

What is the current place of azoles in allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization

Expert Rev. Respir. Med. 6(4), 363–371 (2012)

Ritesh Agarwal

Department of Pulmonary Medicine,
Postgraduate Institute of Medical
Education and Research, Chandigarh,
160012, India

Tel.: +91 172 275 6825

Fax: +91 172 274 8215

riteshpgi@gmail.com

Evaluation of: Chishimba L, Niven RM, Cooley J, Denning DW. Voriconazole and posaconazole improve asthma severity in allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization. *J. Asthma* 49(4), 423–433 (2012).

Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary disorder caused by hypersensitivity to *Aspergillus fumigatus* that usually complicates the disease course of patients with asthma and cystic fibrosis. Oral corticosteroids are currently the treatment of choice for ABPA. Another active target is the use of azoles, which act by reducing the antigenic stimulus secondary to a decreased fungal burden. Studies suggest that itraconazole compared with placebo can improve symptoms in ABPA, decrease the immunological severity (IgE levels and total eosinophil counts), glucocorticoid requirement and the number of acute ABPA exacerbations. Severe asthma with fungal sensitization, a disorder closely related to ABPA, is a specific phenotype of asthma characterized by severe asthma and evidence of fungal sensitization after exclusion of ABPA. Again, oral itraconazole has been found to improve the quality of life in these steroid-dependent asthma patients. The current retrospective study evaluated the use of newer azoles (voriconazole and posaconazole) in adult asthmatic patients with either ABPA or severe asthma with fungal sensitization, and found the newer azoles to improve asthma control and reduce the severity of ABPA.

KEYWORDS: ABPA • allergic bronchopulmonary aspergillosis • asthma • azoles • steroids

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disorder of the lung caused by *Aspergillus fumigatus* [1,2]. On the other hand, allergic bronchopulmonary mycosis is the occurrence of ABPA-like syndrome due to fungi other than *A. fumigatus*. The interest in ABPA springs from the fact that this condition is extremely treatment responsive, and early diagnosis and treatment can prevent progression to end-stage lung disease [3]. However, if the condition is not diagnosed and/or treated appropriately, widespread bronchiectasis and pulmonary fibrosis can eventually develop, culminating in cor pulmonale and chronic type 2 respiratory failure [4]. Recently, Denning *et al.* have described a new asthma phenotype termed severe asthma with fungal sensitization (SAFS), which is closely

linked to ABPA [5,6] and can be considered as a prelude to the development of ABPA [7,8]. These patients are characterized by severe asthma, sensitization to one or more fungi with no other diagnostic features of ABPA. SAFS and ABPA can be considered as different stages of fungal sensitization due to differing Th2 responses, with the immune responses being quantitatively higher in the latter.

The management of ABPA includes two important facets, namely, institution of anti-inflammatory therapy in the form of glucocorticoids to control the immunologic activity, and use of antifungal agents to attenuate the fungal burden secondary to fungal colonization in the airways. The goals of therapy in ABPA include control of asthma, prevention and treatment of acute

exacerbations of the disease, and prevention of the development of bronchiectasis and pulmonary fibrosis. Current pharmacotherapy for ABPA primarily involves the use of oral corticosteroids (OCSs) and azoles. Oral steroids are currently agreed as the treatment of choice for ABPA, although there are no randomized trials of steroids in ABPA. They are highly efficacious in the management of ABPA [3,9–12]; however, once the steroids are tapered, almost 50% of patients relapse and 20–45% remain glucocorticoid dependent [9,13]. Many patients also develop adverse effects owing to chronic glucocorticoid therapy [14,15]. These problems have led clinicians to look for alternative treatment approaches that would either obviate the need for glucocorticoids or decrease the dose of systemic steroids in the treatment of ABPA. Antifungal agents, especially itraconazole, have been reported to have beneficial effects in therapy of ABPA [16–23]. Itraconazole was also found to have some beneficial effects in the treatment of SAFS. However, not all patients respond to itraconazole and, currently, treatment with itraconazole is associated with a 40% failure rate in ABPA [24]. Moreover, there are numerous adverse events (AEs) described with itraconazole [25]. In a recent retrospective study, Chishimba *et al.* analyzed the effect of newer azoles (voriconazole and posaconazole) as second- or third-line therapies in patients with ABPA and SAFS [26].

Methods

The study by Chishimba *et al.* was a single-center, retrospective study on the efficacy and safety of voriconazole or posaconazole in patients with ABPA or SAFS diagnosis based on contemporaneous criteria [26]. Voriconazole (300–600 mg/day) or posaconazole (800 mg/day; adjusted by plasma-level monitoring) was given for at least 6 months, if tolerated. The target plasma levels used for voriconazole and posaconazole were 1.3–5.7 mg/l (predose) and >0.7 mg/l (random, after steady state was reached), respectively. Some patients received both agents at separate times, and the authors evaluated each course separately.

