Omalizumab as New Modality of Treatment ABPA in Cystic Fibrosis Patient: Case Report

Ibrahim Ali Al-Rashidi

MD, Department of Pediatric Qassim University

Abstract: Background Allergic bronchopulmonary aspergillosis (ABPA) is a severe complication in patients with cystic fibrosis (CF), resulting in deterioration of lung function and impairment of overall prognosis. Standard therapy consists of high dosage, long-term corticosteroid treatment. This carries the risk of serious side effects such as immune suppression, diabetes and osteoporosis. Antifungal drugs such as itraconazole may cause interactions with other drugs and drug levels need to be monitored. Omalizumab treatment has been tried in several case studies.

Methods: This is a retrospective analysis of patients with CF and ABPA receiving treatment with omalizumab from May 2014 to May 2015. A patient was treated at the Department of Paediatric Pulmonology of the king faisal special Hospital and research center the patient gave his written informed consent for retrospective analysis of their ABPA history. Diagnosis of CF in the patient was approved by cystic fibrosis transmembrane conductance regulator (CFTR) mutations.

Results/discussion: patient showed clinical and laboratory stability or even an improvement within the treatment and post-treatment observation period, although .Side effects of systemic steroids were reduced.

Conclusion: Omalizumab has the potential to be an additional and solitary treatment option in patients with CF and ABPA. Early onset treatment may be beneficial and patients with early stage of lung disease seem to be more benefit.

Keywords: ABPA; Aspergillus; cystic fibrosis; itraconazole; omalizumab.

1. INTRODUCTION

Approximately 1–25% of patients with cystic fibrosis (CF) develop allergic bronchopulmonary aspergillosis (ABPA) during their lifetime. A higher incidence may happen during pulmonary colonization with Aspergillus fumigatus, sensitization and genetic susceptibility for atopy [Stevens et al. 2003]. Progressive deterioration of lung function is the major complication of this disease and relapses occur more frequently [Baxter et al. 2013]. Recommended treatment with systemic steroids usually results in severe side effects, like immune suppression, hyperglycemia, cataracts and osteoporosis [Wong et al. 2013]. Antifungal drugs, like itraconazole, used to reduce the antigen burden, require monitoring of drug levels, may interact with other medications or may result in side effects themselves [Ranhawa et al. 2009; Elphick and Southern, 2012].

The pathogenesis of ABPA has still not been understood, but the presence of pathogenic immunoglobulin E (IgE) is one diagnostic hallmark of this disease [Kanu and Patel, 2008]. Omalizumab is a recombinant humanized monoclonal anti-IgE antibody and is an established treatment modality in allergic asthma. First case studies exist reporting the use of omalizumab for the treatment of ABPA in CF patients, with different results [Randhawa et al. 2009; Brinkmann et al. 2010; Zirbes and Milla, 2008; Van der Ent et al. 2007; Lebecque et al. 2009a, 2009b]. The aim of this study was to describe our experience with omalizumab in patient with CF and ABPA.
2. CASE REPORT

An 11-year-old Saudi boy had been diagnosed with cystic fibrosis after birth because of neonatal presentation. From infancy, he had mild to moderate lung problem requiring admission and antibiotic treatment 2 to 4 times a year. In September 2005, he was colonized with pseudomonas aeruginosa. At age of 11 years, he had more severe form of cough in which he developed pulmonary infiltrates and bronchiectasis and signs of severe airflow obstruction and admitted to pediatric ward at King Faisal Special Hospital and research center and started on antibiotics after obtaining cultures and other investigations for this patient. Then he was diagnosed as ABPA and received treatment with omalizumab from 2014 to 2015. Patients gave his written informed consent for retrospective analysis of their ABPA history. Diagnosis of CF in patient was approved by cystic fibrosis transmembrane conductance regulator (CFTR) mutations and the diagnosis of ABPA was based on the criteria of the ABPA Consensus Conference [Stevens et al. 2003] which includes at least five criteria: (a) asthma/bronchial obstruction; (b) immediate cutaneous reactivity to Aspergillus species; (c) elevated total serum IgE levels (>417 IU/ml or 1000 ng/ml); (d) elevated serum IgE to Aspergillus fumigatus; (e) immunoglobulin G (IgG) to A. fumigatus (precipitines); and (f) central bronchiectasis, new pulmonary infiltrates or mucus plugging. Omalizumab was administered subcutaneously at fortnightly intervals. Dosage was individually adapted to body weight and IgE level at the beginning of treatment – referring to the prescribing recommendation of omalizumab for allergic asthma. If IgE levels were above the limits of the licence, the maximum possible dosage of omalizumab with reference to the body weight was administered (600 mg fortnightly). Treatment was started after approval of off-label therapy by our hospital.

