Effect of dupilumab for the therapy of atopic dermatitis and the effect on serum TARC, HBD2 and SEA-IgE levels and peripheral blood T helper cell subtypes

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Received May 6, 2023; Accepted January 2, 2025

DOI: 10.3892/etm.2025.12888

Abstract. Atopic dermatitis (AD) presents as a prevalent chronic, relapsing, inflammatory skin condition. While dupilumab has proven effective in treating moderate-to-severe AD, some patients still experience unsatisfactory outcomes with this therapy in clinical settings. Patients with AD receiving dupilumab were selected for inclusion in the present study for prospective observations. Over an 8-week period, the patients underwent monitoring and changes in serum biomarkers and circulating T helper (Th) cell levels were analyzed using questionnaires, ELISA and flow cytometry. The Scoring Atopic Dermatitis (SCORAD), Objective-SCORAD, Itch Numeric Rating Scale (NRS), Dermatology Life Quality Index, Patient Oriented Eczema measure and Atopic Dermatitis Control Tools scores in patients with AD significantly decreased at week 8 compared with those before treatment (P<0.05). Moderate positive correlations were demonstrated between serum thymus and activation-regulated chemokine (TARC) and human β-defensin 2 levels and Eczema Area and Severity Index (EASI) and SCORAD scores (P<0.05). A weak negative correlation was shown between serum IgE against *Staphylococcus aureus* enterotoxin A level and the EASI and SCORAD scores, although these were not statistically significant (P>0.05). There was a notable increase in the proportion of Th2 cells in peripheral blood at week 2 (P<0.05). The proportion of Th22 cells in the peripheral blood was weakly correlated with the NRS score (P>0.05). Patients were categorized into rapid or slow groups depending on whether they achieved EASI-75 scores by week 8. The proportion of Th17 cells in peripheral blood in the rapid group at week 8 of treatment was lower than that compared with the slow group at week 2 (P<0.05). The SCORAD scores of the rapid group were significantly lower compared with those of the slow group at week 8 of treatment (P<0.05). The conventional dupilumab treatment regimen led to a marked remission in patients with exogenous AD after 8 weeks of therapy. Significant correlations were observed between serum TARC levels and clinical disease scores (P<0.05), which changed notably during treatment and remained valuable for monitoring disease progression at follow-up. Additionally, the elevated ratio of Th17 cells in peripheral blood at week 2 of treatment showed potential for predicting the attainment of EASI-75 by week 8 after treatment.

Introduction

Atopic dermatitis (AD) is a type of chronic, recurrent, inflammatory dermatological condition. Previous studies have demonstrated that genetic and environmental influences, impaired skin barrier, microbial imbalance on the skin and immune dysfunction collectively contribute to the pathogenic mechanisms of this condition (1-3). These genetic and environmental elements enable skin microbes to penetrate the compromised epidermal barrier, instigating immune disturbances that exacerbate the condition associated with the deteriorated skin barrier function (4-8). The dysregulation of T cell subsets is crucial to the development of AD. The shift towards T helper (Th) 2 cells increases the level of secretion of IgE by B cells and plasma cells, leading to allergic inflammation and itchiness. AD has also been linked to certain types of allergic disorders, such as food allergies, allergic rhinitis and asthma (9). In acute AD lesions in adults, Th22 subsets become highly active, and the increased production

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Key words: atopic dermatitis, dupilumab, serum biomarkers, circulating T helper cell subtypes, prospective cohort study

of IL-22 by these cells can result in epidermal thickening and further barrier damage (10,11). Th17 cell subsets may have a less critical role in the pathogenesis of AD and could exert protective effects, helping to regulate the skin's immune response and maintain the skin's health status (12). Previously published Chinese clinical guidelines indicate the presence of diverse subtypes of skin inflammation in patients with AD, with Th2-type inflammation observed in children with AD, a combination of Th2/Th22-type inflammation in adults and a Th2/Th17-type mixed inflammation in Asian patients (13,14).

A number of AD-related biomarkers have been identified, and these biomarkers are important for the understanding of AD pathogenesis, identifying patient phenotypes, evaluating clinical therapeutics and patient prognoses. *Staphylococcus aureus* enterotoxin A (SEA), a superantigen secreted by *S. aureus*, can mediate IgE immune responses to cause chronic inflammation and aggravate Th2-type AD (15). SEA-induced IgE can activate mast cells, basophils, eosinophils and dendritic cells, all of which express high-affinity IgE receptors, and SEA can induce high expression of IL-22, aggravating immune inflammatory responses (16,17). Human β-defensins (HBDs), which are components of the skin chemical barrier, have both antimicrobial activity and complex immunoregulatory functions. It has been reported that HBD2 can inhibit the damage caused by *S. aureus* proteases to the skin barrier (18). In patients with Th2-type AD, the HBD levels in skin lesions are markedly reduced by IL-4 and IL-13 compared with those in healthy individuals or patients with psoriasis, whereas serum HBD levels are significantly elevated and correlate with disease severity (19,20). Thymus and activation-regulated chemokine (TARC) and C-C motif chemokine ligand 17 facilitate the homing of Th2 cells, and their serum concentrations are associated with AD severity (21,22). Presently, TARC serves as the most effective biomarker for monitoring AD treatment responses and ensuring treatment success (23).

The role of molecular targeted therapy in treating AD is of clinical importance. Dupilumab, a human monoclonal antibody targeting the IL-4 and IL-13 receptor α subunit (IL-13Rα) signaling pathways, has been reported to be effective for managing moderate-to-severe AD and has been recognized as a safe treatment (24). Dupilumab enhances skin barrier functions, diminishes epidermal thickness in damaged skin, reduces epidermal hyperplasia, increases the expression levels of genes related to barrier and differentiation, suppresses the expression of genes associated with type 2 inflammation, lowers serum levels of the Th2 chemokine TARC and total allergen specific IgE, improves skin flora balance, reduces *S. aureus* colonization and increases microbial diversity (25,26).

However, some patients with AD still experience unsatisfactory outcomes with dupilumab in clinical settings (27). The potential involvement of heterogeneity in this disease warrants further investigation. The present study aimed to assess the therapeutic impacts of dupilumab on patients with AD, examining its effects on serum TARC, HBD2 and SEA-IgE levels and peripheral blood Th cells to provide information to refine individualized and precise treatment strategies for patients with AD.

Materials and methods

Patients and study design. The present study included patients with AD who were treated with dupilumab in Guangzhou Dermatology Hospital (Guangzhou, China) between May 2021 and January 2022. The inclusion criterion was patients with AD who were diagnosed according to the Williams criteria (total IgE, >87 IU/ml) and treated with dupilumab for the first time (28). The exclusion criteria were as follows: i) Pregnant women; ii) patients with serious diseases, such as active infections, autoimmune disease, endocrine disease, cardiovascular and cerebrovascular disease or abnormal liver and kidney function diseases; iii) patients who used corticosteroids or immune inhibitors within the previous 28 days; iv) vaccinated patients; and v) patients who were allergic to dupilumab. A total of 7 male and 6 female patients with AD, aged 12 to 57 years (mean ± SD, 29.8±14.2 years), were recruited, 12 of whom had a personal or family history of allergic disease.