Response was evaluated in clinical, immunological (decrease in IgE levels [total and *A. fumigatus* specific] and peripheral blood eosinophilia), lung function and radiological features, with clinical improvement considered as the most important outcome. Clinical improvement was defined as improvement in symptoms of breathlessness, cough, wheeze, chest tightness, nocturnal awakening and/or asthma control (as defined by the global initiative for asthma criteria that include: reductions in dosage and courses of oral and inhaled corticosteroids [ICSs], exacerbations, daytime or nocturnal symptoms and number of hospitalizations or emergency room visits; improvement in exercise tolerance and lung function in terms of forced expiratory volume in the first second [FEV₁]; and improvement in the overall quality of life).

Results

The study included 25 patients (20 ABPA and five SAFS; ten men) with a median age of 58 years (range: 20–80 years). Of the 20 patients with ABPA, 12 had bronchiectasis on computed tomography of the chest. All patients with SAFS had fixed airway obstruction with the mean FEV₁% predicted being 52.8% (range: 27.8–75%). All patients had previously received

itraconazole, but treatment was discontinued owing to adverse reactions (n = 13), lack of clinical efficacy (n = 11), low serum concentrations (n = 2) or itraconazole resistance in *A. fumigatus* (n = 2). Thirty-three courses of therapy were administered, 24 with voriconazole (19 ABPA and five SAFS) and nine with posaconazole (all ABPA). Posaconazole was administered in those experiencing side effects (n = 5), lack of response (n = 3) or *in vitro* resistance of *A. fumigatus* (n = 1) to voriconazole. The mean treatment duration of voriconazole and posaconazole was 16.7 months (range: 2–48 months) and 16.3 months (range: 3–36 months), respectively.

Overall clinical improvement to voriconazole therapy was observed in 17 (13 [68%] ABPA, four [44%] SAFS) of 25 patients at 3 months, 15 (75%) of 20 patients at 6 months and 12 (70.6%) of 17 patients at 12 months, compared with seven out of nine (78%) at 3, 6 and 12 months for posaconazole. There was reduction in requirement of OCSs, and at 12 months 88% of those receiving voriconazole and 43% of those requiring posaconazole could discontinue the OCSs. There was a decline in the requirement of rescue inhalers and healthcare utilization owing to asthma, with improvement in overall health status. There was also a decrease in the number of hospital admissions and acute exacerbations in both the voriconazole and the posaconazole arms. There was statistically significant decline in both total and *A. fumigatus*-specific IgE values after 12 months of therapy. There were modest improvements in the radiological findings, although there was no significant improvement in pulmonary function (FEV₁ values).

AEs were encountered in 11 (55%) patients taking voriconazole, and the most common were skin photosensitivity (n = 11) and visual light flashes (n = 10). Most of these side effects were transient and mild, lasting less than 1 week. Significant AEs resulting in discontinuation of treatment included depression and sleep disturbance (n = 1), photosensitivity (n = 4), visual hallucinations (n = 2) and peripheral neuropathy (n = 1). Two patients with posaconazole experienced AEs, including insomnia (n = 2), gastrointestinal disturbances and mild liver impairment (n = 1). No patient discontinued posaconazole because of side effects.

Expert commentary & five-year view

This is the first study reporting the use of newer azoles (particularly voriconazole in SAFS and posaconazole in ABPA) in patients with ABPA and SAFS. Although the results of the study suggest that newer azoles may be tried in a subgroup of ABPA patients unresponsive to itraconazole, it is limited by its retrospective design and small number of patients. Nevertheless, voriconazole and posaconazole represent newer treatment options in the armamentarium of physicians managing this chronic and debilitating disorder. OCSs are highly effective in the treatment of ABPA and are considered the cornerstone in the management of ABPA [27]. However, many patients either require high doses or a long duration of therapy with these agents, and the well-known AEs of long-term steroid treatment indicate the necessity of alternative therapies [28].

The classical understanding of ABPA rests on the assumption that the disorder results from noninvasive colonization by *A. fumigatus*

and release of antigens, which trigger immune responses in a genetically predisposed host. The inconsistent recovery of *A. fumigatus* from sputum samples in ABPA or SAFS patients (0–63%) [29–33] led to the notion that antifungals would not be very helpful in ABPA. However, in a recent study, *Aspergillus* DNA was detected in sputum in almost 80% of patients with ABPA compared with none by culture [32]. As the inflammatory responses in ABPA (and SAFS) are mounted against antigens of *A. fumigatus*, antifungals would intuitively attenuate the resulting immune response by decreasing the fungal burden, whether or not the fungi is demonstrated in culture. Therefore, antifungals definitely have a place in the treatment of ABPA. The apparent benefits of azoles are, however, confounded by the fact that azoles themselves have direct and profound immunologic effects [34–40], and itraconazole can also increase the levels of glucocorticoids, thereby potentiating the steroid effect [41–43]. Therefore, it is not settled whether it is the antifungal action of the azole alone or the coexistent anti-inflammatory property of the drug that leads to improvement in patients with ABPA/SAFS. In many patients, antifungals alone are not effective because the disorder is not due to the fungi *per se* but due to the profound immunological activity, and anti-inflammatory therapy with OCSs would be warranted. It is also likely that in patients with milder forms of ABPA, particularly in those without bronchiectasis (or minimal bronchiectasis) or mucoid impaction, monotherapy with antifungals would also be effective. However, there are no data on azole monotherapy in acute stages of ABPA. A randomized controlled trial comparing monotherapy of itraconazole versus prednisolone in ABPA (MIPA study; ClinicalTrials.gov identifier: NCT01321827 [101]) is underway, which aims to evaluate itraconazole monotherapy in various subgroups of ABPA patients.

