

## **Changes of Thymus and Activation-Regulated Chemokine in Type 2 Inflammatory Disease Patients with Dupilumab Treatment**

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**Palabras clave:** Citoquina de activación regulada del timo. Enfermedad inflamatoria tipo 2. Dermatitis atópica. Dupilumab.

### **To the Editor,**

Type 2 inflammatory diseases, such as atopic dermatitis (AD), asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and eosinophilic esophagitis (EoE), share a similar pathogenesis, with multiple cytokines involved, including interleukin (IL)-4, IL-5 and IL-13[1]. Thymus and activation-regulated chemokine (TARC), also referred to as CCL17, can be generated by macrophages, dendritic cells, keratinocytes, and fibroblasts. Through the recognition of chemokine receptor (CCR) types 4 and 8 on T helper 2 (Th2) cells, TARC plays a vital role in the development of T cells[2]. Current studies have demonstrated that TARC could be involved in the pathogenesis of AD and asthma[2,3]. Dupilumab is a fully human monoclonal antibody, which blocks IL-4 and IL-13 pathway[4]. With increasing use of dupilumab, cytokines or biomarkers trends 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 patients treated with dupilumab. To comprehensively investigate the TARC trends in these patients, we performed this meta-analysis.

Publications were selected from six databases, and details were in the Supplementary materials (sFigure 1). The standardized mean difference (SMD) was used to assess the trends. According to the between-study heterogeneity, a fixed or random effect model was chosen in the data merge.

Nine studies were included, all of which could be considered as high quality. The characteristics of the included studies were in sTable 1. TARC levels decreased significantly after dupilumab treatment. When dupilumab was used for a duration within 4 weeks, the TARC level had decreased, with SMD=-0.41 (95%CI: -0.65, -0.16). Then, at weeks 4, 8, 12, 16, 43, 48 and 52, TARC levels all showed significant decreases ( $P<0.05$ ), with SMDs=-1.04 (95%CI: -1.47, -0.61); -0.98 (95%CI: -1.50, -0.46); -1.29 (95%CI: -1.89, -0.70); -1.48 (95%CI: -2.27, -0.69); -1.06 (95%CI: -1.34, -0.79); -0.58 (95%CI: -0.68, -0.47), respectively. When dupilumab was used for longer than one 52 weeks, the level was still lower than baseline, with SMD=-0.91 (95%CI: -1.24, -0.59). At weeks 6, 10, 14 and 15, no significant difference was observed. However, only one included study covered these weeks (sFigure 2). Moreover, in the sensitivity analysis at different weeks, when each study was ignored seriatim, the significance did not change, indicating that the results were robust.

Then we performed subgroup analysis to evaluate the changes based on different characteristics. In subgroup analysis by disease (Asthma, AD, CRSwNP, EoE), when dupilumab was used for less than 4 weeks, there was a significant decrease in the total effect ( $P<0.05$ ), but no obvious decrease was shown in the AD group ( $P=0.05$ ). At week 12, a significant decrease was shown in the total effect ( $P<0.05$ ), but no obvious decrease was shown in the EoE group ( $P=0.05$ ). In subgroup analysis by study type (RCT, observational studies), the effect in each subgroup was identical to the total effect in each comparison. In subgroup analysis by dose, at week 4, a significant decrease was shown in the total effect ( $P<0.05$ ), but no obvious decrease was shown in the subgroup with a mixed dose of 75/150/300 mg qw ( $P=0.06$ ). At week 4 and under, 6, 10, 12, 14, 15, and 16, the dose of 200 mg qw was included, however, no significant decrease was shown in this subgroup ( $P=0.05$  or  $P>0.05$ ). In subgroup analysis by single or combined use, when dupilumab was used for less than 4 weeks, there was a significant decrease in the total effect ( $P<0.05$ ), but no obvious decrease was shown in single use group ( $P=0.05$ ). Then, at weeks 6, 10, 14 and 15, studies with single use of

dupilumab were included exclusively, but no significance was shown ( $P>0.05$ ). The results indicated that combined use of dupilumab and other treatments may enhance the impact on TARC. Details were presented in the Supplementary materials (sFigures 3–6).

Our study evaluated changes of TARC levels for patients under dupilumab treatment. The serum level of TARC can decrease significantly, and this decrease can last during the whole treatment duration. Compared to traditional methods, biological agents inhibit pathways more accurately. Thus, better efficacy can be obtained. Meanwhile, the impact to the biomarkers or cytokines should be emphasized. Evidence-based results suggest that TARC is a valuable biomarker to assess the severity and predict the prognosis of AD[5]. Clinically, TARC detection could be meaningful for patients using dupilumab. In Japan, serum TARC has been applied to monitor response to treatment in AD patients[6]. Currently in China, measurement of TARC is rarely used as a routine for dupilumab treatment. Through meta-analysis, we found that TARC level decreased significantly for type 2 inflammatory diseases patients after dupilumab treatment. Besides, through subgroup analysis, we found that the effect of dupilumab to TARC may be dose-dependent. Dupilumab also showed effect on blood eosinophils. A transient increase of blood eosinophil counts could be observed after dupilumab treatment. The inhibition of TARC may contribute to the change of eosinophil counts [7]. The actions between the cytokines and chemokines were complex. When the IL-4 and IL-13 were blocked, the interaction may be altered. Therefore, further studies were needed to investigate the change of the interactions after dupilumab treatment.

There were limitations in our study. Most of the patients suffered from AD and asthma. However, only two study groups included CRSwNP and EoE, which limited our further analysis by diseases. Furthermore, the included studies did not exclusively focus on children or the elderly.

In conclusion, for patients on dupilumab, TARC has excellent potential to be used for severity assessment before treatment, efficacy evaluation during treatment and

prognosis prediction after treatment. However, future studies with a larger sample size, more focused on different diseases and age groups are need.

**Conflict of interest**

The authors have no conflict of interest to declare

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