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Letter to the Editor

Case series of allergic bronchopulmonary aspergillosis treated successfully and safely with long-term mepolizumab

Dear Editor,

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic pulmonary disease characterized by hypersensitivity to *Aspergillus fumigatus*, manifesting with asthma along with eosinophilic inflammation. ABPA does not remit completely once expressed, and thus many patients with ABPA require long-term treatment. Systemic corticosteroids (SCSs) and itraconazole are currently the treatment of choice for ABPA,¹ but both SCSs and itraconazole are associated with numerous adverse events.

It is also unclear whether treatment with corticosteroids and itraconazole will improve long-term outcomes. Here, we report two cases of ABPA treated successfully and safely with mepolizumab (a monoclonal antibody against interleukin [IL]-5) for long periods without SCSs or itraconazole.

Case 1

A 54-year-old Japanese woman was referred to our hospital because of poorly controlled severe asthma although she had been treated with an inhaled corticosteroid/long acting beta-agonist (ICS/LABA) and a leukotriene receptor antagonist (LTRA). The laboratory examination revealed eosinophilia (1365 cells/ μ L), a marked increase in the total serum IgE level (2145 IU/mL), and positive *A. fumigatus*-specific IgE (0.74 KUA/l; Class 2). The FEV_{1.0} was 2.39 l before mepolizumab treatment. Chest computed tomography (CT) showed central bronchiectasis and mucoid impaction (Fig. 1A). The patient was diagnosed with ABPA based on the history of bronchial asthma, elevated total IgE levels (>1000 IU/mL) and specific IgE antibody to *A. fumigatus*, elevated total eosinophil count (>500 cells/ μ L), and radiographic pulmonary opacities consistent with ABPA according to the International Society for Human and Animal Mycology (ISHAM) Working Group's criteria.^{1,2} In this case, the patient was worried about adverse events of SCSs and itraconazole and refused those agents for the treatment of ABPA. We administered mepolizumab (100 mg/month) at least to control her asthma in addition to the same ICS/LABA and LTRA.

After 6 months of mepolizumab treatment, the patient's peripheral blood eosinophil was decreased, and chest CT revealed that the mucoid impaction was attenuated (Fig. 1A). The ACT score was increased to 25 (by 4 points) (Table 1). Spirometry showed that the FEV_{1.0} was increased to 2.48 l. The serum total IgE level did not change after mepolizumab treatment. She has undergone

mepolizumab treatment for 24 months without SCSs or itraconazole and has good control.

Case 2

A 61-year-old Japanese woman was diagnosed with bronchial asthma. Initially, she had good control of asthma with an ICS/LABA. At 66 years old, she was suffering from severe uncontrolled asthma despite treatment with a high-dose ICS/LABA and LTRA. Her laboratory data showed eosinophilia (1856 cells/ μ L), normal total serum IgE level (162 IU/mL), positive *A. fumigatus*-specific IgE (3.88 KUA/l; Class 3), and positive precipitating IgG antibodies to *Aspergillus*. Chest CT demonstrated bronchial wall thickening with mucoid impaction (Fig. 1B).

We diagnosed ABPA based on the patient's history of bronchial asthma, elevated specific IgE antibody to *A. fumigatus*, the presence of precipitating antibody against *A. fumigatus* in serum, elevated total eosinophil count (>500 cells/ μ L), and radiographic pulmonary opacities consistent with ABPA despite the IgE titer <1000 IU/mL according to the ISHAM Working Group's criteria.^{1,2} The patient refused SCSs for the treatment of ABPA because she had previously experienced serious adverse events of SCSs to treat her ulcerative colitis. We initiated mepolizumab (100 mg/month) to control asthma in addition to the high dose ICS/LABA and LTRA.

After 2 months of treatment with mepolizumab, the patient's peripheral blood eosinophil count was decreased. After 4 months of mepolizumab treatment, chest CT demonstrated the improvement of bronchial wall thickening and mucoid impaction (Fig. 1B). The patient continued mepolizumab for 21 months without any adverse events. Her symptoms (cough and sputum) improved and the ACT score remained at 24 points (Table 1). The serum total IgE level did not change after mepolizumab.

In our cases, mepolizumab that was administered to control severe asthma coincidentally resolved ABPA. To the best of our knowledge, these are the first reported cases of patients with ABPA treated successfully and safely with long-term mepolizumab.

