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Systematization of the two-decade world experience using tacrolimus ointment off-label. Fundamental information on the product, its use in vitiligo and fibrosing connective tissue diseases

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Developed in the 1990s and introduced into clinical practice in the first decade of the 21st century, tacrolimus ointment (known worldwide under the trade name Protopic®) became the first and most potent member of the class of topical calcineurin inhibitors (TCIs) and the first alternative to topical corticosteroids (TCSs) in terms of its anti-inflammatory activity in half a century. Its unique mechanism of action (selective T-cell immunosuppressant) and the absence of side effects typical of TCSs have made it a valuable tool in the therapeutic arsenal of dermatologists. Today, tacrolimus ointment is included in all possible international and national clinical guidelines for the treatment of atopic dermatitis, which is the only registered indication, and has the highest level of evidence (1A). Unfortunately, for a number of reasons, mostly commercial in nature, the manufacturer did not invest in a clinical trial program that would have allowed the registration of tacrolimus ointment for other indications. However, it is clear that the T-cell immune response plays a crucial role in pathogenesis of a wide range of dermatoses, and the pharmacodynamics of tacrolimus are well-suited for their treatment. In this regard, over the past two decades, hundreds of clinical studies have been conducted by independent investigators including well-designed double-blind randomized studies that have provided the evidence base for including tacrolimus ointment in the clinical guidelines for a wide range of off-label indications. The purpose of this review is to systematize the aforementioned global experience in order to raise awareness of clinicians and make more rational practical use of the valuable clinical tool, that is tacrolimus ointment. The first part of this review (the second part will be published later) provides general information on tacrolimus ointment including the history of its development, pharmacological characteristics and clinical applications as well as addressing off-label drug use. The evidence base for the use of tacrolimus ointment in the treatment of vitiligo and fibrosing connective tissue diseases will be analyzed.

Keywords: **tacrolimus ointment; topical application; off-label indications**

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Систематизация мирового опыта двух десятилетий применения мази такролимуса по незарегистрированным показаниям (off-label). Фундаментальные сведения о препарате, применение при витилиго и фиброзирующих заболеваниях соединительной ткани

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Созданный в 1990-е годы и вошедший в клиническую практику в первой декаде XXI в. препарат такролимуса в форме мази (известен во всех странах под торговым названием Протопик®) стал первым и наиболее активным представителем класса топических ингибиторов кальциневрина (ТИК) и первой за полвека альтернативой топическим глюкокортикостероидам (ТГКС) по своей противовоспалительной активности. Уникальный механизм действия (селективный Т-клеточный иммуносупрессант) и отсутствие характерных для ТГКС побочных эффектов сделали его ценным инструментом в терапевтическом арсенале дерматологов. На сегодняшний день мазь такролимуса входит во все возможные международные и национальные клинические рекомендации по лечению атопического дерматита, являющегося единственным зарегистрированным показанием к применению, имея наивысший уровень доказательности (1А). К сожалению, по ряду причин, преимущественно коммерческого характера, компания-производитель не стала инвестировать в программу клинических испытаний, которые позволили бы зарегистрировать мазь такролимуса по другим показаниям; в то же время очевидно, что Т-клеточный иммунный ответ играет ключевую роль в патогенезе широкого спектра дерматозов и фармакодинамика такролимуса полностью отвечает задаче их лечения. В связи с этим за два минувших десятилетия независимыми исследователями были проведены сотни клинических исследований, включая высокодоказательные двойные слепые рандомизированные, обеспечившие доказательную базу, которая позволила включить мазь такролимуса в клинические рекомендации по широкому спектру незарегистрированных показаний. Цель данного обзора — систематизация упомянутого мирового опыта для повышения осведомленности о нем клиницистов и более рационального практического использования ценного клинического инструмента, коим является мазь такролимуса. В первой части данного обзора (вторая будет опубликована позднее) приведены общие сведения о мази такролимуса, включая историю разработки, фармакологические характеристики и особенности клинического применения, а также затронута проблема off-label применения препаратов. Будет проанализирована доказательная база по применению мази такролимуса для лечения витилиго и фиброзирующих заболеваний соединительной ткани.

Ключевые слова: **мазь такролимуса; наружное применение; незарегистрированные показания**

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Introduction

Since the appearance of topical glucocorticosteroids (TCS) in dermatological practice, which revolutionized the treatment of the widest range of inflammatory, allergic and autoimmune skin diseases, several new important classes of external medications have appeared — retinoids, vitamin D analogues, Janus kinase inhibitors, phosphodiesterase inhibitors, aryl hydrocarbon receptor agonists, etc.

Among them, topical calcineurin inhibitors (TCIs) occupy an important place, as they were the first real alternative to TCS for 50 years in terms of their anti-inflammatory and immunosuppressive effect, while lacking adverse effects typical for glucocorticosteroid hormones [1–4]. The first and most active representative of the TCI class was tacrolimus in the formulation of ointment (Protopic®) [5, 6], approved for the treatment of moderate and severe atopic dermatitis in 2000 in Japan, in 2001 in the USA, in 2002 in the EU and in 2011 in the Russian Federation.

Today, a large body of evidence has been accumulated on the use of tacrolimus ointment for the treatment of atopic dermatitis, including several meta-analyses, which summarize the data of many high-quality double-blind randomized controlled clinical trials involving, in total, tens of thousands of patients [6–11], which provides the highest level of evidence from the standpoint of evidence-based medicine; accordingly, the Russian federal clinical guidelines for the treatment of atopic dermatitis include it with the level of evidence 1a (the highest possible).

