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Publisher Informa Healthcare

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Journal of Asthma

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597262>

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Online Publication Date: 01 June 2009

To cite this Article Randhawa, Inderpal, Chin, Terry and Nussbaum, Eliezer(2009)'Resolution of Corticosteroid-Induced Diabetes in Allergic Bronchopulmonary Aspergillosis with Omalizumab Therapy: A Novel Approach',*Journal of Asthma*,46:5,445 — 447

To link to this Article: DOI: 10.1080/02770900902849871

URL: <http://dx.doi.org/10.1080/02770900902849871>

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CASE REPORT

Resolution of Corticosteroid-Induced Diabetes in Allergic Bronchopulmonary Aspergillosis with Omalizumab Therapy: A Novel Approach

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Keywords allergic bronchopulmonary aspergillosis, omalizumab

INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) occurs in up to 15% of patients with cystic fibrosis (CF) (1). Clinically, the disease manifests by symptoms consistent with bronchial asthma along with wheezing, pulmonary infiltrates, and bronchiectasis. Variable immunologic responses to *Aspergillus fumigatus* antigens are observed including peripheral blood eosinophilia, prick skin test reactivity, increased levels of total serum immunoglobulin (IgE), the presence of precipitating antibodies and increased specific serum IgE and IgG antibodies to *A. fumigatus* (2,3). Treatment of ABPA targets the inflammatory and immunological activity with corticosteroids in concert with an overall reduction of airway fungal load with antifungal agents (4). Long-term treatment is often required because of repeated exacerbations when corticosteroid treatment is tapered. Owing to chronic systemic corticosteroid use, serious adverse events frequently include insulin resistance, hyperglycemia, and chronic diabetes (5).

Allergic bronchopulmonary aspergillosis frequently results in severe worsening of the respiratory condition in patients with chronic obstructive lung disease, particularly cystic fibrosis. Treatment can result in steroid dependency and serious adverse events (6). Several case reports of improvement of respiratory symptoms and lung function after treatment with anti-IgE antibody (omalizumab) in cystic fibrosis patients with ABPA have been described (7,8). While previous benefits of omalizumab have been noted in ABPA, this report focuses on the subgroup of CF patients with steroid-induced hyperglycemia. As systemic corticosteroids are a mainstay of therapy in ABPA, this subgroup requires intensive glucose monitoring while on steroids. We report a case of corticosteroid-induced diabetes in a patient with CF and ABPA subsequently treated with omalizumab.

CASE HISTORY

R.H. is a 14-year-old African American male with F191V/R1070W CF mutations and positive *P. aeruginosa* bronchial cultures. He was in a usual state of health with baseline forced expiratory volume one second (FEV₁) 60% predicted and was hospitalized with progressive pulmonary infiltrates. He had no prior history of ABPA. His pulmonary function values (% predicted) were decreased at FEV₁ 26%, forced vital capacity (FVC) 56%, FEV₁/FVC 46%, forced expiratory flow during the middle half of the forced vital capacity (FEF_{25–75})₀ 7%, peak expiratory flow (PEF) 39%, respiratory volume (RV) 152%, and RV/total lung capacity (TLC) ratio 0.39. Total serum IgE was 2487 IU/mL (normal 0–150 IU/mL), presence of precipitating antibodies, increased specific serum IgE and IgG antibodies to *A. fumigatus*, and positive bronchoalveolar fluid culture with *A. fumigatus*. Chest radiograph demonstrated worsening left upper lobe infiltrates. Chest computed tomography showed increased bronchiectasis particularly in the left upper lobe.

