ORIGINAL RESEARCH

Clinical Implications of Interleukin-4 and C-reactive Protein in Atopic Dermatitis and Their Changes Before and after Dupilumab Treatment

Tian Zhao, MM; Yinglei Wu, MM; Zhina Shi, MM; Jing Zhang, MM; Chunjie Geng, MM; Yanan Jia, MM; Yaohui Yuan, MD

ABSTRACT

Objective • To analyze the clinical implications of C-reactive protein (C-reactive protein) and interleukin-4 (IL-4) in atopic dermatitis and their correlations with the therapeutic effect of Dupilumab (DU).

Methods • Seventy-four cases of atopic dermatitis (intervention group) were admitted to Xingtai Third Hospital between May 2021 and January 2023, and 55 concurrent healthy controls (control group) were selected as research participants. Atopic dermatitis patients were treated with a DU injection of 600 mg for the first time after diagnosis. Peripheral blood IL-4 and C-reactive protein levels before and after treatment in the intervention group and their levels at admission in the control group were comparatively analyzed, and their predictive value for the occurrence, clinical efficacy, and adverse reactions of atopic dermatitis were determined. Additionally, alterations in C-reactive protein and IL-4 levels before and after treatment in the intervention group and their relationship with the Scoring Atopic Dermatitis (SCORAD) index were discussed.

Results • The intervention group exhibited higher C-reactive protein and IL-4 levels than the control group. The diagnostic sensitivity and specificity of C-reactive protein + IL-4 detection for atopic dermatitis were 74.32% and 94.55%, respectively ($P < .05$). The post-treatment C-reactive protein and IL-4 were lower in the intervention group, and the test results were positively correlated with SCORAD before and after treatment ($P < .05$). In addition, C-reactive protein + IL-4 detection showed excellent predictive effects on the therapeutic efficacy of DU and adverse reactions.

Conclusions • IL-4 and C-reactive protein are closely related to atopic dermatitis, which can be used as the evaluation indexes for disease development of atopic dermatitis and therapeutic effects of DU in the future. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Atopic dermatitis, a common chronic, recurrent skin inflammation characterized by dry skin, eczema-like rash, and intense itching, has become a widespread public health problem worldwide.[1] In the past 3 decades, the incidence of atopic dermatitis has been increasing yearly, with the new sufferers exceeding 300 000 in 2021.[2] The disease usually begins in infants and young children, with more than 50% of patients presenting before the age of one year.[3] Though remaining to be further defined, its specific pathogenesis is clinically believed to be attributed to multiple reasons such as heredity, immunity, environment, and skin barrier dysfunction.[4] As an allergic reaction, atopic dermatitis is often difficult to cure completely, and its recurring nature leaves sufferers and their families afflicted.[5] Clinically, it is considered that finding an effective atopic dermatitis condition assessment index can provide a more effective reference for the clinical diagnosis and treatment of atopic dermatitis.

Inflammation is a typical pathological reaction of atopic dermatitis, so abnormal changes in the levels of inflammatory factors may contribute to further clinical understanding of the development process of atopic dermatitis.[6] C-reactive protein (C-reactive protein) and interleukin-4 (IL-4), both classic inflammatory cytokines in clinical studies, have been confirmed to present abnormal expression in atopic dermatitis in previous studies. Also, C-reactive protein and IL-4, as cytokines secreted by type II helper T cells (Th2 cells), play key roles in the regulation of humoral and adaptive immunity, which are particularly important for atopic dermatitis.[7] However, as inflammatory reactions

involve multiple tissues and organs of the human body, they do not have the ability to effectively identify atopic dermatitis.[8]

We suspect that the combined detection of IL-4 and C-reactive protein may make up for their limitations and help to improve their disease assessment ability in atopic dermatitis. Still, there is no research to confirm our view. Accordingly, this study carries out relevant research and analysis for validation. Meanwhile, to further understand the correlation of IL-4 and C-reactive protein with atopic dermatitis, we also analyze their changes before and after treatment to provide more comprehensive reference and guidance for clinical use.

MATERIALS AND METHODS

Study Participants

Seventy-four cases of atopic dermatitis (intervention group) were admitted to Xingtai Third Hospital between May 2021 and January 2023, and 55 concurrent healthy controls (control group) were selected as research participants. The ethics committee of the hospital approved this study, and all participants provided informed consent. All atopic dermatitis patients were scored and graded for disease severity using the Scoring Atopic Dermatitis (SCORAD; 0-103 points) Index,[9] with 0-24 as mild, 25-50 as moderate, and 51-103 as severe.

