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Letter to the Editor

Successful concomitant therapy with mepolizumab and dupilumab for atypical eosinophilic granulomatosis with polyangiitis

Dear Editor,

Eosinophilic granulomatosis with polyangiitis (EGPA) is a necrotizing granulomatous vasculitis with eosinophilia that presents with asthma and various other symptoms. Mepolizumab, a humanized monoclonal antibody against interleukin (IL)-5, significantly reduces exacerbation of severe eosinophilic asthma, which results in a longer period of disease remission in a higher proportion of patients with EGPA.^{1,2} Dupilumab, a humanized monoclonal antibody against the alpha subunit of the IL-4 receptor, can reduce severe exacerbations, improve airflow limitation, and decrease fractional exhaled nitric oxide (FeNO) levels in patients with eosinophilic asthma.³ The interaction between IL-5 and IL-4/13 pathways in the pathogenesis of EGPA remains unclear. Herein, we report a case in which EGPA became apparent after switching from benralizumab to dupilumab, and asthma symptoms could not be controlled with high dose mepolizumab alone, but with concomitant use of both mepolizumab and dupilumab.

A 42-year-old man presented with severe asthma. He was diagnosed at 36 years of age, accompanied by hypereosinophilia and an absolute blood eosinophil count of 2420/ μ L. He was treated with inhaled corticosteroid with a combination of long-acting beta-2 agonist, long-acting muscarinic agonist, and oral prednisolone (PSL), and subsequently with omalizumab at 37 years and quit smoking 20 cigarettes per day at 38 years. However, omalizumab was discontinued due to insufficient efficacy. At age 40, because of uncontrolled asthma, biologics were restarted with mepolizumab (100 mg, monthly) and then benralizumab (30 mg, every two months) at age 42; however, his asthma was difficult to control, and the dose of PSL could not be reduced below 15 mg/day. The biologic agent was switched to a 600-mg loading dose of dupilumab, followed by a 300-mg dose every 14 days. Three weeks later, he was admitted to our hospital with a fever of over 38 °C, the presence of sinusitis, and patchy infiltration shadows in both lung fields on chest computed tomography (Fig. 1A). Laboratory test results revealed elevated white blood cell count and C-reactive protein level but no elevation of eosinophils or IgE (Supplementary Table 1). Proteinase 3-antineutrophil cytoplasmic antibodies (ANCA), which had been positive only once, three years before the onset of EGPA, was negative, and myeloperoxidase-ANCA was also negative. Histological examination of the transbronchial lung biopsy specimen revealed the features of eosinophilic pneumonia (Fig. 1B) and possible features of healed arteritis (damage due to a previous episode of arteritis) (Fig. 1C). Although necrotizing

granulomatous inflammation was not identified, these histologic features were compatible with a case of EGPA. There were no findings suggestive of renal or cardiac dysfunction, peripheral neuropathy, gastrointestinal disorders, or skin rash. He was finally diagnosed with EGPA, based on the American College of Rheumatology 1990 criteria.⁴ The patient was then treated with high-dose corticosteroids (methylprednisolone [mPSL], 1000 mg, daily for three days, followed by oral PSL therapy), intravenous cyclophosphamide (IVCY; 1000 mg, monthly), and mepolizumab (300 mg, monthly) instead of dupilumab. His systemic manifestations, as well as the patchy infiltration shadows in the lung (Fig. 1D), improved quickly. However, 16 weeks after the treatment for EGPA was initiated, his asthma control test (ACT) score dropped from 19 to 14, and his forced expiratory volume in one second (FEV1) decreased from 3.77 L to 2.27 L. Furthermore, his FeNO rose from 34 ppb to 208 ppb. Regardless of the improvement in systemic manifestations due to vasculitis, worsening of asthma was observed. Because of the highly elevated FeNO, indicating the involvement of the IL-4/13 pathway,⁵ we decided to administer dupilumab (300 mg, every 14 days) as a concomitant treatment of mepolizumab. After initiation of dupilumab, the dyspnea was relieved, and FEV1 improved from 3.84 L to 4.43 L in three months. No adverse events related to the biologic agents have been observed until the last follow-up (Fig. 2).

