Topical tacrolimus in adult atopic dermatitis: a consensus based on a 15-year experience

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ABSTRACT

Atopic dermatitis (AD) is one of the most common cutaneous inflammatory diseases both in adults and in children. It is a chronic, remitting-relapsing dermatitis, primarily managed by dermatologists, but also by allergists and primary care physicians. Due to coexistence of comorbidities, often a multidisciplinary team is required. Topical calcineurin inhibitors (TCIs - i.e. tacrolimus and pimecrolimus) are a class of steroid-sparing, anti-inflammatory agents that have been shown to be efficacious for the treatment ofAD acute flares and in maintenance therapy. In particular, the application of tacrolimus ointment twice daily reduces AD severity and pruritus. Moreover, maintenance therapy with an intermittent application of tacrolimus to recurrent skin sites (proactive therapy) decreases frequency and severity of relapses. Many studies have also assessed the efficacy of TCIs in disorders other than AD. Although US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) issued a "black box warning" regarding the possible cancerogenic activity of these drugs, there is currently no strong evidence of an increased rate of malignancy in treated patients, and observational data from postmarketing surveillance studies have shown no safety concerns.

A panel of dermatologists have thoroughly discussed the use of tacrolimus in AD after 15-year experience. The experts focused on AD flare treatment, maintenance therapy and management of side effects. Consensus was reached on some areas of interest, namely the stages of AD in which tacrolimus is recommended, the amount of drug to be applied, how to manage side effects, and how to improve patient's compliance. Moreover, the panel of experts recommended to perform randomized clinical trials to confirm the efficacy of tacrolimus off-label use, which led to successful outcomes in other skin diseases.

Key words: atopic dermatitis; calcineurin inhibitors; tacrolimus; lymphoma; skin tumors, topical therapy

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting approximately 5-20% of children and 3-8% of adults, in Western countries[1-3]. A recent international survey showed that the prevalence of adult with AD in the overall/treated populations is 4.9%/3.9% in the US, 3.5%/2.6% in Canada, 4.4%/3.5% in Europe, and 2.1%/1.5% in Japan[3]. Notably, the prevalence of adult AD in Italy results to be two-four times higher than other countries, reaching the value of 8.1%[2-4].

Both dysfunction of the epidermal barrier and dysregulation of the immune system are known to play a role in the pathogenesis of AD. In particular, loss-of-function mutations in the epidermal filaggrin gene and activation of T-helper type 2 (Th2) cell cytokine pathway are reported to be the main mechanisms involved in the pathogenesis[5].

The disease occurrence is generally lower in males than in females and is decreasing with age. The proportion of subjects with the severe form of AD is less than 10%, those with moderate are 10-20%, and those with mild disease are more than 70%. AD can be associated with other allergic conditions such as asthma, rhino-conjunctivitis, and food allergies[6].

The disease, in its moderate to severe form, has recently shown to be one of the most burdensome illness among all dermatological conditions,[6] with a relevant impact on the quality of life (QoL) of affected patients and their families[7]. Although much of the detrimental effects on QoL are driven by symptoms such as itch and pain, the burden of AD is complex, with influences on self-esteem and personal relationships. Multidimensional effects, higher with greater AD severity, have been described and include not only cutaneous symptoms, but also sleep disturbances, reduction in work and study productivity and may also interfere with sexual life[3,8]. The financial impact of AD is high, including medications price, physician visits, emergency department visits, and hospitalization[9].

The undesirable effect of AD on QoL in the paediatric population is comparable to that of debilitating diseases such as cystic fibrosis, while in adulthood the detrimental effect is similar to that of psoriasis[8].

Treatment of the disease is closely related to its severity. Indeed, while in mild forms topical treatment with emollients and anti-inflammatory drugs is sufficient, in mild-to-severe cases systemic drugs are needed (Tab. 1)[7].

However, the topical treatment with emollients remains the basis of any treatment, due the impairment of cutaneous barrier that is at the basis of the pathogenesis of AD[10].

Effective topical therapy depends on three fundamental principles: sufficient strength, sufficient dosage and correct application[10]. Topical corticosteroids (TCS) are considered the first-line therapy for AD, but their long-term use can be associated with relevant side-effects, and patients may be reluctant to continue this therapy given the risk of adverse events (AEs), ultimately contributing to treatment failure[7].

