CASE REPORT

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Dupilumab suppresses relapsing chronic eosinophilic pneumonia with severe asthma

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ABSTRACT

Dupilumab-induced hypereosinophilia is mediated by blockade of the IL-4/IL-13 pathway, which reduces eosinophil migration from peripheral blood. The increase in peripheral blood eosinophils may lead to chronic eosinophilic pneumonia (CEP) and/or eosinophilic granulomatosis with polyangiitis, but a direct causal connection between dupilumab and eosinophilic lung diseases has not been established. A 33-year-old Japanese woman with bronchial asthma since age three was treated with fluticasone propionate plus salmeterol twice daily after several asthma exacerbations at age 17. Her course was complicated by CEP at age 33 which resolved without the need for systemic steroids. However, in the four months following resolution of her CEP, the patient had three asthma exacerbations, and a recurrence of CEP, with blood leukocytes of 8500/μL, of which 25.0% were eosinophils. She was treated with prednisolone 50 mg/day, but she could not continue this dose due to the onset of myalgia. Then she had relapsing CEP twice within three months. She was treated with prednisolone 15 mg/day for CEP, but she had persistent asthma for more than one month; dupilumab was added at 600 mg, followed by 300 mg every two weeks. In the first month of treatment with dupilumab, the patient's asthma symptoms resolved completely, and she had only one relapse of CEP. In 12 months of follow-up, she had neither an asthma exacerbation nor another relapse of CEP. Dupilumab may be a promising treatment for patients with refractory asthma complicated by recurring CEP and undesirable steroid side effects.

Keywords: chronic eosinophilic pneumonia, dupilumab, eosinophils, severe asthma, biologic drugs

Abbreviations:
CEP: chronic eosinophilic pneumonia
EGPA: eosinophilic granulomatosis with polyangiitis
GGO: ground-glass opacities
PSL: prednisolone

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INTRODUCTION

Dupilumab is one of five biologics licensed in Japan for the treatment of severe asthma. Dupilumab blocks type 2 inflammation by targeting the IL-4/IL-13 pathway.[1] IL-4 and IL-13 are key mediators of type 2 immune responses in which allergens act as the main antigen drivers. The aberrant expression and secretion of IL-4 and IL-13 have been implicated in the pathophysiology of allergic diseases, including asthma.[2] Dupilumab has been reported to be effective in severe asthma with baseline blood eosinophil count >150 cells/μL, FeNO >25 ppb, or both.[3]

In patients with severe asthma and a baseline peripheral blood eosinophil count ≥500 cells/μL, dupilumab suppresses asthma exacerbations and improves forced expiratory volume in one second (FEV_1).[4] Hypereosinophilia, with counts of 1500/μL or greater, is attributed to reduced eosinophil migration via IL-4/IL-13 pathway blockade[1]; it has been observed at least once during follow-up in some patients receiving dupilumab.[5] An association between dupilumab-induced elevated peripheral blood eosinophil counts and chronic eosinophilic pneumonia (CEP),[6] eosinophilic granulomatosis with polyangiitis (EGPA),[7,8] and eosinophilic gastroenteritis[9] has been reported, but these three diseases are likely to coexist with severe asthma, and the role of dupilumab in their pathogenesis remains unclear.

Here we report the case of a woman with recurrent, severe asthma and multiple relapses of CEP who developed peripheral blood eosinophilia during treatment with dupilumab, but whose asthma and CEP were well controlled.

CASE PRESENTATION

A 33-year-old Japanese woman had a two-year history of allergic rhinitis and mild bronchial asthma since age three; her several exacerbations per year responded to short-acting β-agonists. She presented to our hospital with persistent fever to 38.0 °C for four days, generalized malaise, sore throat, productive cough, and chest pain. She denied arthralgia, myalgia, and numbness. Her past medical history was notable for several asthma exacerbations during her pregnancy with her first child at age 17, for which she was prescribed fluticasone propionate (250 μg) plus salmeterol (50 μg) twice daily and the leukotriene receptor antagonist montelukast. She subsequently gave birth to her second and third children at ages 22 and 28 without recurrence of her asthma.

