

Topical tacrolimus during systemic therapy for severe atopic dermatitis in the clinical practice

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Abstract. – OBJECTIVE: To evaluate the role of tacrolimus ointment in the management of patients on dupilumab therapy for severe atopic dermatitis, in a real-life setting.

PATIENTS AND METHODS: Consecutive patients with severe AD treated with dupilumab were enrolled. Topical treatment was associated according to the clinical practice. Eczema Area and Severity Index (EASI), itching and sleep Numerical Rating Scale (NRS) and Dermatologic quality of Life (DLQI) were recorded at baseline and after 4, 16 and 52 weeks of treatment with dupilumab.

RESULTS: Overall, 342 patients were enrolled, and 307 were evaluable. Tacrolimus was used by 6.5% (n=20) of patients at baseline, 11%, 13.5%, and 11.3% after 1, 4 and 12 months, respectively; the mean time to introduce tacrolimus after initiation of dupilumab was 8.3 ± 0.3 months. Low EASI score (<7; mild disease) after 1 month of systemic therapy was more frequent in patients who applied tacrolimus at baseline than in patients who did not (72.2% vs. 55.8%, $p=0.027$). Female sex, low DLQI scores, low age at dupilumab initiation, and non-generalized AD were correlated with an increased probability to start tacrolimus at any time during the study.

CONCLUSIONS: Data suggested that early treatment of localized areas with tacrolimus improves systemic treatment efficacy.

Key Words:

Atopic dermatitis, Tacrolimus, Combined treatment, Skin barrier.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory, multifactorial and immune-mediated disease that can affect all ages groups and impact on the quality of life. Recent research on its etio-pathogenesis showed that impairment of the skin barrier function plays an important role in activating the immunological response. Therefore, topical emollient therapy, aiming at restoration

of the skin barrier, is a very important aspect of AD therapy. Emollient creams should be regularly used by patients with AD, even when topical and/or systemic anti-inflammatory treatment is administered. Available evidence showed that an improved therapeutic response may be obtained with the combination of systemic and topical therapy, both emollient and anti-inflammatory, in the early stages of AD¹. Indeed, the new biological therapies, such as dupilumab, were safe and had a better clinical response after 16 weeks of treatment and the results were maintained for up to 52 weeks, in patients who had received dupilumab in combination with topical steroids²⁻⁴.

Topical corticosteroids are the first-line topical anti-inflammatory therapy for this condition; however, they can be associated with significant adverse effects when used chronically and they may even cause additional damage to the skin barrier⁵. Calcineurin inhibitors, including pimecrolimus and tacrolimus, are an alternative to topical steroids, especially for long-term AD stabilization as they do not damage the skin barrier. A meta-analysis of studies on patients with AD found that topical tacrolimus 0.03% was superior to moderate-to-potent topical corticosteroids, and had a good tolerability profile⁶.

Tacrolimus ointment in 0.1 and 0.03% formulations is routinely used particularly in relapsing AD, and in critical areas such as the face, hands, and folds of the limbs. In the event of a severe relapse, an initial treatment with a topical steroid of moderate potency is necessary, followed by the application of tacrolimus. In moderate/severe AD with an Eczema Area and Severity Index (EASI) >16 or with localization in a sensitive site (face, hands, genitals) or an itching Numerical Rating Scale (NRS) or sleep NRS (S-NRS) ≥ 7 or a Dermatology Life Quality Index (DLQI) >10, systemic therapy is recommended⁷. Recently, the association of tacrolimus with or without topical corticosteroids on the face, in association with

dupilumab, was found to be effective and safe; the rate of improvement of the head/neck EASI score significantly correlated with the rate of improvement of the overall EASI score⁸.

The objective of this monocentric, retrospective observational study was to evaluate the role of tacrolimus in the management of patients on dupilumab therapy for severe AD and to identify the most suitable strategy for this association in a real-life setting.

Patients and Methods

Patient data were retrospectively collected from June 2018 to December 2020 at our center, which is dedicated to AD management, in Milan (Italy). Patients with a severe form of AD, eligible for dupilumab therapy, according to the Italian Drug Agency (AIFA) recommendations (EASI ≥ 24 ; contraindication, side effects, or failure to cyclosporine therapy), and who had used topical corticosteroids or tacrolimus for up to 16 weeks as local treatment during dupilumab therapy were recruited in this study. All patients were treated with self-administered subcutaneous dupilumab 300 mg every other week following a loading dose of 600 mg subcutaneously. All patients received common emollient and moisturizing creams. Patients who had received systemic anti-inflammatory drugs were excluded.

