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Dupilumab treatment for allergic bronchopulmonary aspergillosis: A case series

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TO THE EDITOR:

Allergic bronchopulmonary aspergillosis (ABPA) is a Th2-hypersensitivity reaction to *Aspergillus fumigatus*. The hallmark is bronchial mucoid impaction secondary to eosinophilic infiltration, often resulting in bronchiectasis and fibrosis in untreated subjects.[1] For the 2.5% of severe asthmatics with ABPA, treatment has been limited to oral corticosteroids (OCS) and antifungal agents.[1] Despite these therapies, ABPA never remits completely, with exacerbation rates of >20% in the 2 years after treatment.[2]

ABPA is considered an extreme form of type 2 inflammation driven by fungal specific IgE. Marked eosinophilia is found throughout the lower airways, and the peripheral blood absolute eosinophil count (AEC) is approximately 1000 to 3000 cells/μL during exacerbations.[3] Similarly, IgE production is consistently elevated[1] with serum IgE often >1000 IU/mL.

These biologic characteristics suggest a role for anti-IL-4/13 therapy in ABPA. Here, we describe the clinical course of 3 subjects with ABPA treated with dupilumab over 6 months (summarized in Table I).

Patient 1 was 60 years at initial presentation, with longstanding atopic asthma. In the year before assessment, she experienced significant worsening of control. Forced expiratory volume in 1 second (FEV1) was 63% predicted, and fractional exhaled nitric oxide (FeNO) at 113 ppb despite optimal management. She received frequent OCS courses without perceptible improvement. Her peak AEC was 1620 cells/mL. Total IgE was 682 IU/mL with sensitization to *A. fumigatus*. Chest computed tomography (CT) demonstrated cylindrical bronchiectasis. She was started on omalizumab along with maintenance OCS, but had incomplete response in terms of lung function and symptoms. Also, AEC and FeNO progressively increased with continued treatment. She was then switched to mepolizumab, which enabled wean off maintenance OCS, but she continued to have frequent acute flares requiring OCS. She was then initiated on dupilumab, and asthma symptoms completely

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resolved at 2-month follow-up with normalization of FEV1. FeNO was 38 ppb off OCS. However, AEC was highest recorded at 3400 cells/μL (down to 1090 cells/μL at 4 months). At 6 months, she continues to do well without further OCS.

Patient 2 was a female with childhood asthma that progressively worsened through the years. At 42 years, she had clinical deterioration with expectoration of broncholiths, and required hospitalization for respiratory distress. Serum IgE was >2000 IU/mL with the AEC of 1040 cells/mL. Spirometry at the time was nonobstructive. Chest CT demonstrated bilateral central bronchiectasis. A marked eosinophilic infiltrate and fungal elements were found on bronchoscopy. She also had positive intradermal testing to *Aspergillus*. She improved after 6 months of OCS, but developed a flare shortly thereafter. Her clinical course continued to be punctuated by multiple protracted courses of OCS and itraconazole therapy for acute exacerbations. She was started on mepolizumab without efficacy and serum IgE remained >2000 IU/mL. She was unable to taper below 50 mg prednisone without breakthrough symptoms. Therefore, she was switched to dupilumab and successfully tapered off OCS within 3 months. AEC remained stable after OCS discontinuation, and IgE trended down from >2000 IU/mL on OCS to 384 IU/mL at 6 months of treatment. She reports complete symptom control and has not required further OCS.

Patient 3 was a 22-year-old man with Klinefelter syndrome and severe asthma. He was incidentally found to have cylindrical bronchiectasis in the right upper lobe and diffuse mild bronchiectasis on a chest CT obtained for chest pain. The CT scan also demonstrated a chronic right-sided pneumothorax, and he underwent decortication and right upper segmentectomy. The surgical pathology demonstrated eosinophilic inflammation and many fungal hyphae. He was started on voriconazole with some improvement. However, he continued to have significant consolidative opacities on CT scans of the chest, persistently elevated AEC to a peak of 1750 cells/mL and a serum IgE of 11,290 IU/mL. At 33, the patient was evaluated in the asthma clinic and diagnosed with ABPA. He was initiated on dupilumab, but 1 week later was hospitalized for an asthma exacerbation likely related to dupilumab-induced hypereosinophilia. AEC at the time was 2700 cells/μL. After a course of steroids, the patient improved and repeat CT scan of the chest showed complete resolution of mucus impaction and consolidative opacities.

