

Clinical Communications

Combination omalizumab and mepolizumab therapy for refractory allergic bronchopulmonary aspergillosis

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Clinical implications

- This is the first report to demonstrate mepolizumab as an additional and effective treatment option for severe allergic bronchopulmonary aspergillosis resistant to corticosteroids, antifungal therapy, and omalizumab. It also demonstrates a potentially synergistic effect of using mepolizumab with omalizumab.

TO THE EDITOR:

Allergic bronchopulmonary aspergillosis (ABPA) is a complex hypersensitivity reaction to *Aspergillus fumigatus* characterized by histologic and physiologic features of asthma along with eosinophilic inflammation, bronchiectasis, mucoid impaction, and bronchocentric granulomatosis.¹ Here, we report the case of a 58-year-old woman with severe, treatment refractory ABPA successfully treated with combination therapy of omalizumab (an anti-IgE mAb) and mepolizumab (an anti-IL-5 mAb).

The patient was born in Pakistan and developed upper and lower respiratory tract disease in her early 20s. Symptoms started with intermittent, then persistent nasal congestion, cough, wheeze, and dyspnea with exertion. She was empirically treated for “tuberculosis” without improvement, and received intermittent inhalers and systemic corticosteroids (SCSs) with some improvement. She moved to the United States in 2004 and was diagnosed with asthma and started on inhaled corticosteroids (ICSs) and albuterol with symptomatic benefit. In October 2013, she had significant clinical deterioration and was hospitalized for hypoxemic respiratory distress. Her chest computed tomography demonstrated bronchiectasis, upper lobe fibrosis, scattered nodules, and mucus plugging (Figure 1). She was treated with intravenous antibiotics and SCSs and discharged on 2 mg/kg daily prednisone, moderate dose ICS, a long-acting β_2 -agonist, and albuterol.

Over the next year she was unable to taper below approximately 1 mg/kg of prednisone without developing severe dyspnea, wheezing, and cough. Her symptoms progressively worsened and she developed new-onset hemoptysis, prompting presentation to our tertiary care institution in November 2014. Spirometry showed severe obstructive lung disease with an FEV₁ of 0.74 L (31% predicted), forced vital capacity of 1.48 L (50% predicted), and FEV₁/forced vital capacity ratio of 0.50. On SCSs, her serum IgE level was 1730 IU/mL, absolute eosinophil count was 1100 cells/ μ L, and *Aspergillus fumigatus* IgE was 13.0 kIU/L. On the basis of history of asthma with recurrent exacerbations, radiographic evidence of central bronchiectasis, IgE concentration greater than 417 IU/mL, and

elevated *A. fumigatus* IgE and total eosinophil count of more than 500 cells/ μ L, she was diagnosed with ABPA.² She was continued on 1 mg/kg prednisone daily, long-acting β_2 -agonist, and her ICS was increased to double conventional maximum dosing. She also had mold remediation work done in her home.

Several attempts to taper prednisone led to exacerbation of symptoms. On follow-up in March 2015, she showed no clinical improvement and had dyspnea, limiting her activities of daily living. Her FEV₁ declined to 0.62 L and chest imaging was unchanged. She had corticosteroid-related side effects of weight gain, edema, and hyperglycemia. She was treated with itraconazole for 3 months; however, she was unable to taper prednisone and her condition continued to deteriorate. She developed *Candida* esophagitis, was transitioned to voriconazole, and moved to a new home in an effort to avoid any mold exposure but still showed no improvement. In August 2015 she began omalizumab 300 mg every 2 weeks. At her third injection she was dyspneic and hypoxemic at rest with an oxygen saturation of 82%. She was hospitalized, started on continuous supplemental oxygen, and began physical and pulmonary rehabilitation. Omalizumab was increased to 375 mg every 2 weeks and voriconazole was discontinued secondary to perceived lack of effect. After 5 months of maximum dose omalizumab, she had been able to taper prednisone to 20 mg daily, her lowest dose in 3 years. She was no longer having daily symptoms of wheezing and her albuterol use had markedly decreased. Although her clinical deterioration stabilized, she remained wheelchair bound, oxygen-dependent, and with significant limitations in exercise capacity despite ongoing rehabilitation efforts. Attempts to taper prednisone below 20 mg per day led to recurrence of wheezing and dyspnea.

