

Two atopic dermatitis patients in whom dupilumab improved aberrant epidermal protease activities

Dear Editor,

Atopic dermatitis (AD) is a chronic pruritic inflammatory skin disease characterized by barrier dysfunction, an allergic property that involves mainly Th2-type inflammatory response, and pruritus.¹ Dupilumab, a fully human IgG4 monoclonal antibody that inhibits both interleukin (IL)-4 and IL-13 signaling, has recently been used for the treatment of adult patients with moderate-to-severe AD.² Dupilumab has been shown to progressively improve systemic and cutaneous abnormalities in patients with AD.³ Here we report two cases of AD patients for whom dupilumab treatment was effective and improved epidermal aberrant serine protease activities.

Patient 1, a 24-year-old Japanese man, suffered from severe AD since childhood (Figure 1A, B). He had previously received cyclosporine 200 mg/day, but the result was not satisfactory. We therefore treated him with dupilumab using a standard regimen (600 mg initial dose then 300 mg q2 weeks). His pruritus quickly improved, and his Eczema Area and Severity Index (EASI) score gradually decreased, as expected (Figure 1C-E). Similarly, his serum IgE level fell (Figure 1F). We measured the serine protease activities of the scales on his forearm, using specific substrates (this treatment was approved by the ethics committee of Okayama University, approval no.1611-002). Both trypsin- and chymotrypsin-like serine protease activities decreased with the dupilumab treatment at the standard dose, similarly to the EASI and the IgE level (Figure 1G, H).

Patient 2, a 31-year-old Japanese man with a lifelong history of severe AD, was treated with cyclosporine 150 mg/day but it was stopped, and at the same time, dupilumab was started at the standard dose (600 mg initial dose then 300 mg q2 weeks) (Figure 1I, J). For the initial 3 months, his EASI score did not change greatly; this was probably due to the discontinuation of cyclosporine. After the initial 3 months, both the EASI score and the IgE level gradually decreased (Figure 1K-N). The patient developed conjunctivitis, but an antihistamine eye drop was effective and he was thus able to continue receiving dupilumab. Both trypsin- and chymotrypsin-like serine protease activities on his forearm decreased, similarly to the EASI and the IgE level (Figure 1O, P).

