Benralizumab use in chronic eosinophilic pneumonia with eosinophilic bronchiolitis and chronic airway infection

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Abstract
Chronic eosinophilic pneumonia (CEP) is a rare disorder characterized by marked accumulation of eosinophils in lung tissues and/or bronchoalveolar lavage fluid (BALF). Patients with CEP usually respond well to corticosteroids. However, more than half of these patients relapse while tapering and/or after discontinuing corticosteroids. Long-term adverse effects of corticosteroids can be serious. We report a case of comorbid CEP, severe bronchial asthma, eosinophilic bronchiolitis, and chronic airway infection. Corticosteroid treatment induced remission of the CEP, but recurrent exacerbation of the chronic airway infection occurred. Thus, she was treated with benralizumab, a monoclonal antibody against the alpha-chain of interleukin-5 receptor. After the initiation of benralizumab, the steroid was stopped successfully and her CEP, asthma, and airway infection remained well controlled. Micronodular nodules on high-resolution computed tomography (HRCT) reflecting bronchiolitis were also improved with benralizumab treatment. Benralizumab may be a treatment option for patients not tolerating steroids.

Introduction
Chronic eosinophilic pneumonia (CEP) is an idiopathic disorder characterized by an abnormal accumulation of eosinophils in the interstitium and alveolar spaces of the lungs. The standard treatment for CEP is the administration of corticosteroids, but drug-related complications occur often. Here, we report a case of successful benralizumab treatment for comorbid CEP, severe bronchial asthma, and chronic airway infection.

Case Report
An 83-year-old female never-smoker was referred to our hospital for evaluation of persistent productive cough and an abnormal lung shadow on chest imaging. She had been diagnosed with bronchial asthma more than 20 years earlier. She used a medium-dose inhaled corticosteroid (ICS) plus a long-acting β2-agonist and a leukotriene receptor antagonist. Her oxygen saturation in ambient air was 97% with few rhonchi. Chest radiography revealed scattered infiltrates with peripheral predominance on both lung fields (Fig. 1A), and chest high-resolution computed tomography (HRCT) showed bilateral consolidation with a micronodular shadow mainly in the right upper lobe (Fig. 2A). A pulmonary function test demonstrated forced expiratory volume in 1 sec (FEV1) of 0.77 L and FEV1/forced vital capacity (FVC) of 52.0%. The dose of ICS was increased due to poor bronchial asthma control after admission. A laboratory analysis revealed eosinophilia (white blood cell count: 4540/μL; eosinophils: 1580/μL) and elevated immunoglobulin E (842 IU/mL). Aspergillus-specific immunoglobulin E was negative and central bronchiectasis was not observed. Both myeloperoxidase-anti-neutrophil cytoplasmic antibody (ANCA) and proteinase 3-ANCA were negative. Computed tomography (CT) showed mucosal thickening of maxillary sinus, but any other sign or symptom of vasculitis was not observed. Connective tissue disease-related autoantibodies were absent. The medication history did not suggest drug-induced interstitial lung diseases. Moderate infiltration of eosinophils in the alveolar wall was confirmed by transbronchial lung biopsy. Bronchoalveolar lavage fluid...
(BALF) from the right B4 segment showed increased eosinophils (74%). Based on these findings, we diagnosed CEP. Concurrently, *Pseudomonas aeruginosa* was isolated from culture of BALF.

After the initiation of 20 mg of daily prednisolone, her symptoms improved, and the consolidation on chest X-ray and micronodular shadows on HRCT partly disappeared (Figs. 1B, 2B). However, three weeks after initiating corticosteroid, the productive cough worsened and new infiltrates appeared on chest X-ray, accompanied by elevated C-reactive protein and neutrophils in her peripheral blood (Fig. 1C). Sputum culture yielded *Moraxella catarrhalis* and *P. aeruginosa*. Garenoxacin treatment cured the bacterial pneumonia and prednisolone was tapered gradually to 7.5 mg. However, 12 weeks after initiating corticosteroid treatment, she developed another bacterial pneumonia. Her asthma has not been well controlled despite undergoing step 5 treatment according to the Global Initiative for Asthma guideline. Thus, she was given benralizumab to spare the steroid and to get better control of asthma. After
initiating benralizumab, prednisolone was stopped successfully without any obvious exacerbation of CEP and bronchiolitis (Figs. 1D, 2C). Her asthma got well controlled, and her FEV₁ increased to 1.24 L 10 months after commencing benralizumab.

Discussion

Patients with CEP usually respond well to corticosteroids. However, more than half of these patients relapse while tapering and/or after discontinuing corticosteroids. Long-term adverse events including infections caused by steroids are serious issues. No alternative therapy for CEP has been established. Benralizumab, a monoclonal antibody against the alpha-chain of interleukin (IL)-5 receptor, induces nearly complete depletion of eosinophils through enhanced antibody-dependent natural killer cell-mediated cytotoxicity. Benralizumab reduces exacerbations and improves lung function in patients with severe eosinophilic asthma. It also shows oral corticosteroid-sparing effect in patients relying on oral corticosteroids for severe asthma associated with eosinophilia [1]. In addition, efficacy of benralizumab and mepolizumab, anti-IL-5 monoclonal antibody, has been reported in eosinophilic granulomatosis with polyangiitis and the hypereosinophilic syndrome. Eosinophilic involvement of the lung was often observed in these diseases. Benralizumab decreases mucosal/submucosal eosinophils by more than 95% and peripheral eosinophils by 100% within 12 weeks of administration [2]. Although the pathogenesis of CEP remains poorly elucidated, its histopathology is characterized by both interstitial and alveolar exudates with eosinophils. Thus, benralizumab may be a reasonable treatment option for depletion of eosinophils accumulated in lung tissues.

In this case, micronodular shadows suggestive of bronchiolitis were observed on HRCT. Positive BALF and sputum cultures strongly suggested a chronic airway infection. However, the micronodular shadows on HRCT improved with corticosteroid treatment, and did not relapse after benralizumab administration. The clinical course suggested coexisting eosinophilic bronchiolitis. Eosinophilic bronchiolitis is a rare disorder, which is defined based on the following criteria: (1) blood eosinophil cell count >1 G/L and/or bronchoalveolar lavage eosinophil count >25%, (2) persistent airflow obstruction despite high-dose bronchodilators and corticosteroids, and (3) eosinophilic bronchiolitis at lung biopsy and/or direct signs of bronchiolitis (centrilobular nodules and branching opacities) on CT [3]. Our patient fulfilled all these criteria. Long-term oral corticosteroids were needed in reported cases. There were two case reports of successful treatment in eosinophilic bronchiolitis patients using mepolizumab, a monoclonal anti-IL-5 antibody [4,5]. On the other hand, as far as we are aware, there were no reports on using benralizumab to eosinophilic bronchiolitis patients. In conclusion, benralizumab may be a treatment option for CEP and eosinophilic bronchiolitis patients especially with steroid-sensitive comorbidities. Further prospective studies are needed to confirm its effectiveness.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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Author Contribution Statement

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