The antifungal agents with known efficacy in the management of ABPA include aerosolized amphotericin B and the azoles (itraconazole, voriconazole and posaconazole). Natamycin and ketoconazole have been evaluated in the past, but due to their limited efficacy against *A. fumigatus*, they were not very effective [44–46]. The currently available azoles have fewer side effects and seem an attractive choice in the management of ABPA. A systematic review of the PubMed and EmBase databases yielded 12 studies that have evaluated itraconazole ($n = 10$) or voriconazole ($n = 2$) in five or more patients of ABPA, and three studies evaluating azoles in five (one fluconazole and two itraconazole) or more patients with SAFS (TABLE 1) [6,16–23,47–51]. No study was found evaluating voriconazole in SAFS or posaconazole in ABPA or SAFS. Itraconazole has fewer side effects and a wider spectrum of activity than ketoconazole [52]. In ABPA, the majority of the studies evaluating itraconazole have been observational, with only two randomized trials. The results of these observational studies suggest that itraconazole treatment in ABPA is associated with favorable results (TABLE 2). Similarly, the use of voriconazole in two studies has been beneficial in ABPA [49,50]. The use of azoles in ABPA has been associated with clinical and immunological improvement, with significant decline in the requirement of systemic corticosteroids. Preliminary studies have also reported beneficial effects with the use of itraconazole in SAFS [6,51].

When to initiate azoles in ABPA

Although studies evaluating azoles show positive results in the management of ABPA, not only are most of the azole trials observational and limited by small sample size, but also no study has reported long-term outcomes, particularly the occurrence of relapses after therapy. Two randomized controlled studies ($n = 84$) have evaluated itraconazole in ABPA [21,23]. In one study, 55 patients with ‘glucocorticoid-dependent’ ABPA were randomized to receive either itraconazole 400 mg/day or placebo for 16 weeks (followed by 200 mg/day itraconazole for 16 weeks in all patients during the open phase). Although the difference between the two groups was significant in terms of overall response (reduction in corticosteroid dose by $\geq 50\%$, decrease in total IgE values by $\geq 25\%$ and at least one of the following: increase in exercise tolerance by $\geq 25\%$, improvement in results of pulmonary function tests by $\geq 25\%$ and resolution of pulmonary infiltrates in the itraconazole group), the analysis failed to reach statistical significance when each outcome was examined separately [21]. The other study included 29 ‘clinically stable’ ABPA patients randomized to receive either itraconazole or placebo. There was a significant decline in sputum inflammatory markers and serum IgE levels in the itraconazole group. The study also demonstrated a decrease in the number of exacerbations warranting glucocorticoid usage [23]. Pooled analysis showed that itraconazole could significantly decrease IgE levels by $\geq 25\%$ compared with placebo but did not cause significant improvement in lung function [53]. Neither study reported outcomes for more than 8 months with regard to relapses of ABPA; therefore the long-term benefits of azole therapy remain unknown. In addition, there are no randomized trials on azole monotherapy in acute exacerbations or long-term treatment with azoles in ABPA. Thus more trials are required before a firm recommendation can be made for the long-term use of itraconazole in ABPA. Moreover, studies are required to define the characteristics of ABPA patients who are likely to maximally benefit from the efficacy of azoles. Importantly, one needs to remember that OCSs are effective in all patients with ABPA [10–12], whereas the efficacy of azoles varies from 60 to 85% depending on the agent [26,53]. Many patients with ABPA require long-term treatment, and both OCSs and azoles have numerous adverse effects [6,14,15,25,26]. Whatever treatment approach is adopted (systemic steroids or azoles), it should provide maximum benefit to the patient with least propensity for adverse reactions.

In our clinical experience, we have observed that ABPA patients with mucoid impaction, extensive bronchiectasis and/or uncontrolled asthma would generally benefit from treatment with high doses of OCSs or a combination of OCSs and azoles. In those with recurrent exacerbations, one should definitely consider azole therapy, where they can be used either alone to maintain remission (after achieving clinical response with OCSs) or in combination with OCSs. The first choice of azole in ABPA should be itraconazole, and the newer azoles (voriconazole or posaconazole) should be reserved for those patients who experience no or poor response with itraconazole, or those who encounter adverse effects with the use of itraconazole.