This is the first report of successful treatment of severe refractory asthma caused by EGPA using concomitant mepolizumab and dupilumab therapy. IL-5, which aids in the activation, proliferation, and maturation of eosinophils, is an essential type 2 cytokine involved in the pathogenesis of severe asthma, and its blood level is known to be elevated in patients with EGPA. Mepolizumab, which blocks the IL-5-dependent pathway, could therefore ameliorate the clinical course of EGPA.⁶ The IL-4/13 axis may also play an important role in the pathogenesis of EGPA. Increased levels of type 2 cytokines, including IL-4 and IL-13, have been reported in the blood of patients with EGPA.⁵ Moreover, mRNA levels of not only IL-5 but also IL-4 were elevated in the bronchoalveolar lavage fluid obtained from patients with active EGPA.⁷ A case of dupilumab improving the airway goblet cell metaplasia in the bronchi of a patient with severe asthma associated with EGPA was reported, suggesting that the activation of the IL-4/13 pathway may affect the pathogenesis of EGPA.⁸

In our case, systemic manifestations of EGPA, such as fever and lung infiltration shadow, improved with a high-dose corticosteroid, IVCY, and mepolizumab therapy. However, the rising FeNO level and airflow limitation, which consequently deteriorated the patient's asthma control, could not be managed with mepolizumab

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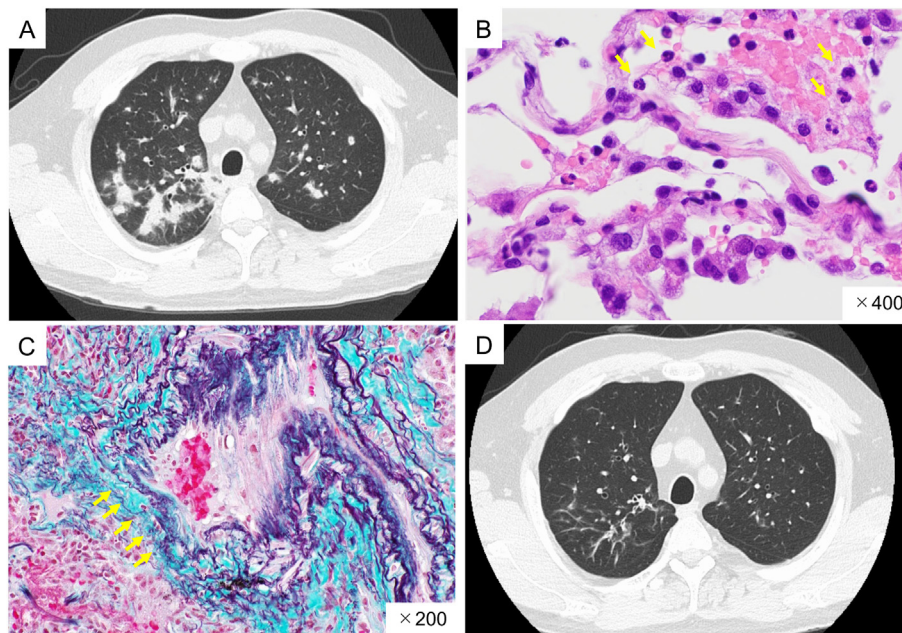


Fig. 1. Representative images of the case. **A:** Chest computed tomography scan on admission. **B:** Pathological findings (hematoxylin and eosin stain) of a lung specimen showing an alveolar-filling process consisting of eosinophils (yellow arrows) and macrophages and mild interstitial inflammation with numerous lymphocytes and scattered eosinophils. **C:** In the small-sized artery without cellular infiltration of the artery wall, elastic Masson-Goldner staining shows fibrous thickening of the intima and tunica media thinning, with disorganized arrangements and focal loss of elastic lamina (yellow arrows) without arterial wall cellular infiltration. **D:** Chest computed tomography image acquired 12 weeks after initiation of treatment for eosinophilic granulomatosis with polyangiitis.

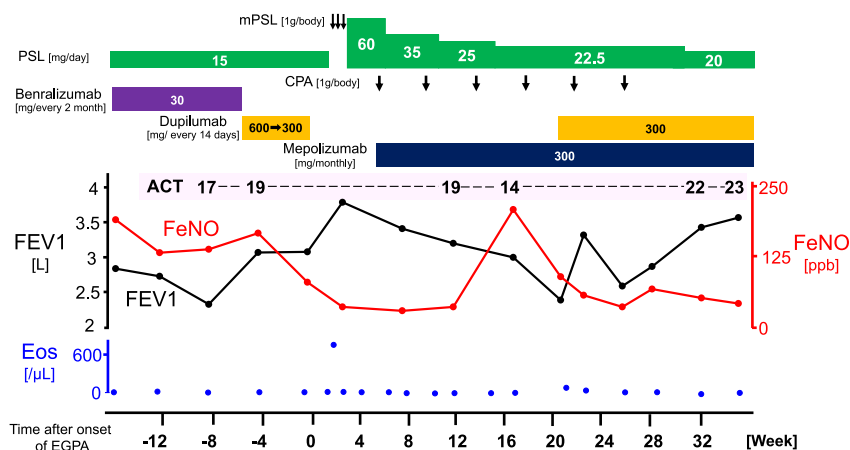


Fig. 2. The clinical course of the case. The X-axis indicates the time after eosinophilic granulomatosis with polyangiitis (EGPA) onset. The top column presents the duration and dose of each treatment. The lines for FEV1 (black), FeNO (red), and absolute blood eosinophil count (blue) are presented; the lower column shows the ACT score. mPSL, methylprednisolone; PSL, prednisolone; CPA, cyclophosphamide; ACT, asthma control test; FEV1, forced expiratory volume in one second; FeNO, fractional exhaled nitric oxide; Eos, absolute number of eosinophils in peripheral blood; EGPA, eosinophilic granulomatosis with polyangiitis.

