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Letter to the Editor

Cycling therapy with benralizumab and dupilumab for severe eosinophilic asthma with eosinophilic chronic rhinosinusitis and eosinophilic otitis media

Dear Editor,

Eosinophilic inflammation plays a crucial role in the development of not only severe asthma but also eosinophilic chronic rhinosinusitis (ECRS) or chronic rhinosinusitis with nasal polyp (CRSwNPs) and eosinophilic otitis media (EOM).^{1,2} Amelink *et al.* reported that the prevalence of CRSwNP was more than 50% in patients with severe asthma.³ Biologics such as omalizumab, mepolizumab, benralizumab, reslizumab, and dupilumab have emerged as effective treatments for severe asthma. Recent studies have reported on “super-responders” those who have an excellent response to biologics, resulting in complete cessation of exacerbations and allowing for discontinuation of systemic steroids.⁴ However, patients with severe asthma may not become “super-responders” with only one biologic. In this situation, recent studies have reported using dual biologics.⁵ This report aims to introduce a new treatment option of cycling therapy using 2 biologics (benralizumab and dupilumab) for severe eosinophilic asthma with ECRS and EOM.

We describe the case of a 43-year-old woman, non-smoker, diagnosed with asthma at the age of 22. She was not aspirin intolerant. She complained of hearing loss and otorrhea and was diagnosed with EOM at the age of 36. Omalizumab was started at a dose of 300 mg once monthly due to recurrent asthma exacerbations 2 months after the diagnosis with EOM. Her body weight at this time was 53.5 kg, and total IgE level was 171 IU/mL. She did not experience asthma exacerbations for 2 years after the initiation of omalizumab. However, subsequently, she experienced recurrent asthma exacerbations. Thus, 5.5 years after the initiation of omalizumab, her medication was changed to mepolizumab 100 mg once monthly. Despite the new medication, she continued to have recurrent asthma exacerbations. She was then referred to the Department of Respiratory Medicine of Tango Central Hospital 8 months after the initiation of mepolizumab. Her body mass index was 21.7 kg/m². Her blood eosinophil counts were 1.4% (80/μl), and FeNO level was 30 ppb. Her total IgE level was 225 IU/mL, whereas specific IgE levels for Japanese cedar, cypress, alder, cockroach, dog dander, and cat dander were all negative. She complained of loss of smell in addition to wheezing and shortness of breath. Sinus computed tomography findings were scored according to the Lund–Mackay score (LMS) system,⁶ resulting in total LMS of 9 points with predominant opacification of the ethmoid

sinuses (Fig. 1A). Peak blood eosinophil counts were 14.6% before the initiation of mepolizumab. According to the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) score system,¹ the JESREC score was 15 points; thus, she was diagnosed with severe ECRS. Her % predicted FEV₁ and FEV₁/forced vital capacity were 33.3% and 50.0%, respectively. Figure 2 shows the status of exacerbations of asthma and EOM, the status of using systemic steroids, and changes in blood eosinophil counts, % predicted FEV₁, total LMS, asthma control test score, and FeNO levels after the referral. She was receiving four puffs of fluticasone 125 μg/formoterol 5 μg twice daily and tiotropium (soft mist inhaler) 5 μg once daily. We modified the inhaled corticosteroid therapy to four puffs of budesonide 160 μg/formoterol 4.5 μg twice daily with a technique of nasally exhaling after inhaling at “fast” inspiratory flow⁷ and added montelukast 10 mg once daily and prednisone 15 mg every other day. After 3 months, prednisone was discontinued. At this time, the patient's sense of smell slightly improved, and total LMS decreased to 6 points (Fig. 1B). 4.5 months after the referral, the patient developed an asthma attack requiring the use of systemic corticosteroids without exacerbations of ECRS and EOM. This prompted a shift of medication from mepolizumab to benralizumab 30 mg every 8 weeks after an initial three doses given every 4 weeks. After the initiation of benralizumab, no exacerbations of asthma were noted. However, 14 months after the initiation of benralizumab, exacerbations of ECRS and EOM with the reduced sense of smell and hearing and otorrhea were noted without asthma exacerbations. Total LMS increased to 12 points (the 8th injection of benralizumab) (Fig. 1C). As the patient needed prednisone (5 mg once daily) for one week, we shifted from benralizumab to dupilumab 300 mg (initial dose of 600 mg) every 2 weeks. Three months after the initiation of dupilumab, the patient's sense of smell and hearing improved, and otorrhea was reduced. Total LMS decreased to 10 points (Fig. 1D). However, blood eosinophil counts increased from 0% to 25.3% (the 7th injection of dupilumab). No sensory disturbance and motor weakness were noted. Chest x-ray revealed no remarkable abnormalities. Eosinophil counts continued to increase, and she experienced twice asthma attacks requiring the use of systemic corticosteroids without exacerbations of ECRS and EOM. Therefore, cycling therapy was initiated 5.5 months after the initiation of dupilumab (the 11th injection of dupilumab), which comprised of a cycle of dupilumab administration four times every 2 weeks a month after a single administration of benralizumab. Total LMS decreased to 0 point