There is a considerable body of evidence that supports the use of biologics in ABPA, specifically omalizumab, but also anti-IL5 therapies.[4] A specific role for IL-4R blockade was suggested nearly 2 decades ago, based on increased sensitivity of Th2 cells to IL-4 and upregulation of CD23 on B cells in patients with ABPA.[5] Furthermore, *A. fumigatus* has high serine protease activity that induces the *Muc5ac* gene through the stimulation of epidermal growth factor receptors.[6] *Muc5ac* is one of the mucin genes that contributes to the formation of inspissated mucus plugs in the bronchi where *A. fumigatus* resides. IL-13 is known to upregulate *Muc5ac* production, and the inhibition of IL-13-induced periostin attenuates *Muc5ac* expression in airway epithelium.[7] This pathway provides another mechanism for potential intervention with dupilumab.

One of the diagnostic criteria for ABPA is a total IgE concentration of ≥416 IU/mL.[1] It is important to note that this high level of IgE is not *Aspergillus* specific, but secondary

to polyclonal B-cell activation. Serial IgE measurements are recommended every 6 to 8 weeks after initiation of ABPA treatment with the goal of at least 35% reduction. This has been shown to correlate with improvement.[1] An IgE-driven etiology for ABPA is further supported by recent reports of clinical improvement in patients with ABPA treated with omalizumab.[8] However, omalizumab therapy may be precluded by high total IgE that exceeds dosing parameters.

Although dupilumab appears to be a promising approach for ABPA therapy, 2 of 3 patients developed worsening hypereosinophilia early into treatment. Although a higher AEC is predictive of responsiveness to dupilumab, the exaggerated peripheral eosinophilia associated with ABPA may render patients especially susceptible to the tendency of dupilumab to increase blood eosinophils. In contrast, overlapping OCS as in patient 2 may be protective against the development of hypereosinophilia and may be warranted during initiation of dupilumab in ABPA.

Also, the effect of dupilumab on tissue eosinophil counts is yet unknown. In a subset analysis of patients with nasal polyps, dupilumab was shown to decrease type 2 biomarkers, including total IgE and markers of eosinophil activation (eotaxin-3 as well as eosinophil cationic protein), in nasal secretions and polyp tissues.[9] These data suggest that in addition to decreasing mucosal IgE production through antagonism of IL-4Rα, dupilumab also decreases eosinophil recruitment to the airways via suppression of eosinophil chemokine release. Although this has been postulated to explain the transient peripheral eosinophilia associated with initiation of therapy, patient 3 developed an asthma exacerbation coincident with AEC spike concerning for airway eosinophilia.

Thus, dupilumab appears to have a role in facilitating disease control in ABPA, with reduced symptoms and OCS use. However, there may be potential for worsening of hypereosinophilia. Larger future studies should clarify the true implications of dupilumab therapy such as decreased exacerbations and/or cumulative OCS dosing in ABPA over a longer period of time.

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Clinical Implications

- Dupilumab may have a role in facilitating disease control in allergic bronchopulmonary aspergillosis, with reduced symptoms and oral corticosteroid use; however, there may be potential for worsening of hypereosinophilia.

TABLE I.

Patient characteristics

Characteristic	Patient 1	Patient 2	Patient 3
Age at treatment with dupilumab (y)	60	51	33
Sex	Female	Female	Male
Ethnicity	African American	Caucasian	Caucasian
Baseline chest CT findings	Cylindrical bronchiectasis	Bilateral central bronchiectasis	Mild diffuse bronchiectasis
FEV1 at baseline	1.52 L (58%)	2.75 L (95%)	1.97 L (37%)
FEV1 at 3 mo	2.18 L (99%)	2.82 L (97%)	2.33 L (56%)
Baseline IgE (IU/L)	561	>2000	11,290
IgE at 3 mo	380	384	1637
Baseline AEC	90	90	1750
AEC at 3 mo	3400	160	690

AEC, Absolute eosinophil count; *CT,* computed tomography; *FEV1,* forced expiratory volume in 1 second.