

CORRESPONDENCE

Dupilumab treatment reduces serum SCCA2 levels in patients with atopic dermatitis

The eczema area and severity index (EASI) and other indices are used internationally to evaluate the severity of atopic dermatitis (AD), but the results may vary among different physicians.

Therefore, there has been a need for a biomarker that can be easily and reproducibly measured in a blood test and that changes sensitively to reflect disease activity. Serum thymus and

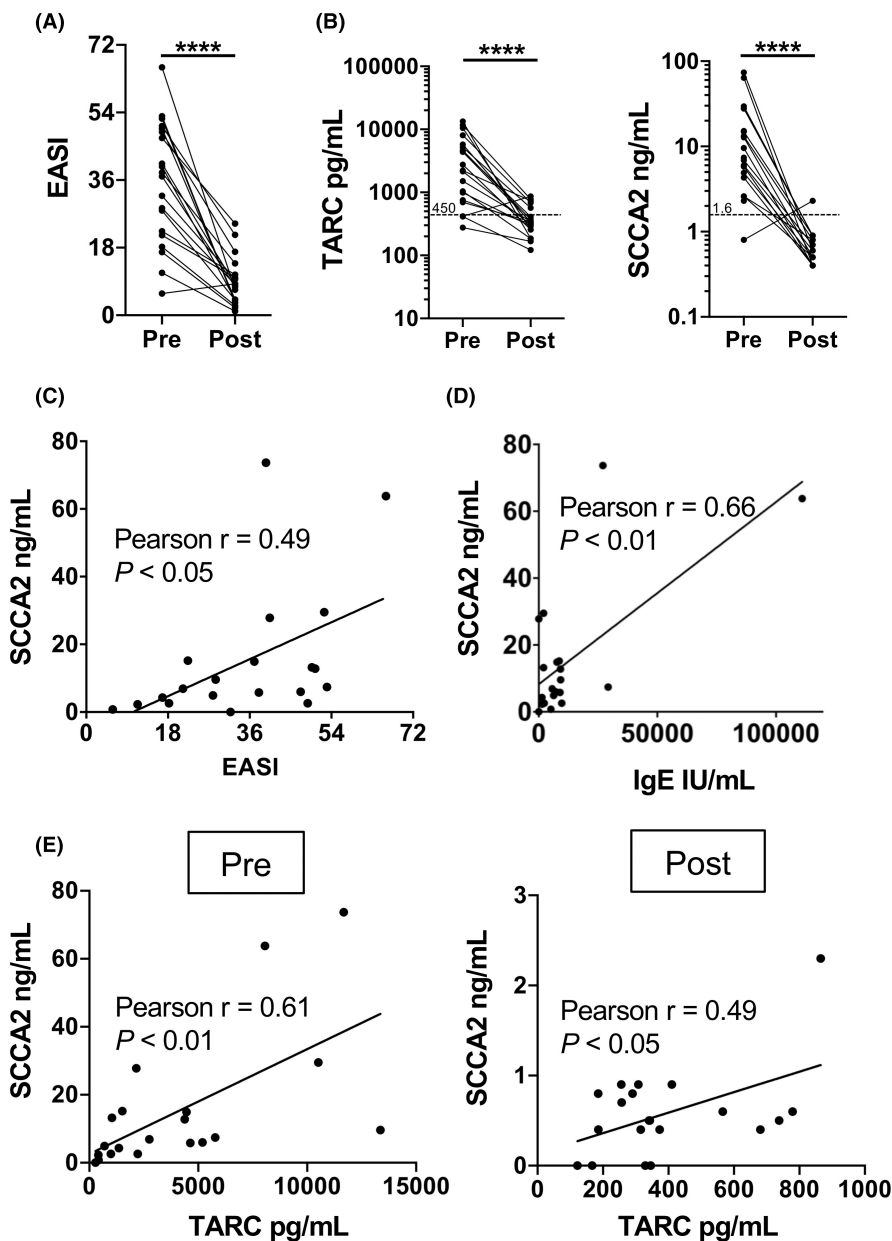


FIGURE 1 IL-4/13 signaling is necessary and sufficient for squamous cell carcinoma antigen2 (SCCA2) expression in patients with atopic dermatitis. (A, B) Changes in Eczema Area and Severity Index (EASI) scores (A) or serum TARC/SCCA2 levels (B) before (pre) and 16 weeks after (post) dupilumab treatment. Values below the dashed lines are normal. (C-E) Comparison of (C) serum SCCA2 levels and EASI scores, or (D) serum SCCA2 levels and serum IgE levels, or (E) serum SCCA2 levels and serum thymus and activation-regulated chemokine (TARC) levels before (pre) and 16 weeks after (post) dupilumab treatment. (A-E) Each dot represents a value for each patient. Blood samples were obtained in our hospital and sent to SRL Laboratory (Tokyo, Japan). The data were analyzed using GraphPad Prism version 8 (GraphPad Software Inc.). The Wilcoxon matched-pairs signed rank test (A, B) or the Spearman rank correlation test (C-E) were used to assess statistical significance. **** $p < .0001$. r , Pearson correlation coefficient.

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activation-regulated chemokine (TARC) levels have been used as biomarkers for AD in clinical practice, but they have the disadvantage that the reference values vary with age. On the contrary, serum squamous cell carcinoma antigen 2 (SCCA2)¹ level is not affected by age and is covered by health insurance as a biomarker for pediatric AD in Japan.² In vitro studies have reported that stimulation of keratinocytes with IL-4/13 results in the production of SCCA2.