

Allergic bronchopulmonary aspergillosis successfully treated with benralizumab

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Clinical Implications

- This is the first report of the successful treatment of allergic bronchopulmonary aspergillosis (ABPA) with benralizumab, which was well tolerated and had rapid efficacy in the 60-year-old female patient. Benralizumab could be an alternative agent for ABPA treatment.

TO THE EDITOR:

Allergic bronchopulmonary aspergillosis (ABPA) is an immunological pulmonary disease characterized by hypersensitivity to *Aspergillus fumigatus*, manifesting as uncontrolled asthma, eosinophilia, and lung infiltrations. Once expressed, ABPA does not remit completely. Many patients with ABPA require long-term treatment. Systemic corticosteroids (SCSs) and itraconazole are the current treatment for ABPA,¹ and the responses to SCSs and itraconazole are usually good. However, the exacerbation rates are >20% in the 2 years after SCSs or itraconazole treatment.² When long-term SCS use is needed, adverse events such as weight gain, sleep/mood disturbance, cataracts, osteoporosis, infections, and diabetes mellitus are serious problems. Safer and more effective agents that are tolerable over a long term are desired for ABPA treatment.

Here, we report the case of a patient with ABPA successfully treated with benralizumab, which is a monoclonal antibody against the alpha subunit of the IL-5 receptor. The patient was a 60-year-old Japanese woman who came to our hospital because of cough, sputum, and abnormal chest radiograph findings. Four months earlier, she was diagnosed with pneumonia at another hospital. Although she received pneumonia treatment, her symptoms did not improve, and she had been suffering with the cough and sputum for 4 months at her first visit to us. She had been diagnosed with bronchial asthma 1 year earlier and had never smoked.

Her laboratory data on admission showed eosinophilia (972 cells/ μ L), elevated total IgE level (537 IU/mL), and positive *Aspergillus*-specific IgE (1.59 UA/mL; Class 2). The total leukocyte count, lactate dehydrogenase (LDH), and C-reactive protein (CRP) were normal. The β -D-glucan and aspergillus galactomannan results were negative. Bacterial culture of sputum detected only normal flora. Chest radiography revealed air space consolidation and ground glass opacity (Figure 1, A).

Chest computed tomography (CT) demonstrated bronchial wall thickening, centrilobular nodules, air space consolidation, and mosaic attenuation (Figure 1, B). On the basis of these findings including parenchymal radiological changes, we diagnosed asthma with ABPA—not severe asthma with fungal sensitization—despite

the IgE titer <1000 IU/mL.² At the first visit, we initiated high-dose fluticasone furoate/vilanterol (inhaled corticosteroid/long-acting β -agonist) and montelukast sodium (a leukotriene receptor antagonist) for the treatment of asthma. At the second visit 1 month later, chest CT showed worsened centrilobular nodules, air space consolidation, and mosaic attenuation, and new laboratory data showed an increased level of eosinophils (Figure 2). Benralizumab (30 mg subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks) was initiated for the treatment of the patient's asthma with ABPA exacerbation.

At 1 month of benralizumab treatment, chest radiography showed that the air space consolidation and ground glass opacity had improved (Figure 1, A). The peripheral eosinophil level had decreased to 0 cells/ μ L (Figure 2), and the total IgE level had decreased to 415 IU/mL. Chest CT showed an improvement of centrilobular nodules, air space consolidation, and mosaic attenuation (Figure 1, B), and after 2 months of benralizumab treatment, the patient's cough and sputum improved. This result suggested that the parenchymal radiological changes were caused by eosinophilic inflammation, not infection, which was consistent with ABPA.

To the best of our knowledge, this is the first case of ABPA to be successfully treated with benralizumab. We observed rapid and dramatic improvement in chest images (Figure 1) and a depletion of peripheral eosinophils (Figure 2).

Immune-mediated mechanisms in ABPA are not fully understood. The immune reaction to *A. fumigatus* in patients with ABPA is thought to be a Th2 CD4⁺ T-cell response with IL-4 and IL-5.¹ IL-4 induces IgE-secreting B cells, and IL-5 induces eosinophil activation. A Th2 inflammatory reaction with IgE and eosinophils is thought to be the main pathogenesis in ABPA. IL-5 is one of the cytokine mediators that induce eosinophil development, activation, and proliferation. Eosinophils activated by IL-5 form mucoid impactions and impair the bronchial wall in ABPA.

