatoses

In the last decade a lot of new immunosuppressive drugs and immunomodulators have become available in medicine (8). They are primarily used in prevention of organ and skin transplants rejection, but a few of them (for example, cyclosporin A and corticosteroids) are administered systemically in the treatment of numerous dermatoses (8). Unfortunately, all these drugs have inconvenient features or a potential for serious, usually unavoidable, adverse effects that limit their use (8). Because topical application of drugs frequently reduces the unwanted effects of systemic administration, topical formulations are generally preferred. The ideal drug for the treatment of chronic inflammatory skin disease should therefore be topical, highly effective, simple in use and with as few side effects as possible. Topical corticosteroids were introduced about 50 years ago and brought significant improvement in treatment of various types of dermatitis. They do, however, have numerous potential adverse effects including skin atrophy, striae, telangiectases, hirsutism and even suppression of growth in children (16). Therefore, there is a great need of safe, anti-inflammatory non-steroidal agent for topical use in skin diseases.

The new topical immunomodulators (TIMs) may provide an alternative to corticosteroids and revolutionize the way that inflammatory dermatoses are treated and managed (8). This group of drugs includes two main agents that share a macrolactam structure: tacrolimus (formerly named FK506) and pimecrolimus (also known as SDZ ASM981). They are calcineurin inhibitors. The way of action is similar to that of cyclosporin A; however, they are effective when used topically (16). We review the current knowledge of these substances, covering the mechanisms of action, clinical efficacy and possible adverse events.

Tacrolimus, the key substance of macrolactam immunomodulators, was first extracted in 1984 from the fermentation product of *Streptomyces tsukubaensis*, a soil bacterium found in Tsukuba, Japan. The name of tacrolimus is a neologism derived by taking the 't' for Tsukuba, 'acrol' for macrolide and 'imus' for immunosuppressant (13). Pimecrolimus is a newer ascomycin derivative. It was isolated in the early 1960s as a fermentation product of *Streptomyces hygroscopicus* var. *ascomycetus* (16). Firstly, its antifungal properties were studied and more than 20 years later its immunomodulatory activity was discovered (9). Tacrolimus has an empirical formula of $C_{44}H_{69}NO_{12}\cdot H_2O$ and molecular weight of 822.05 D, whereas pimecrolimus has chemical structure of $C_{43}H_{68}ClNO_{11}$ and 810.48 D (7, 9).

Although the structure of tacrolimus and pimecrolimus differs from the tertiary complex structure of cyclosporin, the mechanism of action and biologic properties *in vivo* and *in vitro* appears to be similar (8, 13). Functionally, however, there do exist important differences between the agents. First of all, unlike tacrolimus, cyclosporin does not have the ability to be absorbed through the skin and secondly,

it has been demonstrated *in vitro* that tacrolimus has 10 to 100 times higher immunosuppressive ability compared with cyclosporin (8). Initially, tacrolimus known by its experimental name, FK506, was used for systemic immunosuppression of patients to prevent allograft transplants rejection (8). Oral tacrolimus has also been used in dermatology. At the beginning, in systemic lupus erythematosus mice models tacrolimus has been shown to increase survival, decrease lesions, atypical cells and proteinuria (8). The first report on systemic tacrolimus in humans was published in 1992 and described reduction in symptoms in 7 patient with severe recalcitrant psoriasis after 1 week and complete resolution after 4 weeks of oral tacrolimus (8). Because of the efficacy of the systemic treatment, tacrolimus has been extensively investigated as a topical agent and very impressive effects of this formulation have been observed for various dermatoses (8). Since then, multicentre, randomized double-blind clinical trials with topical formulation of tacrolimus have shown its efficacy in moderate to severe atopic skin disease in both children and adults (8, 13). Pimecrolimus also shows promising results (1).

Tacrolimus ointment has two concentrations available for adults, 0.03% and 0.1%, while for children aged 2 to 15, only the 0.03% is recommended (7). Pimecrolimus is currently available only as 1% cream for both adult and pediatric population (10).

MECHANISM OF ACTION

Calcineurin inhibitors act on the signal transduction pathways and block gene transcription of T cells decreasing their activation and thus responsiveness to various antigens. First of all, they inhibit the production of proinflammatory cytokine genes, which is dependent on the transcription factor called NF-AT (nuclear factor of activated T cells) by blocking the catalytic function of calcineurin. Calcineurin is the calcium dependent serine-threonine phosphatase that regulates the translocation of cytosolic components of nuclear factor to the cell nucleus.