It is well known that Th2 cytokines affect skin barrier functions. We reported that IL-4 and IL-13 increase the expression and function of the kallikrein-related peptidase 7 (KLK7, chymotrypsin-like serine protease) in epidermal keratinocytes.⁴ Herein we observed both trypsin- and chymotrypsin-like serine protease activities on the forearms of two AD patients treated with dupilumab. The decrease in chymotrypsin-like protease activity by dupilumab is consistent with our previous in vitro finding.⁴ Dupilumab treatment also decreased the trypsin-like serine protease activity in our patients. In vitro, IL-4, and IL-13 did not directly change the expression or activity of KLK5 (trypsin-like serine protease).⁴ Further investigation is required to clarify the mechanism underlying the effect of dupilumab. This is the first report that dupilumab affects the epidermal serine protease activities of AD patients. Our patients' cases suggest that this biologic agent not only contributes to a decrease in Th2-dominant inflammation but also improves the epidermal barrier function of AD patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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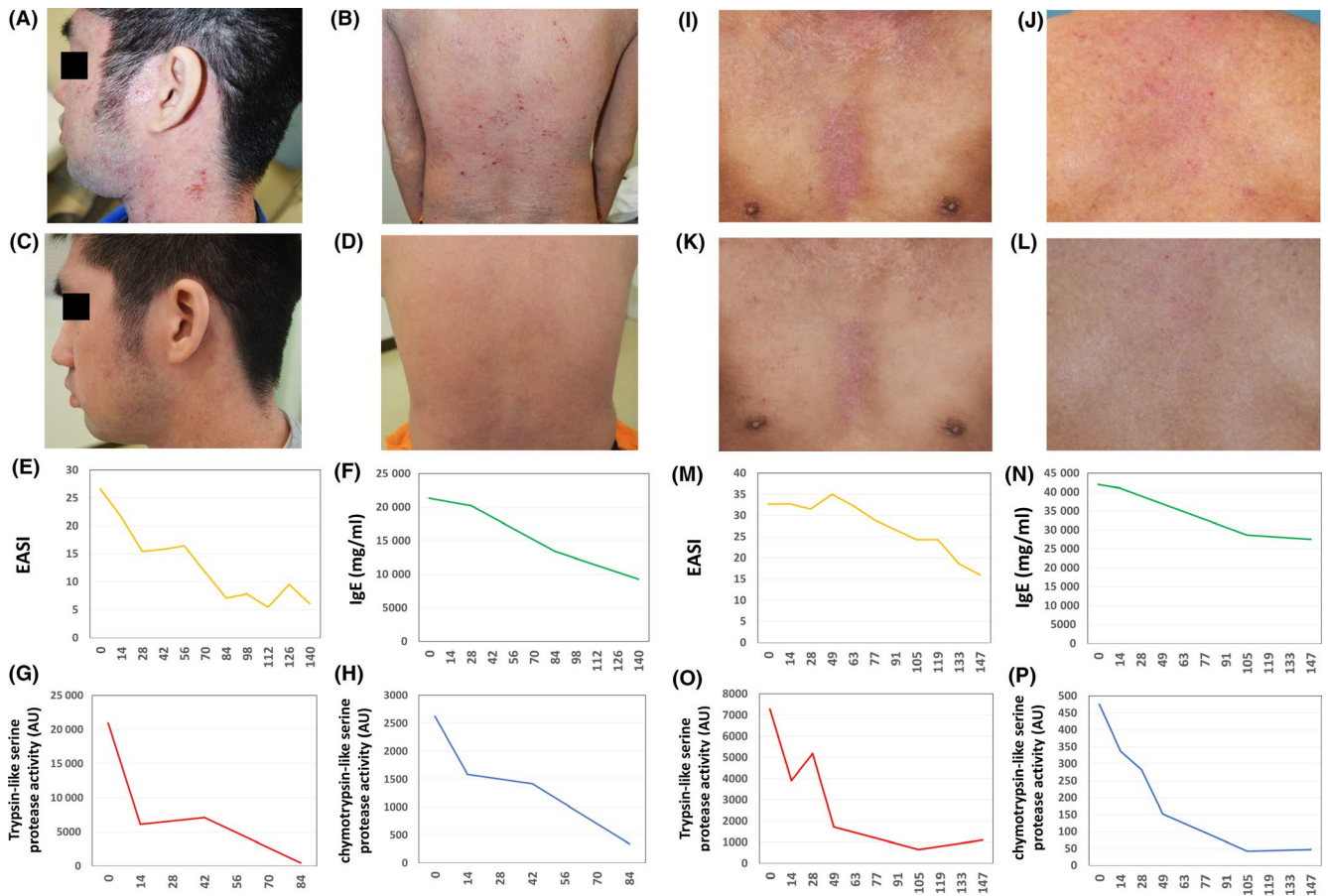


FIGURE 1 A-H, Clinical and laboratory findings of Patient 1. The clinical findings on the face and back before (A, B) and after (C, D) the dupilumab treatment. The time course of the EASI score (E), serum IgE level (F), trypsin-like serine protease activity (G), and chymotrypsin-like serine protease activity (H) in the stratum corneum. I-P, Clinical and laboratory findings of Patient 2. The clinical findings on the chest and back before (I, J) and after (K, L) the dupilumab treatment. The time course of the EASI score (M), serum IgE level (N), trypsin-like serine protease activity (O), and chymotrypsin-like serine protease activity (P) in the stratum corneum. The x-axis shows the number of days after the first dupilumab treatment

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