CASE REPORT

Daily dose of itraconazole 100 mg to treat allergic bronchopulmonary aspergillosis (ABPA) related eosinophilia: a case report

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Abstract

Background: Itraconazole can be used in the treatment of allergic bronchopulmonary aspergillosis (ABPA), as add-on therapy to antiasthmatic medications.

Description of the case: The case of an 83-year-old male with asthma, newly diagnosed with ABPA, is presented. A daily itraconazole dose of 100 mg managed to efficiently control eosinophilia and reduce his total IgE count, while these laboratory findings relapsed three months after stopping itraconazole. When the dose was reduced to 100 mg of itraconazole every other day, it was proved insufficient to control eosinophilia. Moreover, one year later, he is being efficiently treated with 100 mg itraconazole daily.

Conclusions: The dose of itraconazole 100 mg can effectively treat some cases of ABPA with asthma. HIPPOKRATIA 2017, 21(3): 144-146.

Keywords: Allergic bronchopulmonary aspergillosis, ABPA, asthma, itraconazole

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Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic reaction to *A. fumigatus* causing a pulmonary disorder, which occurs mainly in patients with asthma or cystic fibrosis[1,2]. ABPA complicates the course of these diseases and patients usually present with poorly controlled asthma, recurrent pulmonary infiltrates, and bronchiectasis[2]. Differential diagnosis from eosinophilic allergic asthma with sensitization to *Aspergillus* can be challenging, especially when there is imaging with evidence of bronchiectasis.

Treatment of ABPA in people with asthma is based on the stage (acute, remission, exacerbation, corticosteroid dependent or fibrotic) of the disease and aims to control asthma and its exacerbations, but also to prevent deterioration in lung function[3,4]. Systemic corticosteroids are the usual medications, while the use of inhaled corticosteroids (ICS) is controversial since they cannot control complicated cases of ABPA[1-4]. However, ICS can successfully control ABPA with mild/moderate asthma[1,2]. Antifungal treatment with itraconazole is used as add-on therapy, managing to reduce exacerbations, glucocorticoid dose, and eosinophilic count[5,6].

We report the case of a male patient with asthma, who was referred to our Clinic for consultation due to eosinophilia. He was found to have a sensitivity to *Aspergillus* and was treated with low dose itraconazole, following a novel therapeutic scheme.

Case Report

An 83-year-old male was referred for investigation of mild eosinophilia (eosinophils: 1,023 /mm^3) that had been discovered accidentally two years before his presentation and had persisted ever since. He had been diagnosed with asthma 23 years before. He did not report wheezing or dyspnea; however, he had an intermittent cough for the preceding ten years, which was often resistant to the anti-asthmatic treatment. During hospitalization, ten years ago, he had been investigated with bronchoscopy and computed tomography of the chest, with findings of central pulmonary infiltrates in both lower lobes and bronchiectasis in the apical segment of the left lower lobe and the medial segment of the right middle lobe.

He was under fluticasone plus salmeterol (500+50 μg/dose) twice daily and tiotropium (18 μg/dose) once daily. He also reported history of nasal polyps (he had nasal polypectomy twice), hypertension, and benign prostatic hyperplasia. The patient had never smoked, he did not drink alcohol, and he lived in the countryside, though near an urban area. He owned dogs and gardening was his main hobby.

His physical examination showed no abnormal find-

ings, and nasal examination did not reveal nasal polyps. Spirometry was normal. Skin prick tests (SPT) were performed, using the standard battery for airborne allergens of our Clinic and monosensitivity to *A. fumigatus* was revealed. Although mild eosinophilia could have been the outcome of asthma, the SPT results set the probable diagnosis of ABPA. Workup included a chest X-Ray (CXR) and laboratory tests.

Upon his second visit, the eosinophilic count was similar (966 /mm^3) and total IgE (tIgE) was high (890 IU/mL). High specific IgE (sIgE) levels of m3 allergen [ImmunoCAP (Phadia AB, Uppsala, Sweden): 15.8 kUA/L] confirmed hypersensitivity to *A. fumigatus*, while IgM/IgG antibodies were negative. Antibodies and stool microbiological examination for common parasites were also negative, and blood chemistry was normal. Bronchiectasis was noted on his CXR (similar distribution to his previous chest CT). His antiasthmatic treatment was continued and a nasal spray (fluticasone furoate 27.5 μg/dose, twice daily) was prescribed for three months, with advice for regular follow-up. Finally, in order to control eosinophilia, a daily dose of itraconazole 100 mg was prescribed for six months.

