Original Article

DOI: 10.5582/ddt.2022.01046

The clinical significance of dupilumab-induced blood eosinophil elevation in Japanese patients with atopic dermatitis

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SUMMARY This study aims to clarify the clinical significance of dupilumab-induced elevation of blood eosinophil in Japanese patients with atopic dermatitis (AD). Eosinophil elevation was defined as ≥ 5% increase of eosinophil percentage within one year after dupilumab initiation. Seven patients (15.7%) were shown to have eosinophil elevation, six of whom developed dupilumab-associated conjunctivitis (DAC) and were accompanied with DAC more frequently than those without eosinophil elevation, with statistically significant difference. Eosinophil percentage resolved spontaneously in all seven patients, including the one without DAC, despite the continuation of dupilumab treatment. None of the patients with eosinophil elevation had cardiac or pulmonary complications attributable to the hypereosinophilia. The patients with eosinophil elevation were all male. Furthermore, none of four patients in whom efficacy of dupilumab was < 25% showed eosinophil elevation. Childhood onset tended to be more common in patients with the elevation of eosinophil. This study suggests that most eosinophil elevation is associated with DAC, and that the eosinophil ratio is a biomarker for DAC.

Keywords Atopic dermatitis, eosinophil, conjunctivitis

1. Introduction

Dupilumab is a fully human monoclonal antibody against the α subunit of the IL-4 receptor (IL-4Rα), which inhibits the IL-4/13 signaling pathway. This pathway is involved in various pathological conditions of atopic dermatitis (AD) including B-cell differentiation, IgE production, activation of eosinophils, basophils, or mast cells, Th2 immune response, goblet cell metaplasia and proliferation, epidermal barrier dysfunction, and inhibition of the production of anti-microbial peptides (*1,2*).

Biologic therapies such as dupilumab inhibit specific cytokine pathways and suppress inflammation in target organs, but sometimes paradoxically induce or increase inflammation in other organs, which are called paradoxical reactions (*3*). Blood eosinophil elevation is a known adverse effect of dupilumab in patients with AD, but it has not yet been the focus of any studies. This study aims to compare the clinical characteristics of patients with AD with and without the eosinophil elevation, and to clarify its clinical significance.

2. Methods

2.1. Patients

This study was approved by the Wakayama Medical University Institutional Review Board (No.3423), and written informed consent was obtained before patients were entered into this study, in accordance with the Declaration of Helsinki.

Medical information was collected from 46 patients with AD (thirty-four males and twelve females) who were treated with dupilumab between May 2018 and February 2022 at our institute. Their clinical features are shown in Table 1.

2.2. Clinical assessment

Patients who met the previously described diagnostic criteria (*4*) and who showed the characteristic features (pruritus, eczema with typical morphology and age-specific patterns and chronic or relapsing history, xerosis, atopic predisposition such as elevated IgE, medical history of allergic diseases, and family history) were defined as having typical AD.

As in a previous study (*5*), moderate, severe, and very severe AD before dupilumab were defined by Eczema Area and Severity Index (EASI) score ≥ 7, ≥ 21.1 and ≥ 50.1, respectively. In this study, efficacy of dupilumab was evaluated by the percentage improvement in EASI scores after the treatment compared to those before the

treatment. Blood eosinophil elevation was defined as ≥ 5% increase of eosinophil percentage within one year after initiation of dupilumab without any other causes.

The diagnosis and severity of conjunctivitis was evaluated based on clinical manifestation and ophthalmologic examination.

2.3. Statistical analysis

Statistical analysis was carried out with Fisher's exact probability test (2 × 2-table) and Pearson's chi-square tests (m × n-table) to compare percentages. Mann-Whitney tests were used to compare medians between the two groups. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical characteristics of patients with AD in the present study

Forty-six patients (34 males and 12 females, average age of 51.3 years), were diagnosed with AD based on previously published guidelines (*4*) (Table 1). Approximately 70% of them showed typical clinical manifestation with erythema, papules, scales, lichenification-based eczema lesions, characteristic rash distribution, atopic predisposition such as elevated IgE, medical history of allergic diseases, and family history. The past history of other allergic diseases was seen in 34.8% of the patients, among which allergic rhinitis (19.6%) and asthma (23.9%) were the most frequent. The childhood onset was in 13.0% of our patients, although the onset was not recorded for 24% patients. In terms of severity of AD before dupilumab initiation, 30.4% were moderate, 54.4% were severe, and 15.2% were very severe. More than 25% efficacy of dupilumab treatment was seen in nearly 90% of the patients. These results are consistent with previous large studies published in 2021(*6*) except for the percentage of childhood onset (13.0% *vs.* 37-39% respectively).