Benralizumab is approved as add-on therapy to standard care for patients with severe asthma. Benralizumab is a humanized, afucosylated monoclonal antibody against IL-5 receptor-alpha that induces a depletion of eosinophils through enhanced antibody-dependent cell-mediated cytotoxicity.^{3,4} It is reported that benralizumab rapidly decreased the blood eosinophil count³ and sputum eosinophils in severe asthma. In our patient's case, at 1 month of treatment with benralizumab the level of peripheral eosinophils had decreased to 0/ μ L and her chest images were dramatically improved.

Several reports described cases of patients with ABPA treated with biological formulations such as mepolizumab,⁵ omalizumab,⁶ and the combination therapy of these 2 agents.⁷ IL-5 and IgE are considered to be the main mediators of Th2 inflammation that contributes to ABPA. The elevated levels of IgE suggest the efficacy of omalizumab for patients with ABPA. Omalizumab is an effective and safe agent for patients with ABPA, despite their high serum IgE levels.⁸ The eosinophilia in patients with ABPA also suggest that anti-IL-5 agents (ie, benralizumab, mepolizumab, and reslizumab) would be effective. In fact, mepolizumab has been reported to be effective for patients with ABPA.^{5,7}

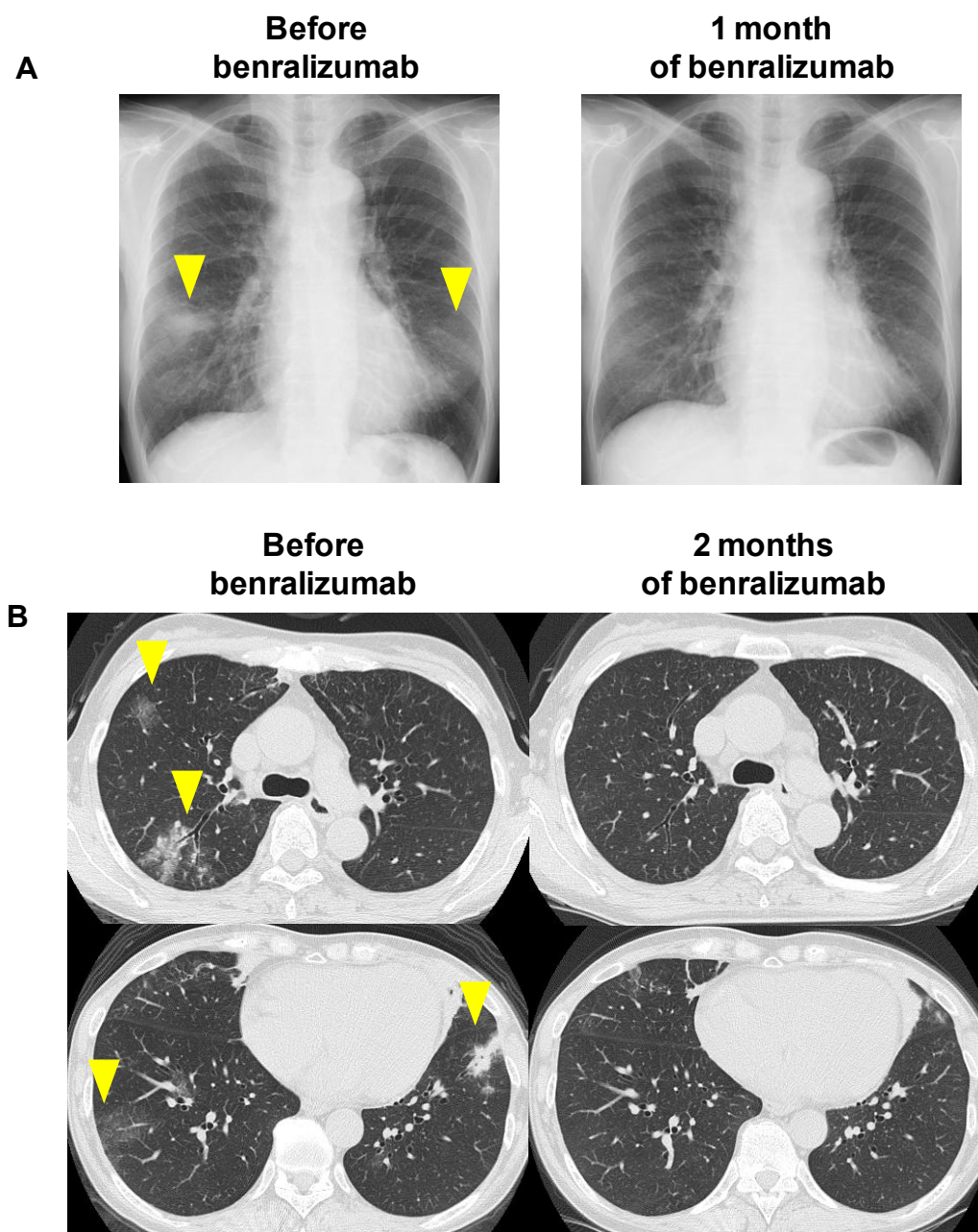


FIGURE 1. **A**, Chest X-ray findings of the patient, a 60-year-old woman, showed air space consolidation and ground glass opacity (indicated by yellow arrows) attenuated after 1 month of benralizumab treatment. **B**, Chest computed tomography showed that bronchial wall thickening, centrilobular nodules, air space consolidation, and mosaic attenuation (yellow arrows) had improved after 2 months of benralizumab treatment.

In our patient's case, we chose benralizumab because the patient was worried about adverse events of SCSs and itraconazole and refused to be treated with those agents. We also expected benralizumab to be effective in light of her eosinophilia. In fact, her ABPA dramatically improved after the benralizumab treatment. The rapid and dramatic improvement might have occurred because her case was ABPA-serologic, which is a milder or earlier stage of ABPA without bronchiectasis.¹

