

Instrumental evaluation of skin barrier function and clinical outcomes during dupilumab treatment for atopic dermatitis: An observational study

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Abstract

Background: Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by pruritus, xerosis, and skin barrier dysfunction. Skin barrier alteration is associated with an increase in trans-epidermal water loss (TEWL) and reduction in skin hydration. Dupilumab is a monoclonal antibody targeting interleukin-13 modulating pro-inflammatory signal transduction, which has been approved for moderate to severe AD. The aim of this study is to evaluate the effects of Dupilumab on skin barrier functions, using non-invasive instruments and clinical evaluation.

Materials and methods: Thirty patients affected by moderate-severe AD, who had been administered dupilumab, were evaluated by clinical examination and through the instrumental measurements of TEWL and corneometry at the baseline (T0) and 8 weeks (T1) on lesional skin. The clinical evaluation was performed using the Eczema Area and Severity Index (EASI) score. Moreover, a Dermatology Life Quality Index (DLQI) and 7-day numeric rating scale (NRS) questionnaires were administered to each patient.

Results: The instrumental parameters of skin barrier recovery confirmed the clinical improvement outcomes with a statistically significant reduction of TEWL at T1.

Conclusion: Our data confirm the clinical outcomes already reported in the literature and show that there was an inverse proportional correlation between TEWL levels and clinical severity after 8 weeks of treatment with dupilumab.

KEYWORDS

atopic dermatitis, dupilumab, skin barrier, trans-epidermal water loss

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic, recurrent, inflammatory skin disease characterized by pruritus, xerosis, and skin barrier dysfunction. It is most commonly observed in pediatric populations, although it can persist or develop in adults. Its pathogenesis is both multifactorial

and environmental where genetic and immunologic factors can play a crucial role. Atopic dermatitis has a significant social and psychological impact on the people affected, with a reduction in the quality of life. In atopic dermatitis, the alteration of skin barrier is associated with reduced ceramide levels, with a consequential increase in trans-epidermal water loss (TEWL) and reduction in skin hydration.¹

Nowadays, available therapies include emollients and moisturizers, corticosteroids, topical calcineurin inhibitors, phototherapy, and systemic immunotherapies (eg, cyclosporine).

In 2017, the US Food and Drug Administration (FDA) approved dupilumab for the treatment of moderate to severe AD.² Dupilumab is a monoclonal antibody targeting interleukin-13 (IL13): It binds to IL-4R α , a component of both the IL-4 and IL-13 receptors, and modulates pro-inflammatory signal transduction.

The aim of this observational study is to evaluate and clinically correlate the effects of Dupilumab on skin barrier functions in patients with moderate to severe AD, using non-invasive instruments and clinical evaluation.

2 | MATERIALS AND METHODS

Thirty adult patients affected by moderate to severe AD assigned to monotherapy with dupilumab, aged between 20 and 61 years of age (median age 36.1), were enrolled in this study: 19 males and 11 females.

All patients voluntarily agreed to participate, with informed consent being obtained from each participant.

Inclusion criteria were as follows: moderate to severe AD (EASI > 24), age >18 years of age, AD resistant to common systemic treatments.

Exclusion criteria were as follows: age <18 years of age, mild AD (EASI < 24), participation in another clinical study, patients not eligible for dupilumab.

All the enrolled patients were evaluated by means of a clinical examination and instrumental measurements of TEWL and corneometry at the baseline (T0) and 8 weeks (T1) after the start of dupilumab treatment. The clinical evaluation was performed using the Eczema Area and Severity Index (EASI) score, which is a tool used to evaluate the extension and the severity of atopic dermatitis. Four body regions (head and neck, trunk, upper limbs, and lower limbs) were assessed separately in order to calculate the percentage of skin affected and the presence of signs of severity (erythema, papulation/edema, excoriations, and lichenification).³

Moreover, a Dermatology Life Quality Index (DLQI) questionnaire was administered to each patient in order to measure the impact of AD on the quality of life. Patients assessed pruritus intensity using the 7-day numeric rating scale (NRS) scoring from 0 (no pruritus) to 10 (the most intensive pruritus) and the quality of their sleep following a numeric rating scale ranging from 0 ("best possible sleep") to 10 ("worst possible sleep"), known as 7-day non-restorative sleep scale (NRSS).

Non-invasive instrumental evaluation of skin barrier biophysical parameters was performed by means of a Tewameter™ 300® (CK Courage Kazaka Electronic), which was used to calculate the water evaporation rate in g/h/m² and a Corneometer CM 820® (CK Electronic), which was used to assess the water content in the stratum corneum (arbitrary units—a.u.).

At each visit, instrumental measurements were conducted on the same lesional skin of the volar surface of the forearm.