On presentation with the current illness, she had grade I wheezing and fine crackles, but lacked multiple polyneuropathies and skin involvement. Laboratory tests in this patient revealed white blood cells (6800/μL, of which 14.0% were eosinophils), elevated C-reactive protein (3.21 mg/L), high KL-6 (189 U/mL, normal range <500 U/mL), and were negative for myeloperoxidase-antineutrophil cytoplasmic antibodies. The serum total IgE level was 1660 IU/mL (normal: 173 IU/mL or less). Antigen-specific serum IgE to mites and cedar (*Cryptomeria japonica*) was detected at greater than 100 UA/mL; orchard grass, 50.1 UA/mL; alder, 49.3 UA/mL; ragweed, 38.3 UA/mL; aspergillus, 0.25 UA/mL; cat, 1.78 UA/mL. A chest radiograph revealed consolidation, ground-glass opacities (GGO) in the right upper and left upper and lower lung fields, and bilateral bronchial wall thickening. Chest computed tomography images showed continuous GGO and subpleural predominant, non-segmental consolidation concentrated in the right upper lobe, and continuous GGO from the pleura of the lower lobes bilaterally. Analysis of the bronchoalveolar lavage (BAL) fluid revealed 21.9% eosinophils, 27.8% lymphocytes, 14.3% monocytes, and 36.0% macrophages. A transbronchial lung biopsy showed interstitial pneumonia and alveolitis, eosinophil and lymphocyte infiltration and edema in the interstitium and alveoli, and intraluminal fibrosis. Examination of the bronchial mucosa revealed thickening of the airway

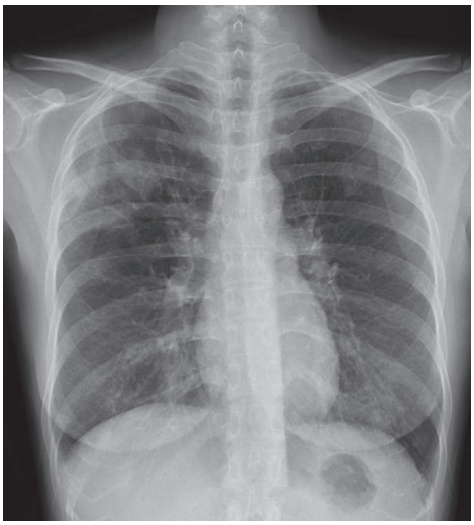

Fig. 1 Chest radiography on presentation to the hospital
Consolidation and ground-glass opacities (GGO) are present in right upper and left upper and lower lung fields. Bronchial wall thickening is visible in both lungs.

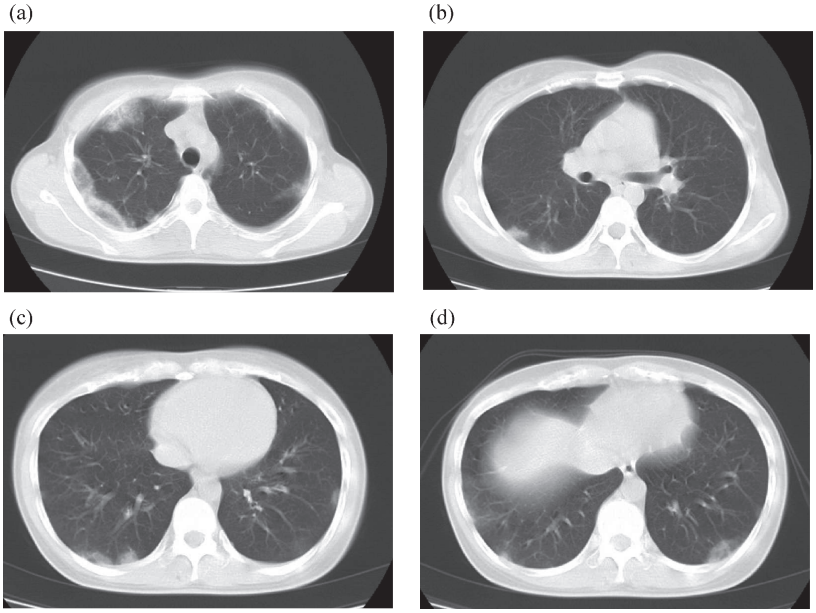

Fig. 2 Computed tomography of the chest during the first hospital visit
Fig. 2a, 2b: Upper lobes in the lung. Continuous GGO and pleural-based, non-segmental consolidation are prominent in the right upper lobe.
Fig. 2c, 2d: Lower lobes in the lung. Continuous GGO from the pleura can be seen in the lower lobes on both sides.
GGO: ground-glass opacities

