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# Mepolizumab use in cystic fibrosis-associated allergic bronchopulmonary aspergillosis

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## Abstract

Allergic bronchopulmonary aspergillosis (ABPA) is common in cystic fibrosis (CF). Treatment is challenging and the relapse rate is high. Standard therapy is oral steroids and antifungals. However, long-term systemic steroid often results in adverse effects and drug interactions between azoles and CFTR modulators are a potential concern. Mepolizumab, an anti-interleukin (IL)-5 monoclonal antibody, can benefit patients with severe eosinophilic asthma and there are reports of mepolizumab use in ABPA but not in ABPA complicating CF. We present the case of an adult with CF who had recurrent ABPA and intolerable treatment side effects with steroid, azole, and omalizumab. Mepolizumab was well tolerated and led to significantly improved clinical stability and symptomatic improvement. To our knowledge, this is the first report of successful mepolizumab treatment for ABPA in CF. Mepolizumab may be an important adjunctive treatment for difficult to control ABPA in CF.

## Introduction

Cystic fibrosis (CF) is an autosomal recessive condition that causes chronic airway inflammation, infection, and premature lung function decline. Allergic bronchopulmonary aspergillosis (ABPA) is a form of severe eosinophilic airway inflammation characterized by an exuberant Th2 hypersensitivity response to *Aspergillus fumigatus*. ABPA affects 7–9% of patients with CF [1]. The clinical presentation of ABPA includes dyspnoea, wheezing, pulmonary infiltrates, bronchiectasis, peripheral eosinophilia, raised serum immunoglobulin (Ig) E, and specific IgE to *Aspergillus* [1].

Standard ABPA treatment comprises of oral steroids and azoles that are often complicated by drug-related side effects. Mepolizumab, a monoclonal interleukin (IL)-5 antibody, targets the eosinophilic inflammatory pathway and improves symptom control in severe eosinophilic asthma [2]. A recent case series highlighted its potential benefit in adult CF patients with an eosinophilic inflammatory profile [3]. Here, we report a case of successful mepolizumab use in an adult with recurrent CF-related ABPA and significant side effects from standard ABPA treatment.

## Case Report

A 43-year-old lady had severe CF-related bronchiectasis, recurrent ABPA, asthma, and gastro-oesophageal reflux. Baseline forced expiratory volume in the first second ($FEV_1$) was 47% predicted. Her airway microbiology was complex, including chronic colonization of *Mycobacterium avium*, *A. fumigatus*, and *Aspergillus niger*, and intermittent colonization with *Stenotrophomonas maltophilia*, *Chryseobacterium gleum*, *Escherichia coli*, and *Haemophilus influenzae*. She further developed *Mycobacterium abscessus* lung disease in 2017 and was commenced on treatment. Her medications included inhaled budesonide/formoterol (400/12 μg) two puffs twice daily, ciclesonide (80 μg) daily, omeprazole, clofazimine,

clarithromycin, nebulized dornase alpha, and hypertonic saline.

The patient had five previous ABPA exacerbations (2007, 2010, 2013, and 2015) characterized by: (1) protracted exacerbation with peripheral eosinophilia ($1.12–1.68 \times 10^9$/L) unexplained by alternative causes; (2) elevated serum IgE (3224–4730 kU/L) and *Aspergillus*-specific IgE (48–63 kU/L); and (3) recurrent lobar collapses with mucus plugging refractory to standard therapy [1].

She had received high-dose prednisolone, azole, and omalizumab for recurrent ABPA exacerbations with significant drug-related complications: Prednisolone caused uncontrolled gastro-oesophageal reflux, fluid retention, weight gain, insomnia, low mood, fatigue, and oral candidiasis. Itraconazole caused visual disturbance. Voriconazole and omalizumab were associated with severe arthralgia and myalgia.

In June 2018, she represented with dyspnoea, chest tightness, productive cough with mucus plugs, peripheral eosinophilia ($1.85 \times 10^9$/L), elevated IgE (1021 kU/L), and positive *Aspergillus* IgE (38.8 kU/L) (Fig. 1). Sputum cultures showed chronic *M. avium* infection. $FEV_1$ remained unchanged (40% predicted). Chest X-ray demonstrated left lower lobe collapse with mucous plugging. The clinical presentation fulfilled the ABPA diagnostic criteria [1]. Prednisolone (50 mg oral daily) was started and inhaled corticosteroid dose was increased (budesonide 1600 μg daily/ciclesonide 160 μg daily). Steroid again caused the aforementioned adverse effects, with substantial functional impact. Steroid weaning between June and September 2018 was complicated by symptomatic decline and IgE rise (2747 kU/L), which required re-escalation of steroid dose. Given her previous intolerance to azole and omalizumab, mepolizumab 100 mg was commenced in October 2018 as an adjunctive therapy to facilitate steroid taper.

