Efficacy of Mepolizumab Extended Interval Dosing For Two Asthmatic Cases with Chronic Eosinophilic Pneumonia

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Chronic eosinophilic pneumonia (CEP) is characterized by infiltration of eosinophils into the lung tissue, 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 CEP development [2]. Mepolizumab, a humanized anti-IL-5 monoclonal antibody, has been shown to be effective in a retrospective study [3] and 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 two patients with steroid-refractory CEP with asthma, who could discontinue corticosteroid treatmentfollowing treatment with mepolizumab. In addition, extended interval dosing (EID) of mepolizumab from 4 weeks to 8 weeks did not produce asthma exacerbation or CEP relapse for over a year.

The first case was a non-smoker, 24-year-old man. In 2006,he was diagnosed with asthma and CEP and started taking 25 mg/day of prednisolone.

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CEP was diagnosed based on infiltration shadows in the bilateral upper lobes of the lungs in a computed tomography (CT) scan, and eosinophilia. Transbronchial lung biopsy (TBLB) and bronchoalveolar lavage fluid (BALF) were not performed. In May 2011, he was relocated to our hospital, and prednisolone treatment was tapered and discontinued in August 2015.In February 2016, he visited our hospital due to dyspnea lasting for 2 weeks. His chest CT scan showed peripherally predominant ground glass shadows in the left upper lobe, and peripheral blood eosinophil countwas1,220/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 CEP relapse according to the CEP diagnostic criteria [7], and prednisolone was reintroduced at 25mg/day. He was also treated with inhaled 100 μg fluticasone furan carboxylate /25 μg and vilanteroltrifenatate once daily, 10 mg/day montelukast sodium, and 300 mg/day suplatasttosilate for asthma. In January 2017, his peripheral blood eosinophil counts were still high at 730/μl on 4 mg prednisolone (Figure 1A Supplementary).Therefore,100 mg subcutaneous mepolizumab every 4 weeks was started. The percentages of predicted forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) examined using spirometry before mepolizumab treatment were 97.7% and 89.9%, respectively. After

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introduction of mepolizumab, no asthma attack or exacerbation of the shadow was observed. Prednisolone was discontinued 10 months after the introduction of mepolizumab. There was no subsequent relapse, and 14 months after introduction, the administration period of mepolizumab was changed to once every 8 weeks. Currently, 3 years have passed since the first administration of mepolizumab, and about 2 years have passed since the administration was changed to once every 8 weeks, and no clear CEP relapse has been observed (Figure 1ASupplementary).

The second case was a non-smoker, 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%). Transbronchial lung biopsy (TBLB) was not performed. Prednisolone was reduced to 7 mg/day, but further dose reduction was difficult, due to increase in peripheral blood eosinophils. In November 2017, she relocated to our hospital. In July2018, blood eosinophil levels increased to 1130/μl and CT scanning showed peripherally predominant infiltrative shadows in both lungs when prednisolone was reduced to 5 mg/day. The patient was diagnosed with CEP relapse, and subcutaneous treatment with 100 mg of mepolizumab every 4 weeks was started. Her asthma was treated with 160 μg inhaled budesonide /4.5 μg formoterol fumarate hydrate, two inhalations

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at a time, twice a day, 10 mg/day montelukast sodium, and200 mg/day suplatasttosilate. Predicted FVC and FEV_1 percentages, examined using spirometry before mepolizumab treatment were 63.9% and 53.1%, respectively. After introduction of mepolizumab, no asthma attack or exacerbation of CEP shadows was observed, and prednisolone was discontinued 7 months after mepolizumab introduction. There was no subsequent relapse, and 12 months after its introduction, the administration period of mepolizumab was changed to once every 8 weeks. No disease progression was subsequently observed. Two years have passed since the first administration of mepolizumab, and about 1 year since the administration period was changed to once every 8 weeks. No clear CEP relapse has been observed (Figure 1B Supplementary). Respiratory functions of both patients are shown in Figure1Supplementary. Both patients showed improved respiratory functions with no obvious adverse events after introduction of mepolizumab.

We have shown the efficacy of mepolizumab on steroid-refractory CEP with asthma. Suplatasttosilate can suppress IL-4 and IL-5 production from T helper 2 (Th2) cells and was administered expecting it to be effective in the treatment of both asthma and eosinophilic pneumonia. One reason why mepolizumab is effective in CEP is the formation of eosinophil abscesses in the alveolar lumina [8].Drugs with a strong ability to remove eosinophils from

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peripheral blood, such as mepolizumab, are more effective than corticosteroids that suppress inflammatory cells because CEP is localized in the alveolar lumina, which have an abundant blood flow. Mepolizumab has been reported in diseases such as EGPA, caused by eosinophil infiltration into systemic organs, at 300 mg every 4 weeks, three times the dosage used for asthma [9]. EID in mepolizumab is possible because mepolizumab maximally reduces the blood eosinophils count until the 57th day when 75mg is administered intravenously, equivalent to 100mg administered subcutaneously[10]. The effect of mepolizumab in reducing eosinophils may persist beyond 4 weeks. The interval dosing 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 of mepolizumab for CEP.

We first reported the successful treatment of asthma patients with steroid-resistant CEP using EID of mepolizumab. We found no asthma exacerbation or CEP relapse following mepolizumab EID compared to previous studies. Mepolizumab may contribute to reducing medical costs and patient burden for asthma patients with CEP.

Conflict of interest

No potential conflict of interest was disclosed.

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