About 15 years ago the use of the TCIs (Topical Calcineurin Inhibitors) for the treatment of AD was introduced in paediatric and in adult population[6]. Tacrolimus and pimecrolimus, the two marketed drugs of the therapeutic class, have shown different pharmacodinamic and efficacy profiles[7].

The selection of a specific TCIs should be based on a number of factors which differentiate tacrolimus from pimecrolimus[7]. According to a recent multinational Position Paper, the choice of tacrolimus is driven by its superior efficacy in comparison with pimecrolimus (Table 2), probably due to the pharmacodynamic profile which shows high affinity for intracellular ligand protein macrophillin-12, also called FKBP, able to suppress the synthesis of pro-inflammatory cytokines[7].

Moreover, the lipophilic vehicle of tacrolimus allows better penetration and enhances the pharmacological activity compared with the hydrophilic vehicle of pimecrolimus. Nevertheless, for some specific areas (e.g. face, and especially during summer), patients may prefer an agent with a lower activity but with a more comfortable application, such as the pimecrolimus cream.[7] These characteristics of tacrolimus, together with its favourable pharmacokinetic profile, may be associated with a cost-saving for the healthcare system, as compared with pimecrolimus[7]. The cost-effectiveness of proactive therapy with tacrolimus has been demonstrated for moderate AD and is even higher in severe AD in a recent study on adult patients[11].

Proactive tacrolimus ointment therapy has been shown to be safe and effective for up to 1 year in reducing the number of flares and improving the QoL both in adults and in children[10,12,13]. This disease management

strategy did not lead to an increase in the incidence and number of adverse events during the 12-month treatment period[7,13]. High-quality long-term safety data have recently been published on a 4-year tacrolimus study[14]. The proven TCIs effectiveness has also led to the extension of their use in off-label setting[15].

In 2005, due to concerns on the possible increased risk of malignancy, the labelling of TCIs class was revised and a boxed warning addressing this problem was included in the package leaflet[6]. This warning was based on insufficient data and evidence. A number of studies have not confirmed this correlation[1,6,16]. Indeed, it has been demonstrated that lymphoma incidence in TCIs-treated patients is not higher than in the general population and no causal relationship has been demonstrated between TCIs use and an increase risk of lymphoma or other malignancies[7].

Considering all the above-mentioned issues, a Committee of Italian experts has been involved to obtain their consensus on the optimal use of tacrolimus ointment in adults with AD.

Methods

The Consensus Committee, consisting of expert Italian dermatologists, met twice. During the first session, the clinical needs and the statement questions have been identified. During the second meeting the consensus statements have been formulated. No systematic literature review has been performed.

The questions the group agreed to answer are the following:

1) In which stages of adult AD tacrolimus ointment should be recommended?

2) How much tacrolimus ointment should be applied by the patient?

3) How side effects should be managed?

4) How patient compliance can be increased?

5) In which off-label condition is tacrolimus also effective?

For each question one/more statements of consensus were agreed between participants.

Discussion and consensus statements

Tacrolimus is available in two strengths: 0.03% and 0.1% ointment[17]. In paediatric patients the 0.03% formulation should be used. The drug is indicated in adults, adolescents and children from the age of 2

years for the treatment of flares of moderate to severe AD patients who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids[17].

Tacrolimus is also indicated in the above-mentioned population for the prevention of AD flares and the prolongation of flare-free intervals in patients experiencing high number of disease exacerbations (i.e. occurring 4 or more times per year) who have had an initial response up to 6-week treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected)[17].

When applying tacrolimus ointment, it is not recommended to apply emollients to the same area within 2 hours.[17] Moreover, the concomitant use of other topical preparations has not been evaluated and there is no data regarding the concomitant use of systemic steroids or immunosuppressive agents.[17] Since the use of tacrolimus ointment under occlusion has not been evaluated, occlusive dressings are not recommended.[17]

1) ***In which stages of the AD tacrolimus ointment should be recommended?***

Clinical tools for assessing the severity of AD as objectively as possible are the SCORing Atopic Dermatitis (SCORAD) indexThe sum of the scores assigned to the extent/intensity of eczema and subjective symptoms (itching and sleep loss)[18] will determine the severity of the AD (mild <25, moderate ≥25 and ≤50, severe >50)[7] and the Eczema Area and Severity Index (EASI)[19].