Initial treatment included inhaled albuterol, fluticasone, alpha dornase, hypertonic saline (6.5%), intravenous tobramycin (with serum levels 2.3–16.6 µg/mL), cefepime, lansoprazole, multivitamins, pancreatic enzymes, itraconazole 200 mg bid and prednisone 1 mg/kg/day (30 mg twice daily). Standard airway clearance protocols were followed. Initial serum glucose was 110 mg% and HgA1c 5.5%. After 10 days of therapy, all pulmonary function test (PFT) values improved, and there was no radiographic evidence of change. After 3 weeks of inpatient treatment, his serum IgE increased to 19506 IU/mL and PFT values had reached a plateau. Serum itraconazole levels by liquid chromatography were 1.3 µg/mL and hydroxyitraconazole serum level 2.8 µg/mL on 500 mg daily. His serum glucose levels were consistently elevated with a peak over 500 mg%. Despite short- and long-acting insulin therapy, glucose control was difficult to achieve. Insulin antibody (<1.0 U/mL), islet cell antibody (<1:4), glutamic acid dehydrogenase antibody (<1 U/mL), thyroglobulin antibody (<33 IU/mL), thyroperoxidase antibody (<33 IU/mL), thyroid stimulating hormone (2.96 IU/mL), and serum cortisol 16 mg% were all within

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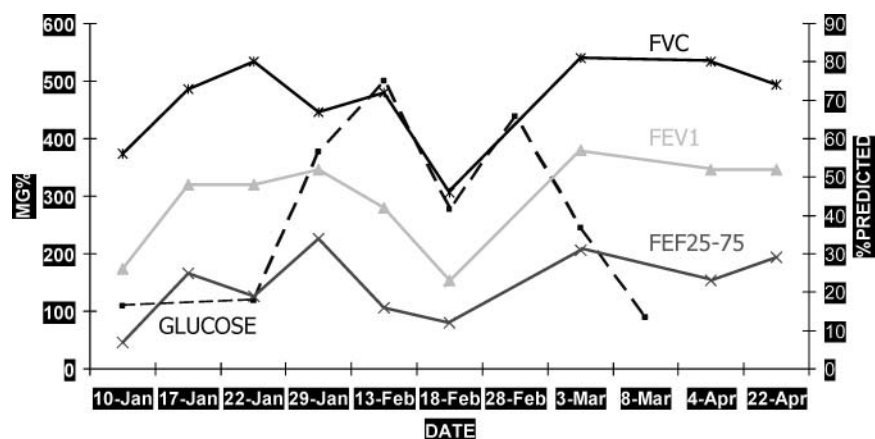


FIGURE 1.—Clinical parameters of blood glucose (preprandial or fasting) and pulmonary function. Insulin treatment started January 29. Prednisone taper began February 18 with discontinuation on March 8. Omalizumab treatment started March 3. Insulin was discontinued on April 4.

normal values. Owing to steroid-induced hyperglycemia, prednisone dose was gradually tapered from 1 mg/kg/day (30 mg twice daily) to 0.15 mg/kg (10 mg every other day) over 5 weeks resulting in improved serum glucose levels varying from 106 to 244 mg%. However, after steroid reduction, pulmonary function values began to worsen (FEV_1 40% predicted). The pulmonary infiltrates and PFTs demonstrated a significant improvement with systemic steroid therapy. Hence, we accepted the adverse effect of volatile hyperglycemia that was targeted with a sliding scale insulin regimen. After 5 weeks of this in-patient intensive regimen, PFT values improved markedly and pulmonary infiltrates cleared.

After discharge, his hyperglycemia persisted despite home insulin sliding scale therapy. In an effort to reduce steroid-induced hyperglycemia, omalizumab 375 mg subcutaneously twice a month was initiated in concert with high-dose itraconazole (500 mg/day). Both objectives of glucose control and maintenance of pulmonary function were accomplished (see Figure 1).

Subsequent PFTs over a 6-month course on omalizumab were consistently near pre-exacerbation baseline (Figure 1). Chest radiographs 1 to 6 months after discontinuation of prednisone have shown resolution of infiltrates. He remains off insulin since the institution of omalizumab. His serum glucose level remains consistently 70 to 90 mg%. Currently, 11 months after omalizumab treatment, the patient has not shown a decline in lung function, symptoms of hyperglycemia, or a need for systemic steroids.