The main pathophysiology of ABPA is considered an immune response with Th2 inflammation. The immune response to *A. fumigatus* is a Th1 CD4⁺ T-cell response in normal lung. However, in ABPA patients the response to *A. fumigatus* is mediated mainly by Th2 CD4⁺ T cells generating IL-4 and IL-5. A Th2 inflammatory reaction with eosinophils and IgE is considered to be the main pathogenesis in ABPA.³

Mepolizumab is approved as add-on therapy to standard care for patients with severe eosinophilic asthma.⁴ Mepolizumab is a monoclonal antibody against IL-5 that attracts and activates

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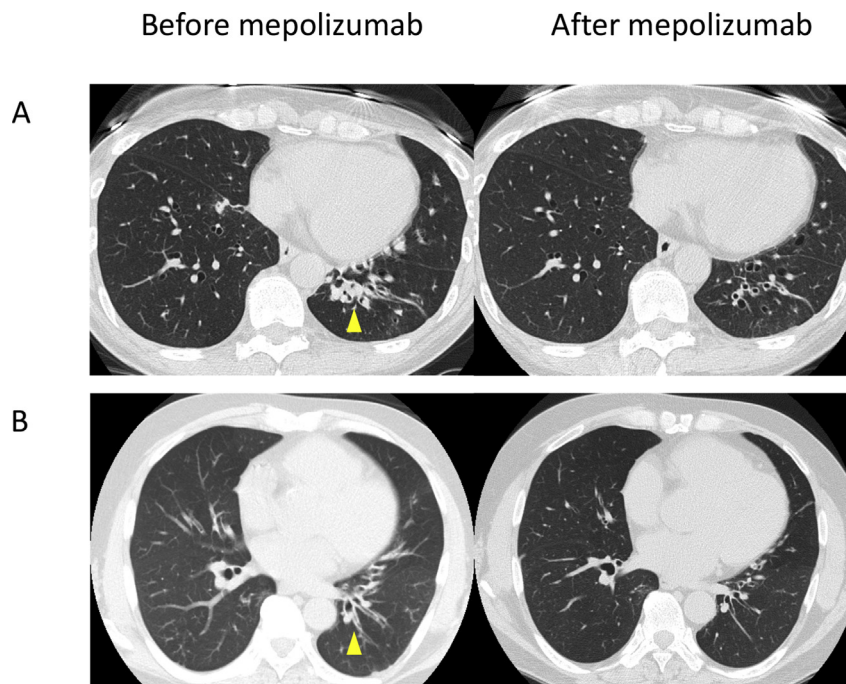


Fig. 1. Chest CT findings. Left-side CT findings before mepolizumab treatment. Right-side CT findings after mepolizumab treatment. **A:** Case 1 (ABPA), showing central bronchiectasis and mucoid impaction (yellow arrows). **B:** Case 2 (ABPA), showing bronchial wall thickening and mucoid impaction (yellow arrows).

Table 1
Outcome of ABPA in patients treated with long-term mepolizumab.

Case#	Duration of Mep treatment (months)	Current Mep dose	No. of eosinophils (cells/ μ l) (before $\rightarrow$ after Mep)	ACT (before $\rightarrow$ after Mep)
1	24	100 mg/mo. SC	1365 $\rightarrow$ 73	21 $\rightarrow$ 25
2	21	100 mg/mo. SC	1856 $\rightarrow$ 32	24 $\rightarrow$ 24

Mep, Mepolizumab; ACT, Asthma Control Test; SC, subcutaneous.

eosinophils. The pulmonary eosinophilic inflammation and tissue damage mediated by eosinophils in ABPA patients suggest that treatment with mepolizumab would be effective against ABPA. In fact, we used mepolizumab to control asthma and obtained good responses to ABPA in these 2 cases.

Several reports described cases of ABPA patients treated with mepolizumab. Oda *et al.* reported the case of an ABPA patient treated with mepolizumab and tapering SCSs for 9 months.⁵ The improvement of a patient's ABPA exacerbation treated with mepolizumab for 4 weeks was described by Terashima *et al.*⁶ Altman *et al.* stated that mepolizumab treatment for 7 months was effective as an additional treatment for ABPA resistant to SCSs, ITCZ, and omalizumab.⁷ Here we have reported two cases of individuals with ABPA who were successfully and safely treated with mepolizumab for the longest periods among all of the present and past reports (24 months and 21 months).

Mepolizumab is approved as add-on therapy to standard care for patients with severe eosinophilic asthma⁴ and eosinophilic granulomatosis with polyangiitis (EGPA),⁸ and it was shown to have a significant glucocorticoid-sparing effect.⁹ Mepolizumab was also reported to be safe and effective as a corticosteroid-sparing agent in hyper-eosinophilic syndrome (HES).¹⁰ The long-term safety and efficacy of mepolizumab treatment has been reported in patients with severe eosinophilic asthma for 12 months.⁴

The most frequent adverse events were minor effects such as headache and nasopharyngitis, and there as yet are no reports of significant adverse reactions to mepolizumab such as serious cardiac, vascular, or ischemic events.⁹ Our patients did not experience any adverse events of mepolizumab treatment. We observed the safety and efficacy of mepolizumab for long periods (24 and 21 months) in ABPA patients.

SCSs and itraconazole, the only other available treatment for ABPA, can cause serious side effects. Little is known about the long-term effects of SCSs and itraconazole, and a safer and more effective alternative treatment of ABPA is needed. Mepolizumab has fewer adverse events than SCSs and itraconazole. We observed that ABPA could be controlled with long-term mepolizumab treatment without the need for SCSs or itraconazole. The present two cases indicate that mepolizumab could be an alternative treatment that is tolerable and effective as a long-term corticosteroid-sparing agent for ABPA.

Conflict of interest

The authors have no conflict of interest to declare.

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