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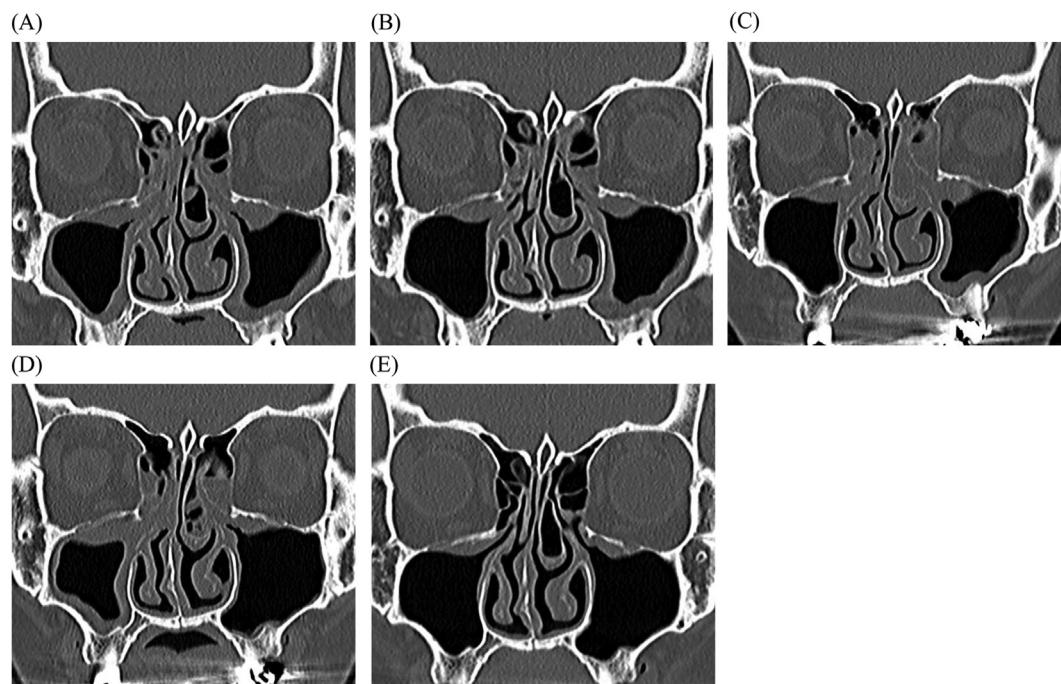


Fig. 1. Sinus computed tomography images at the time of referral (A), 3.5 months after the referral (B), 14 months after initiation of benralizumab (C), 3 months after initiation of dupilumab (D), and 8 months after initiation of cycling therapy (E).