DISCUSSION

Our CF patient had a recent diagnosis of ABPA with recurrent pulmonary exacerbations, significantly elevated total IgE, and deteriorating lung function. He failed frequent and prolonged courses of moderate-dose oral corticosteroids. He also failed adjuvant therapy with itraconazole despite its adequate serum levels. The patient had no prior history of CF-related hyperglycemia until he required oral corticosteroid use. The patient's glucose control with insulin after starting oral corticosteroids was poor and particularly labile such that he required prolonged hospitalization. Omalizumab

improved glycemic control by allowing the patient to taper off systemic corticosteroids.

The pathophysiology of ABPA and *Aspergillus* colonization in CF airways has been previously described (9–10). ABPA has been classically categorized into five stages. Stage 1 represents acute disease with upper or middle lobe infiltrates with acutely elevated total serum IgE. Stage 2 disease indicates clinical remission without pulmonary infiltrates after discontinuation of prednisone for 6 months. Stage 3 disease describes the clinical exacerbation of recurrence (similar to stage 1). Stage 4 disease is defined by intermittent infiltrates, elevated IgE, and corticosteroid dependence. Stage 5 disease represents end-stage fibrocavitary lung disease (11). The mainstay of therapy includes systemic corticosteroids with many patients requiring prolonged treatment courses to control the disease. The use of antifungal therapy has been recommended as a mean to decrease the fungal burden in the airway. Chest radiographs, blood eosinophils, and IgE levels are measured frequently as improvement indicators, characterized by resolution/stabilization of infiltrates, decline in sputum eosinophils, and a stabilization of total IgE (12). Particularly as steroid-sparing therapy, a trial of itraconazole for 4 to 6 months has been recommended. Itraconazole therapy requires monitoring drug levels, liver enzymes, triglyceride, and potassium levels (13). Standard stage 1 therapy with prednisone and itraconazole demonstrated the usual recovery in lung function and radiographic resolution in our case. However, the steroid induction of insulin resistant diabetes did not allow for optimization of the standard treatment regimen.

Systemic glucocorticoid therapy impairs the suppression of glucose production and stimulation of glucose utilization (14). The aspect insulin resistance has been described in depth in solid organ transplantation. The frequency of steroid-induced diabetes was as high as 46% in renal transplant recipients who received high-dose steroid regimens (15). Steroid-induced insulin resistance is potentially multiplied in cystic fibrosis. In CF patients without diabetes, insulin sensitivity is variable (16). While most of these patients are sensitive to insulin at baseline, infection and inflammation increase insulin resistance (17). In episodes similar to

ABPA, insulin resistance can become acutely severe during infectious exacerbations (17). Hence, particularly in CF, baseline insulin resistance compounded with systemic corticosteroid use places these patients at greater risk to develop diabetes and redirects therapy toward steroid-sparing agents.

The use of omalizumab to treat ABPA in cystic fibrosis has been previously reported in a case series (18). The efficacy and safety of omalizumab, a recombinant anti-IgE antibody, has been established in severe allergic asthma (19). The pharmacodynamics of omalizumab in allergic asthma include downregulation of IgE receptors and the reduction of unbound serum IgE (20). A clinical response was achieved in our case without a dose escalation of omalizumab despite a significantly elevated serum IgE. While the pathogenesis of IgE in ABPA is not fully understood, the attenuation of the hyper-IgE response in ABPA has been reported clinically (7). Before the start of omalizumab, our patient failed to achieve complete disease control after prolonged courses of what could be considered standard therapy. The limitation in therapy was primarily steroid-induced diabetes. Unlike previous reports with a prolonged history of stage 4 ABPA, our patient demonstrated rapid clinical improvement and a diminished corticosteroid requirement in stage 1 ABPA. Based on this experience, omalizumab has a potential role as adjuvant therapy in stage 3 ABPA. Omalizumab may also be a steroid-sparing agent in the initial therapy of stage 1 ABPA, particularly in CF patients who are pre-diabetic or prone to insulin resistance. The specific health care cost utilization of ABPA is not known. Nevertheless, the cost of in-patient ABPA therapy in our patient paled in comparison to outpatient omalizumab treatment. This therapeutic option certainly merits further investigation in both cystic fibrosis and other chronic lung disease models prone to ABPA.

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