

Research Article

Improvement of Nonlesional Skin Tone and Skin Barrier in Severe Atopic Dermatitis after Dupilumab Treatment

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Dupilumab, approved for the treatment of moderate-to-severe atopic dermatitis (AD), has been proven to improve skin barrier and postinflammatory hyperpigmentation on nonlesional areas. Previous studies, however, are only based on subjective visual assessments rather than objective biophysical measurements. We aimed to objectively measure transepidermal water loss (TEWL) and skin tone improvements after dupilumab treatment through bioengineering devices. Nineteen patients with severe AD were enrolled. Biophysical measurements were conducted in three nonlesional skin areas, the cheek, forearm, and lower abdomen, on a monthly basis for 5 months since the first dupilumab injection. TEWL was measured using a Tewameter®. Skin tones represented by L^* (lightness), a^* (redness), and b^* (yellowness) parameters were measured by the spectrophotometer®; the erythema and melanin index measured by the narrow-band reflectance spectrophotometer® were additionally assessed. Improvement from baseline was evaluated by the Wilcoxon's rank-sum test and Bonferroni correction. Correlation among biophysical parameters was evaluated by Pearson's correlation. $p < 0.05$ was considered statistically significant. TEWL and skin tone parameters in all anatomical regions showed significant improvement. The L^* and a^* values of the arm and trunk significantly improved after 2 months of dupilumab therapy and the face 3 months after. Similarly, b^* value of all anatomical regions significantly decreased after 1 month of treatment, and the TEWL did so after 2 months. When compared between anatomic regions, the trunk demonstrated higher improvement in L^* value, the arm in erythema index, and the face in melanin index. TEWL positively correlated with erythema index ($r = 0.51$, $p < 0.05$), melanin index ($r = 0.45$, $p < 0.05$), and a^* ($r = 0.50$, $p < 0.05$); negative correlation was observed with L^* ($r = -0.48$, $p < 0.05$). On top of AD symptom relief, dupilumab objectively improves the skin barrier and skin tone of nonlesional areas.

1. Introduction

Atopic dermatitis (AD) is a heterogeneous disease that has differences among various ethnic and racial groups [1]. Clinical presentation can also vary among racial subgroups; darker-skinned patients tend to have postinflammatory hyperpigmentation [2]. Dupilumab, which is approved for the treatment of moderate-to-severe AD, appears to provide significant improvement of skin barrier function and hyperpigmentation in nonlesional skin [3] and for clinical improvement of hyperpigmentation on nonlesional skin [2] as well as for treating AD symptoms. However, to our knowledge, no previous study has evaluated changes of skin tone, erythema, pigmentation, and transepidermal water loss (TEWL) after dupilumab treatment.

2. Materials and Methods

A total of 19 patients with severe AD (14 males, 5 females) aged 20–41 years (mean age, 28.95) received a 600 mg loading dose of dupilumab and continued to 300 mg every two weeks. The baseline eczema area and severity index (EASI) score of the patients was above 21. Written informed consent was obtained from all patients. Before and after treatment with dupilumab, measurements of skin tone, erythema, pigmentation, and TEWL were taken every month for five months and were approved by the institutional review board (KHUH 2022-04-051). A spectrophotometer (CM-2600d, Konica Minolta, Japan), L^* , a^* , b^* , and the narrow-band reflectance spectrophotometer (Cortex Technology, Hadsund, Denmark), erythema index, and