Table 1. Studies describing the use of azoles in allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization.

Study (year)	Type of study	Patients (n)	Underlying diagnosis	Concomitant oral steroids	Azole dose	Duration of therapy	Drug levels	Ref.
<i>Allergic bronchopulmonary aspergillosis</i>								
De Beule <i>et al.</i> (1988)	Prospective and observational	5	Asthma	Four patients	50–400 mg/day (I)	43–239 days	No	[16]
Denning <i>et al.</i> (1991)	Prospective and observational	6	Three CF and three asthma	All	400 mg/day (I)	4 months	Yes	[17]
Germaud and Tuchsais (1995)	Retrospective and observational	12	Asthma	Six patients	200 mg/day (I)	6 months (longer in two patients)	No	[18]
Nepomuceno <i>et al.</i> (1999)	Retrospective and observational	13	CF	12 patients	Not mentioned (I)	Not mentioned	Yes	[19]
Salaz <i>et al.</i> (1999)	Prospective and observational	14	Asthma	All	200 mg/day (I)	12 months	No	[20]
Stevens <i>et al.</i> (2000)	Prospective, double-blind and RCT	55 (28 I and 27 placebo)	Asthma	All	400 mg/day and then 200 mg/day (I)	16 weeks and then 16 weeks (open, all patients)	No	[21]
Skov <i>et al.</i> (2002)	Retrospective and observational	21	CF	Nine patients	200–600 mg/day (I)	Median 33 months (range: 6–54 months) and 5 years in seven patients	No	[22]
Wark <i>et al.</i> (2003)	Prospective, double-blind and RCT	29 (15 I and 14 placebo)	Asthma	Ten (five in each group) patients	400 mg/day (I)	16 weeks	No	[23]
Rai <i>et al.</i> (2004)	Retrospective and observational	13	Asthma	All	200 mg/day (I)	6 months	No	[48]
Hilliard <i>et al.</i> (2005)	Retrospective and observational	13	CF	Nine patients	200–400 mg/day depending on bodyweight (V)	22 weeks (range: 1–50 months)	No	[49]
Glackin <i>et al.</i> (2009)	Retrospective and observational	10	CF	All	200–400 mg/day depending on bodyweight (V)	6 weeks to 3 months	No	[50]
Pasqualotto <i>et al.</i> (2009)	Retrospective and observational	11	Asthma	Five patients	100–450 mg/day (median 300; I)	6 months (range: 6–60 months)	Yes	[51]
<i>Severe asthma with fungal sensitization</i>								
Ward <i>et al.</i> (1999)	Prospective, double-blind and RCT	11 (six F and five placebo)	Trichophyton asthma with cutaneous mycosis	All	100 mg/day	5 months	No	[47]
Denning <i>et al.</i> (2009)	Prospective, double-blind and RCT	58 (29 I and 29 placebo)	Severe asthma	Six (two itraconazole group) patients	100 mg/day (F)	5 months (open, all patients)	Yes	[6]
Pasqualotto <i>et al.</i> (2009)	Retrospective and observational	22	Af-sensitized asthma	Five patients	400 mg/day (I)	32 weeks	Yes	[51]
Af: <i>Aspergillus fumigatus</i> ; CF: Cystic fibrosis; F: Fluconazole; I: Itraconazole; RCT: Randomized controlled trial; V: Voriconazole.								

Table 2. Results of studies describing the use of azoles in allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization.

Study (year)	IgE values (total)	IgE values (Af)	IgG values (Af)	Steroid dose	Exacerbations of ABPA or asthma	Af culture	Lung function	Eosinophil count	Hospital admission	Adverse events	Others	Ref.
<i>Allergic bronchopulmonary aspergillosis</i>												
De Beule <i>et al.</i> (1988)				0		Negative in three patients					Remission (n = 2), marked, moderate improvement (n = 1 each) and unchanged (n = 1)	[16]
Denning <i>et al.</i> (1991)	↓ (S)	NS	NS	↓ (p < 1.01)			↑ FEV ₁ (p < 0.05)			Minimal	Clinical improvement (S)	[17]
Germaud and Tauchais (1995)	↓ (S)	NS		Discontinued in five patients				↓ (S)			Improvement in 11 patients (S)	[18]
Nepomuceno <i>et al.</i> (1999)				↓ (S)	↓ (S)							[19]
Salez <i>et al.</i> (1999)	↓ (p < 0.05)			↓ (S); discontinued in all	↓ (p < 0.01)		↑ FEV ₁ (p < 0.005)	↓ (p < 0.05)		None significant	Marked improvement	[20]
Stevens <i>et al.</i> (2000)	↓ similar to placebo			↓ similar to placebo	↓ similar to placebo		↑ similar to placebo	↓ similar to placebo		Similar to placebo	Overall response in favor of itraconazole but NS when outcomes examined separately	[21]
Skov <i>et al.</i> (2002)	↓ by 42% on monotherapy and 56% on combination	NS	NS			↓ p < 0.05	NS	NS		Minor elevation in liver enzymes		[22]
Wark <i>et al.</i> (2003)	↓ (S)	↓ (S)			↓ (p = 0.03)		NS				↓ in sputum eosinophilia and ECP levels (S)	[23]
Rai <i>et al.</i> (2004)				↓ (S)	↓ (S)						↓ in bronchodilators dose (S)	[48]