All the measurements were obtained according to standardized conditions with controlled temperature and humidity levels and by the same evaluator in order to achieve objective and reproducible values.

2.1 | Statistical analysis

All statistical analyses were performed using SPSS statistical software version 21 (SPSS Inc.). We considered *P*-values of less than .05 to be statistically significant.

Being interested in temporal comparisons, we verified the differences between the continuous variables using the Wilcoxon test or Student *t* test for paired data, according to the nature of the distributions.

3 | RESULTS

All the patients completed the study. No adverse events were recorded or reported. At the baseline, the (T0) EASI score showed an average value of 35.25 (range between 23 and 52), DLQI showed an average value of 27.5 (range between 22 and 30), and NRSS an average value of 8.75 (range between 7 and 10) and itch NRS had an average value of 8.8 (range between 7 and 10). At T1, the EASI score showed an average value of 17 (range between 8 and 24), DLQI an average value of 12.6 (range between 1 and 20), NRSS an average value of 2.2 (range between 0 and 5), itch NRS an average value of 3.37 (between 1 and 8). According to these data, clinical evaluations showed a significant reduction in the degree of severity of all parameters at T1 (*P* < .0001) (Figure 1).

The instrumental parameters of skin barrier recovery confirmed the clinical improvement outcomes with a statistically significant reduction of TEWL at T1. At the baseline, TEWL on damaged skin of the forearm showed an average value of 31.44 ± 13.52, while at T1 it was 21.8 ± 9.97 (*P* = .004). Corneometry evaluation showed a mild improvement, which was not statistically significant (Figure 2).

4 | DISCUSSION

Atopic Dermatitis is a chronic inflammatory cutaneous pathology with a significant impairment of skin barrier function.^{4,5} Dupilumab is a monoclonal antibody which acts on inflammatory pathways in atopic dermatitis. Several studies have demonstrated that it improves the severity of clinical manifestations in atopic dermatitis with a significant reduction of EASI score and a consistent and significant improvement in DLQI, pruritus, and sleep quality. Several studies showed that mean percentage reduction in EASI after dupilumab was 54.1% after 4 weeks and 71.9% after 12 weeks.⁶ These data strongly suggest that the onset of action is relatively fast with a maximum effect at 4 weeks of treatment, with a improvement through to week 16. Moreover, some authors

FIGURE 1 The distribution of EASI, DLQI, NRS sleep, and NRS itch at baseline and follow-up (Median values, first and third quartile, min and max values)

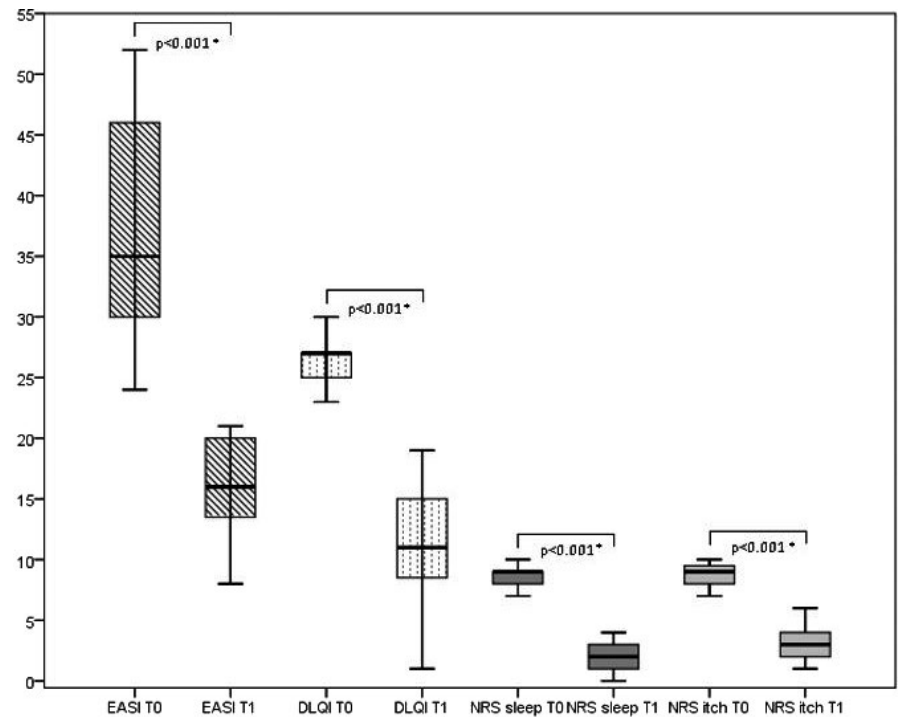
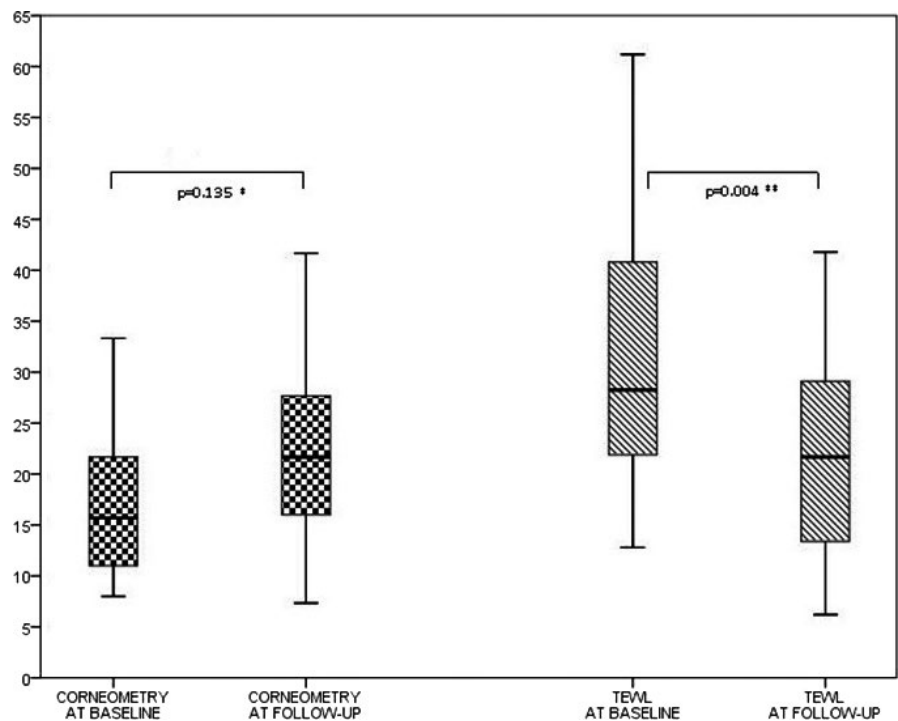


