Case Report

Prolonged Role of Itraconazole in the Treatment of Allergic Bronchopulmonary Aspergillosis

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Received 2 July 2013; Revised 11 August 2013; Accepted 14 August 2013

Abstract

Oral corticosteroids are first-line therapy for allergic bronchopulmonary aspergillosis (ABPA), however, itraconazole has been recognized as an adjunctive treatment. This paper describes the prolonged use of itraconazole in an asthmatic patient with a diagnosis of ABPA. This case report features a patient who showed benefit with a longer duration of itraconazole therapy without demonstrating adverse events related to treatment over nearly eight years. Prolonged treatment with itraconazole may serve as a corticosteroid sparing option for ABPA patients.

Keywords allergic bronchopulmonary aspergillosis; itraconazole

1. Introduction

A 64-year-old patient was diagnosed with ABPA based upon the history of asthma, elevated total IgE level, eosinophilia, elevated Aspergillus fumigatus specific IgE level, and bronchiectasis on a high resolution CT scan of the chest. The patient received prolonged treatment with itraconazole, 200 mg twice a day, over a nearly eight-year period. The patient had ABPA exacerbations after discontinuation of the long-term itraconazole on two separate occasions. The patient demonstrated improvement in symptoms, lower total IgE levels, and no radiographic progression of his disease after resuming long-term therapy with itraconazole at a dose of 200 mg twice a day. This case illustrates how prolonged treatment with itraconazole may serve as a corticosteroid sparing option for ABPA patients.

2. Case presentation

A 64-year-old patient was referred for management of allergic bronchopulmonary aspergillosis (ABPA). The patient was a lifetime non-smoker with a history of asthma and dog allergy since age four. Medications included monteleukast, fluticasone/salmeterol (Advair) 500/50 one puff twice daily; and theophylline 200 mg at bedtime. The patient had been on various doses of prednisone for five years, stopping three years before the initial visit. While on systemic corticosteroids, the patient complained of feeling moody, weight gain, and generalized swelling.

The patient was diagnosed with ABPA based on the history of asthma, elevated IgE level (up to 8,691 KU/L), elevated eosinophil count of 1,944 cells/MCL, elevated Aspergillus fumigatus specific IgE level and bronchiectasis on a high resolution CT scan of the chest.

The patient returned four years later, after recently completing a seven-month course of prednisone for worsening respiratory symptoms. The patient’s serum IgE level was 7,000 KU/L and the most recent CT chest showed lobular and nodular ill-defined parenchymal densities and areas of central bronchiectasis all consistent with progressive disease in the upper lobes. The patient was started on a trial of itraconazole 200 mg twice daily. Six months later, the patient was feeling well and total serum IgE level had decreased to 2,636 KU/L. Chest imaging remained unchanged. Itraconazole was discontinued.

Four months later, the IgE level had risen again to 6,343 KU/L with worsening asthma symptoms and decreased pulmonary function tests. FVC was 4.34 liters (90% predicted) and FEV1 was 2.43 liters (64% predicted), from 4.77 liters and 2.69 liters four years earlier. Itraconazole 200 mg twice daily was resumed.

The patient remained on itraconazole for the next six years with significant clinical improvement and no side effects. IgE levels were routinely monitored and remained between 1,000 KU/L and 2,000 KU/L during this time. Imaging studies suggested the patient’s disease remained stable. Itraconazole was stopped again. Seven months following the cessation of itraconazole the patient relapsed; the IgE level had increased to 5,333 KU/L. The patient reported increased brown-colored sputum, generalized fatigue, and exercise intolerance. Chest X-ray showed a new infiltrate for which he received a course of cefuroxime axetil without improvement.
Itraconazole was resumed but at a lower dose of 200 mg daily. Shortly after starting another course of itraconazole, his third, the patient’s symptoms slightly improved, however still reported fatigue and increased sputum production. IgE level declined from 5,333 KU/L to 5,114 KU/L. Pulmonary function tests mildly improved, with FVC of 3.99 liters (85% predicted) and FEV1 of 2.53 liters (69% predicted). During this time, CT chest showed bronchiectasis with prominent mucoid impaction within the perihilar left upper lobe region. Itraconazole was increased back to the original dose of 200 mg twice daily. Following this dose adjustment the cough improved, sputum production decreased, pulmonary disease radiographically remained stable, IgE level decreased to 3,949 KU/L, and the eosinophil count decreased from 2,051 cells/MCL to 285 cells/MCL.

3. Discussion

A. fumigatus can be present as a viable organism within airway mucus plugs, where it causes an intense local immune reaction, often resulting in marked re-modeling of the airway. This can lead to fixed airflow obstruction with bronchiectasis [10]. ABPA is characterized by exacerbations in asthma and coughing up thick mucus plugs [5]. The diagnosis of ABPA is based on demonstrating clinical and immunologic reactivity to A. fumigatus. Rosenberg-Patterson diagnostic criteria for ABPA include asthma, immediate skin reactivity to A. fumigatus, a serum IgE level of > 417 IU/mL, radiographic evidence of fleeting infiltrates or central bronchiectasis, and elevated serum levels of A. fumigatus specific IgE or IgG [2]. The disease can progress from the acute phase to stages characterized by exacerbations and corticosteroid dependency and finally to end-stage fibrotic disease [9].

Oral corticosteroids are currently regarded as the most definitive treatment for ABPA [1]. They suppress the immune hyper-function and are also anti-inflammatory. However, no prospective studies with corticosteroids have been conducted to evaluate efficacy rates, optimum dose, and duration or relapse rate [5]. The long-term benefits of corticosteroids in ABPA are unclear [9].

It was hypothesized that using anti-microbial agents to reduce the fungal burden in the respiratory tract would decrease chronic antigenic stimulation, reducing the inflammatory response, and possibly the long-term risk of progression of ABPA [9]. In short term use, up to six months, administration of itraconazole, an oral triazole, decreased steroid use and improved pulmonary function, along with exercise tolerance [9].

Optimal duration of itraconazole therapy has not been established [1]. A randomized, double blind, 16 week placebo-controlled study found that in subjects with clinically stable ABPA, defined as no deterioration in symptoms and no increase in the use of asthma medications or antibiotics for chest disease, the addition of itraconazole 400 mg daily reduced airway inflammation, as well as systemic immune activation. It significantly decreased total IgE and IgG antibodies to A. fumigatus, and resulted in fewer severe exacerbations requiring treatment with prednisone [10]. Denning et al. described clinical improvement and reduction of IgE levels in six patients treated with itraconazole for 3.9 months [3].

4. Conclusion

This case highlights the role of prolonged antifungal agents in the treatment of ABPA. Oral itraconazole has been shown to be effective in our patient as an adjunctive therapy for ABPA, reducing the need for corticosteroids. Corticosteroids have been first-line therapy for ABPA, reducing the immune response mounted to the presence of Aspergillus in the airways. The role of long-term systemic corticosteroid therapy has been questioned with only limited evidence that it prevents the progression of lung destruction and it may be ineffective in end-stage fibrosis [8]. Itraconazole has been shown to reduce exacerbations, improve lung function parameters, and prevent disease progression, and our patient demonstrates that control can be maintained for much longer periods of time than previously shown. There are four published studies, including two double-blind, randomized, placebo-controlled studies, describing the use of itraconazole for time ranges of four to twelve months [6, 7, 9, 10]. No adverse events developed over the last eight years, our patient has been (mostly) on and off (less than a total of twelve months) itraconazole. 

References
