Review paper

Application of tacrolimus in the treatment of skin diseases other than atopic dermatitis

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Abstract

In dermatological therapy, a basic group of drugs with immunosuppressive and anti-inflammatory effects is the glucocorticoids. Their mechanism of action may lead to numerous side effects. The discovery of cyclosporin A, tacrolimus and pimecrolimus has created an alternative to steroid therapy in dermatology. A common feature of calcineurin inhibitors is inhibition of the activity of immunocompetent cells, which are responsible for inflammatory processes in the human body. Most studies on this group of drugs concern their effectiveness in the treatment of atopic dermatitis (AD). This paper presents a review of the literature concerning the use of tacrolimus in therapy of diseases other than AD.

Key words: tacrolimus, calcineurin inhibitors, skin diseases.

Introduction

For more than half a century immunosuppressive preparations have been used to treat inflammatory diseases and in transplantation to obtain long-term tolerance of the transplanted organ. In dermatological treatment the main drugs of anti-inflammatory and immunosuppressive action are corticosteroids (CS). Their prolonged use may lead to numerous side effects (e.g. skin atrophy, telangiectasia, perioral dermatitis, metabolic disorders). Often the phenomenon of tachyphylaxis and also exacerbation of skin lesions after discontinuation of the preparation may be observed [1]. A breakthrough for treating inflammatory conditions was the introduction of tacrolimus. It is a macrolide, formerly known as FK-506. It was first isolated in 1984 from the bacterium *Streptomyces tsukubaensis* [2]. The drug has strong immunosuppressive properties, which have been used in transplantation. In dermatology, the fact that tacrolimus can be used topically is very important. In 1994 initial reports describing the effectiveness of calcineurin inhibitor for the treatment of atopic dermatitis (AD) were published [3]. The drug was registered in Poland 10 years ago, and currently is available in the form of an ointment: 0.03% and 0.1%. Tacrolimus proved to be particularly effective in the treatment of localized lesions within the face and neck, where the use of local CS resulted in many side effects. Several multi-centre, short-and long-term studies in patients with atopic dermatitis were performed, on both adults and children, and quick resolution of the inflammation and reduction of itching after using tacrolimus were detected [4-8]. Recently, there have been more reports concerning proactive therapy in patients with a diagnosis of AD. A study conducted by Reitamo *et al.* showed good results after application of tacrolimus twice a week within the skin after resolution of active lesions [9]. Long-term use of anti-inflammatory preparations in small doses can prevent relapse, improve the quality of life of AD patients and reduce treatment costs. Prominent local efficacy in the treatment of AD has led to attempts to use tacrolimus in the treatment of other dermatological diseases.

Mechanism of action of tacrolimus

Tacrolimus belongs to the macrolide group, which exert their effect by inhibiting the activation of calcineurin. During the presentation of antigen to T cells there occurs an increase of calcium ion concentration and the induction of synthesis of the cytoplasmic portion of the lymphocyte-stimulated nuclear factor (nuclear factor of activated lymphocytes – NFAT). Calcium ions bind to calmodulin. This complex activates calcineurin, which causes dephosphorylation of the cytoplasmic NFAT fragment. This leads to its penetration into the nucleus and

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connection with a fragment of nuclear NFAT. This complex, by affecting the promoter regions of multiple genes, allows transcription of proinflammatory cytokines such as interleukin (IL)-2, IL-3, IFN-γ, and TGF-β, and increased expression of receptors such as the receptor for IL-2. The described mechanism involves lymphocytes, mast cells and neutrophils. The action of tacrolimus depends on its connection to the cytoplasmic protein macrophilin 12, also called FKBP (FK binding protein), forming a complex that blocks calcineurin, preventing dephosphorylation of the NFAT cytoplasmic portion, and inhibits the further stages of lymphocyte activation. As a result, there is no transcription of mRNA for proinflammatory cytokines. The strength of binding of tacrolimus to FKBP is approximately three times greater than pimecrolimus [10, 11] (Fig. 1).

Side effects of tacrolimus

Side effects of tacrolimus concern mainly the reactions occurring immediately after drug application. They are itching and burning. Those complaints are transient and are reduced in continued use. No increased incidence of bacterial, viral or fungal infection while treating with tacrolimus was detected [12]. There was no effect of tacrolimus on inhibition of the cutaneous immune response [4]. In 2006, the Food and Drug Administration (FDA) accepted the supplemented information about calcineurin inhibitors, concerning the possible, but uncertain risk of developing skin cancer and lymphoma. However, most dermatological societies found that the FDA's concerns are unfounded and not supported by relevant clinical evidence [13]. There are single reports of diagnosis of Kaposi's varicelliform eruption in a child with atopic dermatitis during treatment with another calcineurin inhibitor, pimecrolimus [14]. It is worth emphasising that combining application of tacrolimus with exposure to UV is not recommended. This medicine is not photosensitive. Tacrolimus does not inhibit collagen synthesis, does not provoke atrophy of the epidermis, and does not damage the skin barrier. It can be safely used for many months, including around the face and neck, both in adults and children [15].

