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Letter to the Editor

Successful management of eosinophilic chronic rhinosinusitis complicated by severe asthma using dupilumab, following negative initial results with benralizumab

Dear Editor,

Eosinophilic chronic rhinosinusitis (ECRS) is a subtype of refractory chronic rhinosinusitis (CRS) characterized by ethmoid-predominant sinusitis with eosinophilic infiltration, and frequent complicated by asthma.^{1,2} Although appropriate endoscopic sinus surgery (ESS) and post-operative management are necessary, there are currently no well-established treatments.

An anti-IL-4R α monoclonal antibody, dupilumab, was approved for the treatment of atopic dermatitis, severe asthma and refractory CRS with nasal polyps (CRSwNP). We herein report the case of a patient with severe asthma complicated with ECRS, whose ECRS symptoms improved after the administration of dupilumab, but not benralizumab, an anti-IL-5R α monoclonal antibody.

A 49-year-old male, who had aspirin sensitivity and allergic rhinitis to house dust mite, presented with nasal discharge, nasal obstruction and hyposmia. At 25 years of age, he had been diagnosed with asthma, and initiated inhaled corticosteroids (ICS)/long-acting beta-agonist (LABA) treatment. At 49 years of age, nasal polyps (NP) in the bilateral middle nasal meatus were detected at another clinic, and he was referred to our hospital. The blood eosinophil percentage was 16.3% and total IgE level was 314 IU/mL. The pathological finding of NP tissue showed enriched infiltration of eosinophils (135 eosinophils/HPF). The sinus CT scan revealed soft-tissue shadows in the bilateral paranasal sinuses. Based on these findings, we diagnosed him as having severe ECRS complicated by asthma. We performed ESS and short term oral corticosteroid (OCS) treatment. After the operation, his nasal symptoms and asthma control improved, but they gradually worsened with the reduction of OCS treatment. At 1 year after the operation, CT scan and endoscopic findings showed a relapse of ECRS (Fig. 1A, B). Additionally, his asthma control also declined, despite his regular use of high-dose inhaled fluticasone furoate/vilanterol trifenatatec (200 μ g/day) and pranlukast hydrate, and the occasional use of OCS. We consulted with respiratory physician about his condition, and initiated biologics therapy for refractory asthma complicated by a recurrence of ECRS.

Before the initiation of biologics, he showed a high level of eosinophil numbers in blood and NP tissue and high exhaled fraction of nitric oxide (FeNO) level. Based on his eosinophilic dominant status, we initiated benralizumab at first. After the initiation, blood eosinophils immediately decreased. At 4 months after the

initiation, the infiltrated eosinophils in NP were not detected, however the size of NP did not improve (Fig. 1E, F). Lung function test and FeNO levels were not changed, but serum IgE levels gradually increased. Eventually, his symptoms and CT scan did not improve (Table 1, Fig. 1D). We judged that benralizumab treatment was not effective on his asthma and ECRS conditions, and change the biologics from benralizumab to dupilumab.

After the initiation of dupilumab, blood eosinophils significantly increased, peaking at 8 weeks, before rapidly decreasing to just below the baseline levels. On the other hand, total IgE levels decreased to the normal level. At 4 months after the initiation of dupilumab, lung function test had not changed, but FeNO level and the numbers of infiltrated eosinophils in NP decreased compared to the baseline (Table 1, Fig. 1I). His nasal and asthma symptoms, endoscopic findings and CT scan showed great improvement (Fig. 1G, H).

In the 12 months that followed after initiation of dupilumab therapy, he continued to receive dupilumab every 14 days for severe asthma. There has been no recurrence of nasal symptoms or exacerbation of asthma. Obviously, his clinical course should be followed for a long time. However, he has no need for OCS or re-operation for maintaining his asthma and ECRS conditions at the time of writing this report.

