Changes in Thymus and Activation-Regulated Chemokine in Patients With Type 2 Inflammatory Disease Receiving Dupilumab

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To the Editor:

Type 2 inflammatory diseases, such as atopic dermatitis (AD), asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and eosinophilic esophagitis (EoE), have a similar pathogenesis, with involvement of multiple cytokines, including interleukin (IL) 4, IL-5, and IL-13 [1]. Thymus and activation-regulated chemokine (TARC), also known as CCL17, can be generated by macrophages, dendritic cells, keratinocytes, and fibroblasts. Through recognition of chemokine receptor types 4 and 8 on type 2 helper T (T_H2) cells, TARC plays a vital role in the development of T cells [2]. Current studies show TARC to be involved in the pathogenesis of AD and asthma [2,3]. Dupilumab is a fully human monoclonal antibody that blocks the IL-4 and IL-13 pathways [4]. With increasing use of dupilumab, changes in cytokines and biomarkers have gained increasing attention. Serum TARC was found to be related to the severity of AD [3]. Thus, changes in TARC levels may be a key indicator for type 2 inflammatory diseases in patients treated with dupilumab. We performed a meta-analysis to comprehensively investigate trends in TARC in this population (Registered in PROSPERO: CRD42022321853).

Publications were selected from 6 databases (see Supplementary materials [sFigure 1] for more details). Trends were assessed using the standardized mean difference (SMD). A fixed or random effect model was chosen in the data merge depending on between-study heterogeneity.

We included 9 studies, all of which could be considered high-quality. The characteristics of the studies included are shown in sTable 1. TARC levels decreased significantly after treatment with dupilumab. When dupilumab was used for less than 4 weeks, the TARC level decreased, with an SMD of −0.41 (95%CI, −0.65 to −0.16). Then, at weeks 4, 8, 12, 16, 43, 48, and 52, TARC levels all decreased significantly ($P<.05$), with SMDs of −1.04 (95%CI, −1.47 to −0.61), −0.98 (95%CI, −1.50 to −0.46), −1.29 (95%CI, −1.89 to −0.70), −1.48 (95%CI, −2.27 to −0.69), −1.06 (95%CI, −1.34 to −0.79), and −0.58 (95%CI, −0.68 to −0.47), respectively. When dupilumab was used for longer than 52 weeks, the level was still lower than baseline, with an SMD of −0.91 (95%CI, −1.24 to −0.59). No significant differences were observed at weeks 6, 10, 14, and 15. However, only 1 study covered these weeks (sFigure 2). Moreover, in the sensitivity analysis at different weeks, when each study was excluded seriatim, the significance did not change, indicating that the results were robust.

We then performed a subgroup analysis to evaluate the changes based on a series of characteristics. In the subgroup analysis by disease (asthma, AD, CRSwNP, EoE), a significant decrease in the total effect was observed when dupilumab was used for less than 4 weeks ($P<.05$), although no obvious decrease was observed in the AD group ($P=.05$). At week 12, a significant decrease in the total effect was observed ($P<.05$), although no obvious decrease was observed in the EoE group ($P=.05$). In the subgroup analysis by study type (randomized controlled trials, observational studies), the effect in each subgroup was identical to the total effect in each comparison. In the subgroup analysis by dose, a significant decrease in the total effect was observed at week 4 ($P<.05$), although no obvious decrease was observed in the subgroup with a mixed dose of 75/150/300 mg/wk ($P=.06$). At week 4 and under and at weeks 6, 10, 12, 14, 15, and 16, the dose of 200 mg/wk was included, although no significant decrease was observed in this subgroup ($P\geq.05$). The subgroup analysis by monotherapy or combination therapy showed a significant decrease in the total effect when dupilumab was used for less than 4 weeks ($P<.05$), but no obvious decrease in the monotherapy group ($P=.05$). Then, at weeks 6, 10, 14, and 15, studies with dupilumab in monotherapy only were included, although no significant differences were observed ($P>.05$). The results indicated that combined use of dupilumab and other treatments may enhance the impact on TARC. The details are presented in the Supplementary materials (sFigures 3-6).

Our study evaluated changes in TARC levels for patients receiving dupilumab. The serum level of TARC can decrease significantly, and this decrease can persist throughout treatment. Biological agents inhibit pathways more accurately than traditional approaches, thus enhancing efficacy. Therefore, the impact on the biomarkers and cytokines should be emphasized. Evidence-based results suggest that TARC is a valuable biomarker for assessing the severity and predicting the prognosis of AD [5]. Clinically, detection of TARC could be meaningful for patients using dupilumab. In Japan, serum TARC has been applied to monitor response to treatment in AD patients [6]. In China, measurement of TARC

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is rarely used as a routine determination in patients receiving dupilumab. Through our meta-analysis, we found that TARC levels decreased significantly for type 2 inflammatory disease after treatment with dupilumab. Besides, through subgroup analysis, we found that the effect of dupilumab on TARC may be dose-dependent. Dupilumab also showed an effect on blood eosinophils, namely, a transient increase in blood eosinophil counts was observed after treatment with dupilumab. Inhibition of TARC may contribute to the change in eosinophil counts [7]. The association between cytokines and chemokines was complex. When IL-4 and IL-13 are blocked, the interaction may be altered. Therefore, further studies are needed to investigate changes in the interactions after treatment with dupilumab.

Our study was subject to limitations. Most of the patients had AD and asthma. However, only 2 study groups included CRSwNP and EoE, which further limited our analysis by disease. Furthermore, the studies included did not focus exclusively on children or the elderly.

In conclusion, for patients receiving dupilumab, TARC has excellent potential for assessment of severity before treatment, efficacy during treatment, and prognosis after treatment. However, future studies with a larger sample size that focus on other diseases and age groups are needed.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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