It has been demonstrated that tacrolimus exerts its biologic effects after entering the cells and binding to its cytosolic ligand the macrophilin 12, formerly called FK506- binding protein (FK-BP), which is one of the immunophilins. This complex gains the ability to bind calcineurin and inhibit its phosphatase activity. Therefore, the tacrolimus-FKBP-calcineurin complex disables the dephosphorylation of nuclear factor cytosolic subunit (cNF-AT) and subsequently blocks its translocation into the nucleus. As a result, the cytosolic subunit can not form a complex with nuclear part of NF-AT which is newly synthesized via T-cell activation signals. It results in inhibition of lymphokine genes transcription. Thus, the production of T-helper 1 cytokines such as interleukin-2 and gamma interferon is blocked resulting in reduction of T-cell-mediated immune response (7, 8, 13). Tacrolimus also inhibits the transcription of genes which encode Th2 cytokines including IL-3, Il-4, IL-5, GM-SCF and TNF-alfa which are involved in the early stages of T-cell activation (8).

Additionally, tacrolimus has been shown to inhibit the release of pre-formed mediators from skin mast cells and basophils, to inhibit the expression of genes involved in leucotriene synthesis, and to down regulate the expression of IL-8 and FcεRI receptor on both Langerhans cells and inflammatory dendritic epidermal cells (IDEC), which play basic role in pathophysiology of various inflammatory dermatoses (7, 8, 13). The drug also decreases the expression of intracellular adhesion molecule -1 and E-selectin on blood vessels endothelial cells (8).

Animal studies with an induced allergic contact dermatitis model in mice reported on reduced RNA levels of IL-1alfa, IL-1beta, GM-CSF, TNF-alfa, INF-gamma, and macrophage inflammatory protein-2 after tacrolimus application (8).

Because pimecrolimus also interacts with macrophilin -12, its clinical effects resemble closely those of tacrolimus(13). It has also been proved that tacrolimus has antifungal activity and acts against *Malassezia furfur* which has been found in greater proportions in skin of atopic dermatitis patients (8).

Although topical tacrolimus is able to penetrate the skin, it is only minimally absorbed into the systemic circulation (13). The percutaneous absorption depends on integrity of the epidermal barrier and it is higher in diseased skin. Therefore, the absorption is limited over the course of the therapy, because the patient's skin will absorb progressively lower quantities of the drug as the lesion heals. Only about 0.5% of tacrolimus applied to the skin can be detected in blood. The absorption properties of tacrolimus are related to relatively high molecular weight and high lipophilicity (8). Low systemic absorption rate and undetectable or subtherapeutic blood levels of tacrolimus have been proved in the majority of clinical cases and randomized studies (8, 13). The lower limit of detection in the blood is 0.05 ng/mL and the therapeutic range after systemic administration is 5 to 15 ng/mL (13). The results from two pharmacokinetic studies have shown the peak tacrolimus blood concentrations from undetectable to 20 ng/mL after single or multiple doses in 49 adult atopic dermatitis patients. In 45 out of 49 patients the peak blood concentrations were lower than 5 ng/mL (7). The result from other study performed in 20 atopic children (aged 6-13 years) showed peak tacrolimus concentrations below 1.6 ng/mL in all patients (7). Only in one particular condition, the Netherton syndrome, an increased percutaneous absorption of tacrolimus ointment has been documented. The syndrome is an autosomal recessive disease characterized by erythroderma, failure to thrive and ichthyosis. Although, as already noted, topical tacrolimus is effective in treating skin involvement with the Netherton syndrome, it is recommended that either patients with this condition should avoid the therapy with tacrolimus or blood levels of the drug should be followed closely (13).

There was also no evidence based on blood concentrations that tacrolimus accumulates systemically upon intermittent topical application for periods of up to 1 year (8). Moreover, Etoh reported on the long-term safety of tacrolimus 0.1% application with 80% of patients not having any systemic absorption (under 0.5 ng/mL) during 2 years of therapy (8). Another randomized study with tacrolimus applied twice daily for 3 weeks resulted in blood concentrations below 0.25 ng/mL in most patients (8). It is very important that minimal systemic absorption make interactions with other systemically administered drugs unlikely to occur but they can not be ruled out. Furthermore, it does not seem that the agent accumulates in the skin, although there is no evidence of cutaneous metabolism (8). But the lowest tacrolimus blood level at which systemic effects could be observed is still unknown (7).