Dupilumab (300 mg/vial; Sanofi S.A.) was used in the present study. The standard treatment regimen was based on the manufacturer's instructions for use in China and on Chinese clinical guidelines (29). The prospective cohort study enrolled patients with AD aged ≥12 years and weighing >60 kg. Patients received subcutaneous injections of 600 mg of dupilumab (administered as two 300 mg injections) at week 0, followed by 300 mg of dupilumab at weeks 2, 4 and 8. Participants were required to complete questionnaires, and their clinical data were assessed using Scoring Atopic Dermatitis index (SCORAD), objective (Obj)-SCORAD, Eczema Area and Severity Index (EASI), Itch Numeric Rating Scale (NRS), Dermatology Life Quality Index (DLQI), Patient Oriented Eczema Measure (POEM) and Atopic Dermatitis Control Tools (ADCT) scores. Blood samples were collected prior to the administration of dupilumab and analyzed using ELISA and flow cytometry. All participants completed 8 weeks of prescribed dupilumab therapy.

The present study was reviewed and authorized by the Ethics Committee of Guangzhou Dermatology Hospital (approval no. 201913). Written informed consent was obtained from all patients or their legal guardians.

EASI score. The severity of the symptoms of the skin lesions in different parts of the patient, the size of the area occupied, and the proportion of the affected area compared with the total body area were used to calculate the EASI (Table SI). The specific calculation methods were as follows.

Clinical manifestation score. The severity of four clinical manifestations were scored, which included erythema, infiltration/oedema or papule, epidermal exfoliation and lichen planus. The severity of each clinical manifestation was scored on a scale of 0-3: 0, not severe; 1, mild; 2, moderate; and 3, severe. Half-point increments (0.5 points) were allowed between the different symptom scores, and the total score for each affected site was obtained by summing the individual scores.

Skin lesion area size score. The body was divided into four parts: Head and neck, upper limbs, trunk and lower limbs. The area covered by the lesions in the four body parts was converted into the proportion of the body part occupied for scoring and was estimated by using the size of the patient's individual palm as 1% of the body surface area. The score was

provided on a scale of 0-6 as follows: 0, no rash; 1, <10% of the area; 2, 10-19% of the area; 3, 20-49% of the area; 4, 50-69% of the area; 5, 70-89% of the area; and 6, 90-100% of the area.

Calculating the total score. The total score of each site was calculated as follows: Total score of clinical manifestations x area score x area proportion coefficient. Then, the total score of each site was added to the total score of the severity of EASI lesion symptoms. The area ratio coefficients of each site were different according to the proportion of each part of the body to the whole body in children aged >8 and 0-7 years.

SCORAD and obj-SCORAD scores

Scoring of the extent of skin lesions. The body surface area was divided according to different ages and parts of the body. For adults, the surface area was divided as follows: Head and neck and bilateral upper arms, 9.0%; anterior and posterior trunk, 13.5%; and bilateral lower limbs, 22.5%. For children aged <14 years, the body was divided as follows: Head and neck and bilateral upper arms, 9.0%; and the anterior and posterior trunk and the bilateral lower limbs, 18.0%. For children aged <2 years, the body was divided as follows: Head and neck, 17.0%; bilateral upper arms, 9.0%, the trunk 18.0%; and bilateral lower limbs, 12.0%. A total of 1 point for each 1% of the body surface area involved in the lesions was scored, and the total range of lesions was scored as A.

Severity of skin lesions. A total of 6 signs were scored for severity, including erythema, papules or oedema, oozing or crusting, epidermal exfoliation, erythroderma and dry skin (uninvolved skin only). Each sign was scored as 0-3 depending on the severity of the lesions, and the total severity of the lesions was scored as B.

Itching and degree that sleep was affected. The visual analogue scoring method was used to evaluate the degree of itching and how sleep was affected. Each item was scored as 0-10 points, with 0 corresponding to no itching/no sleep disturbance and 10 corresponding to the worst itching that the patient could imagine/no sleep. The average score of itching and sleep disturbance degree of the prior 3 days scored as C.

Total SCORAD score. The total SCORAD score was calculated as follows: A/5+7B/2+C. Grading was classed as mild (<25 points), moderate (25-50 points) or severe (≥50 points).

Obj-SCORAD score. The Obj-SCORAD score was calculated as follows: A/5+7B/2. Grading was classed as mild (<15 points), moderate (15-40 points) or severe (≥40 points).

NRS score. Patients were asked to select the most appropriate number from 0-10 that was considered an approximate representation of their level of affectedness according to the level of itching experienced over the previous 24 h.

DLQI score. The DLQI score was used to measure the extent to which the patient's daily life was affected in the past week due to the skin disorder (Table SII). This score was assessed based on the answers to 10 questions, with 1 point awarded for each answer and 0 points for an incorrect or irrelevant response. The total score ranges from 0-30 points.

POEM score. Patients were asked to quantify the frequency of occurrence of seven eczema-related symptoms over the prior week (Table SIII). Each associated symptom was assigned a grade on a 5-point scale (scored as 0-4). The total score ranged from 0-28 points.

ADCT score. The patients evaluated 6 potential issues related to the AD over the prior week (Table SIV). Each item was scored on a scale of 0-4, with a total score ranging from 0 to 24. A total score of <7 was indicative of disease control, while a score of ≥7 was indicative of disease activity.

ELISA. The peripheral blood of patients with AD was collected, and the serum was separated by centrifugation at 1,800 x g at 25˚C for 15 min. According to the manufacturer's instructions, ELISA kits were used to detect the serum levels of SEA-IgE (Jiangsu ELISA Industry Co., Ltd.; cat. no. MM-51969H2), HBD2 (Cloud-Clone Corp; cat. no. SEA072Hu) and TARC (RayBiotech, Inc.; cat. no. IQH-TARC-1). The optical density at 450 nm was detected using a microplate reader (NanJing DeTie Laboratory Equipment Co., Ltd.) and the data were analyzed using the standard curve.

Flow cytometry. Mononuclear cells from the peripheral blood mononuclear cells (PBMCs) of patients with AD were separated and cultured under standard conditions in RPMI-1640 medium (Gibco; Thermo Fisher Scientific, Inc.; cat. no. 11875) supplemented with 10% fetal bovine serum (Gibco; Thermo Fisher Scientific, Inc.; cat. no. 16000) and 1% penicillin-streptomycin (Gibco; Thermo Fisher Scientific, Inc.; cat. no. 15140). Cells were cultured at 37˚C in a humidified incubator with 5% CO_2. PBMCs were stimulated using anti-CD3/CD28 beads (Dynabeads; Invitrogen; Thermo Fisher Scientific, Inc.; cat. no. 11131D) at a 1:1 bead-to-cell ratio and incubated for 4-6 h in the presence of 10 μg/ml brefeldin A (BioLegend, Inc.; cat. no. 420601) to block cytokine secretion. The following antibodies were used for flow cytometric analysis: FITC-conjugated anti-CD3 (BioLegend, Inc.; cat. no. 981002; diluted 1:100), PerCP/Cyanine 5.5-conjugated anti-CD8 (BioLegend, Inc.; cat. no. 980918; diluted 1:100), APC-conjugated anti-IFN-γ (BioLegend, Inc.; cat. no. 506510; diluted 1:100), PE-conjugated anti-IL-22 (BioLegend, Inc.; cat. no. 366703; diluted 1:100), APC-conjugated anti-IL-4 (BioLegend, Inc.; cat. no. 500811; diluted 1:100), and PE-conjugated anti-IL-17A (BioLegend, Inc.; cat. no. 512305; diluted 1:100). PBMCs were stained with the antibodies and analyzed using a FACSCanto II flow cytometer (BD Biosciences; cat. no. 642198) equipped with BD FACSDiva™ software (version 9.0; BD Biosciences). Th1 cells were defined as $CD3^+CD8^-IFN\text{-}\gamma^+$, Th2 cells as $CD3^+CD8^-IL\text{-}4^+$, Th17 cells as $CD3^+CD8^-IL\text{-}17A^+$ and Th22 cells as $CD3^+CD8^-IL\text{-}22^+$.