At the same time, due to a number of reasons, mainly of commercial nature, the companies producing tacrolimus ointment and pimecrolimus cream (Astellas and Novartis, respectively) have not invested in the program of clinical trials of these drugs for the treatment of other skin diseases, which is necessary for the approval of new indications. At the same time, the mechanism of action (selective suppression of the T-cell immune response) pathogenetically justifies the use of TCIs in a wide range of other dermatoses, and the accumulated clinical experience, including a large number of high-quality randomized trials conducted by independent groups of researchers, suggests the efficacy and prospects for the use of TCIs in many other indications besides atopic dermatitis.

In 2013 and 2014, Professors Olisova O.Yu. et al. [13] and Kruglova L.S. et al. [14] published two excellent literature reviews on the use of tacrolimus ointment for unregistered indications (off-label); similar works are also found in foreign literature, e.g., Hengge UR, 2013 [15]. At the same time, a large amount of new clinical data on this topic has been accumulated over the past decade, which actualizes their systematization in the new review.

Tacrolimus — general information

Speaking about the class of calcineurin inhibitors, it is necessary to characterize the immunophysiological role of the key target of their action — serine-threonine phosphatase calcineurin, which is widely distributed in eukaryotic cells and plays an important and multifaceted biological role. Calcineurin has many substrates, including transcription factors (in particular, NFAT, FOXO, MEF2, TFEB), a number of receptors and their channels, some mitochondrial proteins, including those involved in the regulation of cell death processes, and microtubules, which makes it important for a number of systems and their functions; these include higher nervous activity (learning, memory), cardiovascular physiology, renal physiology, muscle fiber development, and, of course, the immune system [16–19].

From the perspective of human physiology and the pharmacodynamics of calcineurin inhibitors class, the most important function of this phosphatase is its role in the immune response. Activation of the T-cell receptor following antigen presentation to a naive T-lymphocyte by an antigen-presenting cell triggers a signaling cascade that activates phospholipase C-gamma, which hydrolyzes phosphatidylinositol-4,5-bisphosphate to form the secondary messengers, diacylglycerol and inositol-1,4,5-trisphosphate; the latter binds to receptors located on the endoplasmic reticulum and causes the release of calcium ions into the cytoplasm. Increase in cytoplasmic calcium concentration leads to calcineurin activation — a complex "calcineurin + calcium + calmodulin" is formed, which causes dephosphorylation of the cytoplasmic fragment of transcription factors belonging to the NFAT (Nuclear Factor of Activated T-cells) family. It should be noted that the NFAT family of factors in its hyperphosphorylated form is the main substrate for calcineurin in immune cells, as well as cardiomyocytes and skeletal myocytes. Dephosphorylation of NFAT causes conformational changes that enable translocation of these factors into the cell nucleus, and also increases their affinity for certain DNA sequences. After that, NFAT translocates into the nucleus, where it interacts with regulatory elements, stimulating gene expression of key cytokines and chemokines for the T-cell immune response, including IL-2,3,4,5,13,17, IFN-γ, TNF-α, etc. Continuous calcineurin activity is required for NFAT to remain in an activated state; decreased calcium levels in the cytoplasm (e.g., upon cessation of antigenic stimulation) or pharmacologic inhibition of calcineurin leads to rephosphorylation of NFAT and its release from the cell nucleus back into the cytoplasm [19–23].

Based on the described mechanism, it is obvious that inhibition of calcineurin will lead to the inability to activate NFAT factors and, thus, T-lymphocyte activation, preventing the development of a T-cell immune response. This premise was the basis for the emergence of a new class of immunosuppressive agents — calcineurin inhibitors.

The first representative of this class was cyclosporine, discovered in 1976, which had a slightly different mechanism of action from tacrolimus but had the same result — inhibition of calcineurin. Its use in transplantology made a real revolution, because it caused powerful T-cell suppression, but at the same time, unlike previously used methotrexate, azathioprine, etc., it did not have cytostatic properties and practically had no myelotoxic effect [20, 24, 25].

In 1983, the Japanese company Fujisawa opened a research laboratory in Tsukuba Science Park, focused on the search for biologically active metabolites with immunomodulatory properties. Using the mixed lymphocyte reaction as a screening assay, this laboratory tested more than 10,000 samples of metabolites produced by soil-derived microorganisms, and in 1984, a member of the *Streptomyces* genus, *Streptomyces tsukubaensis* (named after the mountain where it was found), was isolated from a soil sample taken from Mount *Tsukuba*, which produced a macrolide compound that showed potent immunosuppressive effects. This compound was given the cipher FK506 and subsequently the INN tacrolimus; this INN is, de facto, an abbreviation in which T is taken from the English spelling of the name of Mount Tsukuba, -acrol- — macrolide and -imus — immunosuppressant [1,

26, 27]. In addition, two macrolide compounds produced by *Streptomyces hygroscopicus* strains that also had the ability to inhibit calcineurin were isolated; however, they had much less immunosuppressive activity than tacrolimus and therefore their development was discontinued [28, 29]. Nevertheless, this species, *Streptomyces hygroscopicus*, was later used to produce a compound that was given the INN pimecrolimus; despite its threefold lower activity compared to tacrolimus (one publication called it a "minor variant of tacrolimus" [4]), this agent has also found its way into clinical practice [4, 30].

