Efficacy of Mepolizumab Extended Interval Dosing for 2 Asthmatic Patients With Chronic Eosinophilic Pneumonia

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Chronic eosinophilic pneumonia (CEP) is characterized by infiltration of eosinophils into lung tissue, which is often preceded by or concomitant with allergic diseases such as asthma and allergic rhinitis [1]. Interleukin (IL) 5 is involved in eosinophil proliferation, migration, and activation, and perhaps also in development of CEP [2]. Mepolizumab, a humanized anti–IL-5 monoclonal antibody, was shown to be effective in a retrospective study [3] and in several case reports [4-6]. Although standard interval dosing (SID) of mepolizumab for asthma is every 4 weeks, the appropriate interval for CEP has not yet been investigated. We present 2 patients with corticosteroid-refractory CEP and asthma who were able discontinue corticosteroid treatment following treatment with mepolizumab. In addition, extended interval dosing (EID) of mepolizumab (4 weeks to 8 weeks) did not lead to asthma exacerbations or relapse of CEP for over a year.

The first patient was a nonsmoking 24-year-old man. In 2006, he was diagnosed with asthma and CEP and started prednisolone at 25 mg/d. CEP was diagnosed based on infiltration shadows in the bilateral upper lobes of the lungs in a computed tomography (CT) scan and the presence of eosinophilia. Transbronchial lung biopsy (TBLB) and bronchoalveolar lavage fluid (BALF) samples were not taken. The patient was relocated to our hospital in May 2011, and prednisolone treatment was tapered and discontinued in August 2015. In February 2016, he visited our hospital with a 2-week history of dyspnea. His chest CT scan showed peripherally predominant ground glass shadows in the left upper lobe, and his peripheral blood eosinophil count was 1220/μL. There were no diagnostic findings of other eosinophilic lung diseases, such as parasitic infections, vasculitis, allergic bronchopulmonary aspergillosis, or drug-induced pneumonia. He was diagnosed with relapse of CEP according to reported diagnostic criteria [7], and prednisolone was reintroduced at 25 mg/d. He was also treated with inhaled 100 μg fluticasone furan carboxylate/25 μg vilanterol trifenatate once daily, montelukast sodium 10 mg/d, and suplatast tosilate 300 mg/d for asthma. In January 2017, his peripheral blood eosinophil counts were still high at 730/μL with prednisolone 4 mg (Supplementary Figure 1A). Therefore, subcutaneous mepolizumab was started at 100 mg every 4 weeks. Spirometry showed the percentages of predicted forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) before treatment with mepolizumab to be 97.7% and 89.9%, respectively. After introduction of mepolizumab, no asthma attacks or exacerbations of the shadow were observed. Prednisolone was discontinued 10 months after the introduction of mepolizumab. There was no subsequent relapse, and 14 months after introduction, dosing of mepolizumab was reduced to once every 8 weeks. Three years have passed since the first dose of mepolizumab, and about 2 years have passed since dosing was changed to once every 8 weeks; no clear relapse of CEP has since been observed (Supplementary Figure 1A).

The second patient was a nonsmoking 26-year-old woman. In 2013, she was diagnosed with asthma and CEP, and treatment was started. CEP was diagnosed based on bilateral lung infiltration shadows on a CT scan, eosinophilia, and increased eosinophils in BALF (48.5%). TBLB was not performed. Prednisolone was reduced to 7 mg/d. Further dose reduction was difficult, however, owing to the increase in peripheral blood eosinophils. In November 2017, the patient was referred to our hospital. In July 2018, her blood eosinophil levels had increased to 1130/μL, and the CT scan showed peripherally predominant infiltrative shadows in both lungs when prednisolone was reduced to 5 mg/d. The patient was diagnosed with relapse of CEP, and treatment was started with subcutaneous mepolizumab 100 mg every 4 weeks. Her asthma was treated with inhaled budesonide 160μg/ formoterol fumarate hydrate 4.5 μg (2 puffs, twice daily), montelukast sodium 10 mg/d, and suplatast tosilate 200 mg/d. Spirometry before treatment with mepolizumab showed the FVC and FEV_1 percentages to be 63.9% and 53.1%, respectively. After introduction of mepolizumab, no further asthma attacks or exacerbations of the CEP shadows were observed, and prednisolone was discontinued 7 months after initiation of mepolizumab. There were no subsequent relapses, and 12 months after its introduction, dosing of mepolizumab was changed to once every 8 weeks. The disease did not progress. Two years have passed since the first administration of mepolizumab, and about 1 year since dosing was changed to once every 8 weeks. No clear relapse of CEP has been observed since (Supplementary Figure 1B). The respiratory function of both patients is shown in Supplementary Figure 1. Respiratory function improved in both cases, with no obvious adverse events after introduction of mepolizumab.

We found mepolizumab to be effective for the treatment of corticosteroid-refractory CEP in patients with asthma. Suplatast tosilate can suppress IL-4 and IL-5 production in T_H2 cells and was administered in the hope that it would be effective in the treatment of both asthma and CEP. One reason why mepolizumab is effective in CEP is the formation of eosinophilic abscesses in the alveolar lumina [8]. Drugs with a marked ability to remove eosinophils from peripheral blood, such as mepolizumab, are more effective than corticosteroids, which suppress inflammatory cells, because CEP is localized in the alveolar lumina, where the blood supply is abundant. Mepolizumab has been administered at 300 mg every

4 weeks, ie, 3 times the dosage used for asthma, in diseases such as eosinophilic granulomatosis with polyangiitis, which is caused by eosinophil infiltration into various organs [9]. Tsukamoto et al [10] showed EID to be possible with mepolizumab, because mepolizumab considerably reduced the blood eosinophil count until the 57th day when 75 mg was administered intravenously (equivalent to 100 mg administered subcutaneously) [10]. The effect of mepolizumab in reducing eosinophils may persist beyond 4 weeks. The dosing interval of mepolizumab for CEP could be extended to 4 weeks or longer, depending on the disease type. Further studies are needed to establish an appropriate SID for mepolizumab in the treatment of CEP.

We report the first successful treatment of asthma patients with corticosteroid-resistant CEP using EID of mepolizumab. Compared with previous studies, we found no asthma exacerbations or relapse of CEP following EID of mepolizumab. Mepolizumab may help to reduce medical costs and disease burden in asthma patients with CEP.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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