Prednisolone plus itraconazole in acute-stage allergic bronchopulmonary aspergillosis complicating asthma: is the benefit worth the risk?

Received: 12 Nov 2021
Accepted: 17 Nov 2021

To the Editor:

Treating allergic bronchopulmonary aspergillosis (ABPA) remains a challenge for clinicians, as little high-quality data exists on the optimal treatment regimen. ABPA is widely accepted to correspond to an exaggerated immune response to *A. fumigatus* and oral corticosteroids are the first line of treatment [1, 2]. Oral steroids are often associated with inhaled corticosteroids (ICS), which are mandatory in the management of asthma patients. Antifungal azoles have been proposed as an adjunctive treatment of ABPA in asthma patients for more than two decades [3]. Itraconazole is usually suggested as an add-on therapy in steroid-dependent patients [2], in those with relapsing ABPA and/or in those with insufficient response to oral steroids combined with ICS [1]. Definitive evidence for this approach is currently missing, as previous studies were performed in a small number of patients and over short periods of time [3, 4].

We read with interest the article by Agarwal *et al.* [5] published in the *European Respiratory Journal*. In this single-centre, randomised, open-label study, the authors prospectively compared a 4-month course of prednisolone alone to the combination of prednisolone (4-month course) and itraconazole (6-month course) to treat acute-stage ABPA complicating asthma in treatment-naïve patients. The primary outcomes were exacerbation rates at 12 months and progression to glucocorticoid-dependent ABPA within 24 months after treatment initiation. The authors randomised 191 patients and reported a numerical but non-statistically significant difference in the proportion of subjects experiencing ABPA exacerbation at 1 year (33% *versus* 20.6% in the prednisolone and the prednisolone–itraconazole combination groups, respectively; p=0.054) and 2 years (48.9% *versus* 39.2%; p=0.17). There was no significant difference in the time to first exacerbation, nor in the rate of composite response to treatment, serum total IgE or lung function at 6 weeks. None of the subjects progressed to corticosteroid-dependent ABPA at 2 years. Although patients treated with itraconazole had more elevations of liver enzymes (21.6% *versus* 6.2%), there was no increase in severe adverse events. This study is important since it is the first large randomised controlled trial on combining itraconazole to oral steroids in ABPA complicating asthma. However, some important issues regarding the use of azole therapy in patients with ABPA need to be further discussed.

Agarwal *et al.* [5] suggested that the numerical decrease in the rate of patients experiencing ABPA exacerbations when adding itraconazole was related to a reduction the fungal antigen burden. However, itraconazole is a potent CYP3A4 inhibitor and can increase systemic levels of inhaled fluticasone [6]. In the present study, all patients were treated with inhaled formoterol/fluticasone (6/125 µg twice daily) and the dose of ICS was comparable at study entry between the groups. Thus, patients in the itraconazole plus prednisolone may have experienced greater systemic exposure to steroids as compared to those with prednisolone alone, due to the drug–drug interaction between ICS and itraconazole, which may have contributed, at least in part, to the observed results. The difference in steroid exposure may have even been of greater importance because patients were further instructed to use formoterol/fluticasone as needed for symptom relief; however, there was no monitoring of ICS doses during the treatment period, making it difficult to estimate steroid exposure. This problem could have been diminished by discontinuing itraconazole and oral steroids at the same time during the study (to avoid a longer systemic steroid exposure in the itraconazole group).

Shareable abstract (@ERSpublications)
The effect of adding itraconazole to prednisolone shown in an open-labelled study has no firmly established mechanism and could be related to greater exposure to steroids. The risk of selecting azole-resistant *A. fumigatus* strains should be considered. https://bit.ly/30Nl3zr

Cite this article as: Havette A, Regard L, Roche N, *et al.* Prednisolone plus itraconazole in acute-stage allergic bronchopulmonary aspergillosis complicating asthma: is the benefit worth the risk? *Eur Respir J* 2022; 59: 2102924 [DOI: 10.1183/13993003.02924-2021].

The authors reported only mild elevations of liver enzymes, with no treatment discontinuation due to adverse events, but the risk of hypothalamic-pituitary-adrenal axis suppression was not monitored. This adverse event has been well documented in the literature and is secondary to the interaction of itraconazole and ICS [7]. We suggest that baseline and post-adrenocorticotropic hormone stimulation plasma cortisol levels should be systematically assessed in patients treated with antifungal azoles and ICS. Another potentially important aspect relates to ecological consequences of prolonged azole therapy in patients with aspergillosis: prolonged treatment with itraconazole in subjects with ABPA and cystic fibrosis has been associated with the identification of azole-resistant *A. fumigatus* isolates [8, 9], which have been associated with treatment failure in invasive aspergillosis. Estimating the individual and global impact of this finding is challenging. Of note, no microbiological data were reported in the study by Agarwal *et al.* [5]. Monitoring of fungal load and azole resistance in future trials would appear important to better define the ecological risk of this approach.

The borderline beneficial effect of adding itraconazole to prednisolone shown in this open-label study has no firmly established mechanism and could be related to a reduction in the fungal load but greater exposure to steroids due to drug–drug interaction cannot be excluded. Further assessing the balance between benefit and risk remains complicated, as the individual and collective drawbacks of prescribing azoles in this setting may need to be better assessed before deriving a definitive conclusion.

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Conflict of interest: A. Havette has nothing to disclose. L. Regard has nothing to disclose. N. Roche declares grants (paid to institution) from Boehringer Ingelheim, Novartis, GlaxoSmithKline and Pfizer; consulting fees from Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, Sanofi, Chiesi, Pfizer, Novartis and Teva; and payment or honoraria from Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, Sanofi, Chiesi, Pfizer, Novartis, Teva and Zambon, all in the 36 months prior to manuscript submission. P-R. Burgel declares grants (paid to institution) from Boehringer Ingelheim, Vertex and GlaxoSmithKline; consulting fees from Vertex, GlaxoSmithKline, AstraZeneca and Chiesi; and payment or honoraria from Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, Vertex, Chiesi, Pfizer, Novartis, Insmed and Zambon, all in the 36 months prior to manuscript submission.

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