As this was a real-life study, the authors' clinical routine was used. Topical tacrolimus was prescribed with daily emollients during systemic treatment, to promote a response in localized critical areas, such as face, hands, limb folding, and genitalia, mainly when the global response to systemic treatment was satisfactory. Tacrolimus was associated with topical corticosteroids and systemic therapy in patients with severe disease, who underwent frequent recurrence and exacerbation.

At baseline, demographic characteristics, AD clinical phenotypes, comorbidities, and previous AD treatments were recorded. The following variables were monitored at baseline and weeks 4, 16 and 52: EASI (range: 0-72), itching NRS (range: 0-10), S-NRS (range: 0-10), and DLQI (range: 0-30), and adverse events (AEs).

Ethics

All patients released verbal informed consent to the treatment, which was performed according to the clinical practice and to locally active reg-

ulations. The study was approved by the Ethics Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano area 2, and conformed to the Ethical guidelines of the declaration of Helsinki.

Statistical Analysis

For the descriptive analysis, data are presented as absolute numbers, means and percentages. Standard deviations were calculated. Comparison of data at different time points was evaluated by ANOVA, *t*-test and McNemar test. The probability to use tacrolimus at particular points in time was assessed by the Cox proportional hazards model. The relationship between variables was tested by logistic regression.

Results

Overall Effectiveness of Systemic Treatment

Overall, 342 patients with severe AD and treated with dupilumab were included in this study. Males represented 56% ($n=190$) of the cohort; the mean age was 39 ± 17 years. The mean age at diagnosis of AD was 12 ± 19 years, while the mean age at initiation of treatment with dupilumab was 38 ± 17 years. The clinical features of AD at baseline are reported in Table I. At baseline, 311 (91%) of patients had at least one comorbidity, rhinitis was reported by 248 (72%) patients, conjunctivitis by 176 (51%), asthma by 144 (42%), and food allergy by 54 (16%) patients.

Before this study, 294 (86%) patients had been previously treated with cyclosporine, 273 (80%) with systemic corticosteroids, 152 (45%) with phototherapy, 31 (9%) with methotrexate, 9 (3%) with alitretinoin and 8 (2%) with azathioprine.

Overall, the mean EASI score was 29.5 ± 7.4 at baseline ($n=342$); it was reduced to 8.4 ± 7 after 1 month of study treatment ($n=312$), 5 ± 5 after 4 months ($n=274$), and 3.2 ± 4.9 after 12 months ($n=203$). The EASI score was >21 (severe and very severe form) in 340 (99%) patients at baseline, only 19 (6%) patients after 1 month, 4 (1%) patients after 4 months, and in one (0.5%) patient after 12 months of study treatment. Repeated Measures ANOVA showed that there was a significant ($p<0.001$) reduction of the EASI score from baseline to 12 months of treatment. In addition, the reduction of the EASI score was significant after 1 month as demonstrated by a *t*-test ($p<0.001$).

Table I. Clinical features of atopic dermatitis at baseline.

	Males (n=190), n (%)	Females (n=152), n (%)	Total (n=342), n (%)
Relapsing disease	51 (26.8%)	39 (25.7%)	90 (26.3%)
Persistent disease	80 (47.9%)	87 (57.2%)	167 (48.8%)
Late onset	59 (31.1%)	26 (17.1%)	85 (24.9%)
Classic phenotype	89 (46.8%)	83 (54.6%)	172 (50.3%)
Generalized disease	81 (42.6%)	51 (33.6%)	132 (38.6%)
Nodular prurigo	14 (7.4%)	13 (8.6%)	27 (7.9%)
Nummular eczema	6 (3.2%)	5 (3.3%)	11 (3.2%)
Genitalia	2 (1.1%)	–	2 (0.6%)
Hands	15 (7.9%)	6 (3.9%)	21 (6.1%)
Hands and genitalia	6 (3.2%)	1 (0.7%)	7 (2.0%)
Face	33 (17.4%)	16 (10.5%)	49 (14.3%)
Face and genitalia	7 (3.7%)	2 (1.3%)	9 (2.6%)
Face and hands	72 (37.9%)	84 (55.3%)	156 (45.6%)
Face, hands and genitalia	54 (28.4%)	40 (26.7%)	94 (27.5%)