The expert panel underlines that tacrolimus is often used not only in moderate to severe AD, but also in the mild-to-moderate form not responsive to topical corticosteroids, as indicated by the European and Italian AD guidelines[10,12].

Flare treatment

Regarding the duration of tacrolimus therapy, treatment of adults should be started with tacrolimus 0.1% twice a day and continued until clearance of the lesion. If symptoms recur, twice daily treatment with tacrolimus 0.1% should be restarted[17]. The experts believe that providing specific information to patients on the therapy length is relevant in order to avoid overexposure to the product.

Consensus Committee recommendations:

- *During flares, tacrolimus 0.1% application twice daily until lesion cleared, is recommended*
- *When a significant improvement/clinical healing is achieved, a further week of treatment is recommended;*
- *At baseline, if the area is highly inflamed, an initial treatment with topical corticosteroids for a few days should be considered;*
- *If a concomitant skin infection is suspected, topical and/or systemic antibiotics should be used before applying tacrolimus ointment.*

Maintenance therapy

Regarding the proactive use of topical tacrolimus in adult patients, the Consensus Committee recommends:

- *During maintenance therapy tacrolimus ointment (0.1%) should be applied once a day twice weekly (e.g. Monday and Thursday) to areas commonly affected by AD to prevent progression to flares*[17];
- *Between applications there should be 2–3 days without tacrolimus treatment*[17];
- *If a flare occurs, twice daily treatment should be resumed*[17];
- *After 12 months of treatment, a review of the patient`s response to therapy history should be evaluated and a decision taken whether to continue maintenance treatment in the absence of safety data beyond 12 months*[17].

The experts identified the need of further clinical studies in order to carefully evaluate the efficacy and safety of tacrolimus in term of duration/severity of itching, sleep disturbance, sexuality alteration, other AEs and economic impact.

2) How much tacrolimus ointment should be applied by the patient?

Tacrolimus can be applied to all parts of the body, including the face, neck and flexure areas, in a thin layer[17]. Tacrolimus treatment should begin at the first appearance of signs and symptoms. Each affected region of the skin should be treated until lesions are cleared, almost cleared or partially cleared[17].

The American Academy of Dermatology (AAD) guidelines highlight the "fingertip unit" (the quantity of product corresponding to the distal phalanx of the index of the hand of an adult, equivalent to 2 palms) to be used also for tacrolimus ointment[20].

The Consensus Committee consequently recommends:

- *To use tacrolimus in an amount of fingertip unit to obtain a thin layer.*

All the experts agreed that the total amount of drug to be applied depends on the severity and extent of the disease (SCORAD score, EASI).

3) How side effects should be managed?

The most frequently observed tacrolimus side-effects are transient warmth, tingling, burning/itching at the application site and alcohol intolerance (facial flushing). Some patients experience a transient worsening of skin conditions and paraesthesia. The experts agree to consider the skin burning as the more relevant tacrolimus AE.

In patients experiencing skin burning, the Consensus Committee recommends:

- Consider the use of topical corticosteroids before the application of tacrolimus;
- Consider to start with low 0.03% tacrolimus ointment concentration and then raise to 0.1%;
- Tacrolimus tube can be stored at low temperature (5-7°C) (to obtain a mild cooling effect).

Regarding the possible development of lymphomas or other malignancies during TCIs treatment, there is currently no evidence of an increased rate of malignancy in treated patients and observational data from post-marketing surveillance studies have shown no safety concerns[21]; a recent review article on safety and benefits of tacrolimus ointment for the treatment of adult and pediatric AD concludes that tacrolimus ointment is a safe and effective option for the treatment of AD in both children and adults[21]. Moreover, a systematic review and metanalysis of 24 articles on AD has demonstrated that highly potent steroids, but not TCIs, are associated with a small lymphoma risk[1]. Another study on Danish children with AD do not showed significant increase of incidence in melanoma between the TCIs group (n=34,921) and the topical glucocorticoids group (odds ratio 0.64; 0.2-2.03), nor an increase in lymphoma/leukaemia (OR 1.29; 0.82–2.02)[16]. This was also the case when comparing the TCIs group with the control group on melanoma (OR 0.46; 0.15-1.46) and leukaemia/lymphoma (OR 1.46; 0.94–2.28)[16].