Table 1. Summary of clinical features in AD patients treated by dupilumab (n = 46)

Age at the time of dupilumab initiation (mean years)	51.3
Sex (male)	73.9
Clinical manifestation	
typical	69.6
atypical	30.4
Past history of other allergies	34.8
bronchial asthma	19.6
allergic rhinitis	23.9
Age of onset	
childhood	13.0
adult	63.0
Severity before dupilumab initiation	
moderate	30.4
severe	54.4
very severe	15.2
Mean eosinophilic percentage before dupilumab initiation	9.8
Efficacy of dupilumab	
75-100% improvement	28.3
25-75% improvement	63.0
0-25% improvement	8.7
Adverse effects	43.5
elevation of eosinophil	15.2
conjunctivitis	28.3

Unless indicated, values are percentages.

3.2. Correlation between blood eosinophil elevation and dupilumab-associated conjunctivitis (DAC)

Clinical characteristics were compared between patients with and without blood eosinophil elevation by dupilumab treatment (Table 2). When eosinophil elevation was defined as ≥ 5% increase of eosinophil percentage within one year after dupilumab initiation, seven patients (15.7%) showed the eosinophil elevation. In these patients, there were no evidence of parasitic infections or other hematologic diseases that are known to cause eosinophil elevation.

Six of these seven patients with eosinophil elevation developed DAC, while DAC was seen in only in seven of the 39 patients without eosinophil elevation. Patients with eosinophil elevation were therefore accompanied with DAC more frequently than those without, with statistically significant difference (p = 0.00106, by Fisher's exact test, Table 3). Only one patient with eosinophil elevation did not develop DAC; the patient received chemotherapy for cutaneous squamous cell carcinoma at the same time, but no causes of the eosinophil elevation other than dupilumab treatment could be identified.

When blood eosinophil percentage was compared to severity of conjunctivitis, in three (cases 1, 5, and 6) out of the six patients, the peak of eosinophil percentage mostly coincided with the most serious DAC (Figure 1). In these three cases, the eosinophil percentage decreased and DAC improved at the same time.

Eosinophil percentage resolved spontaneously in all seven patients, including one patient without DAC, despite the continuation of dupilumab treatment. None of the patients with eosinophil elevation had cardiac or pulmonary complications attributable to the hypereosinophilia.

3.3. Correlation of blood eosinophil elevation with other clinical features

There were no significant differences between AD patients with or without eosinophil elevation in mean age, clinical manifestation, past history of other allergies, severity before dupilumab initiation, or efficacy of dupilumab. Mean eosinophil percentage before dupilumab initiation was slightly higher in patients with eosinophil elevation than in patients without elevation.

On the other hand, although not statistically

Table 2. Correlation of clinical features and blood eosinophil elevation in AD patients treated by dupilumab (n = 46)

Items	Patients with elevated eosinophil (n = 7)	Patients without elevated eosinophil (n = 39)	p value
Age at the time of dupilumab initiation	53.3	51.0	0.810
Sex (male)	100	69.2	0.101
Clinical manifestation			1.000
typical	71.4	69.2	
atypical	28.6	30.8	
Past history of other allergies	28.6	35.9	0.479
bronchial asthma	0	23.1	
allergic rhinitis	28.6	23.1	
Age of onset			0.073
childhood	71.4	28.2	
adult	14.3	46.2	
Severity before dupilumab initiation			0.302
moderate	42.8	28.2	
severe	28.6	59.0	
very severe	28.6	12.8	
Mean eosinophilic percentage before dupilumab initiation	10.3	9.7	0.711
Efficacy of dupilumab			0.500
75-100% improvement	42.9	25.6	
25-75% improvement	57.1	64.1	
0-25% improvement	0	10.3	
Adverse effects			0.00106
conjunctivitis	85.7	17.9	

Unless indicated, values are percentages.

