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RESEARCH LETTER

WILEY

IgE levels in patients with atopic dermatitis steadily decrease during treatment with dupilumab regardless of dose interval

To the editor,

Dupilumab is an interleukin-4 receptor α (IL-4Rα)-antagonist that inhibits interleukin (IL)-4 and IL-13 signalling through blockade of the shared IL-4α subunit, thereby reducing the T helper (Th)2-response that is key in the pathogenesis of atopic dermatitis (AD).[1] IL-4Rα is mainly expressed on B-cells, where it plays a crucial role in inducing B-cell proliferation and isotype switching, resulting in high levels of circulating IgE.[2] Consequently, binding of dupilumab to IL-4Rα and thereby blocking its function, has been proven to reduce circulating IgE levels from baseline through week 16[3,4] and week 52[5] in AD patients who are treated with 300 mg dupilumab every 2 weeks.

Dose reduction of dupilumab has been shown to be successful in daily practice in a subgroup of patients with persistently controlled AD.[6] Additionally, we studied the immunological effects of extending the dosing interval of dupilumab and demonstrated that the transition from treatment with dupilumab 300 mg every 4 weeks to 300 mg every 6 weeks results in decreased IL-4Rα binding by dupilumab and concomitant functional changes in skin-homing T cells.[7] In order to better understand the long-term effects of extending the dosing interval of dupilumab, we studied total IgE levels in serum of patients in whom the dosing interval of dupilumab was extended from every 2 weeks (Q2W) to every 4 weeks (Q4W) and eventually every 6 weeks (Q6W). These patients were compared with patients who were treated with dupilumab Q2W for several years as they did not meet the criteria for interval extension and with healthy volunteers.

All included patients participated in the Dutch BioDay registry, which is a prospective registry containing daily practice data regarding dupilumab as treatment of AD (ClinicalTrials.gov identifier: NCT03549416, retrospectively registered 08 June 2018), and provided written informed consent for data extraction from the registry. After 1 year of treatment with the standard dose of 300 mg dupilumab Q2W, the dosing interval was prolonged according to the protocol described previously.[6] In brief, a patient-centered dosing regimen that is guided by the eczema area and severity index (EASI) was applied in which patients were eligible for dose reduction in case of EASI ≤ 7, indicating mild disease activity or less, for at least 6 months. If patients remained in a state of controlled disease (EASI ≤ 7), the dosage was further reduced. As shown in Figure 1A, blood samples were collected from patients before initiation of treatment (baseline), after approximately 1 year of treatment when all patients were treated with Q2W and annually thereafter at time points when patients were treated with dupilumab Q4W and Q6W (group A) or Q2W only (group B).

Additionally, blood samples from 11 adult healthy volunteers without AD or any other atopic disease, were obtained from the Mini Donor Service at the University Medical Center Utrecht, the Netherlands. IgE levels were measured in serum by enzyme-linked immunosorbent assay (ELISA) as described previously.[5]

A total of 21 and 20 patients were included in group A and group B, respectively. An overview of the clinical characteristics is available via https://zenodo.org/record/8172077. There were no differences in both groups except for lower age at baseline in group B (27.9 vs. 47.0, *p*-value 0.027). Mean EASI at start of treatment was similar with a score of 17.24 and 19.37 in group A and in group B, respectively. In both groups, the mean EASI decreased significantly during treatment with dupilumab. It is clearly visible that the mean EASI in group A remains lower compared to group B, which can be explained by the fact that the patients in group A were able to extend the dosing interval due to well-controlled AD, whereas the patients in group B were not (Figure 1B). Total IgE levels in serum of all patients were significantly higher at baseline compared to healthy controls (Figure 1C). A consistent significant decrease of IgE levels was seen in group A when comparing all intervals with baseline (Figure 1C; left). From baseline to Q2W, and also from Q2W to Q4W and from Q4W to Q6W, a significant decrease in IgE levels was observed, indicating a continuing effect of dupilumab. When comparing these data with group B, a similar pattern of IgE decrease, with stabilization over time, was observed (Figure 1C; right). In both groups, a slight increase in IgE levels was observed in three patients when extending the interval from Q4W to Q6W or in the last sample taken when treated with Q2W. An explanation for this may be that these samples were taken during the hay fever season.