ABPA: Allergic bronchopulmonary aspergillosis; Af: *Aspergillus fumigatus*; ECP: Eosinophil cationic protein; FEV₁: Forced expiratory volume in the first second; NS: Not significant; QoL: Quality of life; S: Significant.

Table 2. Results of studies describing the use of azoles in allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization (cont.).

Study (year)	IgE values (total)	IgE values (Af)	IgG values (Af)	Steroid dose values (Af)	Exacerbations of ABPA or asthma	Af culture	Lung function	Eosinophil count	Hospital admission	Adverse events	Others	Ref.
<i>Allergic bronchopulmonary aspergillosis (cont.)</i>												
Hilliard <i>et al.</i> (2005)	↓ (p = 0.003)			NS			↑ FEV ₁ (p < 0.01)			Skin reactions and visual disturbances		[49]
Glackin <i>et al.</i> (2009)	↓ (p < 0.005)			↓ (p < 0.06)			NS			Skin reactions and visual disturbances		[50]
Pasqualotto <i>et al.</i> (2009)	↓ (p = 0.005)	↓ (p = 0.017)		↓ (NS), discontinued in one patient	NS		NS	NS	NS	19%	All key variables were NS at 12 months	[51]
<i>Severe asthma with fungal sensitization</i>												
Ward <i>et al.</i> (1999)				↓ (S)							Decrease in bronchial hyperreactivity (S) and improvement in symptom scores	[47]
Denning <i>et al.</i> (2009)	↓ (p = 0.001)				NS		NS			17 withdrawals	Improvement in QoL	[6]
Pasqualotto <i>et al.</i> (2009)	↓ (p = 0.004)	↓ (p = 0.019)		↓ (NS), discontinued in three patients	NS		NS	↓ (p = 0.017)	NS	19%	All key variables were NS at 12 months	[51]
ABPA: Allergic bronchopulmonary aspergillosis; Af: <i>Aspergillus fumigatus</i> ; ECP: Eosinophil cationic protein; FEV ₁ : Forced expiratory volume in the first second; NS: Not significant; QoL: Quality of life; S: Significant.												

The optimal duration of azole therapy remains unclear, and currently they are either administered as recurrent 16–32-week courses or as long-term therapy, although there is little evidence for the latter approach. One major limitation of long-term treatment with azoles is the development of resistance in *A. fumigatus* [54]. Importantly, resistance to one azole can also lead to cross-resistance to other azoles, and this point should also be kept in mind during long-term therapy [55]. Itraconazole has poor bioavailability, while there are significant drug interactions with voriconazole and posaconazole. Therefore, therapeutic drug monitoring is generally advised, although there is no robust evidence for a direct correlation between drug levels and efficacy. In fact, the doses of azoles in ABPA have never been standardized, and lower doses of itraconazole (200 mg/day) have also been found to be clinically efficacious (TABLE 1). The clinical benefit is maintained only for the duration of therapy, with risk of relapses once treatment is discontinued. Clinicians should also be aware of the interaction between certain ICSs and azoles, which in some patients can even cause adrenal failure if the dose of ICS is not significantly reduced [43].

When to initiate azoles in SAFS

Only three studies have evaluated azoles in patients with SAFS (TABLES 1 & 2) [6,47,51]. The first study, despite being a randomized trial, included 11 highly selected patients with *Trichophyton* asthma with concomitant cutaneous mycoses, and these patients are rarely encountered in clinical practice [47]. One randomized controlled trial and one observational study have evaluated azoles in SAFS; however, in both studies, the benefits were not unequivocal [6,51]. In the only randomized trial that enrolled 58 patients with SAFS, only 41 patients completed 32 weeks of therapy. At 32 weeks, there was an improvement in the quality of life but the confidence intervals were wide, which suggests a modest benefit of

azole therapy. Similar modest improvements were noted in other secondary end points. The results of the study are also limited by the failure to achieve the predetermined sample size. Moreover, the duration of azole therapy remains unclear. Although Denning *et al.* have used itraconazole at a dose of 400 mg/day for 32 weeks [6], it is currently not clear what should be the optimal dose and duration of azole therapy in SAFS patients.