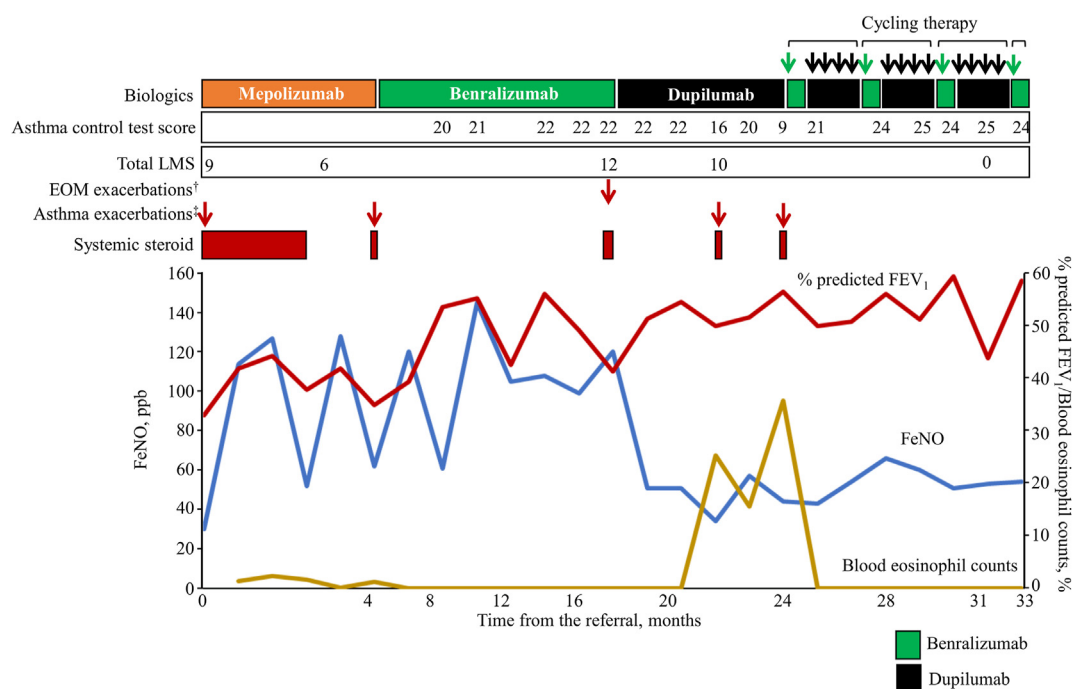


Fig. 2. Status of exacerbations of asthma and EOM, status of using systemic steroids, and changes in blood eosinophil counts, % predicted FEV₁, total LMS, asthma control test score, and FeNO levels after the referral. [†]EOM exacerbations were defined as acute events requiring systemic steroids. [‡]Asthma exacerbations were defined as acute events requiring systemic steroids. EOM, eosinophilic otitis media; LMS, Lund–Mackay score.

8 months after the initiation of cycling therapy (three rounds of cycling therapy) (Fig. 1E). The patient did not use SABA and systemic steroids and did not experience adverse effects during 11 months of follow-up. FeNO levels tended to decline following the initiation of dupilumab (Fig. 2).

In this case, omalizumab did not control asthma in the long term, whereas its biologic effect to ECRS and EOM was unknown.

The patient was a “super responder” to benralizumab, although this biologic did not control her ECRS and EOM in the long term. On the other hand, mepolizumab and dupilumab controlled ECRS and EOM, although these biologics did not control asthma in the short and long term. Finally, the patient was considered a “super responder” to cycling therapy, which achieved good control of both ECRS and EOM. This evidence suggested a benefit in

simultaneously targeting IL-4, IL-5, and IL-13 pathways. During the cycling therapy, benralizumab was administered every 3 months, because a single administration of this drug archived maintenance of low eosinophil counts for up to three months.⁸

The patient was a “super responder” to benralizumab and not mepolizumab. As described in Figure 2, the patient did not experience asthma exacerbations when her blood eosinophil counts were 0. Benralizumab reduces the absolute number of eosinophils in plasma and tissue more effectively than mepolizumab.⁹ This effect is considered to be beneficial to this case.

Dual or even cycling therapy can be used if a single biologic cannot achieve adequate asthma control.⁵ We employed cycling therapy, as we thought it could be more useful than dual biologics therapy for the following reasons. First, cycling therapy costs less than dual biologics therapy; if benralizumab and dupilumab are used as biologics, dual biologics therapy costs, on average, around 500,000 yen per month while cycling therapy using these drugs costs around 130,000 to 360,000 yen per month. Although these therapies are expensive, this can be offset by the reduced cost of hospitalizations and emergency room visits and increase in work productivity. To maximize the cost-effectiveness of these therapies, patients must be carefully selected.¹⁰ Second, if patients respond to dual biologics therapy, cycling therapy represents a useful “step down” from dual therapy. Third, if an adverse event occurs, this causal drug can be more easily identified under cycling therapy than under dual biologics therapy.

Only one biologic cannot control both asthma and comorbidities ECRS and EOM. Cycling therapy using two biologics can create “multi-super-responders” in management and treatment of not only severe asthma but also ECRS and EOM like our patient. Future studies are needed to evaluate the safety, efficacy, and cost-effectiveness when using multiple biologics to treat severe asthma.

Conflict of interest

The authors have no conflict of interest to declare.

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