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Review article

Beneficial effects of Omalizumab therapy in allergic bronchopulmonary aspergillosis: A synthesis review of published literature

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ABSTRACT

Omalizumab, a humanized mAb that binds to IgE, has been an effective therapy for patients with severe allergic asthma; however, there are few clinical trials examining the efficacy of Omalizumab in patients with allergic bronchopulmonary aspergillosis (ABPA) except some case reports. To assess the clinical and immunological effects of Omalizumab in ABPA patients, we made a synthesis review of 102 cases from 30 published literature, analyzed the effects of Omalizumab therapy in ABPA and conducted subgroup analyses to determine factors that influenced the therapy endpoints. We found that Omalizumab treatment not only provided a clinically important reduction in serum IgE, exacerbation rates and steroid requirement, but also showed attenuated asthma symptoms and improved pulmonary function parameters in patients with ABPA. Moreover, further discussion was made when interpretating the results. Double-blind, randomized, placebo-controlled trials are necessary to establish the efficacy and safety of this novel therapeutic intervention for ABPA patients.

Contents

Abbreviations: ABPA, Allergy bronchopulmonary aspergillosis; IgE, Immunoglobulin E; mAb, monoclonal Ab; TB, Tuberculosis; CF, Cystic Fibrosis; FeNO, Fractional Concentration of Exhaled Nitric Oxide; FEF_{25-75}, Forced Expiratory flow from 25%-75% of FVC; FEV1, Forced expiratory volume in one second; FVC, Forced vital capcacity; ACT, Asthma control test; FcεR1, The high-affinity receptor for immunoglobulin E; PBMC, Peripheral Blood Mononuclear Cell; IFN-α, Interferon-α; AE, Adverse events.

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1. Introduction

Allergic bronchopulmonary aspergillosis (ABPA), a severe allergic pulmonary complication caused by *Aspergillus* species [1,2], which occurs almost exclusively in patients with asthma [3–5] or cystic fibrosis [6,7]. The global prevalence of ABPA has been estimated to be as high as 2.5% [8], since its initial description by Hinson in 1952 [9]. Delays in diagnosis or under-treatment of ABPA may lead to pulmonary fibrosis, bronchiectasis with chronic sputum production, and increasingly severe persistent asthma with loss of lung function. Recommend pharmacotherapy for ABPA involves systemic corticosteroids and itraconazole [10], the aim is to prophylaxis against, and treatment of, acute exacerbations, as well as prevention of end-stage fibrotic disease [10]. Although corticosteroids can control the symptoms of most patients, some patients become steroid-dependent, or for others, long-term use may not be possible due to adverse effects [11]. Anti-fungal agents may be an alternative for, or added to, steroids [12]. In an effort to decrease patients' exposure to systematic steroids, many clinicians have tried anti-IgE therapy.

Omalizumab, a humanized mAb that binds to the CH3 domain, near the binding site for the high-affinity type-I IgE Fc receptors of human IgE, can neutralize free IgE and inhibit the IgE allergic pathway without sensitizing mast cells and basophils [13]. Omalizumab has been a useful treatment for severe allergic asthma [14,15], especially for patients with high serum IgE levels. Improvements in asthma symptoms and health-related quality-of-life, and a significant reduction in the frequency of asthma exacerbation as well as significant reductions of inhaled corticosteroids dosage were observed in allergic asthmatic patients after anti-IgE therapy [14,16,17]. Clinical trials and real life experiences that focus on adverse effects of Omalizumab tested its safety [18]. Omalizumab has been found effective for not only allergic asthma but also a number of other atopic conditions including allergic rhinitis and chronic idiopathic urticaria [19].

Since Van der Ent CK first reported the case of Omalizumab therapy in a 12-year-old girl with ABPA which resulted in the rapid and clear improvement of clinical signs and lung function [20], a series case reports of ABPA treatment with Omalizumab have been published [12,20–49]. In total, 116 individuals including 14 stopped during treatment. Although cases reports have been published, there are no randomized, placebo-controlled trials evaluating this treatment approach. Herein, we present a synthesis report of the published cases on the potential efficacy of Omalizumab as treatment for ABPA.

2. Methods

2.1. Search strategy

We searched Medline, Cochrane Database of Systematic Reviews (CDSR), EMBASE, Ovid, and Web of science databases for all reports published from inception until November 2015, using the following search terms: “anti-immunoglobulin E” or “anti-IgE” or “ Omalizumab ” or “ Xolair ” and “ Allergic Bronchopulmonary Aspergillosis ” or “ ABPA ”. Trials were not excluded on the basis of language. All eligible studies were retrieved, and their reference lists were checked for additional articles. To ensure a complete review of the available studies, the abstracts of relevant scientific meetings were also examined. We also contacted authors in cases where relevant data were unclear.

Furthermore, we also searched the ongoing trial registry clinicaltrials.gov for any ongoing trials using “anti-IgE and ABPA” and “Omalizumab and ABPA”.

2.2. Selection of studies

Studies were included only if they evaluated assessment criteria prior to and after Omalizumab use from original description.

2.3. Data management and extraction

For data extraction, we used a standardized data collection form, which included the following items: source (First author, Journal, Location); study methods; participants (No. of cases, sex, age, race, clinic history with TB/Asthma/CF, duration from ABPA diagnosed to use Omalizumab); baseline characteristics (total eosinophil count, serum IgE, specific IgE for *Aspergillus fumigatus*, FeNO, FEF_{25-75}, FEV1%, FVC%, FEV1/FVC%, exacerbation rate, prednisone dose, ACT score), interventions (Omalizumab dose, duration, follow-up time); outcomes (similar to baseline characteristics); results (the decline of total IgE, FeNO, exacerbation rate, prednisone dose; the improvement of ACT score, FEV1%, FVC%, FEV1/FVC%) and adverse outcomes. We resolved any disagreement which arose by consensus discussion. Data was extracted in cases of unpublished reports or multiple publications.

2.4. Data analysis

Total IgE, FeNO, exacerbation rate, prednisone dose, ACT score, FEV1%, FVC%, FEV1/FVC% were primary efficacy endpoints of the present data synthesis. The mean and standard deviation of baseline characters and outcomes were calculated. For single case, we used SPSS17.0 to analyze data and calculated Mean and SD. For cases with calculated median and range (minimum to maximum), we used the following formula [50] to calculate mean(x) and SD(S):

$$\overline{x} \approx \frac{a + 2m + b}{4}$$