Currently, itraconazole in SAFS should be used only in those patients whose asthma remains uncontrolled despite optimal inhaled therapy with ICSs and long-acting β_2 agonists [56], oral montelukast and oral theophylline [7,8]. The other group for which it should be used includes those patients who require a continuous dose of OCSs for asthma control or have required two or more hospital admissions (or courses of OCS) for acute exacerbation within a 6-month period. Although many more patients with severe asthma will meet the criteria for SAFS, in our experience most of these patients generally respond to conventional asthma management. After initiation of itraconazole, the patients should be closely monitored, and if there are no signs of improvement by 6–8 weeks, treatment should be discontinued. In those with clinical improvement, treatment should be continued for a period of 16–32 weeks, and the patient should be closely observed following discontinuation. Finally, the routine use of newer azoles in SAFS should generally be avoided pending more data.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- The use of azoles in allergic bronchopulmonary aspergillosis (ABPA) seems rational, with numerous studies demonstrating short-term efficacy with the use of itraconazole.
- Further investigations are required to define the long-term treatment approach with azoles, and the individuals most likely to benefit from treatment.
- More studies are required to determine whether azoles modify the long-term course of the disorder.
- No trial has evaluated the efficacy of azole monotherapy in acute stages of ABPA. A randomized controlled trial comparing monotherapy of itraconazole versus prednisolone in ABPA (MIPA study; ClinicalTrials.gov identifier: NCT01321827) is underway, which aims to answer this question.
- The use of newer azoles should be restricted in those patients with ABPA who are refractory to itraconazole or demonstrate significant adverse events with itraconazole therapy.
- Azoles should be judiciously used in patients with severe asthma with fungal sensitization.

References

- 1 Agarwal R. Allergic bronchopulmonary aspergillosis. *Chest* 135(3), 805–826 (2009).
- 2 Agarwal R. Allergic bronchopulmonary aspergillosis. In: *Textbook of Pulmonary and Critical Care Medicine*. Jindal SK, Shankar PS, Raoof S, Gupta D, Aggarwal AN, Agarwal R (Eds). Jaypee Publications, New Delhi, India, 947–970 (2010).
- 3 Agarwal R, Garg M, Aggarwal AN, Saikia B, Gupta D, Chakrabarti A. Serologic allergic bronchopulmonary aspergillosis (ABPA-S): long-term outcomes. *Respir. Med.* 106(7), 942–947 (2012).
- 4 Agarwal R, Singh N, Gupta D. Pulmonary hypertension as a presenting manifestation of allergic bronchopulmonary aspergillosis. *Indian J. Chest Dis. Allied Sci.* 51(1), 37–40 (2009).
- 5 Denning DW, O'Driscoll BR, Hogaboam CM, Bowyer P, Niven RM. The link between fungi and severe asthma:

- a summary of the evidence. *Eur. Respir. J.* 27(3), 615–626 (2006).
- ▶ 6 Denning DW, O'Driscoll BR, Powell G *et al.* Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitization: the Fungal Asthma Sensitization Trial (FAST) study. *Am. J. Respir. Crit. Care Med.* 179(1), 11–18 (2009).
 - ▶ 7 Agarwal R. Severe asthma with fungal sensitization. *Curr. Allergy Asthma Rep.* 11(5), 403–413 (2011).
 - ▶ 8 Agarwal R, Gupta D. Severe asthma and fungi: current evidence. *Med. Mycol.* 49(Suppl. 1), S150–S157 (2011).
 - ▶ 9 Agarwal R, Gupta D, Aggarwal AN, Behera D, Jindal SK. Allergic bronchopulmonary aspergillosis: lessons from 126 patients attending a chest clinic in north India. *Chest* 130(2), 442–448 (2006).
 - ▶ 10 Agarwal R, Gupta D, Aggarwal AN, Saxena AK, Chakrabarti A, Jindal SK. Clinical significance of hyperattenuating mucoid impaction in allergic bronchopulmonary aspergillosis: an analysis of 155 patients. *Chest* 132(4), 1183–1190 (2007).
 - ▶ 11 Agarwal R, Gupta D, Aggarwal AN *et al.* Clinical significance of decline in serum IgE levels in allergic bronchopulmonary aspergillosis. *Respir. Med.* 104(2), 204–210 (2010).
 - ▶ 12 Agarwal R, Khan A, Gupta D, Aggarwal AN, Saxena AK, Chakrabarti A. An alternate method of classifying allergic bronchopulmonary aspergillosis based on high-attenuation mucus. *PLoS ONE* 5(12), e15346 (2010).
 - ▶ 13 Patterson R, Greenberger PA, Halwig JM, Liotta JL, Roberts M. Allergic bronchopulmonary aspergillosis. Natural history and classification of early disease by serologic and roentgenographic studies. *Arch. Intern. Med.* 146(5), 916–918 (1986).
 - ▶ 14 Frauman AG. An overview of the adverse reactions to adrenal corticosteroids. *Adverse Drug React. Toxicol. Rev.* 15(4), 203–206 (1996).
 - ▶ 15 Schacke H, Docke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. *Pharmacol. Ther.* 96(1), 23–43 (2002).
 - ▶ 16 De Beule K, De Doncker P, Cauwenbergh G *et al.* The treatment of aspergillosis and aspergilloma with itraconazole, clinical results of an open international study (1982–1987). *Mycoses* 31(9), 476–485 (1988).
 - ▶ 17 Denning DW, Van Wye JE, Lewiston NJ, Stevens DA. Adjunctive therapy of allergic bronchopulmonary aspergillosis with itraconazole. *Chest* 100(3), 813–819 (1991).
 - ▶ 18 Germaud P, Tuchais E. Allergic bronchopulmonary aspergillosis treated with itraconazole. *Chest* 107(3), 883 (1995).
 - ▶ 19 Nepomuceno IB, Esrig S, Moss RB. Allergic bronchopulmonary aspergillosis in cystic fibrosis: role of atopy and response to itraconazole. *Chest* 115(2), 364–370 (1999).
 - ▶ 20 Salez F, Brichet A, Desurmont S, Grosbois JM, Wallaert B, Tonnel AB. Effects of itraconazole therapy in allergic bronchopulmonary aspergillosis. *Chest* 116(6), 1665–1668 (1999).
 - ▶ 21 Stevens DA, Schwartz HJ, Lee JY *et al.* A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. *N. Engl. J. Med.* 342(11), 756–762 (2000).
 - ▶ 22 Skov M, Hoiby N, Koch C. Itraconazole treatment of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. *Allergy* 57(8), 723–728 (2002).
 - ▶ 23 Wark PA, Hensley MJ, Saltos N *et al.* Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: a randomized controlled trial. *J. Allergy Clin. Immunol.* 111(5), 952–957 (2003).
 - ▶ 24 Wark P. Pathogenesis of allergic bronchopulmonary aspergillosis and an evidence-based review of azoles in treatment. *Respir. Med.* 98(10), 915–923 (2004).
 - ▶ 25 Tucker RM, Haq Y, Denning DW, Stevens DA. Adverse events associated with itraconazole in 189 patients on chronic therapy. *J. Antimicrob. Chemother.* 26(4), 561–566 (1990).
 - ▶ 26 Chishimba L, Niven RM, Cooley J, Denning DW. Voriconazole and posaconazole improve asthma severity in allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization. *J. Asthma* 49(4), 423–433 (2012).
 - ▶ 27 Hogan C, Denning DW. Allergic bronchopulmonary aspergillosis and related allergic syndromes. *Semin. Respir. Crit. Care Med.* 32(6), 682–692 (2011).
 - ▶ 28 Wark PA, Gibson PG. Allergic bronchopulmonary aspergillosis: new concepts of pathogenesis and treatment. *Respirology* 6(1), 1–7 (2001).
 - ▶ 29 McCarthy DS, Pepys J. Allergic bronchopulmonary aspergillosis. Clinical immunology. 2. Skin, nasal and bronchial tests. *Clin. Allergy* 1(4), 415–432 (1971).
 - ▶ 30 Chakrabarti A, Sethi S, Raman DS, Behera D. Eight-year study of allergic bronchopulmonary aspergillosis in an Indian teaching hospital. *Mycoses* 45(8), 295–299 (2002).
 - ▶ 31 Fairs A, Agbetile J, Hargadon B *et al.* IgE sensitisation to *Aspergillus fumigatus* is associated with reduced lung function in asthma. *Am. J. Respir. Crit. Care Med.* 182(11), 1362–1368 (2010).
 - ▶ 32 Denning DW, Park S, Lass-Flörl C *et al.* High-frequency triazole resistance found in nonculturable *Aspergillus fumigatus* from lungs of patients with chronic fungal disease. *Clin. Infect. Dis.* 52(9), 1123–1129 (2011).
 - ▶ 33 Agbetile J, Fairs A, Desai D *et al.* Isolation of filamentous fungi from sputum in asthma is associated with reduced post-bronchodilator FEV(1). *Clin. Exp. Allergy* 42(5), 782–791 (2012).
 - ▶ 34 Abruzzo GK, Fromtling RA, Turnbull TA, Giltinan DM. Effects of bifonazole, fluconazole, itraconazole, and terbinafine on the chemiluminescence response of immune cells. *J. Antimicrob. Chemother.* 20(1), 61–68 (1987).
 - ▶ 35 Pawelec G, Jaschonek K, Ehninger G. The anti-fungal agent itraconazole exerts immunosuppressive effects on alloreactivity but not on natural immunity *in vitro*. *Int. J. Immunopharmacol.* 13(7), 875–879 (1991).
 - ▶ 36 Pawelec G, Ehninger G, Rehbein A, Schaudt K, Jaschonek K. Comparison of the immunosuppressive activities of the antimycotic agents itraconazole, fluconazole, ketoconazole and miconazole on human T-cells. *Int. J. Immunopharmacol.* 13(2–3), 299–304 (1991).
 - ▶ 37 Kim JH, Ahn YK. The effects of itraconazole on the immune responses in ICR mice. *J. Toxicol. Sci.* 19(1), 7–15 (1994).
 - ▶ 38 Kanda N, Enomoto U, Watanabe S. Anti-mycotics suppress interleukin-4 and interleukin-5 production in anti-CD3 plus anti-CD28-stimulated T cells from patients with atopic dermatitis. *J. Invest. Dermatol.* 117(6), 1635–1646 (2001).
 - ▶ 39 Ausaneya U, Kawada A, Aragane Y. Itraconazole suppresses an elicitation phase of a contact hypersensitivity reaction. *J. Invest. Dermatol.* 126(5), 1028–1035 (2006).
 - ▶ 40 Simitsopoulou M, Roilides E, Likartsis C *et al.* Expression of immunomodulatory genes in human monocytes induced by voriconazole in the presence of *Aspergillus fumigatus*. *Antimicrob. Agents Chemother.* 51(3), 1048–1054 (2007).
 - ▶ 41 Varis T, Kaukonen KM, Kivisto KT, Neuvonen PJ. Plasma concentrations and