Statistical analysis. Data analysis was performed using SPSS (version 25.0; IBM Corp.) and GraphPad Prism (version 9; Dotmatics). Normally and non-normally distributed continuous variables were expressed as the mean ± SD and median with interquartile ranges (Q_1, Q_3), respectively. The statistical plotting process included creating Tukey box plots, where values exceeding 1.5 times the interquartile range above the upper quartile are defined as outliers. A two-way ANOVA was used to analyze clinical data obtained with or without treatment. Patient data lost to follow-up were either excluded or incorporated into a mixed-effects fitting model. A total

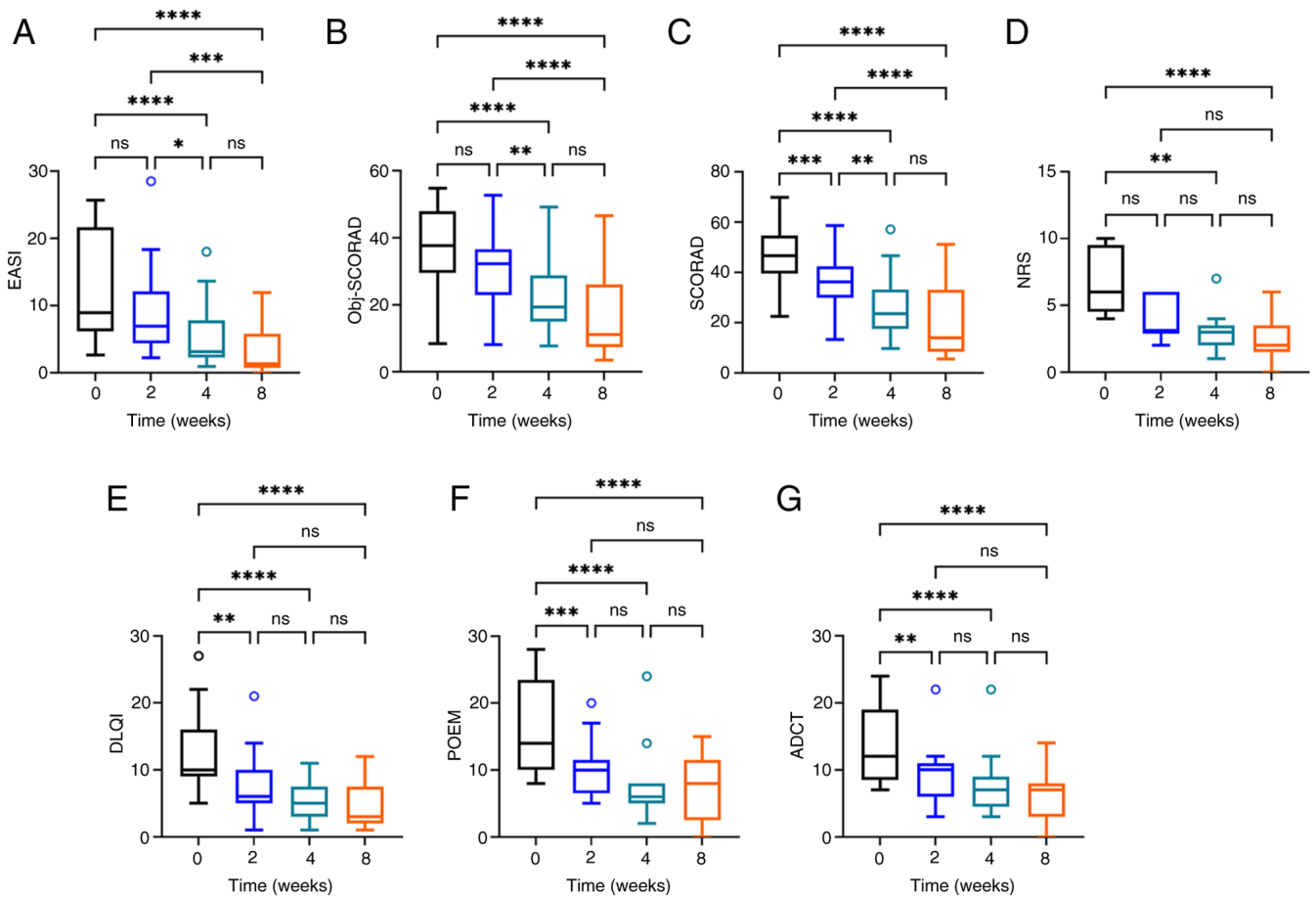

Figure 1. Comparison of the clinical scores of patients with atopic dermatitis treated with dupilumab. (A) EASI score, (B) Obj-SCORAD, (C) SCORAD, (D) NRS, (E) DLQI and (F) POEM scores were analyzed using a repeated-measures ANOVA followed by Sidak's test. (G) ADCT scores were analyzed using Friedman's test followed by Nemenyi's test. n=13. Box plots represent median and interquartile range (IQR). Whiskers extend to the most extreme data points within 1.5 times the IQR. Points beyond the whiskers are considered extreme values. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001. ns, not significant. Data are presented as the median with quartiles. EASI, Eczema Area and Severity Index; SCORAD, Scoring Atopic Dermatitis index; Obj-SCORAD, objective-SCORAD; NRS, Itch Numeric Rating Scale; DLQI, Dermatology Life Quality Index; POEM, Patient Oriented Eczema measure; ADCT, Atopic Dermatitis Control Tools.

of 2 patients were excluded from the analysis due to missing follow-up data. In instances where the data normality test was unsuccessful due to the presence of missing data, patients with missing data were excluded and Dunn's multiple comparisons test was employed for multiple comparisons. If the D'Agostino & Pearson normality test was passed, a linear mixed-effects model was fitted to avoid the exclusion of patients with missing data. Multiple comparisons were performed using two-way mixed or repeated measures ANOVA followed by Sidak's test. For data that did not pass the normality test, Friedman test was used for group comparisons, followed by Nemenyi's test for multiple comparisons. Spearman correlation analysis was performed, and according to the correlation coefficient (r value), correlations were defined as strong ($r \geq 0.70$), moderate ($r=0.4$-0.7) or weak ($0.1 \leq r \leq 0.4$). $P<0.05$ was used to indicate a statistically significant difference.