In addition, in 7,457 children with AD enrolled in the Paediatric Eczema Elective Registry study (a total of 26,792 person-years) and treated with topical pimecrolimus no increased risk of malignancy was observed[6].

The Consensus Committee indicates that:

- *Based on literature data and on the evidence of 15 years of real life use, the risk associated to TCIs treatment and malignancies seems to be not clinically relevant, although it cannot be completely excluded;*
- *Subjects with AD, may develop cancer for causes other than TCIs treatment.*

4) How the patient compliance can be increased?

The management of AEs is a critical issue during AD therapy: the patient often does not follow the clinician advises and the compliance to the therapy may be compromised.

The Consensus Committee indicates that:

- *Patient education is essential in order to increase adherence to treatment;*
- *The physician, the patient and the caregiver should be actively trained on tacrolimus use, the possible AEs, their prevention and management;*
- *The role of patient associations may be important in reassuring patients about tacrolimus AEs so to increase therapy adherence.*

5) In which off-label condition may tacrolimus be effective?

Topical tacrolimus has been evaluated in the treatment of many inflammatory disorders other than AD, with favourable results.[15,22-24]

According to the experts' experience, the efficacy of tacrolimus is higher than the standard therapies in several diseases including: vitiligo, inverse psoriasis, contact dermatitis, lichen planus, seborrheic dermatitis, sebopsoriasis, cutaneous lupus erythematosus, lichen sclerosus pyoderma gangrenosum, Zoon balanitis, and perioral dermatitis. In these disorders, tacrolimus is generally used at 0.1% once or twice a day (being small areas to be treated and given the effectiveness of the drug); the duration of treatment varies depending on the type of the disease.

The Consensus Committee indicates that:

- *Randomized control trials are desirable to confirm the efficacy of tacrolimus in diseases other than AD.*

Conclusions

After 15 years of clinical experience, according to the participants 'opinion and the available evidences, tacrolimus represents an effective and safe therapy for adult AD. Consensus was reached among the experts on timing in which tacrolimus use is recommended, amount of drug to be applied, side effects management and patient's compliance improvement. Regarding the possible development of lymphomas or other malignancies during TCIs treatment, the experts agreed that the current data do not show any correlation between them. Finally, tacrolimus when used off-label may lead to successful outcomes in other skin diseases and the Committee encourages randomised clinical trials in order to confirm the effectiveness of the drug in a wider range of inflammatory skin disorders.

Table 1. Treatments for mild, moderate and severe AD (adapted from Remitz A, *et al.*[7])

AD SEVERITY	TREATMENTS		PREVENTION MEASURES
	APPROVED	OFF LABEL	
Severe	• potent topical corticosteroids (TCS)* • cyclosporine (CsA) • topical tacrolimus • dupilumab • PUVA*	• mycophenolate mofetil • methotrexate (MTX) • azathioprine (AZA)	• emollients
Moderate	• topical tacrolimus • topical pimecrolimus • mid potent and potent topical corticosteroids (TCS)* • UV therapy (UVB 311 nm, medium dose UVA1)* • Oral treatment if response is not sufficient as severe forms		• emollients
Mild	• mild and mid potent topical corticosteroids (TCS)* • topical pimecrolimus		• emollients

* Not formally approved but use allowed since long-time

Table 2. - Facts differentiating tacrolimus (T) from pimecrolimus (P)[7]

- More favourable pharmacokinetic (e.g. higher penetration in the skin) and pharmacodynamic (e.g. higher affinity for FKBP) properties of **T** compared to **P**
- Superior efficacy of **T** compared to **P** according to clinical evidence
- Fast and sustained action of **T**
- The ointment formulation of tacrolimus could be an advantage over **P** cream formulation
- **T** is labelled for moderate to severe while **P** for mild to moderate AD
- Potential role of **T** within combination regimens with corticosteroids

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