Criteria for patient enrollment and exclusion

Inclusion criteria: meeting the diagnostic criteria for atopic dermatitis (in line with any of the following two criteria): 1. symmetrical eczema with a course of disease > 6 months, 2. personal and/or family history of atopic disease, 3. elevated serum total IgE and/or peripheral blood eosinophils and/or positive allergen-specific IgE);[10] age ≥ 18; complete medical records. Exclusion criteria: history of glucocorticoid hormone and antihistamine use within 2 weeks; other allergic diseases such as blood disorders, eosinophilia, tumors, scabies, hereditary and immunobullous diseases.

Treatments

Atopic dermatitis patients were treated with a dupilumab (DU) injection (Sanofi, USA) of 600 mg for the first time after diagnosis, followed by a subcutaneous injection of 300 mg every 2 weeks for 16 weeks.

Sample collection and testing

Fasting cubital vein blood (3 mL) was drawn from intervention group patients before and after treatment and healthy controls at admission into coagulation-promoting tubes, and the serum was obtained after room temperature standing (30 minutes) and centrifugation (3000 rpm/min, 4°C), for the determination of C-reactive protein and IL-4 levels in a sterile environment as per the enzyme-linked immunosorbent assay (ELISA) kit (Beijing TransGen Biotech, China) instructions.

Clinical efficacy evaluation

Clinical efficacy evaluation was made by referring to atopic dermatitis treatment guidelines.[11] A reduction in dermatitis area >90%, 60-89%, and 20-59% was considered cured, markedly effective, and effective, respectively, while failure to meet the above criteria or disease worsening was deemed ineffective.

Endpoints

Differences in C-reactive protein and IL-4 levels between groups, as well as their predictive value for the occurrence, clinical efficacy, and adverse reactions of atopic dermatitis, were analyzed. In addition, changes in C-reactive protein and IL-4 levels in the intervention group before and after treatment and their correlations with SCORAD were discussed.

Statistical analysis

The statistical analysis of data used SPSS v 25.0. Patients' gender, family history, and other count data were all described in the form of [n(%)], and a chi-square test was used for comparison between groups. Measurement data such as C-reactive protein and IL-4 levels were recorded in the form of ($\bar{x} \pm s$), and the methods for comparisons between the intervention group and control group and intra-group (before and after treatment) comparisons in the intervention group employed the independent sample t test was and the paired t-test, respectively. Correlations were identified using Pearson correlation coefficients, and diagnostic value was analyzed by ROC. For the joint diagnosis, binary Logistic regression analysis was performed to obtain the joint formula Log(P), followed by ROC analysis. A minimum significance threshold of $P < .05$ was used.

RESULTS

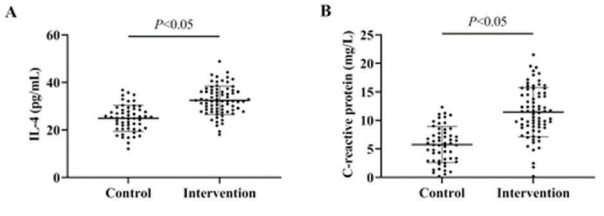
Comparison of IL-4 and C-reactive protein levels between groups

The pre-treatment C-reactive protein and IL-4 in the intervention group were (32.47±6.00) pg/mL and (11.46±4.33) mg/L, respectively, which were significantly higher compared with the control group ($P < .05$, Figure 1).

Diagnostic value of IL-4 and C-reactive protein in atopic dermatitis

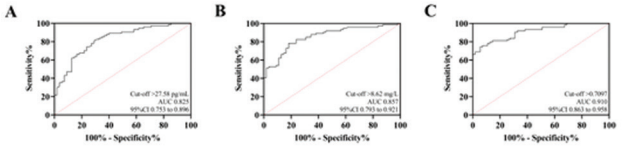
According to ROC analysis, the sensitivity and specificity of IL-4 in the diagnosis of atopic dermatitis were 81.08% and

Figure 1. IL-4 and C-reactive protein levels between groups. A: Comparison of IL-4 in the research and control groups. B: Comparison of C-reactive protein in the research and control groups.



78.38%, respectively, and those of C-reactive protein were 70.91% and 81.82%, respectively (P < .05, 95%CI=0.753-0.896). Then, with the intervention group and control group as dependent variables and the detection results of IL-4 and C-reactive protein as covariates, we obtained the joint formula (IL-4 + C-reactive protein) of Log(P)=-8.543+0.206×IL-4+0.359×C-reactive protein through binary Logistic regression analysis. After calculation, it can be seen that when Log(P)>0.7097, the joint formula had a diagnostic sensitivity of 74.32% and a specificity of 94.55% (P < .05, 95%CI=0.793-0.921, Figure 2).