A noticeable reduction in eosinophilia was noted six months later, with an eosinophil count of 350 /mm^3. His tIgE was reduced to 593 IU/ml, while no changes were seen in a new CXR. He reported no coughing during these months, and his sense of smell had increased. He was advised to stop itraconazole and follow-up was scheduled after six months. At that time his blood test revealed eosinophilia once again (1,030 /mm^3) and similar levels of tIgE (643 IU/ml), so itraconazole 100 mg, every other day (q.a.d.) was prescribed for three months, in an attempt to reduce the risk of adverse effects since long-term administration would be required.

In the follow-up complete blood count, three months later, while he was under the itraconazole q.a.d. scheme, there was no effect on the eosinophil count (1,083 /mm^3); hence itraconazole once daily was prescribed again with a subsequent reduction in eosinophilia (280 /mm^3), three months later. Twelve months after starting the daily treatment, his follow-up has been uneventful, with controlled eosinophilia and unchanged CXR findings.

Discussion

The "ABPA in asthmatics" Working Group of the International Society for Human and Animal Mycology (ISHAM) has set diagnostic criteria for ABPA[7]. According to these, our patient is not considered a case of ABPA since tIgE count was (little) less than 1,000 IU/ml and serum IgG against *A. fumigatus*, was absent. Not fulfilling these criteria he might be considered a case of eosinophilic allergic asthma with *Aspergillus* sensitization. However, our case fulfills the new diagnostic criteria for ABPA proposed very recently[8]. A European Academy of Allergy and Clinical Immunology (EAACI) Task Force, addressing "Fungal Allergy in Asthma" has also proposed broadening of the criteria, in order to include patients with airway disease, allergy to fungi and lung damage[9].

In ABPA oral corticosteroids are administered to control inflammation and the burden of *Aspergillus spp* while they are tapered off to the lowest dose possible[1-4]. Steroids are not necessary for patients at ABPA-S (serological) stage and can be initiated in ABPA-B (bronchiectasis) stages, using spirometry and tIgE levels as decision markers for dose adjustment[2]. In our case, there was no previous corticosteroid administration and hence the dilemma of initiating them, in order to decrease eosinophilia, was set. Since his asthma was well controlled with ICS, we only added antifungal therapy.

Huge progress has been made in the treatment of eosinophilic asthma, and specific anti-eosinophilic therapies (anti-IL5, anti-IL4Ra, anti-TSLP) exist but are indicated only for patients with severe refractory forms of uncontrolled asthma, not responding to ICS[10,11]. Although our patient's asthma was apparently well controlled, we decided to add azoles as add-on therapy, in order to decrease eosinophilia and prevent the undesired effects that the chronic presence of eosinophils can cause on bronchial muscle tone[12]. The fact that his cough improved was a positive clinical sign, while the decrease of blood markers (tIgE and eosinophils) confirmed the efficacy of itraconazole to control the immunological response to *Aspergillus*.

The use of itraconazole is suggested for ABPA and monotherapy can be an option, while no data exist for its use in the treatment of allergic fungal asthma[9]. Main side effects caused by the systemic use of itraconazole are gastrointestinal disorders, skin rash, hypertension, and abnormal hepatic function[13]. To prevent any major side effects, our patient's blood pressure was regularly monitored, and hepatic enzymes were also checked routinely. The only side effect he reported was constipation, which improved after increasing dietary fibers.

In two randomized controlled studies on ABPA's treatment with itraconazole, doses of 200 mg and 400 mg have been used[5,6]. We faced the challenge to balance between side-effects and effective treatment of ABPA, with the use of a 100 mg daily dose. The -lower than usual- administered dose of itraconazole was chosen, in order to minimize the risk of side effects, hypothalamic-pituitary-adrenal (HPA)-axis suppression being one of them. The risk of suppressing the HPA-axis is high when inhaled fluticasone (or other ICS) is combined with itraconazole[14]. Although there is no direct correlation between the degree of HPA-axis suppression and the plasma levels of itraconazole, all reported cases refer to daily doses of 200 mg or higher[14]. However, the use of a lower dose could reduce such a risk.