3. DISCUSSION

We describe here a one case of patients with CF and ABPA whose condition improved after Omalizumab treatment. The patients met diagnostic criteria for ABPA in patients with CF and receive the dose according to IGE level. And after few months of treatment There were decrease in number of Hospitalizations to 1-2 times per year. Also there was clinical improvement and the patient achieved his personal best FEV1 the average FEV1 was around 60% then drop to 45% when he affected with ABPA then show improve after the omalizumab therapy as shown in chart below.

- Chart show improving of FEV1 after receive Omalizumab treatment

Treatment of ABPA with omalizumab should be considered in those CF patients with ABPA who are unresponsive to conventional therapy or require prolonged use of oral steroids.

The risk of developing ABPA is more in patients with CF than in the asthmatic population (1–2%). Within the last two decades, an increase of ABPA in CF patients has been observed. Reasons for this might be awareness of this complicating disease, and availability of diagnostic procedures [Agarwal, 2009]. It is known that sensitization to Aspergillus depends on the mode and frequency of exposure. Also Patients with CF have frequent treatment with antibiotics – systemic and inhaled. Observations suggest that this might be a risk factor for colonization of the bronchial tree with Aspergillus or
other fungi. Moreover, CF patients have abnormal mucus and spores of Aspergillus might be trapped within the bronchial airways, increasing the risk of Aspergillus fumigatus [Stevens et al. 2003]. Furthermore, in CF patients and persons with heterozygous carriage of CFTR mutations, ABPA seems to be more frequent as a result of genetic susceptibility [Stevens et al. 2003; Muro et al. 2013].

Regarding the colonization of aspergillus fumigatus in bronchial tissue It is not clear whether treatment of colonization may reduce the incidence of ABPA development or it is not effected. But many study show that colonization with Aspergillus is associated with deterioration of lung function, increase rates of hospital admissions, increase frequency of colonization with Pseudomonas aeruginosa and pathologic radiologic findings of the lung in CF patients.

There are different line of treatment of ABPA. Systemic steroids are the the first line of ABPA treatment. The anti-inflammatory effects result in inhibition of phospholipase A2-activity, arachidonic acid metabolism, chemotaxis, cell adhesion, tissue infiltration of inflammatory cells and production of interleukin-1 (IL-1) and tumour necrosis factor (TNF) [Stevens et al. 2003].

Second-line of treatment is antifungal drugs, e.g. itraconazole and voriconazole, which reduces the antigen burden. Other treatment like Inhaled steroids or antifungals and oral montelu-kast are not beneficial in ABPA [Moss, 2010; Rundfeld et al. 2013].

Omalizumab is a new medication started to be used in treatment of ABPA which is a monoclonal anti-IgE antibody, thus blocking docking of specific IgE on mast cells and basophilis. During treatment it reduces free IgE, but anti-IgE–IgE complexes may result in elevations of total IgE. Thus, monitoring of total IgE antibody titres alone delivers no sufficient information of disease activity. Moreover, IgE can also be produced against other antigens [Mroueh and Spock, 1994]. Detection of free-IgE levels might be helpful, though only selected laboratories perform this by solid phase immunoenzymetric assay [Zirbes and Milla, 2008].

A down regulation of IgE receptors is an important consequence of omalizumab treatment, thus reducing inflammatory activity [Zirbes and Milla, 2008; ElMallah et al. 2012; Collins et al. 2012]. Moreover, omalizumab reduces airway eosinophilia and decreases IL-4+ cells in allergic asthma. These factors might also be relevant in ABPA [Tanou et al. 2014].

Unfortunately, third party payers provide a challenge to this treatment because omalizumab has not been approved for treatment of ABPA by the Food and Drug Administration, but there are some study like in Europe, a randomized, double-blind, placebo-controlled study assessing omalizumab therapy in CF patients with ABPA is now in progress. If this trial confirms what we have seen in our patients, addition of omalizumab may provide tremendous benefit for patients, similar to those in this report.

**ABBREVIATIONS**

ABPA, allergic bronchopulmonary aspergillosis; CF, cystic fibrosis; CT, computed tomography; FEV1, forced expiratory volume in 1 second.

**REFERENCES**