The mean NRS for a sleep disorder was reduced from 6.8 ± 3.1 at baseline to 0.9 ± 1.9 at 12 months ($p < 0.001$). A 4-point reduction of the NRS for the sleeping disorder was obtained by 193 (62%) subjects after 1 month, 175 (64%) subjects after 4 months, and 149 (73%) subjects after 12 months.

A significant reduction of itching was also obtained in 12 months ($p < 0.001$). The mean NRS was 8.5 ± 1.4 before study treatment, 3.9 ± 2.3 after 1 month of treatment, 3.3 ± 2.5 after 4 months, and 2.9 ± 2.5 after 12 months. A 4-point reduction of NRS for itching was obtained by 66% of patients by 1 month of treatment.

Quality of life was significantly improved by study treatment ($p < 0.001$, baseline vs. 12 months). The mean DLQI was 15.7 ± 6.6 at baseline and it declined to 6.3 ± 5.5 in 1 month, 4.9 ± 4.9 in 4 months, and 3.7 ± 4.7 in 12 months. The DLQI was < 10 only in 16.4% ($n = 56$) patients at baseline, and in up to 94.1% ($n = 192$) after 12 months of study treatment.

Association of Tacrolimus and/or Topical Corticosteroids with Systemic Therapy

In this cohort of patients, 307 of 342 patients were evaluable, while 35 patients were excluded

for non-adherence to the topical therapy. Table II reports the use of topical medications along the study period. At baseline, 136/307 (44.3%) patients received topical corticosteroids, 20 (6.5%) applied tacrolimus, 45 (14.7%) combined corticosteroids and tacrolimus (starting with corticosteroids for 2 weeks and then adding tacrolimus), and 106 (34.7%) applied only emollients.

The proportion of patients receiving topical corticosteroids was reduced from 44.3% at baseline to 32.5% ($n = 92$, $p < 0.001$) after 1 month with dupilumab, 29.8% ($n = 75$, $p < 0.001$) after 4 months, and 17% ($n = 33$, $p < 0.001$) after 12 months.

At baseline, 6.5% ($n = 20$) of patients applied tacrolimus, and this proportion was increased after the introduction of dupilumab (11%, 13.5%, and 11.3% after 1, 4 and 12 months, respectively); the mean time to introduce tacrolimus after initiation of dupilumab was 8.3 ± 0.3 months.

We observed that female sex, lower DLQI scores and a lower age at dupilumab initiation were correlated with an increased probability to start tacrolimus treatment in association with dupilumab at any time during the study observation

Table II. Flowchart of patients for analysis.

Topical medication	Baseline (n=307), n (%)	4 weeks (n=283), n (%)	16 weeks (n=252), n (%)	52 weeks (n=194), n (%)
None	106 (34.5)	127 (44.9); $p = 0.005$	121 (48); $p < 0.001$	124 (63.9); $p < 0.001$
Corticosteroids	136 (44.3)	92 (32.5); $p < 0.001$	75 (29.8); $p < 0.001$	33 (17.0); $p < 0.001$
Tacrolimus	20 (6.5)	31 (11.0); $p = 0.003$	34 (13.5); $p = 0.006$	22 (11.3); $p = 0.061$
Corticosteroids and tacrolimus	45 (14.7)	33 (11.7); $p < 0.001$	22 (8.7); $p = 0.108$	15 (7.7); $p = 0.099$

Data are presented as number and (%). p : comparison vs. baseline.

(DLQI: HR: 0.96, 95% CI: 0.94–0.99, $p=0.011$; age: HR: 0.99, 95% CI: 0.98–0.99, $p=0.031$ and females: HR: 1.5, 95% CI: 1.1–2.2, $p=0.034$). In agreement with these data, the probability to use tacrolimus during treatment with dupilumab was higher in patients with non-generalized AD in comparison to subjects with generalized disease ($p=0.018$).