TOPICAL MACROLACTAMS IN ATOPIC DERMATITIS

Currently topical macrolactam immunomodulators are investigated for the treatment of a wide variety of inflammatory skin diseases. Most of the studies were conducted to show the efficacy of tacrolimus in atopic dermatitis (8, 13). Tacrolimus ointment is indicated for either a short-term or intermittent long therapy of patients with moderate to severe atopic dermatitis, especially in whom the use of conventional therapies (most often corticosteroids) seems to be unadvisable because of potential risk, inadequate response or intolerance. Ointment should be applied to the affected skin areas twice daily and continued for one week after clearing the signs and symptoms of the disease (7). Pimecrolimus 1% cream should only be aimed at patients with mild atopic dermatitis (1).

By the year 2002 the effectiveness of topical tacrolimus had been studied in about 13,000 either pediatric or adult patients with atopic dermatitis in clinical trials (13). The first large European randomized, double-blind vehicle-controlled clinical multicentre trial involving 213 patients with atopic dermatitis confirmed the efficacy of topical tacrolimus for this disease. The severity scores of dermatitis based on a scale from 0 to 3 for a number of features such as erythema, oedema and pruritus present in particular areas of the skin decreased by 75.0%, 83.3% and 66.7%, respectively, for the three concentrations of the drug: 0.3%, 0.1% and 0.03%, after 3 weeks of treatment. In comparison, the

particular areas of the skin decreased by 75.0%, 83.3% and 66.7%, respectively, for the three concentrations of the drug: 0.3%, 0.1% and 0.03%, after 3 weeks of treatment. In comparison, the patients who received the vehicle had a median score decrease of 22.5% (8). Moreover, Hanifin et al. found tacrolimus to be more effective in therapy of moderate to severe atopic dermatitis than vehicle – a 90% or greater improvement from baseline after 12-week therapy was observed in 36.8% of the patients in the 0.1% tacrolimus group, 27% in the 0.03% tacrolimus group and 6.6% in the patients applying the vehicle (8). Hanifin also conducted a study designed to measure the effects of tacrolimus ointment in atopic children. After 3 weeks of therapy 54% of the children receiving tacrolimus experienced a marked or excellent improvement compared with 12% of the children on vehicle ointment (8). The efficacy of long-term application of tacrolimus ointment for atopic dermatitis was also studied in several clinical trials. In an open-label, noncomparative, multicentre phase III study the efficacy and safety profile of 0.1% tacrolimus in 316 adult individuals after 12-month treatment was similar to that of short-term trials – 86% of the patients exhibited either a marked improvement (over 75%) or a total clearance of the disease when evaluated at 12th month. But the most profound difference in symptoms was achieved within the first week of treatment, as measured by a modified EASI (8). Long-term treatment of moderate and severe atopic dermatitis with topical 0.1% tacrolimus has also a been shown to be effective and safe in the pediatric population, aged 2–15. It was observed that the symptoms and signs of atopic dermatitis, total body involvement and patients' subjective rating of pruritus decreased substantially during the first week of therapy. The effectiveness was maintained throughout the course of the study and the therapy received good tolerance from the patients (8). These improvements in skin diseases therapy with tacrolimus also have significant impact upon health-related quality of life in patients with atopic dermatitis. It has been formally documented by Drake et al. in a double-blind, placebo-controlled, quality-of-life study of 985 adult and pediatric patients. With the use of standard Dermatology Life Quality Index, the authors showed marked improvement in the quality of life after treatment with either 0.03% or 0.1% ointments (13).

Overall results of six trials, including 1502 participants directly compared the effectiveness of tacrolimus 0.03% and 0.1% tacrolimus ointment in the treatment of atopic dermatitis. In three of these studies no significant differences between strengths of the drug were found concerning the proportion of patients clear or achieving an excellent improvement at 3 weeks, although following a 12-week observation tacrolimus 0.1% ointment was significantly more effective than tacrolimus 0.03% (1).