Benralizumab was reported to be well tolerated by patients with bronchial asthma.³ The most common adverse events were minor (eg, nasopharyngitis and injection-site reactions). There are few adverse events related to benralizumab treatment for 56 weeks in patients with asthma.³

Medium-dose SCSs were shown to be effective but induced glucocorticoid-related adverse events in 29% of patients with ABPA.⁹ Itraconazole was safer than SCSs, but it was less effective

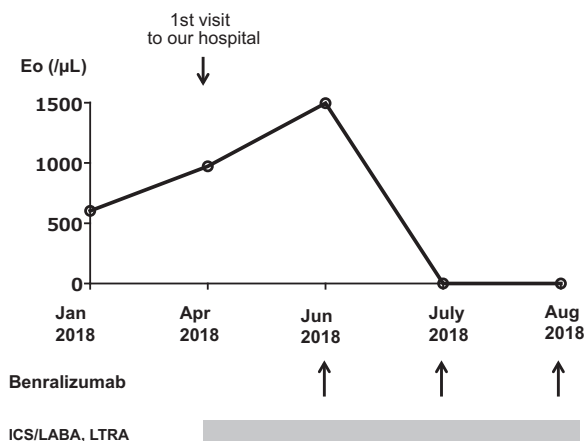


FIGURE 2. The patient's clinical course. After benralizumab administration, the level of peripheral blood eosinophils decreased. *Eo*, Peripheral blood eosinophil count; *ICS*, inhaled corticosteroid; *LABA*, long-acting β -agonist; *LTRA*, leukotriene receptor antagonist.

than SCSs.² An important problem of itraconazole treatment is the risk of azole-resistant *Aspergillus* species, and itraconazole should thus be used only for a short term. It was also reported that ABPA exacerbation rates are >20% in the 2 years after treatment with SCSs or itraconazole.² Thus, safer and more effective agents that can be tolerable for a long term are desired for patients with ABPA.

Regarding the cost-effectiveness relationship of asthma care, adding mepolizumab for severe asthma lowered exacerbation-related medical costs, resulting in a reduction of all service costs.¹⁰ This supports the benefit of treatment with biological formulations for asthma patients with ABPA.

We have described the case of a patient with ABPA treated with benralizumab successfully and rapidly. Benralizumab has fewer adverse effects than SCSs and itraconazole, and it could be an alternative agent for patients with ABPA, especially those who have markedly elevated peripheral blood eosinophil counts. Our findings are limited to a single case, and further studies are needed to confirm the efficacy of benralizumab as ABPA treatment.

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