Results

Evaluation of the therapeutic effect of dupilumab on patients with AD. Following dupilumab treatment, a total of 52 follow-up questionnaires were collected and analyzed using EASI, Obj-SCORAD, SCORAD, NRS, DLQI, POEM and ADCT scores (Table SV). Comparative analyses of the clinical scores of patients across the follow-up visits at weeks 0, 2, 4 and 8 were performed (Fig. 1). Initially, based on EASI scores, AD patient severity was categorized as mild, moderate or severe, with 5 patients in each group at week 0. Following dupilumab therapy, the number of patients with mild-grade AD increased ($P<0.05$), with no patients exhibiting severe-grade AD by week 8 (mild:moderate, 11:2) (Fig. 2A). The EASI scores for each group progressively decreased (Fig. 2B) and by week 8 of treatment, 12 (92.3%), 7 (53.8%) and 2 (15.4%) patients achieved EASI-50, EASI-75, and EASI-90 (representing ≥50, ≥75 and ≥90% improvement in the patient's EASI score compared with baseline), respectively (Fig. 2C). These results suggested that standard dupilumab therapy may cause significant therapeutic effects on patients with AD.

Changes in the serum levels of SEA-IgE, HBD2 and TARC. Blood samples were obtained prior to dupilumab injection, and ELISA kits were used to assess the serum levels of SEA-IgE, HBD2 and TARC in patients with AD at weeks 0, 2, 4, and 8

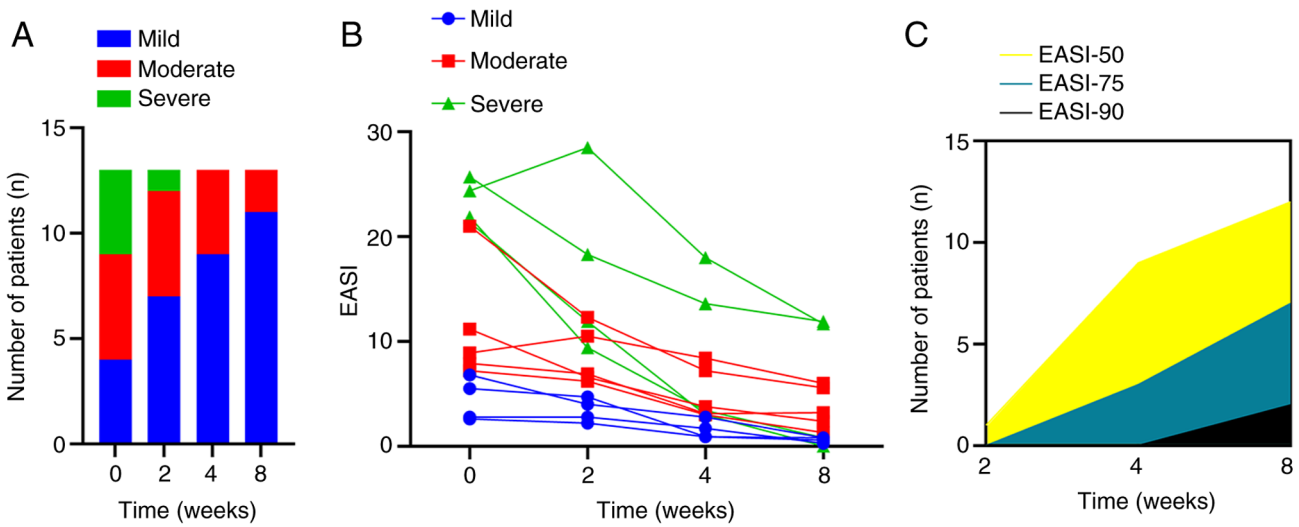

Figure 2. Therapeutic effect of dupilumab on patients with AD based on EASI scores. (A) Number of patients with AD with different severity grades (mild, moderate and severe) at weeks 0, 2, 4 and 8. (B) Changes in the EASI scores of patients with AD with different severity grades (mild, moderate and severe) at weeks 0, 2, 4 and 8. (C) Changes in the number of patients with AD who achieved EASI-50, -75 or -90 at weeks 0, 2, 4 and 8. n=13. EASI, Eczema Area and Severity Index; AD, atopic dermatitis.

(Table SVI). A significant decrease in TRAC levels was demonstrated at weeks 2 (P<0.05), 4 (P<0.001) and 8 (P<0.0001) compared with week 0, and week 2 (P<0.01) compared with week 8 (Fig. 3A). Serum TARC levels were notably elevated in patients with severe AD (Fig. 3D). These findings suggested that TARC may have potential as a biomarker for monitoring the progression of dupilumab treatment in patients with AD. However, changes in serum HBD2 and SEA-IgE levels were not significant following treatment with dupilumab, with some patients consistently exhibiting high levels of these serum biomarkers.

Changes in the proportions of peripheral blood Th cell subtypes. Peripheral blood was collected prior to dupilumab treatments and flow cytometry was used to ascertain the proportions of Th1, Th2, Th17 and Th22 cells in patients with AD (Table SVII; Figs. 4A and S1). Analysis of peripheral blood Th2 cell ratios in patients with mild, moderate or severe disease before dupilumab treatment during the first 8 weeks of treatment was performed (Figs. 4C and S2). Before dupilumab treatment, patients with mild AD exhibited a significantly higher proportion of Th2 cells compared to those with moderate or severe AD (Table SVII). During the 8-week treatment period, Th2 cell proportions increased significantly in patients with mild and moderate AD (P<0.05). This increase was particularly pronounced in the first 4 weeks of treatment, indicating a strong response to dupilumab's mechanism of action (Fig. 4C). By week 8, Th2 cell proportions had stabilized, especially in moderate disease patients, suggesting a shift towards a more balanced immune profile (Fig. S2). The proportions of Th1 cells remained largely unchanged across all severity groups throughout the 8-week period (P>0.05), indicating that dupilumab's effects are more specific to Th2 cell regulation rather than a broad modulation of Th1-mediated immunity (Fig. 4A). The proportions of Th17 cells showed only minor fluctuations during treatment, with a slight reduction in some patients, though these changes were not statistically significant (P>0.05). This suggests that dupilumab does not strongly impact the Th17 axis in AD (Fig. S1). Similar to Th17 cells, Th22 cell proportions exhibited minimal variability throughout the treatment period, with no significant reduction or increase (P>0.05), indicating that dupilumab does not notably affect Th22 cells (Fig. S1). There were no significant changes in the proportions of Th1, Th2, Th17 and Th22 cells and the Th2/Th1 ratio following treatment (Fig. 4D-G).

Correlation analysis of clinical scores, serum biomarker levels and Th cell proportions after dupilumab therapy. Correlation analysis was used to determine the relationships between the clinical scores, serum biomarker levels and Th proportions (Fig. 5). No strong correlation was observed between physicians' objective ratings and patients' subjective assessments, reflecting differences in their evaluation criteria and perceptions. The correlation between TARC and certain clinical scores was moderate, with r values of 0.60 (P<0.05) and 0.67 (P<0.001) when comparing TARC with EASI and SCORAD, respectively. The correlation between TARC and the biomarkers tested was not statistically significant. The correlation between Th1 and Th17 cells was weak (r=0.39; P<0.01) and was modest between Th2 and Th22 cells (r=0.56; P<0.05). The correlation between Th22 cells and NRS was weak (r=0.34; P<0.01).