There are fewer published data on pimecrolimus, but many promising results have recently been reported in various atopic patient populations (1, 10). The topical 1% pimecrolimus has been proved to be significantly superior to placebo in a randomized, double-blind, vehicle-controlled study including 34 atopic patients conducted by Van Leent et al. After 20 days the reduction of symptoms was 71.9% in the group treated with pimecrolimus. In addition, it was shown that application of the drug twice daily is significantly more effective than once daily use (15). SDZ ASM 981 was also reported to be safe and effective in atopic pediatric population aged 3 to 23 months. It was announced that pimecrolimus provides better control of the disease than standard emollient treatment (11).

It was also very important to compare the efficacy of tacrolimus with that of topical corticosteroids in the treatment of atopic patients, but currently there are very few data available. The FK506 Ointment Study Group conducted two comparative studies on the effectiveness of treating atopic dermatitis with tacrolimus and betamethason valerate or aclomethason diproprionate and reported that tacrolimus was as effective as betamethason when applied on trunk and limbs and was significantly more effective than aclomethason in treating the face (8). In a 3-week study Reitamo reported an EASI reduction of 60.1% for 0.1% tacrolimus ointment and 39.8% for hydrocortisone acetate (10). Besides, there are

Tacrolimus 0.1% was also shown to be significantly more effective than 0.1% hydrocortisone acetate in the therapy of atopic dermatitis and, whereas pimecrolimus cream was demonstrated to be less effective than potent topical steroids and there are no data available comparing the drug with mild corticosteroids (1). Following a 3-week study, Luger et al. compared pimecrolimus unfavourably with bethametason valerate – the reduction in EASI score after topical steroid application was 79.6%, whereas for pimecrolimus it was significantly lower (44.9%) (10). The only study directly comparing therapy with 0.03% tacrolimus vs. 1.0% pimecrolimus showed no significant difference in their effectiveness in children with moderate atopic dermatitis (1).

When summarizing the data, it appears that tacrolimus ointment has the efficacy similar to mid-strength glucocorticosteroids. Moreover, both drugs have significantly greater relative reductions in EASI scores than placebo (1).

ADVERSE EFFECTS

When administered systemically, following transplant operations, tacrolimus (FK506) has potency to cause a number of dangerous adverse effects due to its immunosuppressive and calcineurin-blocking activity as calcineurin is required for multiple processes in the body (8, 13). The most serious ones include nephrotoxicity with reduction of the glomerular filtration rate and hyperkalaemia, vasoconstrictive effect with hypertension and various neurotoxic side effects such as encephalopathy, seizures, psychiatric and focal disturbances. These major reactions occur in approximately 5–10% of the individuals. Minor adverse effects are about twice more frequent including headaches, fever, diarrhoea, nausea, constipation and vomiting. Hypersensitivity reactions have also been reported (8).

In comparison, it has been proved in numerous studies that tacrolimus has no systemic toxic effects when used in a topical formulation due to its minimal percutaneous absorption. In all conducted trials tacrolimus ointment has generally been well tolerated and the most common application site events were transient skin burning and pruritus or heat sensation with decreasing frequency of occurrence following the first few days of the therapy (8). These reactions have incidence of approximately 33% to 45% in patients treated with 0.03% ointment and 31% to 61% in those treated with 0.1% ointment, depending on the study (13). They are usually mild and self-limited. It is taken into account that sensitivity of the cutaneous nerves to calcineurin inhibition underlies this common adverse effect. However, the low rate of pimecrolimus- induced skin burning makes this hypothesis difficult to prove (13). A extensive study by Soter et al. also showed burning of the skin to be the most frequently reported adverse event following a 12-week treatment with tacrolimus ointment 0.03% and 0.1% in a group of 631 adult individuals with atopic dermatitis. In addition, 50 patients discontinued treatment due to adverse effects but twice as many were in the vehicle group (8). The data from the study by Reitamo et al. on the long-term (1 year) treatment of atopic dermatitis confirmed that 0.1% tacrolimus ointment is a safe option for these patients and can be used for prolonged periods of time. The safety profile was similar to that of short-term trials. There was no significant increase in adverse effects with repeated applications over the course of the study (8).

Tacrolimus ointment 0.1% was also demonstrated to be safe in a pediatric sample of patients in a 12-month trial conducted by Kang et al. with skin burning (25.9% of children) and itching (23.1%) as the most commonly reported side effects. The most frequent among non-application site events were flu-like symptoms, fever and headache. One patient developed a papular eruption on the face while applying tacrolimus. Furthermore, there were no clinically significant or consistent changes in laboratory variables such as relating to hepatic and renal function or blood cell count (8). Less frequently reported adverse effects include folliculitis, skin rash, alcohol intolerance, acne and cyst formation (13).