I would like to bring some terminological clarity to the term "macrolide", since physicians most often associate it with antibiotics. Macrolides are chemical compounds that have in their structure a macrocyclic ring of carbon atoms closed by lactonization; initially the term "macrolides" was proposed by Woodward to designate antibiotics that have a macrocyclic lactone structure [31], but later it acquired a broader interpretation [32–34]. Many representatives of macrolides have immunomodulatory and anti-inflammatory effects in addition to the main antibacterial or antifungal effect: for example, a wide range of such effects is described for such antibiotics as erythromycin, clarithromycin, roxithromycin [35].

The question also arises, what is the evolutionary meaning of the production of calcineurin-inhibiting compounds by prokaryotes? The point is that these producers compete for habitat and food resources with eukaryotes — fungi, which use calcineurin in their cell cycle; inhibition of calcineurin in fungi prevents their growth and gives a competitive advantage to prokaryotes [4, 36, 37]. Actually, for this reason, drugs of the calcineurin inhibitor class show some antifungal effects as a "positive side effect"; thus, in the early stages of tacrolimus development, it was demonstrated that it had high activity against *Fusarium oxysporum* and *Aspergillus fumigatus*, but had no activity against dermatophytes and yeasts [38]. Later, its activity against fungi of the genus *Malassezia* was found [4, 39, 40], which increases the clinical value of tacrolimus in the off-label treatment of seborrheic dermatitis and tinea versicolor, as well as in the treatment of atopic dermatitis affecting the face and neck, where sensitization to these fungi plays a particularly important role [41].

The compound obtained by Fujisawa scientists — tacrolimus — showed a very high immunosuppressive activity *in vitro*: when comparing the ability to suppress the mixed lymphocytic reaction with cyclosporine A and prednisolone, the IC_{50} value (inhibitory concentration suppressing the reaction by 50 %) in a mouse model obtained values of 0.32 nmol for tacrolimus, 27 nmol for cyclosporine and 17 nmol for prednisolone, while in the human model the values were 0.22 nmol, 14 nmol and 80 nmol, respectively, i.e. the immunosuppressive activity of tacrolimus exceeded that of the comparators by orders of magnitude. Further studies on the ability to inhibit the cytotoxic response of T lymphocytes by suppressing the expression of IL-2 and its receptor gave IC_{50} values of 0.1 nmol for tacrolimus and 10 nmol for cyclosporine, i.e. the activity of tacrolimus was 100 times higher [26,38,42].

This information laid the fundamental basis for the systemic use of tacrolimus in transplantology — the main pathogenetic role in transplant rejection is played by T-cell reactions mediated by $CD8^+$ cytotoxic lymphocytes and "conductors" — Th1 cells. In 1989, clinical trials of tacrolimus in transplantology began, and in 1993 it was first approved under the trade name Prograf®, becoming a new revolution in this field of medicine — its efficacy was significantly superior to its predecessor, cyclosporine A [1, 43, 44]. Subsequently, the efficacy of systemic therapy with tacrolimus was demonstrated in a wide range of autoimmune diseases, including dermatoses — this, in principle, was expected, based on their T-cell pathogenesis [1, 45 , 46]. It is noteworthy that in the early stages of the development of pimecrolimus, attempts were also made to apply it systemically, but later they were abandoned — pimecrolimus is used only topically [47, 48].

An important serendipitous observation for dermatology was an unexpected beneficial effect observed in transplant patients receiving systemic therapy with tacrolimus — in the presence of background atopic dermatitis or psoriasis, a marked improvement in these dermatoses was observed [1,49]. Based on this observation, the concept of topical application of tacrolimus for the treatment of various skin diseases while avoiding systemic side effects was born. In 1996, clinical trials of tacrolimus in ointment formulation began, and in the early XXI century it entered the world markets under the trade name Protopic®. The trade names Prograf® and Protopic® have a certain semantics: "graf" in the name of the systemic drug Prograf® is taken from the English word "graft", i.e. "Pro-graf" = "for graft", and "topic" in the name Protopic® is taken from the English word "topical", "Pro-topic" = "for topical application".

How is the mechanism of action of tacrolimus realized? To manifest calcineurin-inhibitory activity, it must first bind to the immunophilin family protein FKBP (FK-binding protein, from the original code of tacrolimus — FK506), also known as immunophilin-12 [4, 20, 49]. For reference, immunophilins are endogenous cytosolic peptidyl-prolyl cis/trans isomerases (PPIs) involved in protein folding processes and many other cellular functions [20, 50]. The tacrolimus + immunophilin-12 complex inhibits calcineurin, making it impossible to dephosphorylate the transcription activation factor NFAT and thus its translocation to the nucleus, which prevents lymphocyte activation and expression of a wide range of proinflammatory cytokines (see Figure 2) [4, 20, 49]. This fundamentally distinguishes the mechanism of action of tacrolimus from that of glucocorticosteroids — the latter are non-selective immunosuppressants and also cause multiple endocrine and metabolic effects (see Figure 1) [51, 52].

The differences in the mechanism of action explain an important difference between tacrolimus and TCS — the absence of side effects characteristic of GCS, including atrophogenicity and negative effects on the morphofunctional characteristics of the epidermal barrier. Unlike the latter, therapy with tacrolimus ointment leads to the improvement of epidermis structure and thickness, has no negative effect on collagen synthesis, increases hydration, integrity and cohesion of the stratum corneum, reduces protease activity and its pH, leads to a decrease in transepidermal water loss, has a positive effect on the extent of lipid membranes in the intercellular spaces of the stratum corneum (see Table 1) [53, 54]. This valuable property makes it possible to use tacrolimus ointment for a much longer period of time than TCS, including for maintenance therapy, which is important for many dermatoses with chronic recurrent course.