IL-4 and IL-13, produced by TH2 cells, ILC2s, mast cells, basophils and eosinophils have an important role in the development of type 2 inflammation, such as tissue remodeling, mucus hypersecretion, and recruitment of inflammatory cells, in airway inflammatory diseases including asthma and ECRS.^{2–4} It has been reported that the greater clinical effect was observed when dupilumab was initiated for patients with severe asthma who showed high levels of FeNO (≥ 25 ppb) and blood eosinophils (≥ 300 cells/ μ L) in the intention-to-treat population.⁵ Benralizumab, which blocks IL-5-dependent signaling pathways and allows nearly complete depletion of eosinophils by natural killer cell-mediated antibody-dependent cellular cytotoxicity, is approved for severe eosinophilic asthma, and is still undergoing clinical trials for CRSwNP.⁶ It has been reported that the best biomarker to predict the efficacy of benralizumab is blood eosinophils, but not FeNO and total IgE levels.⁷ However, he showed broad type 2-high inflammation status including the high levels of FeNO and total IgE that are useful biomarker for prediction of anti-IL-4/IL-13 therapy, in addition to increased blood eosinophils. This might be one of the reasons that the present case is

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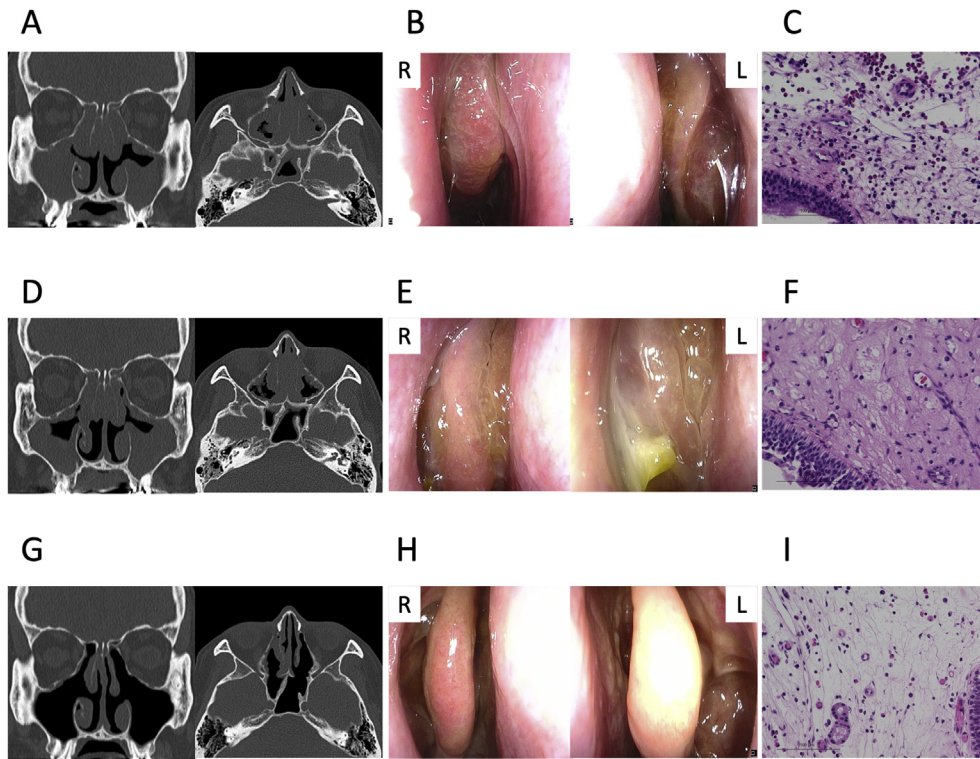


Fig. 1. Sinus computed tomography (CT) images, nasal endoscopic findings of the middle meatus and histological images of hematoxylin-eosin stained nasal polyp (NP) tissue (x400). (**A, B, C**) Prior to biologics treatment, the relapse of eosinophilic chronic rhinosinusitis (ECRS) was observed. CT scans showed soft tissue shadows almost fully occupied in bilateral paranasal sinuses. Nasal polyp and sticky nasal discharge were detected in the both sides of the middle nasal meatus. The massive numbers of infiltrated eosinophils were observed in NP tissue. (**D, E, F**) Four months after the initiation of benralizumab therapy, significant improvement was not observed in CT scan and endoscopic findings, whereas the numbers of the numbers of infiltrated eosinophils in NP tissue disappeared. (**G, H, I**) Four months after dupilumab therapy. CT scans showed clearness in the bilateral paranasal sinuses. Nasal endoscopy showed clear shape of the middle nasal turbinate and remarkable decrease of nasal polyp in the middle nasal meatus and olfactory cleft. The numbers of infiltrated eosinophils in NP tissue decreased in comparison with the baseline level.