In April 2016, mepolizumab 100 mg every 4 weeks was added to omalizumab and her conventional asthma therapies. Three

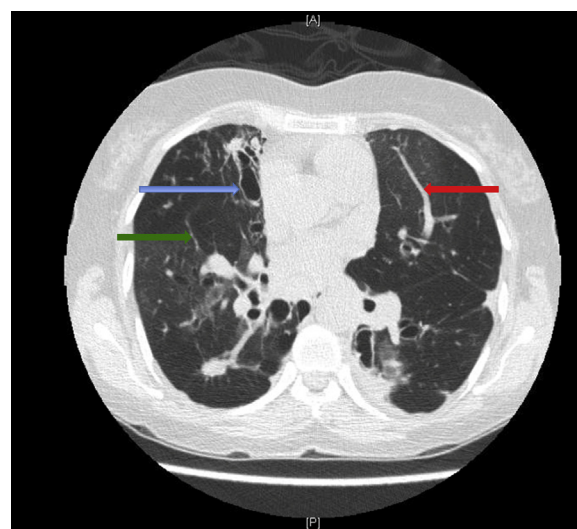


FIGURE 1. The patient's initial chest computed tomography in October 2013 demonstrating bronchiectasis (blue arrow), mosaic attenuation (green arrow), and mucus plugging (red arrow).

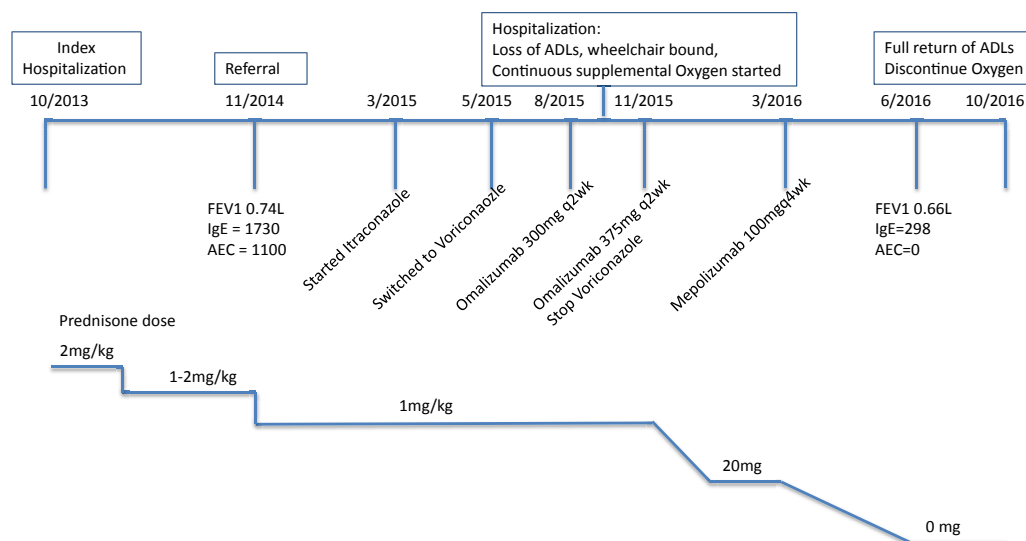


FIGURE 2. Timeline summarizing the patient's clinical course and key treatments. Treatment with omalizumab 375 mg every 2 weeks (q2wk) halted the patient's clinical decline. Addition of mepolizumab 100 mg every 4 weeks (q4wk) led to clinical improvement including discontinuation of oral steroids and supplemental oxygen and return of ADLs. ADLs, Activities of daily living; AEC, absolute eosinophil count.

months after starting mepolizumab, she successfully tapered off SCS. By September 2016 she could perform activities of daily living independently without dyspnea and discontinued supplemental oxygen. Her eosinophil count became undetectable and total serum IgE decreased to 298 IU/mL. Her spirometry has remained unchanged (Figure 2).