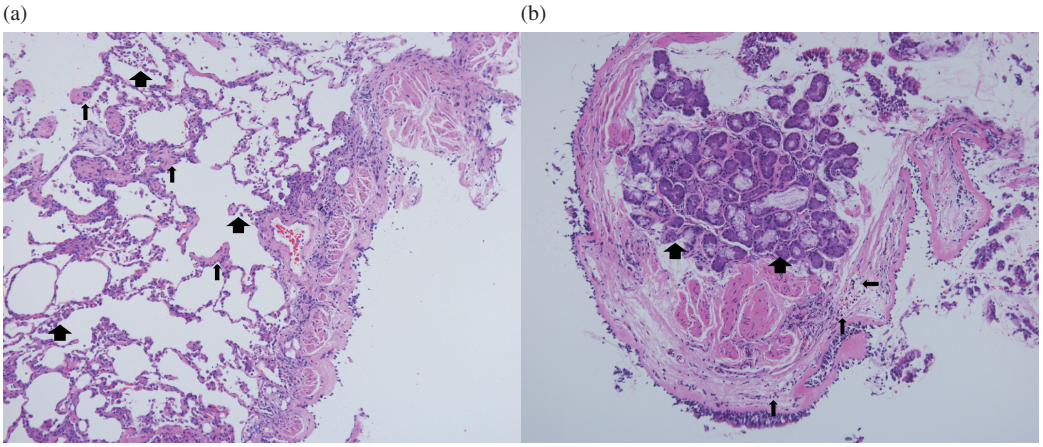

Fig. 3 Histopathology findings in the lungs and bronchi

Fig. 3a: Biopsy of right lower lobe. Infiltrates of eosinophils and lymphocytes are visible in the lung interstitium and alveoli (wide arrows). Intraluminal fibrosis and interstitial edema suggest alveolitis (narrow arrows).

Fig. 3b: Biopsy of bronchi. Bronchial mucosa showing thickening of the airway epithelium basement membrane, and hypertrophy of fibroblasts, smooth muscle cells, and goblet cells (wide arrows). Submucosal eosinophil infiltration (narrow arrows) is also present.

epithelial basement membrane; submucosal eosinophil infiltration; and fibroblast, smooth muscle cell, and goblet cell hypertrophy. Fractional exhaled nitric oxide (FeNO) was 55 ppb. Pulmonary function testing revealed vital capacity (VC) of 2.19 L, 77.1% predicted; FEV_1 of 2.65 L, 98.9% predicted; and maximum expiratory flow rate at 50% of forced vital capacity ($\dot{V}_{50}$) of 3.50 L, 79.2% predicted of 79.2%. Pulmonary function testing demonstrated small airway obstruction. Taken together, the patient's clinical presentation and laboratory results met the diagnostic criteria for CEP as modified by Marchand et al.[10] Whereas the patient's history of chronic sinusitis and maxillary sinus polyps could suggest EGPA, the absence of vasculitis (eg, peripheral neuropathy, skin eruptions, or arthralgias) and negative myeloperoxidase-antineutrophil cytoplasmic antibodies excluded the diagnosis.

After the diagnosis of CEP with asthma, the patient's fever resolved over the course three days without the need for systemic steroids. Her cough disappeared, the peripheral blood eosinophil counts normalized, and the chest radiograph no longer showed GGO in the bilateral upper and left lower lungs. However, in the four months following resolution of her CEP, the patient had three asthma exacerbations, and her FP dose was increased from 1000 μg to 1800 μg. Four months after the increase to FP1800 μg, she had asthma exacerbations and a recurrence of CEP, with blood leukocytes of 8500/μL, of which 25.0% were eosinophils. She was treated with prednisolone (PSL), 50 mg/day, which was tapered to 20 mg/day. After that, her asthma symptoms persisted. However, she could not continue this PSL dose due to the onset of myalgia; the PSL dose was reduced to 10 mg/day for one week and then discontinued. Her CEP improved, but her asthma symptoms persisted, and three months after discontinuing PSL, the CEP recurred, with peripheral blood leukocytes of 7000/μL, of which 21.0% were eosinophils. She was again started on PSL 10 mg/day, after which she defervesced, the GGO on her chest radiograph resolved, the eosinophil count normalized, and her asthma was better controlled. She discontinued the systemic steroids for a month and a half. Two months after stopping the PSL, her fevers and asthma symptoms returned, followed by another relapse of CEP, with leukocytes of

6800/μL and 35.0% eosinophils. PSL 15 mg/day was started after more than one month without improvement in her asthma, but she did not have concurrent CEP, 600 mg dupilumab injected subcutaneously was added, two weeks later by 300 mg every two weeks. In the first month of treatment with dupilumab, the patient's asthma symptoms resolved completely, and she had only one relapse of CEP one month after start of dupilumab.