In addition, low DLQI and female sex were associated with an increased frequency of using tacrolimus at baseline ($p=0.049$ vs. high DLQI and $p=0.003$ vs. male sex, respectively). Interestingly, patients who used tacrolimus at baseline obtained a low EASI score (<7 ; mild disease) by 1 month of treatment with dupilumab in a higher proportion than patients who did not receive tacrolimus at baseline (72.2% vs. 55.8%, $p=0.027$). As shown in Figure 1, after 1 month of treatment with dupilumab, high EASI scores were more frequent in patients who did not receive tacrolimus at baseline in comparison with those who received it.

During treatment with dupilumab, relapsing disease ($p=0.024$) and younger age ($p=0.02$) were correlated with a higher probability to initiate tacrolimus after 1 month of study treatment. In addition, after 4 months of treatment with dupilumab, tacrolimus initiation was more frequent in patients with relapsing disease ($p=0.012$).

The association of topical corticosteroids-tacrolimus was used by 14.7% ($n=45$) of patients at baseline, and this proportion was reduced to 11.7% ($n=33$) after 1 month of concomitant treat-

ment with dupilumab ($p<0.001$), 8.7% ($n=22$) after 4 months ($p=0.108$), and 7.7% ($n=15$) after 12 months ($p=0.099$).

Discussion

This observational study investigated the real-life use of tacrolimus in concomitance with dupilumab in adult patients with severe AD. Our patients were treated according to real-life clinical practice, and we evaluated different association schemes with topical tacrolimus, topical corticosteroids and systemic dupilumab. Overall, we observed a significant and persistent improvement of EASI, sleep disorder NRS, itching NRS, DLQI with dupilumab, alone or with topical therapy, and a reduction in the use of topical corticosteroids after the initiation of systemic treatment, which confirmed the overall improvement obtained.

The proportion of patients prescribed with topical tacrolimus after the initiation of systemic therapy was significantly increased after 4 and 16 weeks, with a persistent trend after one year. This may be linked to our routine practice to use tacrolimus as a local treatment for localized critical areas when the disease is generally well controlled. These results suggest that the response to dupilumab was satisfactory in many patients, who needed further treatment only in restricted areas. Tacrolimus has been indicated at the beginning of the therapy mainly for the management of persistent dermatitis of the face and neck, hands, genitalia and limb folds.

We found that the use of tacrolimus during treatment with dupilumab was more frequent in patients with lower DLQI; we may speculate that these subjects had a good quality of life because their dermatitis was not generalized and was predominantly localized, which could explain the frequent use of topical treatment. Indeed, we generally prescribe tacrolimus to treat localized residual disease in patients who respond to systemic therapy. These patients were predominantly female, and this may be perhaps explained because women are more prone than males to irritant contact dermatitis related to the use of cosmetics or their activities.

Large improvements in AD, i.e., EASI score reduction, were more frequently observed in subjects using tacrolimus. This result is in agreement with previous findings by Matsutani et al⁸, and, in addition, suggests that early treatment of localized critical areas with tacrolimus in association with

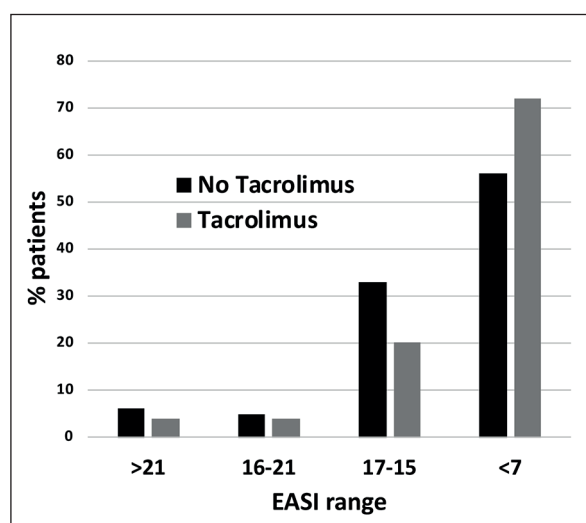


Figure 1. Ranges of EASI scores after 1 month of treatment with dupilumab according to tacrolimus use at baseline (original figure).

