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Calcineurin Inhibitors in the Treatment of Alopecia Areata

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Topical calcineurin inhibitors (TCI) are a relatively new class of drugs used in dermatology. There are two drug forms available – tacrolimus 0.03% or 0.1% ointment and 1.0% pimecrolimus cream. The drugs act by inhibiting synthesis of proinflammatory cytokines. The only approved indication for using TCI is treatment of atopic dermatitis. The TCI may be used as an alternative therapy to corticosteroids. Tacrolimus is used to treat moderate-to-severe atopic dermatitis, pimecrolimus – mild-to-moderate atopic dermatitis. Topical calcineurin inhibitors do not cause skin atrophy and the drug absorption through the skin is minimal. The TCI have been well-studied, their efficacy was evaluated in a number of vast, long-term studies. The anti-inflammatory potency of tacrolimus ointment is similar to a corticosteroid with moderate activity, while the latter is clearly more active than pimecrolimus cream. Topical calcineurin inhibitors significantly relieve pruritus in atopic eczema.

Keywords: topical calcineurin inhibitors, tacrolimus, pimecrolimus

1. Introduction

The history of calcineurin inhibitors is associated with search for immunosuppressive drugs for transplantation. Cyclosporine A was the first introduced calcineurin. Transplants of kidneys, liver, lungs or heart were possible due to drug inhibition of immune reaction against the transplanted organ. Improvement in clinical presentation of skin was observed in patients with psoriasis, atopic dermatitis and other dermatoses when given cyclosporine A after the organ transplant. Cyclosporine A is still used in treating some severe skin conditions but in transplantation it was replaced by tacrolimus, isolated in 1984, for its 10-100 times higher immunosuppressive activity [1]. Tacrolimus is produced by a type of soil bacterium *Streptomyces tsukubaensis* in the *Tsukuba* region of Japan. First known as FK 506, then the name tacrolimus was derived from *Tsukuba* (the mountain the soil sample came from), *macrolide* (the compound is a hydrophobic macrolide) and *immunosuppressive* [1, 2]. Tacrolimus was introduced as an oral drug preventing transplant rejection in 1989. Despite several attempts to treat atopic dermatitis, psoriasis, alopecia areata, pemphigus or eosinophil fasciitis with the drug, it is not commonly used in systemic treatment in dermatology, which may be due to its high costs [3]. Discovery of pimecrolimus, another calcineurin inhibitor, resulted from long studies on ascomycin derivatives (antifungal and immunomodulatory compound) in the Laboratory of Novartis. Pimecrolimus, ascomycin macrolactam, is produced by the fermentation of *Streptomyces hygroscopicus var. ascomycetous*.

Tacrolimus (topical) was launched on the market at the end of 2000, pimecrolimus in 2001. Attempts of topical use of cyclosporine A were not successful due to high molecular weight (about 1200 Da), preventing effective penetration into the skin [4]. Sporadically, the drug is used in the form of eye drops in eye inflammation and for washing the oral cavity in patients with pemphigus vulgaris [5, 6]. Tacrolimus and pimecrolimus have similar both chemical structure and molecular mass (about 800 Da). The molecular structure allows effective skin penetration, not as intense as topical glucocorticosteroids, which prevents higher systemic drug absorption [7].

2. Mechanism of action of calcineurin inhibitors

Mechanism of action of calcineurin inhibitors is suppressing synthesis of pro-inflammatory cytokines. In the cytoplasm of the target cells, pimecrolimus and tacrolimus bind to the intracellular protein macrophilin-12, also called FKBP (FK506-binding protein)[8]. Similarly, cyclosporine A binds to cyclophilin. Immunosuppressive activity results from suppressing calcineurin activity – dependent on calcium and calmodulin (serine-threonine phosphatase). The drug has an anti-inflammatory activity due to T-helper activity affecting synthesis and release of pro-inflammatory cytokines. Cytokine transcription blockage leads to decrease in expression of cytokine Th1 and Th2 dependent among others on interleukin 2, 3, 4 and 5 (IL-2, IL-3, IL-4, IL-5), interferon-γ (INF-γ) and tumor necrosis factor-α (TNF-α). Tacrolimus and pimecrolimus inhibit mast cell and neutrophil activation and release of inflammatory mediators. Tacrolimus affects basophils and eosinophils function as well as function and apoptosis induction of Langerhans cells [9].

3. Indications for use of topical calcineurin inhibitors

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Tacrolimus is available in the form of 0.1% and 0.03% ointment (Protopic) while pimecrolimus in the form of 1% cream (Elidel). The only approved indication for use of topical calcineurin inhibitors (TCI) is atopic dermatitis (AD). However, these preparations are also very effective in treating other dermatoses, particularly seborrheic dermatitis, genital lichen sclerosus, oral lichen planus, psoriasis (face and flexures areas), vitiligo and alopecia areata [10, 11].