Our data suggest that IgE levels continue to decrease over time, and may reach a plateau in some patients. Mean IgE levels in both groups remain above the levels observed in healthy individuals, suggesting that certain patients with AD may not achieve IgE levels as low as those seen in healthy individuals, or that it will take longer for their levels to decrease. This can be explained by the fact that the

immune-modulating effect of dupilumab on B-cells, and thus eventually the decrease in IgE levels is slower than the immune-modulating effects on T-cells.[5] This could also mean that the increase in IgE levels would take some time. However, the mean duration on treatment with Q6W (group A) at time of sampling was 191 days, suggesting that IgE levels do not increase despite the interval prolongation. Previous studies have shown that dupilumab treatment in AD patients also reduces specific IgE levels against food- and respiratory

Summary box

- Overall, dupilumab significantly reduces IgE production up to a median of 2.5 years of treatment.
- IgE levels continue to decrease significantly over time irrespective of treatment interval.

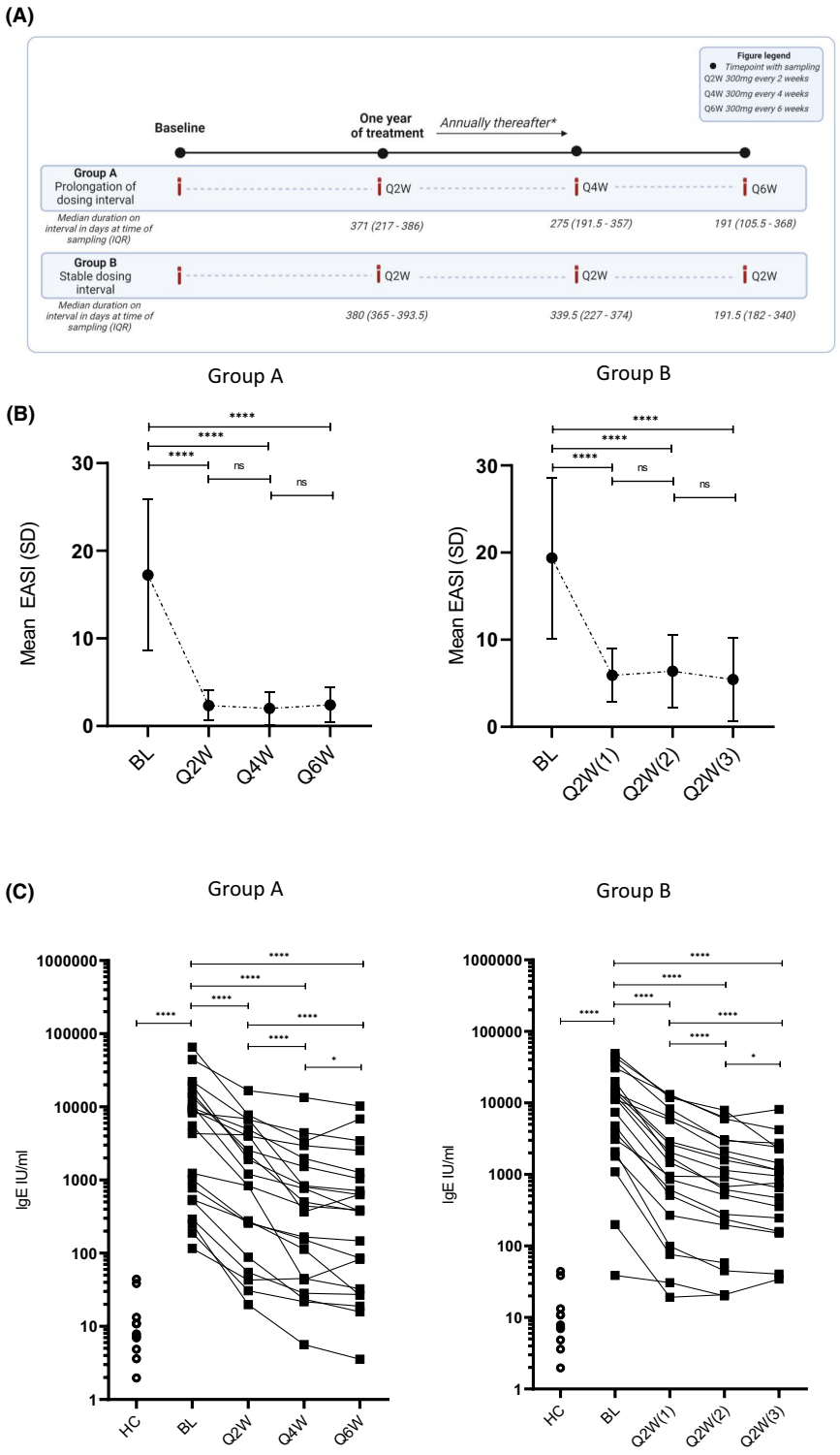

FIGURE 1 (A) Overview of blood sampling during treatment with dupilumab in group A and group B. *The exact time point in the year may vary from patient to patient. The median duration on interval in days at time of sampling is shown in the figure. (B) Mean EASI with standard deviation during treatment with dupilumab in group A (left) and group B (right). (C) Mean IgE in IU/ml during treatment with dupilumab in group A (left) and group B (right). Q2W, dupilumab 300 mg subcutaneously once every 2 weeks; Q4W, dupilumab 300 mg subcutaneously once every 4 weeks; Q6W, dupilumab 300 mg subcutaneously once every 6 weeks; EASI, eczema area severity index; BL, baseline; HC, healthy control; SD, standard deviation. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.005$ and $^{****}p < 0.001$.