At the same time, tacrolimus ointment has some specific side effects characteristic for the TCI class; the most typical are burning and hyperemia of the skin during the first days of treatment, observed in many patients. They are attributed to the release of neurotransmitters, particularly substance

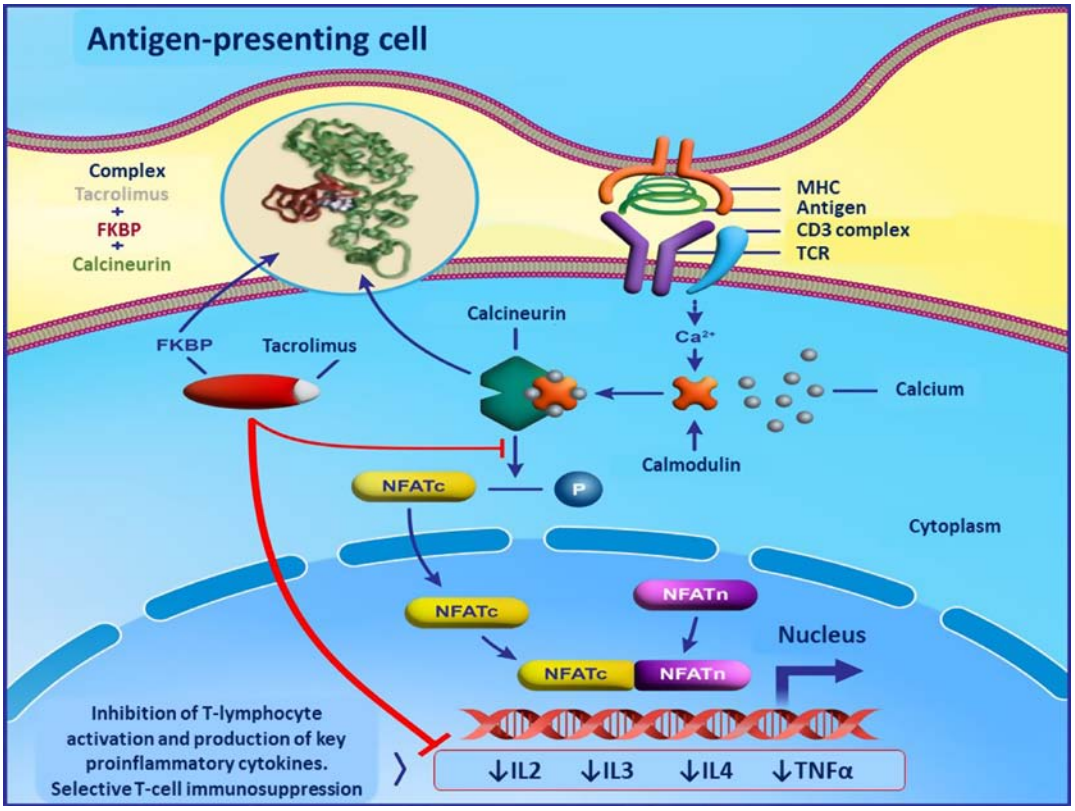

Fig. 1. Tacrolimus mode of action. Selective T-cell immune suppression
Рис. 1. Механизм действия такролимуса. Селективная Т-клеточная иммуносупрессия