Application of tacrolimus

Efficacy of tacrolimus in the treatment of atopic dermatitis is commonly known and confirmed in numerous studies. The preparation can be administered to substitute for moderately potent CS. The results of AD treatment encourage researchers to test tacrolimus in other dermatological disorders which also have an inflammatory background. The first study on the use of tacrolimus in the treatment of psoriasis vulgaris was in 1998. Tacrolimus was used once a day at a concentration of 0.03%. The control group was treated with 0.005% calcipotriol twice a day. A third group of patients used a placebo. No statistically significant difference between the effectiveness of tacrolimus and placebo was observed. It should be emphasized that tacrolimus was applied once a day at a low concentration,

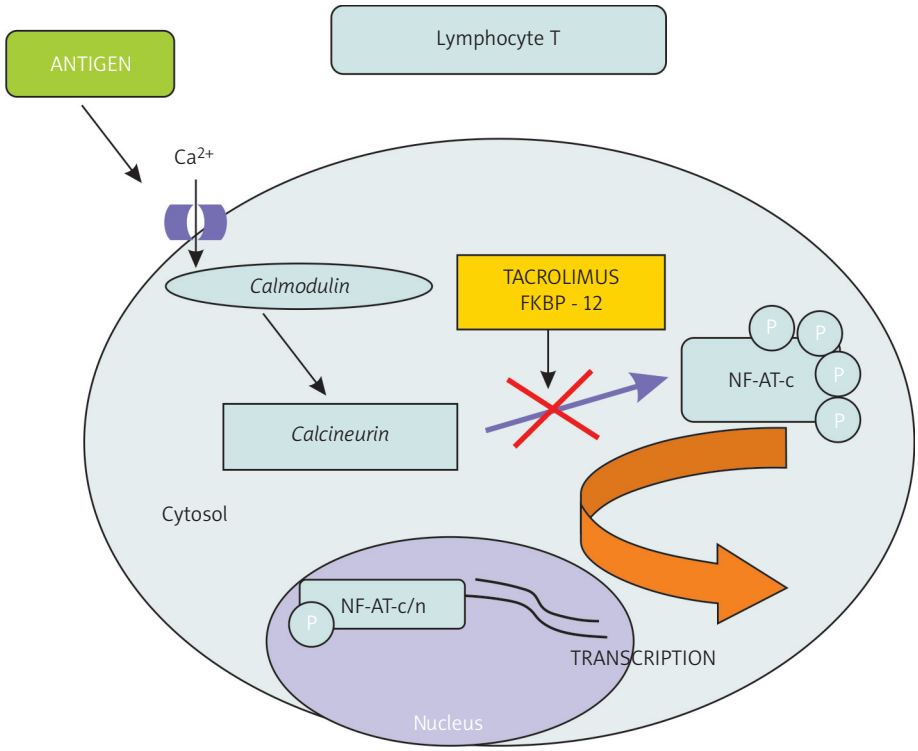

Fig. 1. Tacrolimus mechanism of action

0.03% [16]. A year later another trial was performed on 16 patients with psoriasis vulgaris. The efficacy of tacrolimus, calcipotriol and betamethasone was compared. Tacrolimus was used within the area of the skin where previously an agent increasing penetration was applied. The result was a significant reduction of erythema and infiltration [17]. Subsequent studies have demonstrated significant efficacy of tacrolimus in the treatment of psoriasis occurring within the face and intertriginous areas [18-22]. In 2009 the National Psoriasis Foundation presented the consensus on the treatment of psoriasis, recommending tacrolimus as a preparation for use in case of long-term inverse psoriasis [23]. Another dermatological disorder in which an attempt of treatment with tacrolimus was made is **seborrhoeic dermatitis**, for which a significant improvement or complete resolution of skin lesions was obtained [24-25]. In 2007 the results of a study from the Department of Dermatology, Katowice, was published. Tacrolimus was used as a 0.1% ointment, twice daily for up to a month, depending on clinical improvement. Complete resolution of skin symptoms was obtained in all patients [26]. The positive effect of tacrolimus in seborrhoeic dermatitis stems not only from its anti-inflammatory activity, but also in relation to antifungal *Malassezia furfur* [27]. Tacrolimus was also effective in the treatment of **lichen planus** (LP). There are several studies that have shown high efficacy of tacrolimus in the treatment of erosive lesions located within the oral mucous membrane [28-30]. Local therapy resulted in significant improvement or complete resolution of lesions. The preparation was also effective in cases of LP lesions occurring within the anogenital area [31, 32]. Also satisfactory results were obtained due to the effect of tacrolimus applied to mucosal lesions in the course of **lichen sclerosus** (lichen sclerosus – LS) [33]. It should be noted that tacrolimus resolved complaints of burning and itching [34]. The first report about the good effects of therapy with tacrolimus in **vitiligo** dates from 2002 and concerns the observation of a patient with atopic dermatitis and vitiligo. Tacrolimus used topically because of atopic dermatitis has caused repigmentation [35]. Subsequent research has concerned the planned treatment of vitiligo with tacrolimus [36-38]. Interesting observations were made in 2003, comparing the efficacy of tacrolimus and clobetasol. The percentage of patients who experienced repigmentation was higher in the case of CS. Two-month therapy with clobetasol resulted in adverse effects in the form of telangiectasia and skin atrophy, while after application of tacrolimus only a burning sensation within the treated area was observed [39]. Thus, this confirms the high efficiency and high safety profile of these preparations in comparison to local CS. There have also been studies on combination therapy with tacrolimus and narrow-band UVB irradiation. After several months of therapy, a significant improvement was achieved [40-41]. Good results were also observed after concomitant treatment with the excimer laser [42]. Beneficial effects of treatment with tacrolimus 0.1% were noted in the case of **localized scleroderma**. It should be emphasized that better results were achieved using tacrolimus under occlusion. In patients with a long history of disease a partial