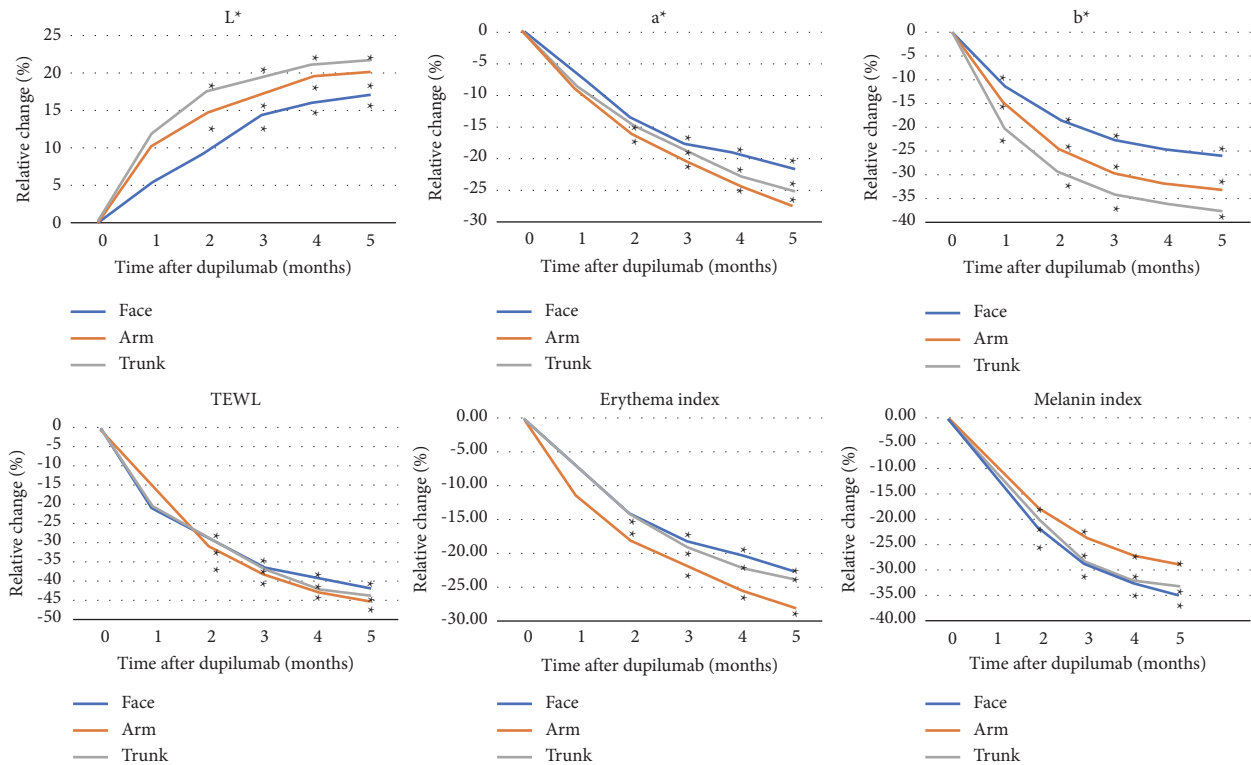


FIGURE 1: A comparison of relative changes in the spectrophotometer (L^* , a^* , and b^*), reflectance spectrophotometer (erythema index and melanin index), and TEWL before and after dupilumab treatment ($n = 19$). TEWL, transepidermal water loss.

melanin index were used to measure the skin tone, erythema, and pigmentation in three sites of the nonlesional skin: the cheek, forearm, and lower abdomen. The Tewameter TM300 probe (Courage + Khazaka, Köln, Germany) was used to measure TEWL. An alternative skin color type classification tool was developed using the individual typology angle (ITA). This classification is based on colorimetric parameters of the Commission Internationale de l'Eclairage (CIE) L^* , a^* , b^* system. In this system, any color can be represented by three variables: L^* the lightness axis, a^* the red-green axis, and b^* the yellow-blue axis [4]. L^* ranges from black (value 0) to white (value 100). a^* reflects the intensity and nature of basic melanic pigmentation as well as the level of natural vascularity of the individual. b^* is related to the intensity of basic pigmentation. It is also reflected in the carotene content and the nature of melanin [5]. Narrow-band reflectance spectrophotometer was developed to measure hemoglobin and melanin in the skin. The red reflectance yields an estimate of the melanin content and allows the calculation of the melanin index. Subtracting the red absorbance due to melanin from the green reflectance estimates the erythema and gives the erythema index [6].

We calculated the relative percentage change from the baseline. Correlations between data were analyzed using Pearson's correlation coefficients. Data were analyzed using the Wilcoxon's rank-sum test. A Bonferroni correction was used to compare the differences between baseline and treatment duration. The statistical significance level was set at $p < 0.05$.

3. Results and Discussion

These results showed an improvement in skin tone, erythema, hyperpigmentation, and TEWL after dupilumab treatment (Figure 1). All the anatomical regions were brightened (Supplementary Figure 1). Comparing the anatomical regions, skin tone showed a relatively large improvement in the trunk, erythema index in the arm, and melanin index in the face. TEWL was correlated with the erythema index ($r = 0.51$, $p < 0.0001$), melanin index ($r = 0.45$, $p < 0.0001$), and a^* ($r = 0.50$, $p < 0.0001$) and negatively correlated with L^* ($r = -0.48$, $p < 0.0001$), but weakly correlated with b^* ($r = 0.28$, $p = 0.0059$) (Supplementary Table 1). In this study, the L^* and a^* showed significant differences from two months after dupilumab on both the arms and trunk and from three months on the face. In all anatomical regions, b^* significantly decreased after one month, and TEWL showed a significant difference from two months (Supplementary Table 2). Nonlesional AD skin is distinct from normal skin with respect to epidermal differentiation and immune abnormalities, suggesting that the overall skin in AD is abnormal [7]. Dupilumab normalized lipid composition and increased ceramide chain length in lesional and nonlesional stratum corneum, thus allows restoration of the skin lipid composition and barrier function [8]. In our study, all results showed continuous improvement as dupilumab treatment continued.

4. Conclusion

In conclusion, this study demonstrates that the skin tone, erythema, hyperpigmentation, and TEWL of nonlesional skin significantly improved after dupilumab initiation. These changes may be more clinically noticeable in Asians with melanin pigmentation.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Supplementary Materials

Supplementary Figure 1: Clinical images of skin tone improvement after dupilumab. Supplementary Table 1: Pearson's correlation coefficient between skin tone, erythema, pigmentation, and skin barrier. Supplementary Table 2: Comparison of changes before and after dupilumab ($n = 19$). (Supplementary Materials)

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