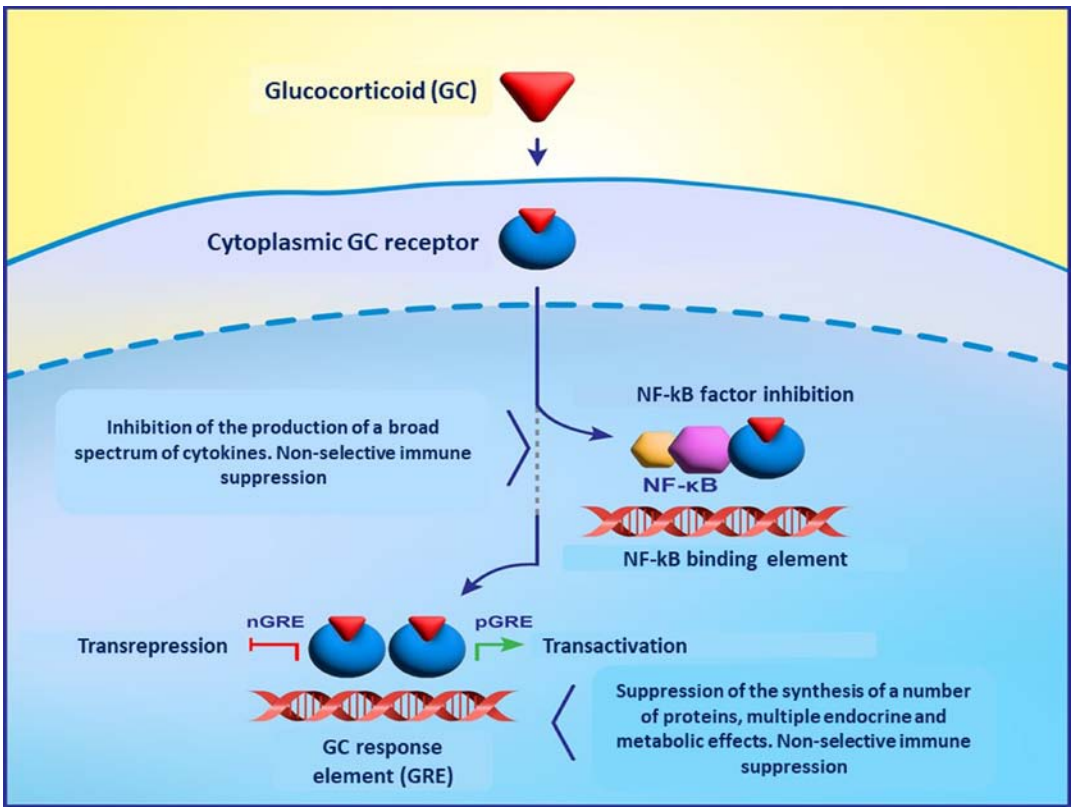

Fig. 2. Glucocorticosteroids mode of action. Non-selective immune suppression, multiple endocrine and metabolic effects
Рис. 2. Механизм действия глюкокортикостероидов. Неселективная иммуносупрессия, множественные эндокринные и метаболические эффекты

Table 1. Effect of therapy with TCS and tacrolimus ointment (Protopic®) on different epidermal barrier parameters (previously published in Kruglova L.S., Petrunin D.D. Impact of topical anti-inflammatory therapy on morpho-functional characteristics of epidermal barrier. Optimization of atopic dermatitis treatment schedules // Vestnik dermatologii i venerologii. — 2018. — Vol. 94. — N. 4. — P. 73-82. [53])
Таблица 1. Влияние терапии ТГКС и мазью такролимуса (Протопик®) на различные параметры эпидермального барьера (на основе [53])

Property	Method/parameter	TCS	Tacrolimus
Structure and thickness of epidermis	OCT*	negative	Trend toward positive
	ULTRASOUND	negative	positive
	Collagen synthesis	negative	positive
Integrity and cohesion of the stratum corneum	Adhesive tape/TEPV removal	negative	positive
	Tight junction proteins	negative	Neutral / negative <TCS
Proteolytic activity in the stratum corneum	Protease activity	negative	positive
Effect on pH	pH-metry	negative	positive
Hydration	Conductivity/corneometry	positive	positive
Lipid lamellae	Biopsy/TEM**	positive	positive >TCS
Disturbance of differentiation	Filaggrin and Na-PC***	negative	Neutral / positive
Expression of antimicrobial peptides	ELISA****	negative	Neutral / positive

* OCT, optical coherence tomography; ** TEM, transmission electron microscopy; *** Na-PC, sodium pyrrolidone carbonate; **** ELISA, enzyme-linked immunosorbent assay.

P, from neurosecretory granules of sensory nerve endings in the skin — one of the suggested mechanisms is phosphorylation of TRPV1; later, as neurotransmitter stores are depleted, the burning subsides and an antipruritic effect is achieved [55, 56]. This side effect limits the possibility of using tacrolimus ointment as a starting therapy in acute inflammatory processes, where it may be aggravated; in such cases, it is preferable to start treatment with TCS, with the possibility of switching to tacrolimus ointment later on.

Use of tacrolimus ointment for unapproved indications (off-label)

Hundreds of skin diseases are characterized by disorders of the T-cell immune response, in which the use of selective T-cell immunosuppressant is scientifically grounded and clinically justified. It is not surprising that the emergence of the TCI class aroused great interest of the medical community, which has led to extensive experience with these agents in indications far beyond those formally approved. The evidence base accumulated to date has made it possible to include tacrolimus ointment in numerous clinical guidelines covering a multitude of nosological units (see Table 2) [57–60].

The following will provide information on the accumulated experience with tacrolimus ointment for specific skin diseases.

Use of tacrolimus ointment in vitiligo

Vitiligo is a chronic disease of unknown etiology characterized by the appearance of depigmented patches and discolored hair on various parts of the body due to the destruction and reduction of melanocytes in the skin.

Although there are a number of theories regarding the pathogenesis of vitiligo, including oxidative, neurohumoral and some others, currently the leading role is attributed to autoimmune mechanisms — about 85 % of genes associated with predisposition to vitiligo encode proteins somehow related to the immune response [61]. Autoreactive $CD8^+$ cytotoxic T lymphocytes and the key cytokine INF-γ produced by them, which induces the production of chemokines CXCL9 and CXCL10 by keratinocytes, are considered to be the main cell population from the point of view of pathogenesis; the latter are necessary for the recruitment of $CD8^+$ lymphocytes to the lesion foci [62-63]. Moreover, the rate of vitiligo recurrence within a year after achieving repigmentation is 40 %; this is attributed to the persistence of tissue-resident $CD8^+$ memory T cells in the skin, the reactivation of which leads to the resumption of the pathologic process [63]. Thus, the use of calcineurin inhibitors as selective T-cell immunosuppressants in vitiligo is pathogenetically justified. In addition, vitiligo usually requires long-term treatment, making the lack of atrophogenic potential and endocrine effects of tacrolimus ointment a definite advantage.

According to informal verbal communications with commercial departments of Astellas and LEO Pharma, in some Central Asian CIS countries prescriptions of tacrolimus ointment for vitiligo treatment by dermatologists often exceeded the prescription for the approved indication, reflecting a high demand for this therapeutic option.

Clinical studies on the use of tacrolimus ointment in vitiligo are so numerous that even a simple listing of them will not fit into the format of a review article; therefore, emphasis will be placed on the results of meta-analyses systematizing accumulated clinical data.