Analysis of the efficacy of dupilumab after 8 weeks of treatment. Patients were categorized into rapid or slow groups depending on whether they achieved EASI-75 scores by week 8. During the 8 weeks of dupilumab therapy, 7 patients achieved EASI-75 scores and were classified as the rapid group, and remaining 6 patients did not achieve EASI-75 scores and were classified as the slow group. The SCORAD scores decreased significantly from week 0 to week 2 in the slow group (P<0.05), and this decrease was maintained through week 8. By contrast, the rapid group exhibited a more substantial and consistent

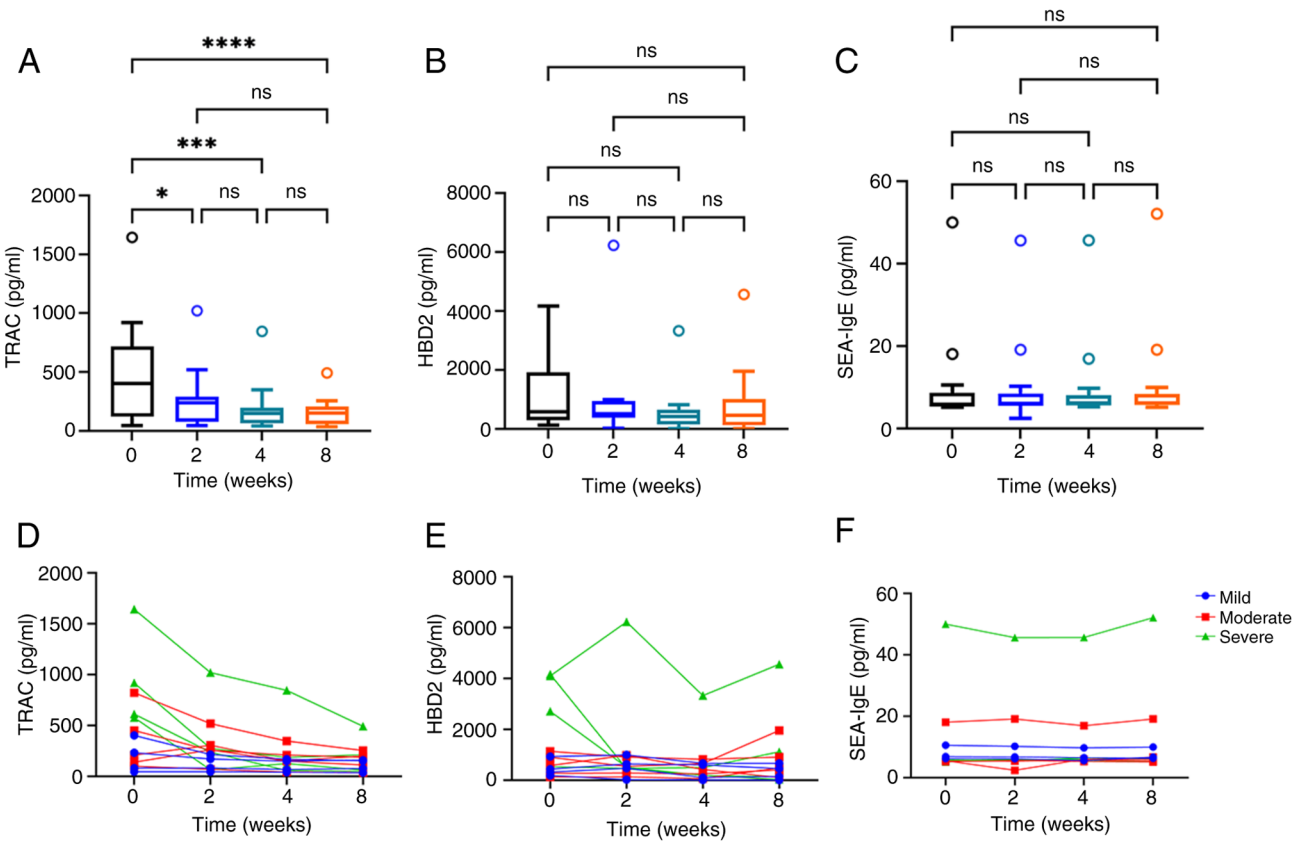

Figure 3. Changes in the serum biomarkers levels of patients with AD treated with dupilumab. Levels of (A) TARC, (B) HBD2 and (C) SEA-IgE in patients with AD treated with dupilumab. Data were analyzed using a repeated-measures ANOVA followed by Sidak's test. Levels of (D) TARC, (E) HBD2 and (F) SEA-IgE in untreated patients with different severities of AD. n=13. *P<0.05; ***P<0.001; ****P<0.0001. Data are presented as the median with quartiles ns, not significant; SEA-IgE, IgE against *Staphylococcus aureus* enterotoxin A; HBD2, human β-defensin 2; TARC: thymus and activation-regulated chemokine.

reduction in SCORAD scores from week 0 to weeks 2, 4, 6 and 8 (P<0.05, P<0.01, P<0.001 and P<0.0001, respectively). The SCORAD scores increased slightly by week 12 in both groups, but the differences were not statistically significant (P>0.05) (Fig. 6A). There was no significant difference between the Obj-SCORAD and NRS scores of the rapid group compared with the slow group (Fig. 6D and F). At week 2, the proportion of Th17 cells in the rapid group was significantly lower compared with that in the slow group (Fig. 6H; P<0.01; Fig. S3).

Discussion

The EASI-50 is an effective index for evaluating the minimum significant change eczema area and severity index in AD (30). In the present study, the EASI-50 of patients with AD receiving dupilumab therapy reached 92.3% at week 8, and no adverse reactions were reported, indicating the efficacy and safety of dupilumab in the treatment of patients with AD. The outliers observed at weeks 2 and 4 may be related to the slow response of some patients to dupilumab treatment. When using Obj-SCORAD scores to evaluate the signs and symptoms of patients with AD (such as lesions, erythema and lichenification), the score changes exceeded some patients' levels of improvement, suggesting that Obj-SCORAD may have better response capability. However, there was no significant difference in Obj-SCORAD scores between week 4 and week 8, indicating that after achieving relatively stable treatment effects within the first 4 weeks, further improvement in subsequent treatment is needed to achieve complete remission. Currently, dupilumab is recommended for the treatment of severe AD, and treatment guidelines have been extended to include moderate to severe AD in patients >6 years old. In the present study, EASI scores significantly decreased in patients with mild, moderate and severe AD, suggesting that dupilumab may also hold promise for treating mild AD.

In line with the Harmonizing Outcome Measures for Eczema guidelines, clinical observations of patients with AD should include symptom scores reported by both physicians and patients, alongside patient quality of life and long-term disease control scores (31,32). In the present study, patients reported low NRS and POEM scores after 2 weeks of treatment, indicating improved control of itching and other symptoms, such as skin lesions, redness, swelling, lichenification, dryness, cracking and exudation, in the early stages of dupilumab therapy. Patient quality of life, assessed by DLQI scores, also showed improvement after 2 weeks, suggesting that rapid symptom control may be achieved with dupilumab therapy. However, ADCT scores at weeks 4 and 8 indicated that half of the patients still exhibited disease activity (≥7 patients), with extreme scores for multiple indices, underscoring the heterogeneity of patients with AD, in addition to scores obtained using subjective evaluations. The appearance of extreme scores suggested the existence of exceptional