Patients with AD, regardless of treatment, are generally at a higher risk of bacterial and viral infections, including eczema herpeticum. Thus, the topical treatment with an immunosuppressive agent such as tacrolimus, was suspected to be associated with an increased incidence of VZV (chicken pox or shingles), HSV and Staphyloccocus aureus infections (7). Atopic skin colonization with *Staph. aureus* is frequent. The bacterium that produces superantigens is involved in the pathophysiology of the disease and the eradication improves the clinical manifestations (3). According to the study conducted by Robinson et al. the local bacterial infection risk is lower with tacrolimus than in case of corticosteroids (3).

Paller et al. following a 12-week trial reported chicken pox and vesiculobullous rash at a low incidence of less than 5% in atopic pediatric patients treated with topical 0.03% tacrolimus; however, it was statistically significant when compared with the vehicle group (8). Fleischer et al. in the year 2002 presented a review in which they reported that tacrolimus ointment is not associated with an increase in herpes simplex virus infections. This study showed that eczema herpeticum is a rare complication in the setting of atopic dermatitis treated with the topical immunomodulator – the rate of the herpes infection was 1.9% (6). Jaracz et al. also reported that tacrolimus does not increase the incidence of cutaneous infections in the atopic patients for up to 1 year therapy (8). In a review of the data on topical calcineurin inhibitors presented by Alan B. Fleischer, MD at the 13th Congress of the EADV in 2004, a theoretical concern that tacrolimus application could affect the immune response, including a response to vaccination, was not substantiated. The author reported that 26 children who were vaccinated with pneumococcal vaccine after 3 weeks of treatment with tacrolimus 0.03% ointment generated a protective antibody response (5).

Unlike topical steroids, tacrolimus has no effect on collagen synthesis and does not decrease skin thickness (Reitamo et al.).The investigators concluded that tacrolimus does not cause skin atrophy, which in contrast may be observed following application of a medium-potency corticosteroid (bethamethason) for 7 days. What is more, tacrolimus does not affect keratinocytes proliferation (8). Furthermore, neither sensitization, phototoxicity nor photoallergicity occur with tacrolimus. The drug does not photosensitize the skin. Although human studies have not shown a potential risk for skin carcinogenesis, avoidance of excess natural or artificial sunlight exposure is recommended in response to hairless mouse model studies in which use of tacrolimus shortened the time of skin tumor formation after exposure to UV radiation (13). Owing to the lack of serious adverse events, tacrolimus can be used to treat AD on all body regions including the most sensitive areas such as the face, the neck and skin folds, whereas corticosteroids will be preferred in thicker areas of the skin where atrophy is less of a worry. The tacrolimus safety for the eye is also proved – in contrast to steroids, there is no evidence of increased ocular pressure when applied to the eyelids (13).

There are no adequate reports on the effects of either oral or topical tacrolimus on pregnant women, although animal models show some negative consequences to both mother and fetus. Tacrolimus is transferred across the placental membrane and is excreted in breast milk (8). The drug has been placed in Pregnancy Category C in terms of safety, which means that it should be only used in pregnant women if the potential benefit to the mother justifies the potential risk to the fetus (7).

OFF-LABEL USE

Topical tacrolimus is currently investigated for the therapy of other inflammatory skin diseases; however, there are few data available so far.

In a pilot study by Zonneveld et al. it was demonstrated that tacrolimus as topical agent is not effective in chronic plaque psoriasis, the most likely because of inability to penetrate the thick hyperkeratotic skin lesion. The authors found no significant difference between topical tacrolimus 0.03% ointment and

a vehicle in alleviating symptoms (8, 13). However, a number of trials proved the efficacy of tacrolimus when applied topically to facial lesions of psoriasis where skin is thinner and to naturally occluded intertriginous regions (inverse psoriasis) where steroid-induced atrophy would be a concern (13). In contrast to the vehicle, tacrolimus 0.03% ointment was also demonstrated to decrease redness, superficial blood flow, infiltration and thickness of psoriatic lesions if applied under occlusion every 2–3 days for 2 weeks (8). Pimecrolimus 1% cream applied under the occlusive condition was also reported to be as effective in chronic psoriatic plaque lesion as clobetasol propionate 0.05% ointment and significantly (13).