Arora CJ et al. [64] conducted a systematic review of randomized clinical trials to evaluate the efficacy and safety of tacrolimus ointment for vitiligo in mono- and combination therapy. A total of 19 studies including 814 patients were included in the analysis. Meta-analysis of two studies using a random-effects model showed that combination therapy with tacrolimus and narrow-band ultraviolet (NB-UVB) was more effective than NB-UVB alone in terms of achieving > 75 % repigmentation [OR 1.34 (95 % CI: 01.05-1.71), P = 0.02]. Tacrolimus and steroids had similar efficacy in this criterion [OR 1.02 (95 % CI: 0.19-5.51), P = 0.98]. A meta-analysis of two studies showed that combination therapy with fractional laser and tacrolimus was not superior to

Table 2. Representation of tacrolimus ointment in clinical guidelines. The GLs of the Russian Society of Dermatovenerologists and Cosmetologists, the European Academy of Dermatology and Venereology (EADV), the European Dermatology Forum (EDF) and the German Society of Dermatology (DDG) were analyzed
Таблица 2. Представленность мази такролимуса в клинических рекомендациях

Clinical guidelines	RSDVC [57]	European [58–60]
Autoimmune photodermatoses	No GL	YES
Balanoposthitis	No GL	YES
Bullous pemphigoid	NO	YES
Vitiligo	YES	YES
Alopecia areata	YES	No GL
Annular granuloma	YES	No GL
Itching	No GL	YES
Contact dermatitis	YES	YES
Lupus erythematosus	YES	YES
Lichen planus	NO	YES
Linear IgA dermatosis	No GL	YES
Lipoid necrobiosis	YES	No GL
Localized scleroderma	YES	YES
Pemphigus	NO	YES
Rosacea	YES	YES
Seborrheic dermatitis	YES	No GL
Lichen sclerosus	YES	YES
Eczema	YES	YES*
Psoriasis	NO	YES

* Hand eczema

tacrolimus monotherapy in achieving > 75 % repigmentation [OR 2.11 (95 % CI: 0.87-5.09), P = 0.10]. The authors stated that the combination of tacrolimus with other treatments such as steroids, phototherapy, and laser therapy may be more effective than tacrolimus alone.

A meta-analysis by Chang HC et al. [65] compared the efficacy of TCI and TCS (as classes) in vitiligo; data from 11 studies including a total of 509 patients were processed. In the pooled analysis, the efficacy of TCI was lower than that of TCS in terms of achieving > 50 % repigmentation (OR 0.72; 95 % CI, 0.58-0.89); however, TCIs were comparable to TCS in terms of > 75 % repigmentation (OR 0.78; 95 % CI, 0.56-1.10). In a subgroup analysis, when TCSs were divided into medium potency and super potent TCSs, TCIs showed a similar effect in terms of > 50 % repigmentation compared with medium-strength TCSs. In addition, no difference in > 50 % and > 75 % repigmentation was found between TCS and TCI when the pediatric group was treated. Subgroup analysis by different TCIs also yielded similar results. Super-high potency TCSTCSs showed greater efficacy than TCIs in terms of > 50 % repigmentation, but TCIs may be a safer alternative to them, especially with long-term use.

A systematic review and meta-analysis by Suo DF et al. [66] analyzed the efficacy of tacrolimus ointment and 308 nm excimer laser in the treatment of facial vitiligo in monotherapy and in combination; data from 19 studies (n=2085) were processed. Combination therapy with tacrolimus ointment and excimer laser was found to be statistically significantly superior to each of the therapeutic options in monotherapy (P < 0.001 by the overall response rate criterion for both comparisons).

Dong Y et al. [67] devoted their meta-analysis to the efficacy of tacrolimus ointment in vitiligo combined with phototherapy, including 11 studies encompassing 588 patients. Compared with phototherapy alone, combined treatment with tacrolimus and phototherapy significantly increased the rate of excellent response (repigmentation ≥ 75 %) (OR = 1.40, 95 % CI 1.16, 1.69; P < 0.001) and decreased the rate of poor response (repigmentation < 25 %) (OR = 0.37, 95 % CI 0.22, 0.61; P = 0.001). However, the frequency of good response (50-75 % repigmentation) (OR = 1.00, 95 % CI 0.59, 1.69, P = 1.000) and moderate response (25-50 % repigmentation) (OR = 0.91, 95 % CI 0.60, 1.38; P = 0.653) did not differ significantly. Subgroup analysis showed that when lesions were localized to the

face and proximal extremities, combination treatment had a higher rate of excellent responses than phototherapy alone. Both NB-UVB and excimer laser, when used in combination with tacrolimus ointment, resulted in significantly higher rates of excellent responses than when used in monotherapy. Meta-regression analysis showed that children had a higher frequency of excellent response to treatment. Other demographic and clinical variables, including gender, disease duration, family history, and type of vitiligo, did not influence the efficacy of therapy. The combination of tacrolimus ointment and phototherapy was more effective than phototherapy alone, especially for lesions located on the face and proximal limbs.

In addition to the above data, an interesting experimental work demonstrating histologic differences in patients receiving monotherapy with narrowband ultraviolet light and combination therapy with NB-UVB and tacrolimus ointment was performed by Gauthier Y et al. [68]. Clinically, intrafollicular repigmentation was observed in the combination therapy group in addition to perifollicular and marginal pattern. Histologically, in addition to the migration of melanocytes from the hair follicle bulb observed in the monotherapy group, dermal melanocyte precursors located in the mid and superficial dermis were first detected in the combination therapy group. The authors note that tacrolimus may not only potentiate the activation of hair follicle and dermal melanocyte precursors by NB-UVB, but also protect them from autoimmune destruction during migration from the dermis to the epidermis.