Tacrolimus is used for treating moderate-to-severe AD when there is no sufficient response or tolerance to conventional treatment, such as topical use of corticosteroids. The drug was also approved for supportive therapy (proactive therapy) of moderate-to-severe AD to prevent relapses and extend periods without recurrence in patients with frequent exacerbations (4 or more times a year) and who initially used to respond to treatment with tacrolimus ointment 2 times a day for maximum 6 weeks. The new proactive therapy has been based on new discoveries in AD pathogenesis. In the course of this inflammatory dermatosis, disorders affecting both the structure and immune function are observed in seemingly unchanged skin. They are reported to be significantly dependent on filaggrin gene mutation. After disappearance of active lesions, the skin still presents features of subclinical inflammation [12].

In remission tacrolimus should be applied on the skin area where most intense lesions were observed in the course of the last exacerbation or where lesions usually appear, one or two times a day for 2 days a week (e.g. Monday and Thursday). Significant effectiveness of proactive therapy in preventing AD exacerbations and lower cost compared with conventional reactive treatment are stressed [13]. So far proactive therapies for the described tacrolimus as well as for two glucocorticosteroids: fluticasone and methylprednisolone have been investigated [12].

4. Pharmacokinetics of topical calcineurin inhibitors

The TCI absorption through the skin into circulation is minimal due to a large molecular size of the drugs. The highest absorption is observed in the initial stage of AD treatment when the inflammatory process is most advanced. When the disease subsides and epidermal barrier recovers, penetration into the skin decreases [14]**.** Increased tacrolimus penetration into circulation was found in dermatoses where profound skin barrier damage is observed e.g. Netherton syndrome [15]**,** lamellar ichthyosis [16], pyoderma gangrenosum [17]**.** Pimecrolimus is more lipophilic than tacrolimus, which results in slow penetration of TCI from the corneal layer rich in lipids into the hydrated lower epidermal layer. The TCI penetrates much lower than topical glucocorticosteroids[8]**.**

Draelos *et al.* [18] compared pimecrolimus and tacrolimus concentrations in the blood from patients given one of the preparations 2 times a day for 13 days. Tacrolimus was detectable in 36% of blood samples whereas pimecrolimus in 12% and the concentration was very low. Subsequent studies on TCI pharmacokinetics confirmed very low absorption into systemic circulation [18]**.**

Undre *et al.* [19] evaluated tacrolimus distribution in the skin and serum after application on the extended surface of the skin. Gradual decrease in the drug concentration in the skin along with the increasing skin depth was found, moreover, the retention time was short after the drug withdrawal. Systemic drug activity was not confirmed; in 64% of patients the concentration was below 1 ng/ml, and in 30% it was undetectable [19]**.**

Pharmacokinetic studies on pimecrolimus carried out on children with moderate-to-severe AD and whose body surface was affected up to 92%, showed 67% of pimecrolimus blood concentrations below 0.5 ng/ml and 97% of samples did not exceed 2.0 ng/ml [20]**.**

In a recent study carried out on a group of very young children (between 3 and 24 months) given 0.03% tacrolimus 2 times daily for 2 years in exacerbation, the concentration of tacrolimus was < 1.0 ng/ml in 98% of blood samples and in > 40% of blood samples, tacrolimus concentration was below the limit of detection (0.0250 ng/ml) [21]**.**

- In the investigated groups of children there was no difference in drug absorption through skin depending on age. No increased risk of systemic or local infection was found. Proper immune response to vaccination in the course of treatment with TCI was observed, which confirms only topical activity of the drug [22]**.**
- ***Cyclosporine A:***

It causes an adverse effect of hypertrichosis in 80% of the patients used, by prolonging anagen phase of hair growth cycle. But, its use in AA has shown conflicting results. Its use is limited because of side effects and high relapse rate [23]**.**

5. Efficacy of topical calcineurin inhibitors

The TCI are a well-investigated class of drugs, their efficacy was assessed in many longitudinal studies on vast populations of patients. First clinical reports on topical tacrolimus and pimecrolimus described the drug significant efficacy in the management of patients with AD.

In the study on a group of 624 children with moderate-to-severe AD, Reitamo *et al.* [24] found that 0.03% tacrolimus ointment is more effective than 1% hydrocortisone acetate [24]. The following investigations carried out by Remitz *et al.*[25] on a group of 466 children at the age of 2-15 years for 30

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months showed effectiveness of tacrolimus in AD management [25]. In 2008, results from a multi-center study on the effectiveness and safety of tacrolimus use, conducted on a group of 782 patients with AD at the age between 2 and 72 years, were published. The treatment was stopped when all skin lesions and pruritus disappeared, in the case of recurrence, the therapy was restarted. After 4 weeks' therapy, 60% of patients or their caretakers evaluated the clinical picture as very good or excellent. In the final stage 75% of participants of the study were satisfied with the treatment [26].

The obtained results from the studies on effectiveness of pimecrolimus are also satisfying. In a double-blind study on a group of 713 children between 2 and 17 years with AD carried out for 12 months, Wahn *et al*. [27] compared effectiveness of treatment with pimecrolimus to conventional topical methods (glucocorticosteroids, emollients). Clinical evaluation was performed after 6 and 12 months of treatment, safety and tolerance to the preparations were also monitored; improvement in the clinical picture was found after both 6 and 12 months of the treatment [27].

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