- effects of oral methylprednisolone are considerably increased by itraconazole. *Clin. Pharmacol. Ther.* 64(4), 363–368 (1998).
- ▶ 42 Varis T, Kivisto KT, Neuvonen PJ. The effect of itraconazole on the pharmacokinetics and pharmacodynamics of oral prednisolone. *Eur. J. Clin. Pharmacol.* 56(1), 57–60 (2000).
- ▶ 43 Skov M, Main KM, Sillesen IB, Muller J, Koch C, Lanng S. Iatrogenic adrenal insufficiency as a side effect of combined treatment of itraconazole and budesonide. *Eur. Respir. J.* 20(1), 127–133 (2002).
- ▶ 44 Shale DJ, Faux JA, Lane DJ. Trial of ketoconazole in non-invasive pulmonary aspergillosis. *Thorax* 42(1), 26–31 (1987).
- ▶ 45 Fournier EC. Trial of ketoconazole in allergic bronchopulmonary aspergillosis. *Thorax* 42(10), 831 (1987).
- ▶ 46 Currie DC, Lueck C, Milburn HJ *et al.* Controlled trial of natamycin in the treatment of allergic bronchopulmonary aspergillosis. *Thorax* 45(6), 447–450 (1990).
- 47 Ward GW Jr, Woodfolk JA, Hayden ML, Jackson S, Platts-Mills TA. Treatment of late-onset asthma with fluconazole. *J. Allergy Clin. Immunol.* 104(3 Pt 1), 541–546 (1999).
- ▶ 48 Rai SP, Panda BN, Bhargava S. Treatment of allergic bronchopulmonary aspergillosis with fluconazole and itraconazole. *Med. J. Armed Forces India* 60(2), 128–130 (2004).
- ▶ 49 Hilliard T, Edwards S, Buchdahl R *et al.* Voriconazole therapy in children with cystic fibrosis. *J. Cyst. Fibros.* 4(4), 215–220 (2005).
- ▶ 50 Glackin L, Leen G, Elnazir B, Grealley P. Voriconazole in the treatment of allergic bronchopulmonary aspergillosis in cystic fibrosis. *Ir. Med. J.* 102(1), 29 (2009).
- ▶ 51 Pasqualotto AC, Powell G, Niven R, Denning DW. The effects of antifungal therapy on severe asthma with fungal sensitization and allergic bronchopulmonary aspergillosis. *Respirology* 14(8), 1121–1127 (2009).
- ▶ 52 Van Cutsem J, Van Gerven F, Van de Ven MA, Borgers M, Janssen PA. Itraconazole, a new triazole that is orally active in aspergillosis. *Antimicrob. Agents Chemother.* 26(4), 527–534 (1984).
- 53 Wark PA, Gibson PG, Wilson AJ. Azoles for allergic bronchopulmonary aspergillosis associated with asthma. *Cochrane Database Syst. Rev.* 3, CD001108 (2004).
- ▶ 54 Burgel PR, Baixench MT, Amsellem M *et al.* High prevalence of azole-resistant *Aspergillus fumigatus* in adults with cystic fibrosis exposed to itraconazole. *Antimicrob. Agents Chemother.* 56(2), 869–874 (2012).
- ▶ 55 Rodriguez-Tudela JL, Alcazar-Fuoli L, Mellado E, Alastruey-Izquierdo A, Monzon A, Cuenca-Estrella M. Epidemiological cutoffs and cross-resistance to azole drugs in *Aspergillus fumigatus*. *Antimicrob. Agents Chemother.* 52(7), 2468–2472 (2008).
- ▶ 56 Agarwal R, Khan A, Aggarwal AN, Gupta D. Is the SMART approach better than other treatment approaches for prevention of asthma exacerbations? A meta-analysis. *Monaldi Arch. Chest Dis.* 71(4), 161–169 (2009).

Website

- 101 ClinicalTrials.gov.
<http://clinicaltrials.gov>