Mepolizumab was well tolerated and prednisolone was ceased six weeks later. Her symptoms remained stable during steroid taper. Her total eosinophil count decreased from $1.2 \times 10^9$ to $0.03 \times 10^9$/L and total IgE remained unchanged at 1100–1500 IU/mL (Fig. 1). $FEV_1$ stabilized at 1.25 L (45%), similar to baseline. Repeat X-ray demonstrated re-expansion of the left lower lobe. The patient remained on monthly mepolizumab and was free from ABPA or asthma exacerbations over the following 20 months (till June 2020). Her maintenance inhaled steroid dose was reduced (budesonide 800 μg; ciclesonide was ceased). Since mepolizumab commencement, there have been four episodes of infective exacerbations caused by *H. influenzae* and *S. maltophilia*, which were treated with intravenous and oral antibiotics. In January 2020, the patient commenced tezacaftor/ivacaftor but no significant symptomatic or spirometry improvements were noted.

## Discussion

We report a case of successful use of mepolizumab in an adult with CF-related ABPA whose treatment was previously complicated by difficulty in steroid wean and drug-related toxicity. Mepolizumab was well tolerated, resulting in symptomatic and radiological improvement and facilitated steroid taper (Fig. 1).

ABPA is a type 2 hypersensitivity inflammatory airways disease triggered by *A. fumigatus*. *Aspergillus fumigatus* is ubiquitous in the environment, and is commonly found in the sputum of patients with CF. Fungal antigens trapped in the tenacious CF airway mucus are processed by antigen-presenting cells bearing HLA-DR2 or HLA-DR5, and presented to T cells in the bronchoalveolar lymphoid tissue. This provokes an exuberant Th2 CD4+ inflammatory response with the release of a cascade of cytokines (e.g. IL-5). IL-5 is a potent chemokine that facilitates recruitment, persistence, and activation of eosinophils. The Th2 CD4+ response also stimulates B cell production of immunoglobulins (e.g. IgE) and leads to mast cell degranulation and eosinophilic airway inflammation.

ABPA therapy aims to down-regulate the exuberant host inflammatory response and reduce fungal burden. Systemic corticosteroid, often prednisolone, is the first-line treatment for CF-related ABPA [1]. Treatment guideline recommended an initial dose of 2 mg/kg/day for a week, reduced to 1 mg/kg/day for one week, followed by alternate day dosing and gradual taper according to symptomatic response [1]. Such prolonged high-dose steroid exposure is associated with toxicity that is often poorly tolerated. Inhaled corticosteroid is ineffective in the treatment or prevention of ABPA.

Azole antifungal therapy improves clinical symptoms, reduces exacerbation frequency, and facilitates steroid weaning in ABPA with asthma [4]. Its safety and efficacy in CF-related ABPA remain less clear. Azole-related complications, such as liver enzyme derangement, are also common. Voriconazole is associated with vision changes, neurological toxicity, and photosensitivity. In CF, azole-related drug interactions, particularly with cystic fibrosis transmembrane conductance regulator (CFTR) modulators, pose an important therapeutic challenge. Azole is metabolized by hepatic cytochrome p450 system. Concurrent use of cytochrome p450 inducers (e.g. lumacaftor) reduces azole serum level. Dose reduction in lumacaftor/ivacaftor is required when initiated in a patient already on azole therapy. Azoles are also potent cytochrome p450 inhibitors that can increase the serum levels of other medications (e.g. ivacaftor or tezacaftor). Dose reduction of tezacaftor/ivacaftor is required during azole therapy. Achieving stable serum azole levels can therefore be challenging due to drug–drug interactions and bioavailability issues in CF.