We also assessed the risk of *Aspergillus* developing resistance when exposed to subinhibitory doses of itraconazole. Such resistance is connected mainly to a mutation in the Cyp51A gene (up to 94 % of the cases)[15]. However, in ABPA, a lower fungal load is expected than in a true infection. Although it could have been helpful with dose adjustments, routine measurement of itraconazole

level was not available at the time of the study. Nonetheless, the efficacy of itraconazole 100 mg daily, when reintroduced, has proved that emergence of resistance had not occurred.

Concluding, eosinophilia relapse and inadequate control after discontinuation of the antifungal or administration of a lower dose, led us to choose the maintenance dose of itraconazole 100 mg daily. It is possible that long-term itraconazole dose in ABPA could be customized considering the i) clinical and biomarker response, ii) side-effects, and iii) emergence of itraconazole resistance. Until now, no guidelines exist to suggest the long-term use of antifungal drugs in cases similar to ours. We suggest that itraconazole on a daily dose could be used with follow-up visits every six months. However, such a recommendation would only be possible after the suggested treatment strategy has been studied in a larger number of patients.

Conflict of interest

Authors declare no conflict of interest.

References

1. Greenberger PA, Bush RK, Demain JG, Luong A, Slavin RG, Knutsen AP. Allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol Pract. 2014; 2: 703-708.
2. Agarwal R, Chakrabarti A. Allergic bronchopulmonary aspergillosis in asthma: epidemiological, clinical and therapeutical issues. Future Microbiol. 2013; 8: 1463-1474.
3. Greenberger PA, Miller TP, Roberts M, Smith LL. Allergic bronchopulmonary aspergillosis in patients with and without evidence of bronchiectasis. Ann Allergy. 1993; 70: 333-338.
4. Muldoon EG, Strek ME, Patterson KC. Allergic and Noninvasive Infectious Pulmonary Aspergillosis Syndromes. Clin Chest Med. 2017; 38: 521-534.
5. Wark PA, Hensley MJ, Saltos N, Boyle MJ, Toneguzzi RC, Epid GD, et al. Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: a randomized controlled trial. J Allergy Clin Immunol. 2003; 111: 952-957.
6. Stevens DA, Schwartz HJ, Lee JY, Moskovitz BL, Jerome DC, Catanzaro A, et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. N Engl J Med. 2000; 342: 756-762.
7. Agarwal R, Chakarbarti A, Shah A, Gupta D, Meis JF, Guleria R, et al; ABPA complicating asthma ISHAM working group. Allergic bronchopulmonary aspergillosis: review of the literature and proposal of new diagnostic and classification criteria. Clin Exp Allergy. 2013; 43: 850-873.
8. Ishiguro T, Takayanagi N, Uozumi R, Baba Y, Kawate E, Kabayashi Y, et al. Diagnostic criteria that can most accurately differentiate allergic bronchopulmonary mycosis from other eosinophilic lung diseases: A retrospective, single-center study. Respir Investig. 2016; 54: 264-271.
9. Denning DW, Pashley C, Hartl D, Warlaw A, Godet C, Del Giacco S, et al. Fungal allergy in asthma-state of the art and research needs. Clin Transl Allergy. 2014; 4: 14.
10. O'Byrne PM. POINT: Will New Anti-eosinophilic Drugs Be Useful in Asthma Management? Yes. Chest. 2017; 151: 14-17.
11. Barnes PJ. COUNTERPOINT: Will New Anti-eosinophilic Drugs Be Useful in Asthma Management? No. Chest. 2017; 151: 17-20.
12. Roufosse F, Weller PF. Practical approach to the patient with hypereosinophilia. J Allergy Clin Immunol. 2010; 126: 39-44.
13. Sporanox® [package insert]. Athens (Greece): Famar for Janssen-Cilag Pharmaceuticals Cop; 2017, available at: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPORANOX-Capsules-pi.pdf, last accessed: 20/9/2017.
14. Gilchrist FJ, Cox KJ, Rowe R, Horsley A, Webb AK, Jones AM, et al. Itraconazole and inhaled fluticasone causing hypothalamic-pituitary-adrenal axis suppression in adults with cystic fibrosis. J Cyst Fibros. 2013; 12: 399-402.
15. Howard SJ, Cesar D, Anderson MJ, Albarrag A, Fisher MC, Pasqualotto AC, et al. Frequency and evolution of Azole resistance in Aspergillus fumigatus associated with treatment failure. Emerg Infect Dis. 2009; 15: 1068-1076.