Another systematic review and meta-analysis of the outcomes of vitiligo TCI treatment was conducted by Lee JH et al. [69]. The evaluation criteria were to achieve a mild (≥ 25 % repigmentation), moderate (≥ 50 %), or marked (≥ 75 %) response to treatment. Forty-six studies with a total sample of 1499 patients were included in the analysis. With TCI monotherapy, at least a mild response was achieved in 55.0 % (95 % CI, 42.2 %-67.8 %) of 560 patients in 21 studies, at least a moderate response in 38.5 % (95 % CI, 28.2 %-48.8 %) of 619 patients in 23 studies, and a marked response in 18.1 % (95 % CI, 13.2 %-23.1 %) of 520 patients in 19 studies at a median treatment duration of 3 months (range 2-7 months). In a subgroup analysis for face and neck lesions, at least a mild response was observed in 73.1 % (95 % CI, 32.6 %-83.5 %) of patients and a marked response in 35.4 % (95 % CI, 24.9 %-46.0 %) of patients. When TCI was used in combination with phototherapy, at least a mild response was achieved in 89.5 % (95 % CI, 81.1-97.9 %) of patients, and a marked response was achieved in 47.5 % (95 % CI, 30.6-64.4 %) of patients. The authors conclude that TCI should be actively used for the treatment of vitiligo, both in monotherapy and in combination with phototherapy.

There are also data on maintenance therapy of vitiligo with tacrolimus ointment by the schedule 2 times a week. Cavalié M et al. [70] conducted a double-blind, randomized, placebo-controlled study that included patients with vitiligo which had previously achieved ≥ 75 % repigmentation. They received therapy with 0.1 % tacrolimus ointment (n = 19) or placebo (n = 16) twice weekly for 24 weeks. When analyzing a sample of patients who completed treatment according to the protocol, it was found that re-depigmentation was observed in 40 % of foci in patients receiving placebo and only 9.7 % in patients receiving tacrolimus ointment (P=0.0075), indicating the efficacy of this approach.

Use of tacrolimus ointment in fibrotic connective tissue diseases

Among dermatoses of this category, the greatest amount of clinical data on the use of tacrolimus ointment was obtained for lichen sclerosus and localized scleroderma.

The pathogenesis of localized scleroderma is multifactorial: the main role is attributed to autoimmune disorders, excessive collagen deposition in the skin and subcutaneous tissue, microcirculatory disorders. Following exposure to trigger factors, T-cells are activated and produce key profibrotic mediators, including transforming growth factor-β, platelet-derived growth factor, connective tissue growth factor, interleukins (IL-4, 6, 8, 17, IFN-γ), and some chemokines. This leads to increased synthesis and deposition of collagen and other connective tissue components in the skin and subcutaneous tissue, impaired regulation of matrix metalloproteinases (MMPs) responsible for collagen degradation, impaired microcirculation. Characteristic histopathologic picture with predominance of lymphocytic infiltrate from CD4+ T-cells and predisposition of scleroderma patients to other autoimmune diseases [71, 72]. Lichen sclerosus is considered by many authors as a type of localized scleroderma with predominantly genital skin lesions and has a similar pathogenesis [71, 72]. Thus, drug-induced suppression of the T-cell response corresponds to the pathogenetic features of this pathology.

The first description of clinical study of tacrolimus ointment application in localized scleroderma belongs to Mancuso G and Berdondini RM [73]. There were 7 patients under observation, which applied tacrolimus ointment 0.1 % twice a day for 3 months on some foci of scleroderma, and on others — vaseline ointment (control). Three months later, all 7 patients showed complete resolution of early foci and significant improvement of late foci (the latter softened, but atrophic and scarring changes remained) treated with tacrolimus; no dynamics was observed in the foci on which vaseline was applied.

The results were further confirmed in a double-blind randomized controlled trial by Kroft EB et al. [74] with a similar design, where 10 patients with plaque form of localized scleroderma were treated with tacrolimus ointment and vaseline (control) for 4 months. The foci on which tacrolimus was applied showed a positive trend, and the differences with vaseline were statistically significant based on the assessment of clinical signs ($p = 0.019$) and on durometry data ($p < 0.005$).

Finally, Stefanaki C et al. [75] conducted an open trial (n = 13) of topical therapy for localized scleroderma with 0.1 % tacrolimus twice daily; an immunohistochemical study was additionally performed. Four patients improved less than 25 %, two patients improved 50–70 %, and the remaining seven patients improved more than 70 %. Patients with dense long-standing lesions responded worse to treatment than patients with less dense and more erythematous lesions. Patients with mild to moderate fibrosis were histologically more likely to improve after treatment, and the lymphocytic infiltrate decreased regardless of the initial degree before treatment. It was concluded that topical tacrolimus therapy can be used in patients with localized scleroderma, especially those with early inflammatory lesions, even as first-line therapy.

Significantly more clinical data have been accumulated on the use of tacrolimus ointment for the treatment of lichen sclerosus.