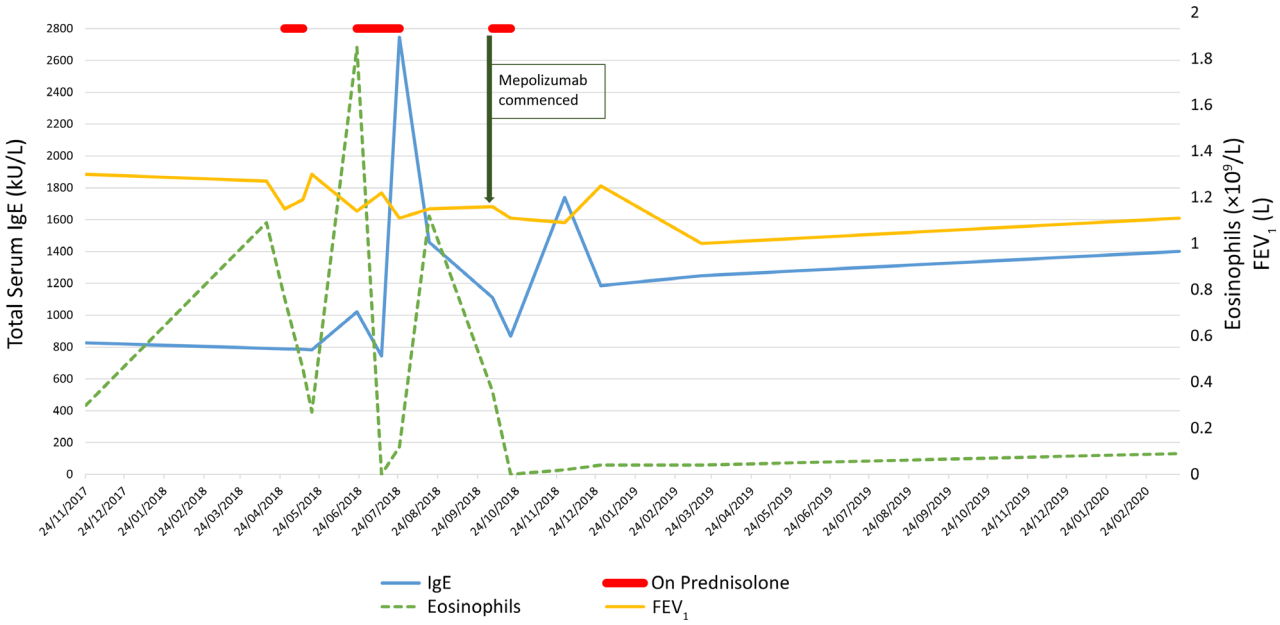


**Figure 1.** Evaluation of total eosinophil count, total immunoglobulin (IgE), and forced expiratory volume in the first second ($FEV_1$) from September 2017 to August 2020 and effect of prednisolone and mepolizumab treatments. After mepolizumab 100 mg was commenced in October 2018, total eosinophil count decreased from $1.2 \times 10^9$ to $0.03 \times 10^9$/L and total IgE remained unchanged at 1100–1500 IU/mL. $FEV_1$ stabilized at 1.25 L (45%), similar to baseline. Prednisolone was ceased six weeks later.

Biologic therapy, which targets the Th2 inflammatory pathways, is an important breakthrough in the management of severe allergic asthma. Omalizumab, a monoclonal IgE antibody, is an effective adjunctive therapy that reduces the rate of exacerbations and hospitalizations in severe atopic asthma [5] but systematic trial data on its use in CF-related ABPA remain lacking. Omalizumab dose is dependent on IgE and weight, and multiple injections are often required. Mepolizumab, a monoclonal antibody against IL-5, is effective in reducing exacerbation frequency and facilitating steroid sparing in refractory eosinophilic asthma. [2]. Zhang et al. reported the clinical benefit of mepolizumab in three adults with CF and eosinophilic airways disease [3]. We here report the successful use of mepolizumab in an adult with CF-related ABPA which was well tolerated. Of interest, whilst Zhang et al. observed normalization in IgE levels in all three patients treated with mepolizumab, our patient's IgE level remained elevated [3]. This might be attributable to ongoing exposure to environmental *Aspergillus* species. Despite serological evidence of persistent fungal exposure/sensitization, her symptoms continued to improve on mepolizumab resulting in further reduction in inhaled corticosteroid dose.

Current ABPA therapy in CF remains challenging due to drug toxicity and drug interactions particularly with CFTR modulator therapies. Further studies are required to further explore the potential role of targeted therapy against type 2 inflammation in optimizing treatment in CF-related ABPA.

## Disclosure Statement

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

## Author Contribution Statement

Dr. Maeve Boyle—CF Fellow. CF Unit in Sir Charles Gairdner Hospital. Lead author and corresponding author. Dr. Siobhain Mulrennan—Consultant CF Physician at Sir Charles Gairdner Hospital. Involved in care of this patient and contributed to review and minor revisions. Sue Morey—Senior CF Nurse at CF Unit Sir Charles Gairdner Hospital. Involved in care of this patient and reviewer of case report. Sona Vekaria and Natalia Popowicz—Pharmacists in CF unit at Sir Charles Gairdner Hospital. Involved in care of this patient and mepolizumab prescription. Reviewers of the article and contributed to minor revisions. Dr. Anna Tai—Consultant CF Physician at Sir Charles Gairdner Hospital. Involved in care of this patient,

application of mepolizumab, reviewer of the article, and final contribution to revisions.

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