proteins.[8,9] The included patients who showed an increase in serum IgE levels reported no complaints of pre-existing atopic comorbidities. Thus, our results suggest that the positive effect of dupilumab on atopic comorbidities persists even with slightly increased IgE levels during treatment compared to healthy controls, independent of the dose of dupilumab.

With the findings of our study it is demonstrated that dupilumab significantly reduces IgE production from baseline up to a median of 2.5 years of treatment. Our findings show that IgE levels continue to decrease significantly over time irrespective of treatment interval. This can play an important supporting role in the decision to extend the dosing interval of dupilumab in patients in whom AD is well controlled.

AUTHOR CONTRIBUTIONS

Conceptualization: CD, MMvdW, DSB, MdBW, FvW; Formal Analysis: CD, MMvdW; Funding Acquisition: FvW, MdBW; Investigation: CD, MMvdW, LvdN; Methodology: CD, MMvdW, LvdN; Resources: CD, MMvdW; Supervision: MdBW, FvW; Validation: FvW; Visualization: CD, MMvdW; Writing – Original Draft Preparation: CD; Writing – Review and Editing: MMvdW, DSB, LvdN, MdBW, FvW.

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CONFLICT OF INTEREST STATEMENT

CD has nothing to disclose. MMvdW has nothing to disclose. LvdN has nothing to disclose. DSB is a speaker for Sanofi Genzyme, Janssen, Novartis and LEO Pharma, all unrelated to this research. FvW is a speaker and/or consultant for Janssen, Johnson & Johnson and Takeda. She has received research funding from Leo Pharma, Takeda, Galapagos, Sanofi and Bristol-Myers Squibb, all unrelated to this research. MdB-W is a consultant, advisory board member and/or speaker for AbbVie, Almirall, Amgen, Aslan, Eli Lilly, Galderma, Janssen, Leo Pharma, Pfizer, Regeneron and Sanofi-Genzyme, all unrelated to this research.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This manuscript has not been published in whole or part elsewhere. The manuscript is not currently being considered for publication in another journal.

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