reduction of sclerosis was observed, while in patients suffering for several months the resolution of skin symptoms was observed [43-44]. Reports on the use of tacrolimus in the treatment of different types of alopecia date back to 1995, when total regrowth was observed in a patient after liver transplantation treated generally with tacrolimus [45]. Subsequent studies concerned treatment specifically targeted at alopecia areata or alopecia universalis. In most cases, partial regrowth was observed as a result of topically used tacrolimus [46-48]. In 2009 the efficacy of tacrolimus and betamethasone was compared. In most patients, better results were observed after CS [49]. Treatment of alopecia requires the patient's self-discipline and patience, because therapy is prolonged. The effects of treatment are seen after several weeks of therapy. **Eczema** is one of the most common dermatological disorders, which repeatedly encounter problems of therapy. There are several studies confirming the efficacy of 0.1% tacrolimus in the treatment of stasis dermatitis and contact dermatitis [50-51]. German researchers have used the presented preparation in patients with eczematous lesions located within the vicinity of the anogenital area with an improvement with twice a day applications [52]. This treatment proved to be safe, without the side effects that accompany the use of steroid preparations. Skin lesions occurring in systemic lupus erythematosus, in its various forms (systemic lupus erythematosus, subacute cutaneous **lupus erythematosus**, discoid lupus erythematosus), often require the use of topical application of CS, even within the face, neck, and upper part of the chest. Treatment is prolonged and without side effects. Studies on the use of tacrolimus in these disorders produced positive results, and now calcineurin inhibitors are perceived as an alternative treatment [53-57].

Treatment of **rosacea** with tacrolimus ointment is ambiguous. In 2003 the results of therapy of steroid-induced rosacea were published. Combined use of oral tetracycline and tacrolimus resulted in an improvement of dermatological status [58]. Another study showed a reduction in erythema, without a reduction of maculopapular lesions [59]. An immunosuppressive effect of tacrolimus on the proliferation of *Demodex folliculorum* is also reported [60]. In the same year a case report concerning induction of rosaceiform dermatitis during treatment of facial inflammatory dermatoses with tacrolimus ointment was published. Three individuals were observed to have changes in the type of rosacea [61]. There are also reports of local therapy with tacrolimus **bullous diseases**. It should be emphasized that good results were obtained after application of tacrolimus 0.03% ointment applied to the conjunctiva in **pemphigus** [62] and a 0.03% suspension in the case of lesions located within the oral mucous membrane [63]. Publications concerning therapy of **bullous pemphigoid** with tacrolimus also confirm the efficacy of the drug [64, 65]. The first report on

the effectiveness of tacrolimus in the treatment of **pyoderma gangrenosum** is from 1991. The drug was applied systemically to yield beneficial effects, in the absence of improvements in relation to other methods [66]. Results with the 0.1% ointment treatment are also satisfactory. Most studies are based on combination therapy with CS [67, 68]. Tacrolimus is a very useful method in reducing subjective symptoms, especially itching [69]. Diseases in which tacrolimus has proved to be an effective method of therapy are **annular granuloma**, **sarcoidosis**, **incontinentia pigmenti**, **pityriasis alba**, **necrobiosis lipoidica**, **keloids**, **angiolymphoid**, and **venous ulcers**. However, reports on those subjects are single. It is necessary to conduct further research. In each case a dermatological improvement was observed.

To conclude, tacrolimus is used in the treatment of many dermatological diseases. It helps to eliminate or partially replace local corticosteroids, especially in such regions as the face, neck, and groin. It is a safe drug, but further studies need to be conducted to confirm the safety and efficacy, and possible extension to new diseases, other than those described.

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