FIGURE 2 Comparisons of the corneometry and TEWL values between baseline and follow-up, according to the site



reported a 51.5%⁷ and 28.3%⁸ decrease of pruritus by means of itch NRS score after 4 weeks of treatment. Our clinical findings confirm the data from literature, highlighting a consistent improvement of EASI and a reduction of pruritus after 8 weeks of treatment (Figure 1).

Guttman et al correlated an impaired barrier function with a proinflammatory cytokine production. In particular, the IL-4 and

IL-13 highly inhibit the expression of barrier-related molecules such as filaggrin (FLG), loricrin (LOR), and involucrin (IVL) with consequential barrier impairment. According to these findings, the authors also reported that topical steroids significantly improve clinical inflammatory features and reduce TEWL in lesional AD skin with the up-regulation of FLG and LOR expression.^{9,10} Subsequently, the same processes have been analyzed in patients with AD during dupilumab

treatment obtaining similar results: FLG and LOR expression were found to decrease in the lesional skin compared to non-lesional skin.

Microscopic and functional improvements of epidermal remodeling and inflammation have been observed with dynamic optical coherence tomography in patients affected by severe AD and treated with dupilumab.¹¹

Previous authors have investigated cutaneous biophysical parameters in atopic dermatitis demonstrating an alteration of skin barrier function followed by a TEWL increase. The loss in skin barrier integrity results in an increase of TEWL both on damaged and non-damaged atopic skin.¹² Addor et al¹³ demonstrated that skin biophysical parameters in atopic non-damaged skin are related to clinical severity of atopic dermatitis. In particular, there was a significant TEWL increase in non-damaged skin and the corneometry values were proportionally reduced to clinical features.

To the best of our knowledge, there is only one study that has evaluated instrumental skin barrier function modification during dupilumab treatment. Furuhashi et al¹⁴ investigated whether or not dupilumab could restore skin barrier function. According to their data, dupilumab probably reduced TEWL but it was unable to increase stratum corneum hydration in lesional skin of patients with atopic dermatitis. The most important limitation regards the limited number of the study population, because they enrolled only 7 patients. Our results support their hypothesis with a bigger number of subjects, suggesting that Dupiluman plays a role in skin barrier recovery.

5 | CONCLUSION

Our data confirm the clinical outcomes already reported in literature and show that there was an inverse proportional correlation between TEWL levels and clinical severity after 8 weeks of treatment with dupilumab. Such findings support the hypothesis that systemic treatment with dupilumab is able to improve skin barrier function. However, further studies including a larger population sample and longer follow-up are needed in order to confirm our preliminary data.

CONFLICT OF INTEREST

The authors declare they have no conflict of interests. The principles of the Declaration of Helsinki have been followed.

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