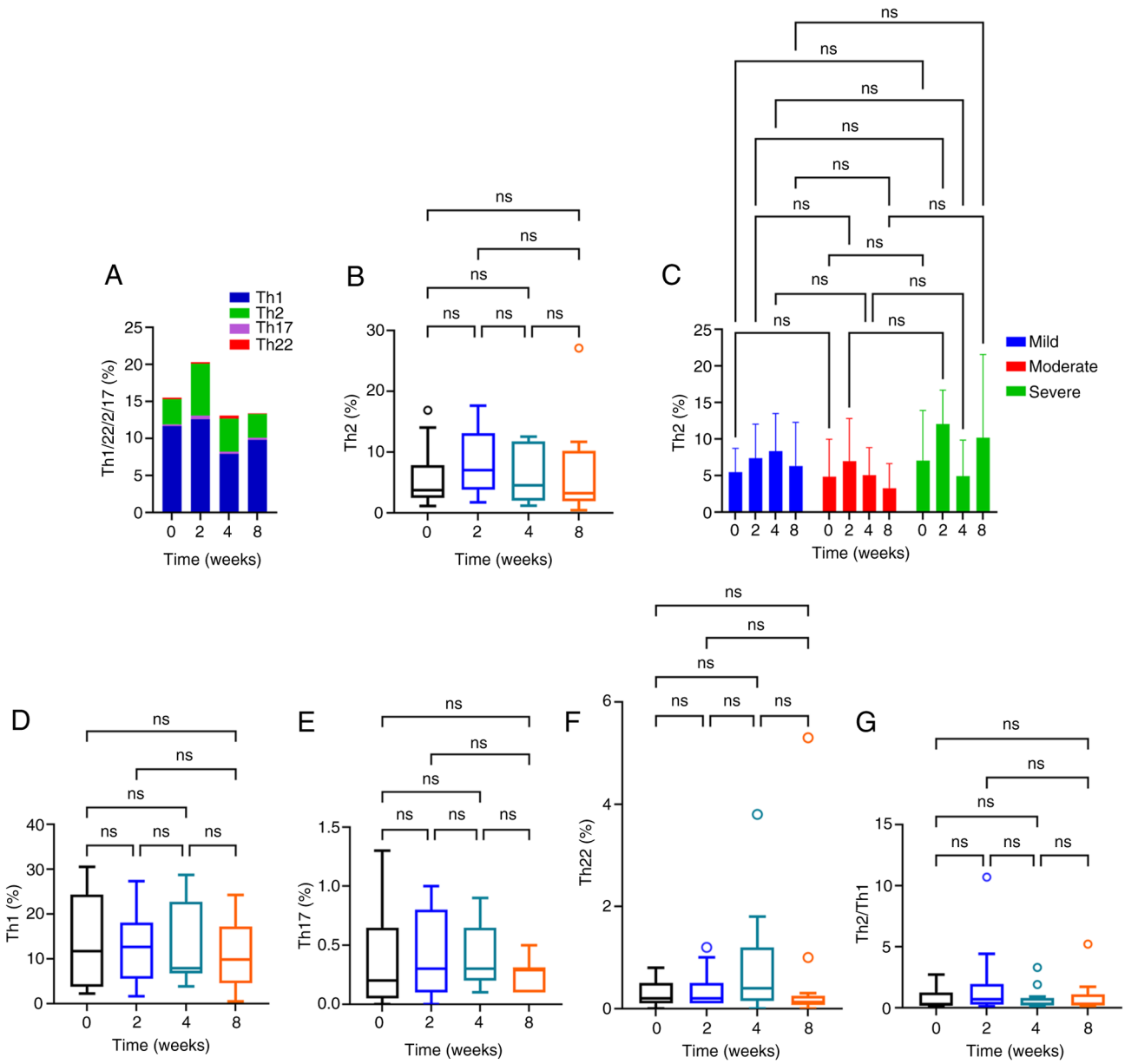

Figure 4. Analysis of the proportion of peripheral blood Th1, Th2, Th17 and Th22 cells in patients with atopic dermatitis treated with dupilumab. (A) The median proportion of peripheral blood Th1, Th2, Th17 and Th22 cells. (B) Compares the proportion of Th2 cells over 0, 2, 4, and 8 weeks of treatment. Data were analyzed using a repeated-measures ANOVA followed by Sidak's test. (C) Changes in the proportion of Th2 cells with different Eczema Area and Severity Index grades (mild, moderate or severe) at weeks 0, 2, 4 and 8 of treatment. Data were analyzed using a two-way mixed ANOVA followed by Sidak's test. Comparison of the proportion of (D) Th1, (E) Th17, (F) Th22 and the (G) Th2/Th1 ratio. n=13. Data in a-b and d-g are presented as the mean ± SD. Data in c are presented as the median with quartiles. ns, not significant; Th, T helper.

cases (those with extreme scores, values or metrics) within the present sample group. Further observation of these cases is necessary to enhance the representativeness of the sample and the reliability of the study. Compared with previous studies, the proportions of patients who achieved EASI-50 and EASI-75 at weeks 2, 4 and 8 were greater in the present study, which may be related to the low baseline EASI of the present patients and the differences in sex, age and baseline total IgE levels (33-35). In the present study, dupilumab rapidly relieved subjective symptoms and objective signs in patients with AD, but it did not benefit all patients.

The serum TARC levels demonstrated a strong correlation with the clinical scoring methods used in the present study obtained from either medical professionals or patients, and the findings of the present study aligned with those reported by a previous study (21). The serum levels of TARC continuously decreased during dupilumab therapy, and the correlation with the EASI score was significant and parallel, the correlation with the Obj-SCORAD score was significant, but the changes appeared to lag behind, and the correlations with the NRS, DLQI, POEM, and ADCT scores were significant, indicating that these scores could be useful for clinical follow-up. Moreover, the serum HBD2 level was correlated with the severity of disease, and there was a negative correlation between SEA-IgE levels and clinical objective scores. However, the changes in the serum HBD2 and SEA-IgE levels were not significant after dupilumab therapy, indicating that dupilumab may have low clinical value for disease follow-up.