Four months after starting dupilumab, the patient's peripheral blood leukocytes rose to 6000/μL, with 26.0% eosinophils, without any asthma symptoms or relapse of CEP. After nine months on dupilumab, the FP dose was reduced from 1600 μg to 1000 μg. In 12 months of follow-up, she did not have an asthma exacerbation or another relapse of CEP. Furthermore, after initiating dupilumab, the FeNO level decreased from 86 ppb to less than 20 ppb, and her small airway obstructive impairment markedly improved, as evidenced by increases in the $\%FEV_1$ and the $\%\dot{V}_{50}$.

The ethics committee at our hospital approved the study (2022-05), and written informed consent was obtained from this patient.

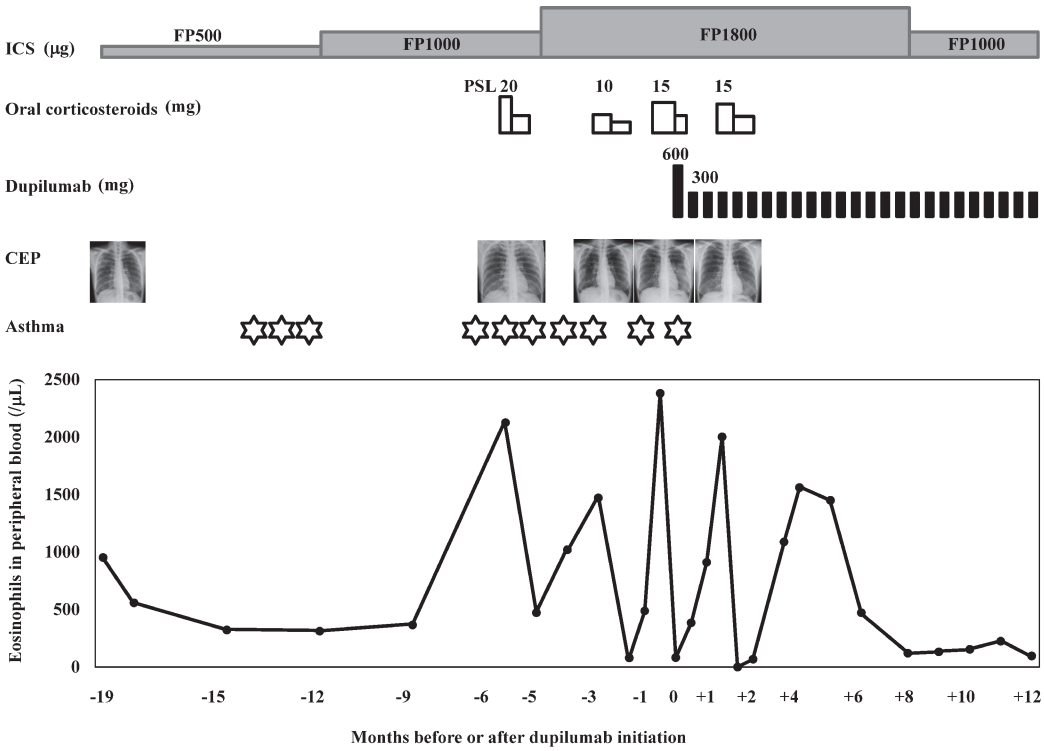

Fig. 4 Clinical course in which dupilumab suppressed CEP relapse

The patient's clinical course from her initial presentation with CEP to her last examination, showing multiple asthma exacerbations and CEP relapses, the time course of her treatments, and the corresponding changes in her eosinophil counts.