Hengge UR et al. [76] conducted a multicenter (10 centers) phase II study of the efficacy and safety of tacrolimus ointment in the treatment of long-term active lichen sclerosus. Eighty-four patients aged 5 to 85 years with histologically confirmed disease were included; all received treatment with tacrolimus ointment 0.1 % twice daily for 16 weeks. The primary endpoint (complete resolution of symptoms) was achieved in 43 % of patients after 24 weeks of treatment; partial resolution was achieved in 34 % of patients. The maximum effect occurred between weeks 10 and 24 of therapy. Treatment resulted in a significant reduction in total lesion area ($P < 0.01$) and a significant reduction in total symptom score ($P < 0.005$). No serious adverse events were observed. Three (9 %) relapses were noted during the follow-up period. The authors concluded that tacrolimus ointment is an effective and safe therapeutic option for the treatment of lichen sclerosus.

Another prospective phase II study by Ebert AK et al. [77], investigated the use of tacrolimus ointment as adjuvant therapy in 20 boys (mean age 9.7 years) with histologically confirmed lichen sclerosus, which had undergone penile surgery (complete excision of the foreskin). Tacrolimus 0.1 % ointment was applied postoperatively to the penile head and meatus twice daily for 3 weeks. During follow-up of a median duration of 13 months, 2 recurrences were recorded, which were completely resolved after a second 3-week course of tacrolimus ointment.

Two studies by Mazzilli S et al. [78] and Li Y et al. [79] were devoted to the use of 0.03 % tacrolimus ointment for the treatment of vulvar lichen sclerosus in children (girls aged 4-9 years (n=10) and 4-11 years (n=14), respectively). Both publications noted the efficacy and safety of the treatment.

Funaro D et al. [80] published the results of a randomized double-blind prospective study involving 55 women with vulvar lichen sclerosus, which were treated with 0.1 % tacrolimus ointment or 0.05 % clobetasol propionate for 3 months. Meaningful improvement was noted in both groups, but efficacy was greater in the clobetasol group ($P < 0.002$). Previously, similar results were obtained by Goldstein AT et al. [81] when comparing clobetasol with pimecrolimus cream — the efficacy of clobetasol was also higher than TCI. At the same time, the question of safety of TCSs of activity class IV remains open, especially in long-term treatment.

In this context, the works devoted to the use of tacrolimus ointment for long-term maintenance therapy of lichen sclerosus are of interest. Thus, in the above-mentioned study by Li Y et al. [79], after a basic 16-week course of treatment, 9 out of 14 patients continued to receive tacrolimus ointment 0.03 % twice a week for 6 months. During follow-up, relapses were noted in 4 of 5 patients which received only the main course of treatment and in only 2 of 9 (22 %) which received maintenance therapy. In another study by Kyriakou A et al. [82], men with genital lichen sclerosus which responded to starting therapy with clobetasol propionate for 8 weeks received maintenance therapy with 0.1 % methylprednisolone aceponate cream twice weekly (n = 17) or 0.1 % tacrolimus ointment once daily (n = 20) until week 20. By the end of treatment, both groups showed a significant decrease in DLQI and mean visual analog scale score, mean IGA score remained 0; there were no significant differences between the comparison groups.

A noteworthy study on the efficacy of 0.1 % tacrolimus ointment in lichen sclerosus of anogenital and extragenital localization was conducted by Kim GW et al. [83]; 10 and 6 patients were included, respectively. Objective response to treatment was achieved in 9 of 10 patients with genital localization, and only 1 of 6 (partial) with extragenital localization. The authors concluded that tacrolimus ointment is an effective treatment for genital lichen sclerosus, but cannot be recommended for extragenital localization.

Thus, the data available to date suggest that tacrolimus ointment is a valuable therapeutic option for the treatment of lichen sclerosus with anogenital localization in children and adults, including long-term maintenance therapy; the effect of treatment in extragenital localization seems unlikely.

Conclusion

Over the past twenty-five years since the introduction of tacrolimus ointment into clinical practice, the drug has firmly taken its place in the arsenal of dermatologists and related specialists. In the first part of the review the history and stages of development of tacrolimus ointment were considered in detail, which allowed to trace the evolution of views on the possibilities and limitations of topical calcineurin inhibitors. Particular attention is paid to the pharmacological characteristics of the drug, including its mechanism of action, pharmacokinetics and interaction with target cells.

The mechanism of action of TCI — selective immunosuppression of T-cell immune response - determines its efficacy in the treatment of a wide range of dermatoses, the pathogenesis of which is based on the activation of certain subpopulations of T-lymphocytes.

An important part of the first part of the review was the discussion of the problem of off-label use of drugs in dermatology, which reflects the current trends of personalized medicine and the desire to expand therapeutic options for patients with chronic and recurrent skin diseases. Using vitiligo and fibrotic connective tissue diseases as examples, this review provides an in-depth evaluation of the evidence supporting the use of tacrolimus ointment beyond its approved indications. The analysis of numerous clinical studies, including randomized controlled trials, confirms the efficacy of the drug, as well as its favorable safety profile in long-term use in adults and children. This allows to consider tacrolimus ointment as one of the important alternative options, especially in cases when standard therapies prove insufficiently effective or carry a risk of adverse events.

In the future, we can expect a significant expansion of the arsenal of topical immunosuppressive therapies — topical inhibitors of Janus kinases, phosphodiesterase-4, aryl hydrocarbon receptor agonists, etc. are undergoing clinical trials and are being introduced into practice, demonstrating similar clinical efficacy, but the important role of tacrolimus ointment is likely to persist, as the extensive evidence base accumulated over 25 years makes it difficult for newer agents to reach this level in the near term and will require large-scale investments and many years of study.

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