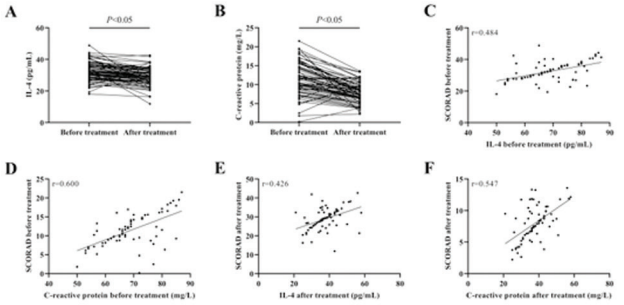
Figure 2. Diagnostic value of IL-4 and C-reactive protein in atopic dermatitis**.** A: ROC for IL-4 diagnosis of atopic dermatitis occurrence. B: ROC for C-reactive protein diagnosis of atopic dermatitis occurrence. C: ROC for IL-4 combined with C-reactive protein diagnosis of atopic dermatitis occurrence.



Changes in IL-4 and C-reactive protein in the intervention group before and after treatment and their correlations with SCORAD

IL-4 and C-reactive protein levels decreased significantly in the intervention group after DU treatment (P < .05). The SCORAD scores in the intervention group before and after treatment were (69.00±9.16) and (37.59±7.66), respectively. Pearson correlation coefficient analysis showed that pre-treatment IL-4 and C-reactive protein were positively correlated with pre-treatment SCORAD (P < .05, r=0.484, 0.600), as was the post-treatment association (P < .05, r=0.426, 0.547, Figure 3).

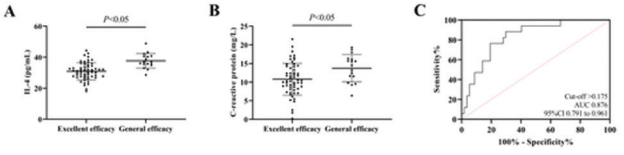
Figure 3. Changes in IL-4 and C-reactive protein in intervention group before and after treatment and their correlations with SCORAD. A: Changes in IL-4 before and after treatment. B: Changes in C-reactive protein before and after treatment. C: Correlation of pre-treatment IL-4 and SCORAD. D: Correlation of pre-treatment C-reactive protein and SCORAD. E: Correlation of post-treatment IL-4 and SCORAD. F: Correlation of post-treatment IL-4 and SCORAD.



Correlations of IL-4 and C-reactive protein with the therapeutic effect of DU

After treatment, 31 cases in the intervention group were cured, 26 cases were markedly effective, 14 cases were effective, and 3 cases were ineffective. Patients with cured and markedly effective treatment were assigned to the excellent efficacy group (n=57), and the others were assigned to the general efficacy group (n=17) for further analysis. By comparison, it can be seen that the excellent efficacy group had lower pre-treatment IL-4 and C-reactive protein levels than the general efficacy group (P < .05). Further, ROC analysis revealed a sensitivity of 88.24% and a specificity of 70.18% of IL-4 + C-reactive protein detection for the prediction of general efficacy (P < .05, 95%CI=0.791-0.961, Figure 4).

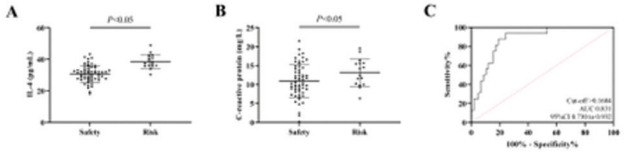
Figure 4. Correlations of IL-4 and C-reactive protein with therapeutic effect of DU. A: Comparison of IL-4 in the excellent and general efficacy groups. B: Comparison of C-reactive protein in the excellent and general efficacy groups. C: Combination of IL-4 and CPR for diagnosis of ROC with general efficacy.



Correlation of IL-4 and C-reactive protein with adverse reactions

During treatment with DU, some patients developed adverse reactions such as urticaria, nausea and vomiting, and dizziness, with an overall incidence of 21.62%. Patients with adverse reactions and those without were included in the risk group (n=16) and the safety group (n=58), respectively. By comparison, the pre-treatment IL-4 and C-reactive protein were higher in the risk group than in the safety group (P < .05). ROC results further showed that the sensitivity and specificity of IL-4 + C-reactive protein detection in predicting adverse reactions during treatment with DU was 93.75% and 75.86%, respectively (P < .05, 95%CI=0.730-0.932, Figure 5).

Figure 5. Correlation of IL-4 and C-reactive protein with adverse reactions. A: Comparison of IL-4 in the risk and the safety groups. B: Comparison of C-reactive protein in the risk and the safety groups. C: ROC for the occurrence of adverse reactions in the combined diagnosis of IL-4 and CPR.