alone but were controllable with concomitant dupilumab therapy. In addition, a previous study has reported a case of EGPA after switching from anti-IL-5 or anti-IL-5R therapy to dupilumab,⁹ which resembles our case. These findings indicate that the IL-5 pathway may play a pivotal role in controlling systemic manifestations of EGPA. These data suggest that the IL-5 and IL-4/13 pathways might be involved in manifesting different phenotypes of EGPA. Inhibiting the IL-4/13 pathway may be beneficial in the phenotypes with elevated FeNO, and inhibiting the IL-5 pathway may be beneficial in the phenotypes with predominant eosinophilic inflammation. As shown in this case, various cytokines may be involved in the pathology of EGPA, and suppression of a single

cytokine may not be sufficient to control the disease in some cases. In this regard, a combination of biologics, such as that used in our case, might be a useful and reasonable treatment option for refractory asthma phenotypes in EGPA.

It has been reported that a one-month transient combination of mepolizumab and dupilumab was successfully used in pediatric cases of refractory asthma in EGPA.¹⁰ In these cases, mepolizumab administration was discontinued one month after the initiation of dupilumab. On the contrary, we continued concomitant therapy with mepolizumab and dupilumab for more than 16 weeks because the patient's EGPA became active immediately after switching from benralizumab to dupilumab. Further accumulation

of cases is desirable to investigate whether transient or long-term combination therapy with dupilumab is preferable for cases of mepolizumab-resistant asthma of EGPA.

In this case, there were no symptoms of vasculitis other than fever, and no active vasculitis could be identified histologically. The clinical course of this case may be atypical for EGPA, but this may be due to the influence of continuous systemic steroids. Therefore, the diagnosis of EGPA in patients using continuous systemic steroids is an issue hereafter.

Herein, we report a case of refractory asthma caused by EGPA. Concomitant use of mepolizumab and dupilumab was safe and effective for the control of disease manifestations. The clinical course of the case suggested the involvement of the IL-5 pathway and IL-4/13 pathways in the independent manifestation of EGPA phenotypes.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2021.11.003>.

Conflict of interest

The authors have no conflict of interest to declare.

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Supplementary Table 1: Laboratory data on admission

Biochemistry			Blood count			Immunologic test		
TP	7.0	g/dL	WBC	16000	/μL	IgG	1334	mg/dL
Alb	3.4	g/dL	Neut	89.3	%	IgE	194	
Na	140	mmol/L	Eosin	0.3	%	KL-6	133	U/mL
K	4.7	mmol/L	Lymp	7.9	%	sIL-2R	548	U/mL
Cl	106	mmol/L	Hb	12.6	g/dL	ANA	<2.0	
Ca	8.9	mg/dL	Plt	580	10 ³ /μL	ss-DNA	<2.0	AU/mL
BUN	12.4	mg/dL	Coagulation test			ds-DNA	<2.0	IU/mL
Crea	0.91	mg/dL	PT	13.1	sec	SS-A	<1.0	U/mL
T-Bil	0.5	mg/dL	APTT	37.6	sec	SS-B	<1.0	U/mL
AST	33	U/L	D-dimer	1.2	μg/mL	PR3-ANCA	<0.5	IU/mL
ALT	38	U/L				MPO-ANCA	<0.5	IU/mL
LDH	260	U/L						
γ-GTP	110	U/L						
ALP	297	U/L						
CK	94	U/L						
CRP	7.74	mg/dL						
BNP	<5.8	pg/dL						

TP : total protein, BUN : blood urea nitrogen, T-Bil : total-bilirbin, AST : aspartate aminotransferase, ALT : alanine aminotransferase, LDH : lactate dehydrogenase, γ-GTP : γ-glutamyl transpeptidase, ALP : alkaline phosphatase, CK : creatine kinase, CRP : C-reactive protein, BNP : brain natriuretic peptide, WBC : white blood cell, Neut : neutrophil, Eosin : eosinophil, Lymp : lymphocyte, Hb : hemoglobin, Plt : platelet, PT : prothrombin time, APTT : activated partial thromboplastin time, KL-6 : sialylated carbohydrate antigen KL- 6, sIL2-R : soluble interleukin-2 receptor, ANA : anti-nuclear antibody, ss-DNA : single stranded DNA, ds-DNA : double stranded DNA, SS-A : Sjögren's syndrome–A, SS-B : Sjögren's syndrome-B, PR3-ANCA : proteinase3- anti-neutrophil cytoplasmic antibody, MPO-ANCA : myeloperoxidase-anti-neutrophil cytoplasmic antibody