Table 3. Comparison of prevalence of conjunctivitis between AD patients with and without blood eosinophil elevation

Items	Conjunctivitis (+)	Conjunctivitis (-)	Total	p value
Elevation (+)	6	1	7	
Elevation (-)	7	32	39	
	13	33	46	0.00106

Eosinophil elevation is defined as ≥ 5% increase of eosinophil percentage within one year after dupilumab initiation. $^{*}p < 0.05$ using Fisher's exact probability test.

significant (p = 0.101 by Fisher's exact test), the patients with eosinophil elevation were all male, while male were only 69.2% of the patients without eosinophil elevation. Furthermore, although insignificant (p = 0.500), none of four patients in whom efficacy of dupilumab was < 25% showed eosinophil elevation.

Additionally, among the patients with eosinophil elevation, the number of patients with childhood onset was five, and adult onset was one (Table 4). Among those without eosinophil elevation, however, 11 had childhood onset and 18 had adult onset. Childhood onset tended to be more common in patients with eosinophil elevation, although without significant difference (p = 0.073).

4. Discussion

Blood eosinophil elevation has been previously reported in patients with AD treated with dupilumab, but the exact percentage of AD patients with the eosinophil elevation is unclear because there is no universally-accepted definition of eosinophilia (*7*).

As the mechanism, blockage of IL-4/13 signaling by the monoclonal antibody in mouse models prevents eosinophils from invading each organ, leading to accumulation of eosinophils in the bloodstream (*8*). Conversely, blood eosinophil elevation is not observed in all AD patients treated with dupilumab, so drug-induced changes of blood eosinophil number may depend on the levels of chemokine suppression by dupilumab and the speed of eosinophil production in each patient (*7*).

In the present study, clinical characteristics were compared between seven patients with (15.2%) and 39 patients without (84.8%) elevation of blood eosinophil. The incidence of DAC was significantly higher in patients with elevation. DAC is one of the most well-known adverse events of dupilumab. The high incidence of DAC by dupilumab is notably seen only in AD, and is less common in other allergic diseases, such as asthma or nasal polyps (*9*). The mechanism of DAC remains unclear, but suppression of goblet cell proliferation and mucin secretion by dupilumab may contribute to its development (*10,11*). Katsuta *et al.* (*12*) also compared the clinical features of AD patients with and those without DAC, and described that blood eosinophil number two month after the dupilumab therapy was significantly higher in those with DAC. Consistently, in the present study, four out of the six patients with DAC also had a peak of eosinophil elevation 2-4 months after administration, and in three out of the four patients, eosinophil percentage was proportional to the activity