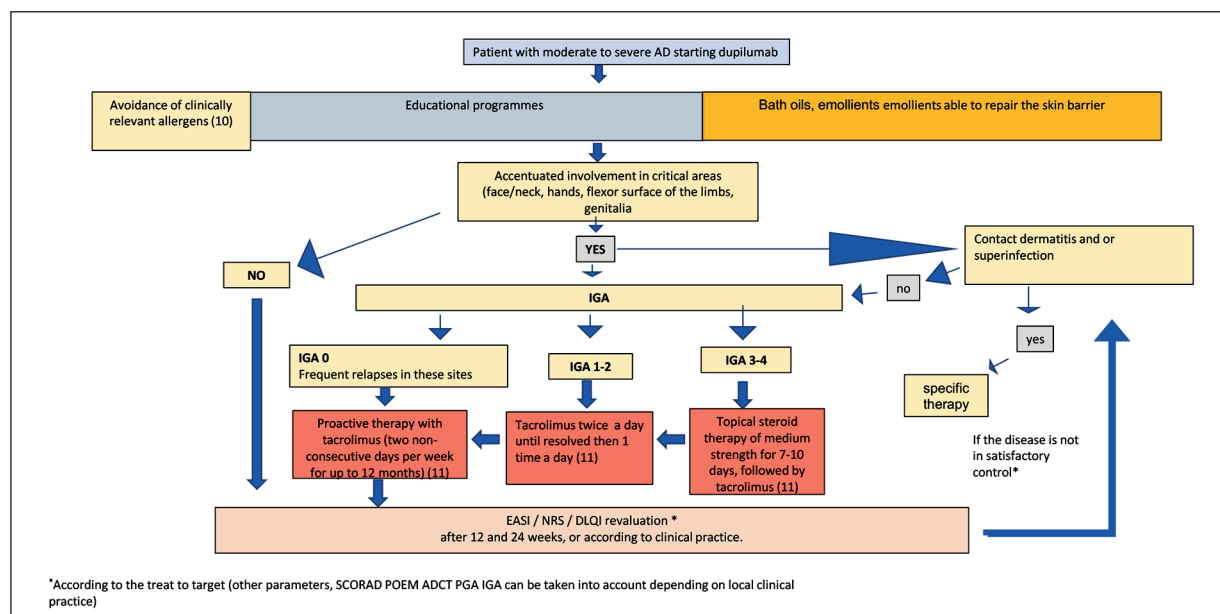


Figure 2. An algorithm for the management of severe AD with systemic and topical treatments (original figure, data from^{12,13}).

dupilumab improves treatment efficacy. Late initiation of tacrolimus, after 4 months of therapy with dupilumab, was frequent in subjects with relapsing disease; this may indicate that many severely affected patients had a relevant clinical improvement with the persistence of lesions only in localized areas.

It is known that the skin barrier function is restored after some weeks of treatment with dupilumab, but before this effect of the systemic therapy is obtained, it is possible that AD lesions in areas such as face, neck, and hands do not respond and may need an additional topic treatment^{9,10}. Based on this consideration and our results, we believe that a barrier repairing therapy should be combined with an emollient treatment in the first phase of the systemic therapy of AD when AD is worsened in special areas¹¹ (Figure 2). If IGA is 1-2, tacrolimus should be applied twice/day up to resolution, followed by proactive application twice/week. If AD is severe, with IGA 3-4, tacrolimus should be preceded by an initial course of about 7–10 days with a medium strength topical steroid. This approach should not be used if dupilumab is initiated in summer.

Conclusions

According to our results, the association of tacrolimus with dupilumab is safe and beneficial. It is mainly useful when initiated early and should

be associated with emollients to facilitate the response in localized critical areas.

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Conflict of Interest

S. Ferrucci has been principal investigator in clinical trials by AbbVie, Sanofi-Genzyme, has served on advisory board, and received honoraria for lectures and research grants from Novartis, Menarini, Almirall. The other authors reported no conflicts of interests.

Data Availability Statement

Data are available by request to the corresponding author.

Authors' Contribution

Study conception and design: SMF; collection of data: LA, EB, ST; interpretation of data: SMF, LA, EB, ST; manuscript drafting: SMF, LA, EB, ST; approval to submit: SMF, LA, EB, ST, AVM.

Ethics Approval

The study was approved by the Ethics Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano area 2, and conformed to the Ethical guidelines of the declaration of Helsinki.

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