At first systemic and now also topical tacrolimus has been used to treat pyoderma gangrenosum. The drug may improve the lesions of this rare skin disorder through the suppression of proinflammatory cytokines such as GM-CSF or IL-8 resulting in the inhibition of neutrophlis chemotaxis which is one of the most important implication in the pathogenesis of the disease. Successful systemic therapy resulting in resolution of ulcers has been described in a number of single case reports including patients with steroid and cyclosporin-resistant disease (13). Tacrolimus was applied under occlusion as monotherapy or was conjunct with oral tacrolimus 0.3 mg/kg/per day (8). Moreover, oral lichen planus appears to be effectively treated with topical tacrolimus. In one of the first trials assessing the response of erosive mucosal lichen planus to topical treatment with 0.1% tacrolimus, 3 of 6 patients had complete resolution of the disease and other 3 participants showed an improvement following a 4-week therapy. One patient was free of the disease for 6 months after cessation of the treatment (8, 13). Similar effectiveness of tacrolimus 0.1% ointment with rapid resolution over a week has been demonstrated in a single case report of lichen planus of the lip (13). Another possible application of topical tacrolimus is a T-cell-mediated graft-versus-host disease in which skin is the most commonly affected. In a case series of 18 patients treated with tacrolimus 0.1% ointment, over 70% showed rapid decrease in erythema and pruritus (13).

Although the systemic tacrolimus as well as systemic cyclosporin are known to have direct stimulatory effect on the hair follicle, inducing anagen and promoting hair growth in various animal models (8, 13), the tacrolimus ointment has been shown in a number of single human case reports to be not effective in alopecia areata (AA) (8, 13). Tacrolimus ointment appears to be especially useful for treatment of contact dermatitis on the face where steroids are contraindicated. In human studies Lauerma et al. assessed the possible inhibition of dinitrochlorobenzene-induced contact allergy reactions by topical FK506. In this investigation 5 patients received pretreatment with 0.1% tacrolimus ointment or with a lower (0.01%) and higher (1.0%) drug concentrations, or vehicle. After exposure to contact allergen, the biopsy and histologic evaluation were performed. The areas of the skin that were treated with vehicle histologically displayed inflammation, whereas in the tacrolimus-treated skin no histologic evidence of inflammation was found (13). Animal models of contact dermatitis have also been employed to test the efficacy of tacrolimus in inhibition of inflammatory skin reactions. Duncan, for example, used guinea-pigs to determine which one of the three topical agents: tacrolimus 0.02% or 2%, cyclosporin A, or rapamycin (sirolimus) is able to control dinitrofluorobenzene (DNFB)- induced hypersensitivity. It was found that *in vivo* only topical tacrolimus suppresses T-cell infiltration and erythema (8).

In 2001 Goldman published a preliminary report on the efficacy of twice daily applied tacrolimus 0.075% ointment in 3 individuals with steroid-induced rosacea. Patients took no other systemic medication at that time. The author described an excellent resolution of erythema, pruritus and tenderness following 7-to 10-day therapy (8). The effectiveness of topical tacrolimus was also confirmed by 12-week open-label clinical trial in which 24 participants with erythrotelangiectatic or papulopustular rosacea were treated with 0.1% tacrolimus ointment twice daily. Over the course of the study erythema was significantly improved in both rosacea subtypes, although there was no improvement and decrease in papulopustular signs (2). Other off-label uses for topical tacrolimus have been studied in a number of

case reports, including recalcitrant leg ulcers associated with rheumatoid arthritis, seborrheic dermatitis, dyshidrotic eczema, hand eczema and ichthyosis linearis circumflexa (13).

According to preliminary results reported at the 20th World Congress of Dermatology (WCD) in July, 2002, topical tacrolimus 0.1% ointment appears to decrease symptoms of seborrheic dermatitis. This pilot study by DiCarlo et al. included 14 participants (male and female) aged 18 or older with at least a 3-month history of clinically evident SD. Following a 6-week treatment with once-daily applied 0.1% ointment, patients were evaluated according to global assessments (subject's and investigator's) and lesional severity (scaling / erythema). The subjects' average improvement was 86.3%, the average improvement of lesional scaling was found to be 86.9%, and the erythema alleviation was 73.3%. The average global improvement measured by investigators was 82.1% (4).