ABPA is a severe form of inflammatory lung disease. Although the pathophysiology is not fully understood, it results in part from a mixed innate and adaptive immune response including intense T_H2 inflammation in susceptible hosts who cannot clear inhaled fungal spores from the respiratory epithelium. The innate immune response to *A fumigatus* in the lung leads to chemotaxis and activation of T_H2 cells. T_H2 cells produce cytokines including IL-4 and IL-5 that drive differentiation of IgE-secreting plasmacytes and attract and activate eosinophils, both of which are key markers of the disease.³⁻⁵ These mechanisms suggest that both anti-IgE therapy and anti-IL-5 therapy may be of benefit in ABPA.

The primary treatment of ABPA is prolonged oral steroids to control and prevent acute exacerbations and limit progression of parenchymal lung damage but steroid side effects limit this approach. Although antifungal therapies are often used to decrease exacerbations and limit corticosteroid use, our patient showed no clinical benefit with this approach. Omalizumab has been reported to have steroid-sparing effects and to decrease ABPA exacerbations.^{4,6-9} Given the high serum IgE values in ABPA, several reports have used the maximum approved dose of omalizumab.

In our patient, maximum dose omalizumab therapy stabilized her clinical decline but was unable to fully control her symptoms or enable complete tapering of corticosteroids. The addition of mepolizumab to her high-dose omalizumab led to a dramatic clinical improvement. This is the first reported case of using mepolizumab to treat ABPA and the first case demonstrating synergistic effects of omalizumab and mepolizumab for a severe

allergic lung disease. Although our findings are limited to a single case and we cannot exclude improvement due to other causes, the time course of improvement was closely associated with initiation of omalizumab and mepolizumab, and her clinical response coincided with her decrease in measurable IgE and peripheral eosinophils. Combination therapy with omalizumab and mepolizumab can be justified from a mechanistic standpoint and could offer a critical treatment option in individuals with severe ABPA and similar severe allergic respiratory diseases. Future studies are needed to further evaluate the utility of this approach.

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

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REFERENCES

- Greenberger PA. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol* 2002;110:685-92.
- Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy* 2013;43:850-73.
- Knutsen AP, Slavin RG. Allergic bronchopulmonary aspergillosis in asthma and cystic fibrosis. *Clin Dev Immunol* 2011;2011:1-13.
- Moss RB. Treatment options in severe fungal asthma and allergic bronchopulmonary aspergillosis. *Eur Respir J* 2013;43:1487-500.

5. Stevens DA, Moss RB, Kurup VP, Knutsen AP, Greenberger P, Judson MA, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis—state of the art: Cystic Fibrosis Foundation Consensus Conference. *Clin Infect Dis* 2003;37: S225-64.
6. Collins J, deVos G, Hudes G, Rosenstreich D. Allergic bronchopulmonary aspergillosis treated successfully for one year with omalizumab. *J Asthma Allergy* 2012;5:65-70.
7. Aydın Ö, Sözüner ZÇ, Soyuyiğit Ş, Kendirinan R, Gençtürk Z, Mısırlıgil Z, et al. Omalizumab in the treatment of allergic bronchopulmonary aspergillosis: one center's experience with 14 cases. *Allergy Asthma Proc* 2015;36:493-500.
8. Tillie-Leblond I, Germaud P, Leroyer C, Tétu L, Girard F, Devouassoux G, et al. Allergic bronchopulmonary aspergillosis and omalizumab. *Allergy* 2011;66: 1254-6.
9. Voskamp AL, Gillman A, Symons K, Sandrini A, Rolland JM, O'Hehir RE, et al. Clinical efficacy and immunologic effects of omalizumab in allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol Pract* 2015;3:192-9.