³ Thus, although it was expected that IL-4/13 would induce SCCA2 expression, it was not clear whether IL-4/13 inhibitors would reduce serum SCCA2 levels in real-world clinical practice. We therefore investigated the effect of anti-IL-4R α monoclonal antibody dupilumab (DUP) on serum SCCA2 levels in AD patients. We measured serum SCCA2 levels before and after DUP administration in 20 adult male AD patients who visited the Department of Dermatology, Hyogo College of Medicine College Hospital (currently Hyogo Medical University Hospital) between April 2018 and March 2020. This study conformed to the Declaration of Helsinki and was approved by the Ethics Review Board of Hyogo Medical University. Patient details are shown in Table S1. The EASI score before the introduction of DUP was 35.3 ± 16.1 (mean \pm standard deviation) and was significantly reduced to 8.6 ± 6.4 after 16 weeks of treatment (Figure 1A). Serum TARC level decreased from $4064 \text{ pg/ml} \pm 3999$ before treatment to 393 ± 216 at 16 weeks after treatment, and serum SCCA2 level decreased from $15.21 \text{ ng/ml} \pm 20.1$ before treatment to 0.58 ± 0.51 at 16 weeks after treatment (Figure 1B). Even though the skin eruptions (EASI scores) had not yet fully disappeared, the mean level of serum SCCA2 was reduced well to below normal (<1.6) by the administration of DUP. Therefore, we speculated that DUP would decrease serum SCCA2 levels directly. In addition, serum SCCA2 levels were positively correlated with EASI scores and IgE levels (Figure 1C,D). Both before and after DUP administration, serum SCCA2 and serum TARC levels were positively correlated (Figure 1E), in accordance with the fact that both SCCA2 and TARC are good biomarkers of type 2 inflammation.^{2,3}

SCCA2 functions as a protease inhibitor,^{4,5} and it has been reported that SCCA2 may be involved in the pathogenesis of AD by affecting epidermal differentiation.⁴ Therefore, we speculated that inhibition of SCCA2 production by IL-4/13 inhibition may also contribute to the restoration of skin barrier function by DUP administration. In this sense, serum SCCA2 levels would represent not just a disease activity marker but also a therapeutic target in AD.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DECLARATION SECTION

Approval of the research protocol: The study protocol was approved by the Ethics Review Board of Hyogo College of Medicine and conformed to the ethical guidelines of the Declaration of Helsinki.

Informed Consent: N/A.

Registry and the Registration No. of the study/trial: 0212.

Animal Studies: N/A.

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SUPPORTING INFORMATION

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