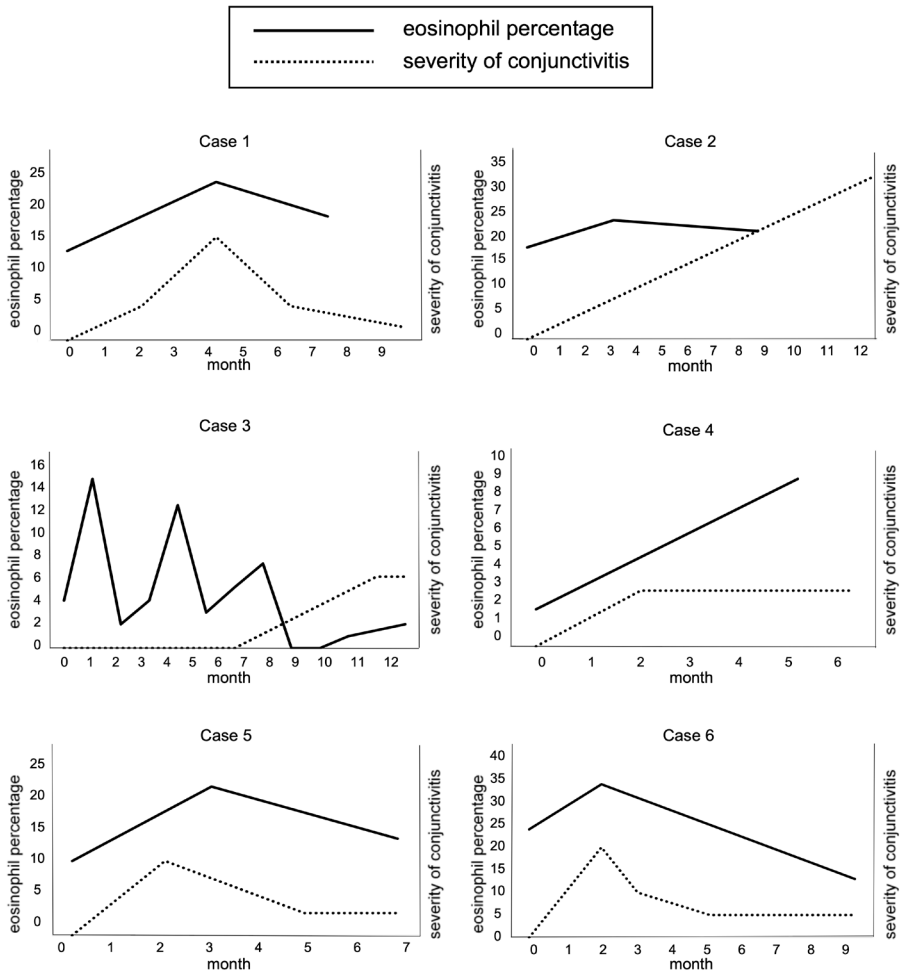

Figure 1. Correlation between eosinophil percentage and severity of conjunctivitis. Vertical axis: severity of conjunctivitis and eosinophil percentage; horizontal axis: month after dupilumab treatment. The solid and dotted lines indicate the eosinophil percentage and the severity of conjunctivitis, respectively. The results were compared for each.

Table 4. Comparison of onset age between patients with and without eosinophil elevation

Items	Childhood	Adult	Total	*p* value
Elevation (+)	5	1	6	
Elevation (-)	11	18	29	
	16	19	35	0.07

of DAC. In these three cases, maximum eosinophil percentage exceeded 20%, which was higher than the other three cases.

Taken together, this is the first report to identify the clinical characteristics of patients with AD with eosinophil elevation, and the results suggest that most eosinophil elevation may be seen in association with DAC. Blood eosinophil percentage can therefore be considered to be a predictive marker for DAC. Moreover, eosinophil elevation by dupilumab does not seem to cause organ damage, and moreover spontaneously disappears, so it is perhaps unnecessary to discontinue dupilumab.

In this study, although not significant, there were no patients showing low efficacy by dupilumab (0-25% improvement) in AD patients with blood eosinophil elevation, while such non-responder was seen only in those without eosinophil elevation. This may also be associated with the action of dupilumab to prevent migration of eosinophils from the bloodstream to the skin. We speculate, for example, that the lack of eosinophil influx into the skin tissue may attenuate the skin inflammation in patients with blood eosinophil elevation.

Similarly, although insignificant, there were more patients with childhood onset among those with eosinophil elevation, perhaps suggesting that the disease duration of AD may correlate with action of dupilumab. Compared with patients with adult-onset, for example, those with childhood onset may tend to have a longer Th2 immune response and increased eosinophil production speed in the bone marrow, resulting in the blood eosinophil elevation after dupilumab therapy. Lack of information of disease duration of several

patients in medical records was a limitation of this comparison.

In conclusion, seven patients (15.7%) among 46 patients with AD were considered to have elevation of blood eosinophil. Those with eosinophil elevation were accompanied with DAC more frequently than those without, with significant difference. Most eosinophil elevation may therefore be seen in association with DAC, and blood eosinophil percentage seems to be a predictive marker for DAC, although further studies with a greater number of patients are required.

Acknowledgements

We acknowledge editing and proofreading by Benjamin Phillis from the Clinical Study Support Center at Wakayama Medical University.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received June 10, 2022; Revised July 28, 2022; Accepted August 16, 2022.

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Released online in J-STAGE as advance publication August 21, 2022.