DISCUSSION

Atopic dermatitis seriously affects patients' daily lives, especially for those with the disease site involving the face, which has a great negative impact on their normal life and communication.[12] Moreover, atopic dermatitis is often associated with allergic diseases such as chronic rhinitis and asthma, increasing the suffering of patients.[13] Hence, rapid and accurate assessment of the onset and development of atopic dermatitis is of great significance to ensure the normal life and health of patients. This study identified a close correlation of C-reactive protein and IL-4 with the onset and progression of atopic dermatitis, which undoubtedly suggests the potential of the two as candidate disease evaluation indexes of atopic dermatitis, thus providing a more reliable guarantee for clinical treatment of atopic dermatitis.

By analyzing peripheral blood C-reactive protein and IL-4 levels in atopic dermatitis patients and healthy controls, we found that both of them were highly expressed in atopic dermatitis cases, suggesting a potential relationship between them and the occurrence of atopic dermatitis. Previous studies have also repeatedly verified the abnormal expression status of C-reactive protein and IL-4 in atopic dermatitis,[14] which can also prove the accuracy of the experimental results. IL-4 has been shown to play a role in the pathophysiological process of atopic dermatitis by binding with IL-4Rα expressed by T cells, B cells, and macrophages to promote Th2 differentiation, activate immunoglobulin conversion to IgE, and induce eosinophil chemotaxis.[15] C-reactive protein, on the other hand, is a nonspecific marker of the acute-phase systemic inflammatory response synthesized by the liver and is usually used in the analysis and evaluation of cardiovascular risk events.[16] In atopic dermatitis, high C-reactive protein expression can cause immune system dysfunction and increase the risk of iron deficiency anemia or chronic blood loss.[17] Through ROC analysis, we found that both of them had a good diagnostic effect on the occurrence of atopic dermatitis, but the general specificity is not high. As we all know, IL-4 and C-reactive protein, as highly sensitive inflammatory factors in the human body, have strong reactions to various pathological changes in the body,[18] which can explain their low diagnostic specificity in atopic dermatitis. However, this situation was significantly improved by the combination of C-reactive protein and IL-4, suggesting that C-reactive protein + IL-4 detection can compensate for the deficiency of both. Moreover, C-reactive protein and IL-4 levels decreased after treatment in atopic dermatitis patients. They were positively correlated with the SCORAD score, which further demonstrated the close relationship between the two and atopic dermatitis progression. We believe that using C-reactive protein and IL-4 as routine clinical examination items can effectively improve the early diagnosis rate of atopic dermatitis so as to provide patients with more reliable intervention treatment in time and control the progression of atopic dermatitis.

On the other hand, DU, as a fully humanized IgG4 subtype monoclonal antibody drug, was approved for atopic dermatitis treatment in 2020 and has achieved excellent results.[19] However, there are still patients who do not respond well to the treatment and experience recurrent atopic dermatitis attacks.[20] Therefore, how to evaluate the therapeutic effect of DU is also one of the focuses of clinical research. Herein, we found that IL-4 and C-reactive protein were closely related to the therapeutic effect of DU and adverse reactions during treatment and showed excellent predictive value for clinical efficacy and occurrence of adverse reactions, further demonstrating that the two not only participate in atopic dermatitis progression but also have important significance for the efficacy evaluation of DU in the treatment of atopic dermatitis. According to studies on the pharmacological mechanism of DU, DU can bind to IL-4 and IL-13 co-receptors on the cell surface and inhibit the expression of inflammatory factors and signal transduction.[21] DU also inhibits the JAK-STAT6 pathway to downregulate the barrier proteins of keratinocytes, reducing the ability of allergens and pathogens to penetrate the epidermis, while the hyperimmune response environment, known for promoting B cell reduction, leads to a decrease in histamine cell secretion, so the levels of IL-4 and C-reactive protein were reduced.[22] We speculate that this is also the reason for the decrease of both C-reactive protein and IL-4 after DU treatment, and the above experimental results also provide a new reference for future clinical evaluation of the therapeutic effect of DU.

However, the small number of cases included may result in the lack of representativeness of ROC analysis results. Besides, due to the fact that we have not followed up on the prognosis, the role of IL-4 and C-reactive protein in evaluating the prognosis and recurrence of atopic dermatitis cannot be determined for the time being. Finally, we still need to carry out basic experiments to confirm the mechanism of IL-4 and C-reactive protein in atopic dermatitis to improve our research.

CONCLUSION

The increase of IL-4 and C-reactive protein in atopic dermatitis was strongly correlated with disease progression, and IL-4 + C-reactive protein detection can effectively diagnose the onset of atopic dermatitis. However, their levels decreased after treatment, demonstrating the excellent predictive value of IL-4 and C-reactive protein for clinical efficacy and adverse reactions after treatment with DU. In the future, IL-4 and C-reactive protein can be used as indicators to assess the disease condition and effectiveness of treatment for atopic dermatitis, thus enabling a more timely and rapid understanding of the development of the disease in patients and providing more efficient guarantees for their diagnosis and treatment.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

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AVAILABILITY OF DATA AND MATERIALS

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

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