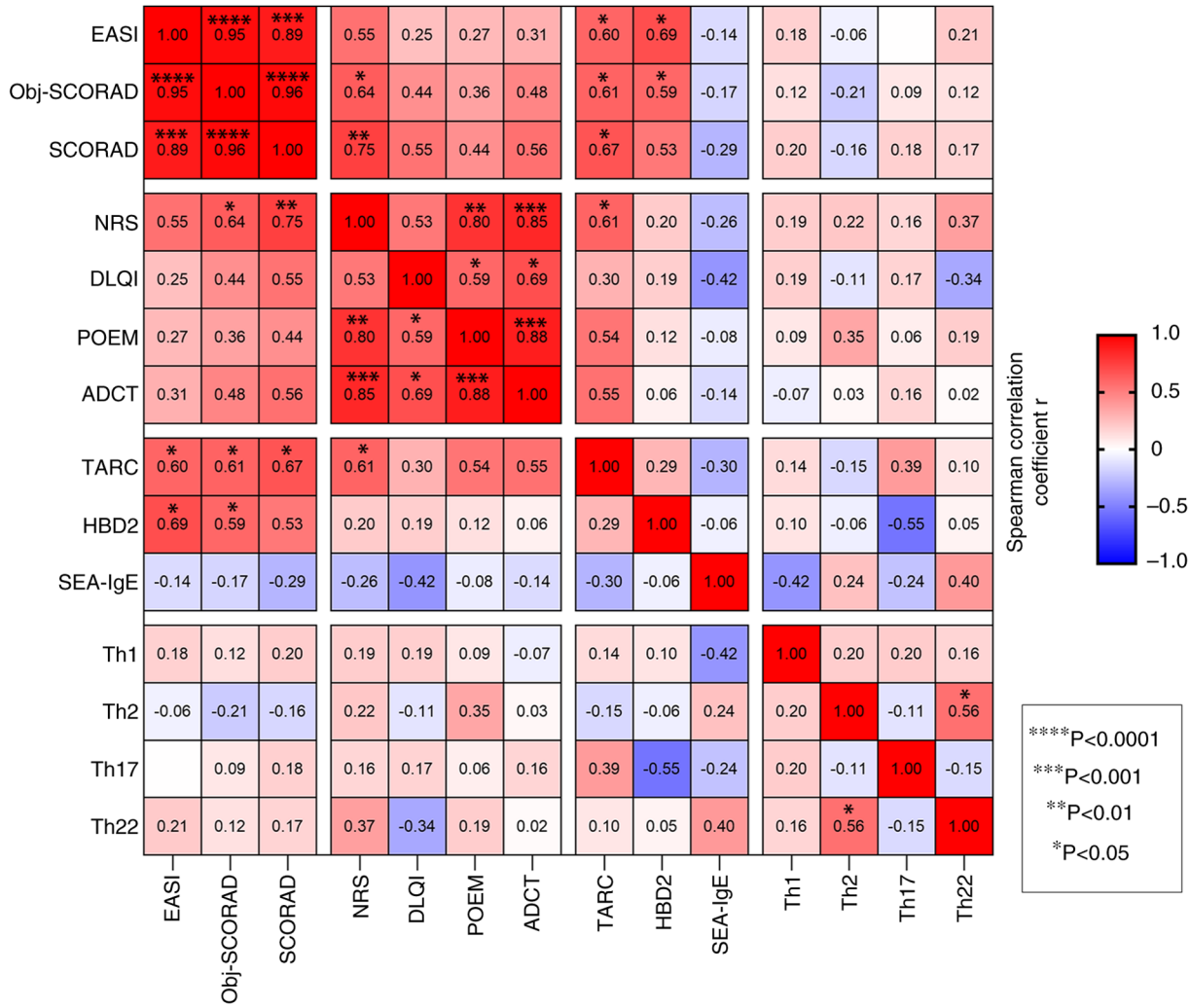

Figure 5. Correlation analysis of clinical scores, serum biomarkers and peripheral blood Th cells. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001. Th, T helper; EASI, Eczema Area and Severity Index; SCORAD, Scoring Atopic Dermatitis index; Obj-SCORAD, objective-SCORAD; NRS, Itch Numeric Rating Scale; DLQI, Dermatology Life Quality Index; POEM, Patient Oriented Eczema measure; ADCT, Atopic Dermatitis Control Tools; SEA-IgE, IgE against *Staphylococcus aureus* enterotoxin A; HBD2, human β-defensin 2; TARC: thymus and activation-regulated chemokine.

Furthermore, consistently elevated levels of serum HBD2 and SEA-IgE were demonstrated in certain patients with AD. However, due to the limited number of patients included in the present study, substantial analysis of the results was not feasible, which restricted the clinical utility for disease follow-up. Nonetheless, prior research indicates a close association between serum SEA-IgE levels and *S. aureus* colonization, with *S. aureus*-targeted treatment proving effective for AD management (36,37). This suggests the presence of clinically diverse patients with AD who exhibit variations in serum HBD2 and SEA-IgE levels. Further data collection and analysis of such patients could potentially reveal new AD subtypes or treatment approaches.

Based on the findings of the present study, the median proportions of Th1 and Th2 cells in patients with AD increased at week 2, while the proportions of Th17 and Th22 cells increased at week 4. An increase in Th2 cells indicates the selective upregulation of the Th2 immune axis during IL-4Rα blockade (38). Additionally, a significant correlation was observed between Th1 and Th17 cells, as well as between Th2 and Th22 cells, which may indicate the mixing of the Th2 and Th22 subtypes of skin inflammation, or the constraints of the flow cytometry design utilized in the present study. However, further studies are warranted to determine the clinical significance of these results. The sequential increase and relationships of Th cells in patients with AD suggested that attention should be paid to the period from the weeks 2-4 of dupilumab therapy, whilst further studies are necessary to explore subsequent therapeutic effects. A correlation was demonstrated between the proportion of Th22 cells and NRS score. This could be linked to the fact that T cells producing IL-22 also produce IL-31, affecting skin barrier function (39-41). Therefore, Th22 cell-related biomarkers may offer insights into exploring the pathogenesis or discovery of novel methods to treat itching in patients with AD.

Patients with AD were categorized into rapid and slow groups based on whether they achieved EASI-75 scores by week 8 of dupilumab treatment. The SCORAD scores in the rapid remission group were monitored for 8 weeks, while those in the slow remission group exhibited a significant decrease at week 2, with remission lagging behind, irrespective of AD severity before treatment. Similar patterns were observed in