Currently ongoing studies also include vitiligo treatment with tacrolimus ointment. Because T cells activation has been shown to play some role in the pathogenesis of progressing vitiligo, several small studies and case reports have discussed the use of TIMs in the treatment of the disease since the year 2002. Through the inhibition of T-cell activation, topical immunomodulators such as tacrolimus and pimecrolimus could be effective in vitiligo therapy. The efficacy of 0.1% tacrolimus ointment versus 0.05% clobetasol applied twice daily was compared in the study by Lepe et al. including 20 pediatric patients aged 4 to 17 with active vitiligo. After a 2-month therapy tacrolimus was found to be as effective as clobetasol. In 25% of individuals treated with either tacrolimus or steroid the percentage of repigmentation was 75%, which is usually defined as a successful treatment. The mean percentage of repigmentation was 49% and 41% for clobetasol and tacrolimus, respectively. Tacrolimus achieved its best responses when used on the face and neck. It appears to be associated with a greater density of hair follicles in these areas, which make a great melanocyte reservoir (12).

In a recent open-label study the efficacy of 0.1% tacrolimus was evaluated following a 6-month therapy. The 75% repigmentation on face and neck lesions was achieved in 68% of the 19 patients. The authors also compared the production of various cytokines such as INF-gamma, TNF-alpha and IL-10 in vitiligo patients and in healthy subjects who were included in the second part of the study. A baseline expression of cytokines in involved and uninvolved skin of vitiligo patients was statistically significantly increased when compared with healthy controls. The post-treatment decrease in TNF-alpha (cytokin which inhibits melanogenesis) expression in both depigmented and adjacent uninvolved skin was observed. This process may play a therapeutic role in vitiligo (12). By the year 2005 only one case report the use of pimecrolimus in vitiligo has been published. The patient treated with 1% pimecrolimus cream for 5 months experienced over 90% repigmentation on his face lesions (12).

According to a small number of studies the efficacy of TIMs in vitiligo is significantly lower than in atopic patients, probably due to a limited penetration of the drugs through the intact epidermis (12).

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SUMMARY

New topical immunomodulators (TIMs), tacrolimus and pimecrolimus, might represent an alternative to glucocorticosteroids in the therapy of chronic inflammatory dermatoses such as atopic dermatitis. They work by inhibiting calcineurin, which regulates the activity of the transcription factors that control the early stages of T cell activation (8). Corticosteroids, although effective, usually lead to several local or systemic adverse events (16). Large, multicentre, randomized, vehicle-controlled clinical trials have shown efficacy and safety of TIMs . There are no data suggesting side effects following long-term therapy (8, 13). This favourable relation between therapeutic and adverse effects will probably result in increased use of topical macrolactams over the next several years. The best established current indication for their application in dermatology is atopic dermatitis. In the future, alopecia areata, lichen planus, facial psoriasis, and pyoderma gangrenosum might become additional indications for topical therapy with these novel drugs (8, 13).

Nowe makrolaktamowe immunomodulatory w leczeniu miejscowym zapalnych chorób skóry

Nowe immunomodulatory do stosowania miejscowego, takrolimus i pimekrolimus, mogą stanowić alternatywę dla glikokortykosteroidów w leczeniu przewlekłych zapalnych dermatoz, takich jak atopowe zapalenie skóry. Działają one przez zablokowanie kalcyneuryny, które reguluje aktywność czynników transkrypcyjnych biorących udział we wczesnych stadiach aktywacji limfocytów T. Kortykosteroidy, chociaż efektywne, zwykle dają zarówno miejscowe jak i ogólnoustrojowe działania niepożądane. Duże, wieloośrodkowe, randomizowane i kontrolowane placebo próby kliniczne wykazały skuteczność i bezpieczeństwo stosowania immunomodulatorów makrolaktamowych. Dostępne w piśmiennictwie

dane wskazują na brak działań ubocznych nawet przy przewlekłej terapii. Korzystna relacja między skutecznością terapeutyczną a działaniem niepożądanym prawdopodobnie przyczyni się do częstszego stosowania makrolaktamów w leczeniu miejscowym w ciągu kilku następnych lat. Obecnie najlepiej poznanym wskazaniem dla stosowania tej nowej grupy leków w dermatologii pozostaje atopowe zapalenie skóry. W przyszłości mogą one znaleźć zastosowanie w leczeniu takich chorób, jak łysienie plackowate, liszaj płaski czy piodermia zgorzelinowa, a także zmian łuszczycowych zlokalizowanych na twarzy.