CEP: chronic eosinophilic pneumonia

FP: fluticasone propionate

ICS: inhaled corticosteroid

PSL: prednisolone

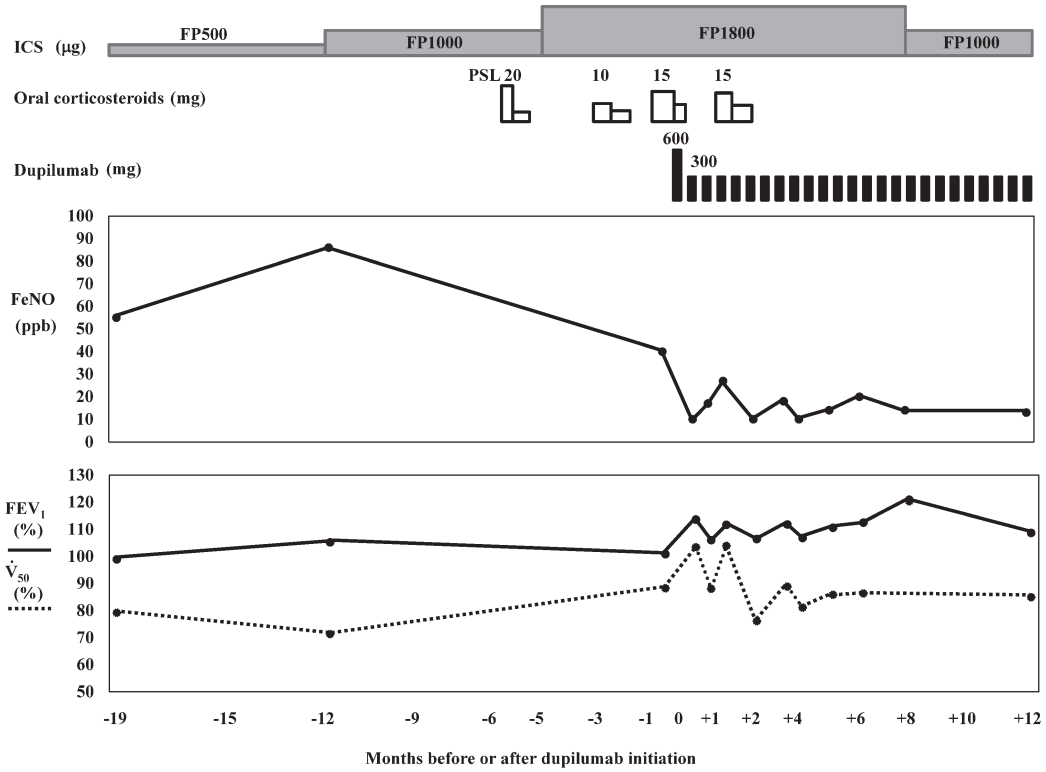

Fig. 5 Changes in FeNO and lung function throughout the course of disease
After starting dupilumab, the FeNO decreased and the $\%FEV_1$ and $\%\dot{V}_{50}$ increased, indicating better asthma control and improved lung function.
FeNO: fraction exhaled nitric oxide
$\%FEV_1$: percent forced expiratory volume in one second
FP: fluticasone propionate
ICS: inhaled corticosteroid
PSL: prednisolone
$\%\dot{V}_{50}$: percent maximum expiratory flow rate at 50% of forced vital capacity

DISCUSSION

Three criteria are needed for a diagnosis of CEP: respiratory symptoms of more than 2 weeks' duration; alveolar eosinophilia >25% on BAL fluid differential cell count or blood eosinophilia >1000/mm^3; and pulmonary infiltrates on chest imaging, usually with a peripheral predominance.[10] In actuality, many cases of CEP do not meet these strict diagnostic criteria.[11] For example, in patients with CEP who present with progressive EGPA, the percentage of eosinophils in BAL fluid varies from 8% to 71%.[12] CEP may be a presenting feature of or overlap with EGPA.[13,14] It is not known what determines whether a patient with asthma who develops CEP will develop EGPA. We previously reported that many patients with CEP also have severe asthma, and proposed that maintaining sufficient regulatory T cells might inhibit EGPA development in patients with asthma and CEP via the action of cytokines such as IL-10 and IL-2 produced by $CD4^+CD25^+$ or $CD4^+CD25^-$ T cells.[15] Guillevin et al described triggering factors that preceded the onset of EGPA by up to several months, including the rapid discontinuation of oral corticosteroids.[16]

Six biologic therapies are currently used overseas for severe asthma, including omalizumab (anti-IgE), mepolizumab (anti-IL-5), benralizumab (anti-IL-5R), reslizumab (anti-IL-5), dupilumab (anti-IL-4Rα), and tezepelumab (anti-thymic stromal lymphopoietin).[17] Asthma exacerbations might be decreased by treatment with omalizumab, mepolizumab, benralizumab, or dupilumab in patients with peripheral blood eosinophils ≥150 cells/μL.[18] As no head-to-head comparisons between these biologics have been attempted, there is no evidence of the superiority of any of these biologic agents over the others.[19] In patients with peripheral blood eosinophils ≥150 cells/μL and FeNO ≥25 ppb, both mepolizumab and dupilumab might inhibit asthma exacerbations.[20] Dupilumab is indicated in children, adolescents, and adults with severe type 2 asthma with FeNO >25 ppb or with peripheral blood eosinophil counts of 150–1500/μL.[3,17]