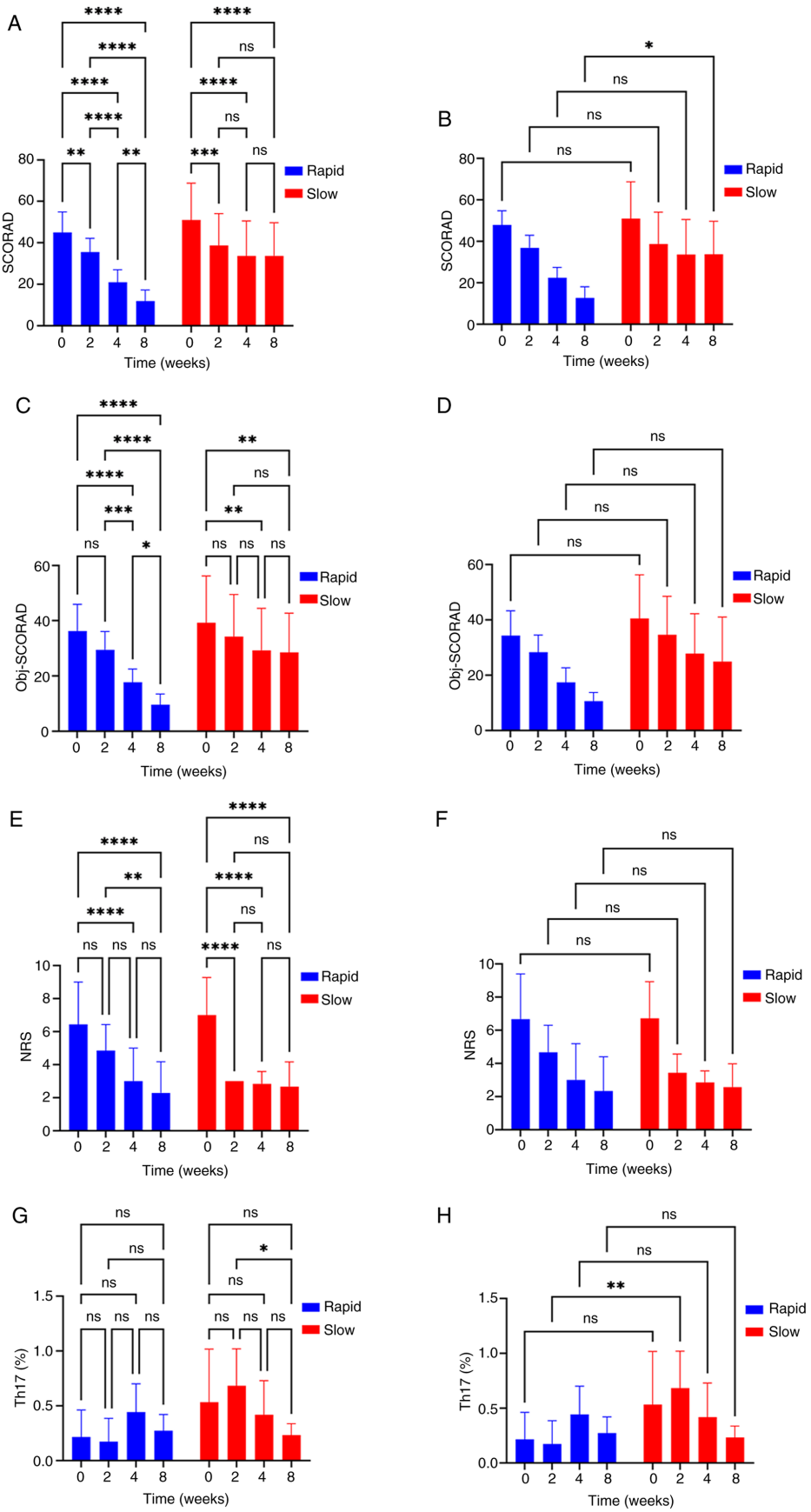

Figure 6. Intra-group and inter-group analysis of the rapid and slow therapeutic effects of dupilumab on patients with atopic dermatitis. (A and B) SCORAD, (C and D) Obj-SCORAD, (E and F) NRS and (G and H) Th17 cells. Data were analyzed using a two-way mixed ANOVA followed by Sidak's test. Subfigures e and f were analyzed using Friedman's test and the Nemenyi/Mann-Whitney tests, followed by the Bonferroni correction. The quantification graphs presented correspond to the same experimental groups but different statistical analyses have been performed. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001. Data are presented as the mean ± SD. ns, not significant; SCORAD, Scoring Atopic Dermatitis index; Obj-SCORAD, objective-SCORAD; NRS, Itch Numeric Rating Scale; Th, T helper.

Obj-SCORAD scores reported by physicians, with remission occurring at week 4 and continuing in the rapid group of patients. However, in the slow group, remission also lagged until week 2, and a number of patients experienced recurrence of symptoms by week 4. Although the slow group showed an decrease in certain symptoms by week 8, the disparity in the speed and extent of symptom relief between the rapid and slow groups suggested that therapy plan adjustments (such as dose adjustment, increased treatment frequency, combination therapy, individualized treatment plan, close monitoring and follow-up) should be considered between weeks 2 and week 4. Similarly, a decrease in the NRS score in the rapid group occurred at week 4, while the decrease in the NRS score in the slow group was slower after strong control of disease symptoms was achieved (NRS ≤3) at week 2, which may potentially be related to the lack of alleviation of symptoms. After week 4, both the rapid and slow groups experienced improved control of pruritus, which improved patient compliance with the clinical application of dupilumab. In the rapid group, SCORAD scores significantly decreased from week 0 to week 2, whilst changes in Obj-SCORAD and NRS scores were less apparent, possibly due to an improvement in the sleep status of patients or the accumulation of subtle score changes. Hence, it could be recommended that SCORAD scores should be measured for the comprehensive evaluation and follow-up of patients with AD undergoing dupilumab therapy. However, the reason for the slow recovery group's lack of improvement or worsening of symptoms after week 2 remained unclear. This could potentially be due to the dosing regimen of dupilumab decreasing from 600 mg at week 0 to 300 mg at week 2.

The patients in the slow response group could be identified by week 4 or earlier, as by week 2, the slow response group exhibited a notably increased proportion of Th17 cells compared with the rapid response group. A previous study reported that a greater prevalence of Th17 cells in the peripheral blood of patients with AD compared with healthy individuals, particularly in acute AD lesions compared with both chronic AD lesions and healthy skin (42). Additionally, Th17 polarization is more pronounced in the skin lesions of Asian patients with AD (14). Hence, it could be suggested that some patients with AD with elevated IgE levels experienced an increase in the proportion of Th17 cells by week 2 after initial dupilumab injection, leading to stagnation or relapse by week 4 and a subsequent failure to achieve EASI-75 by week 8. Moreover, a positive correlation has been reported between SCORAD scores and Th2 cytokine levels in patients with exogenous AD (43). However, the total serum IgE level of patients in the present study exceeded that of healthy individuals before treatment (>87 IU/ml), and the majority of patients reported a personal or family history of allergy. In conclusion, further research is warranted to ascertain a potential causal link between stagnation after week 2 in the slow response group and an increase in Th17 cell proportion. Monitoring Th17 cell proportions of patients during dupilumab treatment could aid in identifying potential patients in the slow response group and allow clinicians to effectively amend their therapeutic strategy. Further research is needed to determine the threshold of Th17 cell proportion increase that indicates treatment effectiveness, and to optimize the treatment approach based on this information.

Although previous studies have dynamically evaluated the therapeutic effect of dupilumab on AD (44,45), the present study provided a more thorough understanding of the changes in Th cells in patients with AD using intracellular staining assays and analyzing the predictive role of heterogeneity of patients with AD over the course of dupilumab treatment. The present study demonstrated that a failure to achieve EASI-75 by week 8 of treatment may be associated with an increased percentage of Th17 cells in peripheral blood at week 2 during the course of dupilumab treatment. However, the present retrospective study, conducted at a single center, had a relatively small sample size, potentially limiting the applicability of its findings. Further exploration of the results in a larger cohort of patients may be necessary to confirm the findings. The present study exclusively utilized the standard dupilumab treatment regimen and omitted other treatments or a control group, making it impossible to compare the efficacy of various treatment protocols. Furthermore, due to its brief 8-week observation period, the present study could not assess the long-term effects and safety of the treatment regime used. Future investigations should strive to broaden the study's scope to generate results with broader practical implications.

To conclude, according to evaluations by both doctors and patients, an increased relief of AD symptoms was observed after 8 weeks of standard dupilumab therapy. The serum TARC levels in patients with AD showed a significant positive correlation with treatment progress and mirrored changes in the EASI score, underscoring the importance of follow-up assessments. While serum levels of HBD2 and SEA-IgE were also correlated with treatment progress, the changes were not statistically significant, warranting further investigation into their clinical relevance.

Acknowledgments

Not applicable.

Funding

The present study was supported by the Science and Technology Program of Guangzhou (grant no. 2023A03J0468), the Science and Technology Planning Project of Guangzhou (grant. no. 202102080317) and the Guangzhou Basic and Applied Basic Research City University (Institute) Enterprise Joint Funding Project.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YL and JW conceived the study design. XT and JuL drafted and edited the manuscript. XL and JiL performed the experimental work. XT, JuL, JW, HX, YY, MX, AG, XZ, LS, JZ, QY, RX, QH, JW and RF participated in the recruitment, treatment and follow-up process of patients, and provided clinical data and samples for the study. XT and JuL confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was reviewed and approved by the Medical Ethics Committee of Guangzhou Dermatosis Preventing & Curing Institute (approval no. 201913). The patients or their legal guardians provided written informed consent for participation in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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