Table 1
The clinical course before and after biologics treatment.

	Before initiation of biologics	Benralizumab treatment				Dupilumab treatment			
		Post 1 month	Post 2 months	Post 3 months	Post 4 months	Post 5 months	Post 6 months	Post 7 months	Post 8 months
Blood test									
WBC (/μL)	4700	3700	3300	3100	3600	5500	8700	4600	5400
Eosinophil (%)	17.4	0.0	0.0	0.0	0.0	25.0	30.5	13.1	10.7
Eosinophil (/μL)	818	0	0	0	0	1375	2654	603	578
Total IgE (IU/mL)	368	547	1300	892	1070	543	365	199	174
Lung function									
FEV1 (L)	3.42				3.29				3.29
%FEV1 (%)	82.81				78.11				79.47
PEF (L/sec)	10.26				9.15				9.46
FeNO									
FeNO (ppb)	95				89				45
Lung symptom									
ACT score	11	15	13	12	11	21	25	23	23
Nasal symptom									
Total score	18	18	19	17	18	9	10	3	3
Nasal polyp tissue									
Numbers of the infiltrated eosinophils (/HPF)	133				0				23

The clinical condition of asthma was evaluated by asthma control test score, lung function test and exhaled fraction of nitric oxide (FeNO). The clinical condition of eosinophilic chronic rhinosinusitis (ECRS) was evaluated by nasal symptom score and biopsy of nasal polyp tissue. We evaluated the degree of patient's nasal discharge, nasal obstruction, post nasal drip, hyposmia and decline in quality of life by visual analog scale (0: none, 1: very mild, 2: mild, 3: moderate, 4: severe, 5: very severe, 6: worst), and defined total score as nasal symptom score. We averaged the numbers of infiltrated eosinophils in nasal polyp tissue in three high power fields (HPF, x400).

sensitive to dupilumab but not benralizumab treatment, however further investigation is needed. Although biologics targeting type 2 inflammation are shown to be effective on severe asthma, the precise way to select the appropriate biologics has not yet been well established.

In spite of eradicating eosinophils from blood and NP, benralizumab did not show favorable clinical response in this case. No previous report has shown that benralizumab increases total IgE level. Meanwhile, total IgE level fluctuates greatly in patients with poor control of asthma, and in clinical practice, systemic corticosteroids, seasonal pollinosis (eg. cedar pollinosis) and cigarette smoking are known as factors affecting total IgE level.^{8,9} Neither factor can be considered as the cause of increase in total IgE level after benralizumab treatment in this case, thus precise mechanism is unknown. On the other hand, dupilumab immediately improved the clinical status in both ECRS and asthma, and reduced total IgE levels, FeNO values and the number of infiltrated eosinophils in NP, although blood eosinophils were elevated. It has been reported that dupilumab treatment was associated with transient eosinophilia, that was observed in 14% of the patients with severe asthma. This phenomenon is speculated that dupilumab inhibits the production of eotaxin and vascular cell adhesion molecule 1 that promote eosinophil migration into tissue.¹⁰ Whereas IL-5 and eosinophils have an important role in pathophysiology of asthma and ECRS, other factors such as IL-4 and IL-13 that drive IgE production from B-cells, promote inducible nitric oxide synthase from airway epithelium and cause tissue eosinophilia, might be considered as the central inflammatory mediators of this patient.^{11,12}

This is the first case report that dupilumab showed the great clinical effect on ECRS complicated by severe asthma, following negative response of benralizumab. Biologics are expected to be an epoch-making treatment choice for refractory airway inflammatory disease, but further investigation including identifying the suitable biomarkers for deciding which biologics, are needed.

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This observational study was approved by Showa University ethical committee (approval number 2862).

Conflict of interest

The authors have no conflict of interest to declare.

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