The hypereosinophilia in patients with asthma receiving dupilumab is due to reduced eosinophil migration from the blood to target tissues mediated by IL-4/IL-13 pathway blockade.[1] Inhibiting eotaxin-3, vascular cell adhesion molecule-1, and thymus and activation-regulated chemokine without simultaneously inhibiting bone marrow eosinophilopoiesis leads to the accumulation of eosinophils in the blood.[1] Dupin et al observed hypereosinophilia ≥1500/mm^3 at least once during follow-up in 16 of 64 patients (25.0%) with severe asthma treated with dupilumab.[5] Elevated eosinophil counts persisted for longer than 6 months in 8 (13%) of them. The increase in blood eosinophil count did not modify the clinical response to treatment during the study period.

It has also been reported that dupilumab reduces the number of peripheral blood eosinophils in eosinophilic esophagitis, one of the hypereosinophilic diseases, and improves the symptoms of esophagitis.[21] However, several cases reported a patient with dupilumab-associated hypereosinophilia who developed CEP.[6,22] Also reported have been eosinophilic pleuritis following administration of dupilumab,[23] and EGPA during treatment with dupilumab for nasal polyposis[7] and severe asthma,[8] and after discontinuing dupilumab.[24] In some asthma patients treated with dupilumab, EGPA has been observed with reduction in their oral steroid dose. However, in a previous report, dupilumab was administered to 26 patients with severe asthma, and only 1 patient (3.8%) developed chronic eosinophilic pneumonia.[25] In QUEST clinical trial,[3] peripheral eosinophilia was observed in 52 (4%) of 1263 patients, and only 2 patients (0.15%) were complicated by severe chronic eosinophilic pneumonia. We considered that eosinophilic pneumonia induced by dupilumab was a rare adverse event. We administered dupilumab instead of mepolizumab or benralizumab to patients for severe asthma and recurrent eosinophilic pneumonia. There were several reasons that this patient had sinusitis as a complication. We expected that she would suppress an increase of eosinophilia in peripheral blood after administration of dupilumab because she treated with systemic corticosteroid already, and so she preferred a biologic that could be self-injected at home. Our patient had a single recurrence of CEP associated with the first transient peripheral blood eosinophilia after initiation of dupilumab. When this patient developed eosinophilic pneumonia, we confirmed that she had no symptoms other than fever and we continued administration of dupilumab.

Dupilumab,[24] omalizumab[26] and benralizumab[27] are all used to improve asthma control. Unlike omalizumab and benralizumab, however, dupilumab has been shown to decrease the estimated rate of severe exacerbations and improve pre-bronchodilator FEV_1 levels; these effects appear to depend on the increase in peripheral blood eosinophil counts.[4] It is not clear whether the increase in blood eosinophils seen in some patients receiving dupilumab can induce CEP or a vasculitis such as EGPA. In many cases, the symptoms of an underlying vasculitis become apparent as the steroid dose is reduced. We previously reported a patient whose severe EGPA and asthma was resistant to mepolizumab, 300 mg per month, but was treated successfully with dupilumab[28]; in this case, dupilumab treated both vasculitis-associated bilateral pulmonary thromboemboli and asthma. We considered that rituximab might contribute to activated B cell reconstruction.

Our prior research demonstrated an association between increased peripheral blood type 2 innate lymphoid cell (ILC2) counts and EGPA disease activity.[29] Furthermore, another study reported that patients whose asthma was treated successfully with the combination of dupilumab and rituximab had lower peripheral blood ILC2 levels than those not receiving dupilumab.[30] Thus, we consider dupilumab to be a good therapeutic option in patients with severe asthma and EGPA, given its ILC2-reducing and type 2 inflammation-suppressing mechanisms of action.[1]

In conclusion, in our patient with severe, inhaled corticosteroid-resistant asthma and multiple relapses of CEP, treatment with dupilumab resulted in good control of her asthma symptoms and only one recurrence of CEP over the course of 12 months. A transient steep rise in her blood eosinophils was not associated with recurrence of her asthma or eosinophilic pneumonia, and her overall condition remained extremely good. However, the effect of dupilumab on eosinophilic pneumonia or EGPA has not been fully explored. We recommend that the efficacy of dupilumab in hypereosinophilic disease be evaluated in prospective studies.

CONFLICT OF INTEREST

No author has any conflict of interest to disclose.

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