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Isavuconazole and voriconazole for the treatment of chronic pulmonary aspergillosis: A retrospective comparison of rates of adverse events

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Summary

Background: Long-term oral triazole antifungal therapy is the cornerstone of management for patients with chronic pulmonary aspergillosis (CPA). Itraconazole is the first-line choice of treatment. Voriconazole, posaconazole or isavuconazole can be used as alternative treatments in case of resistance or intolerance. All of these can cause significant adverse drug reactions.

Objectives: To evaluate how CPA patients tolerate voriconazole and isavuconazole after prior triazole therapy.

Methods: We performed a retrospective observational study at the UK National Aspergillosis Centre. Medical records for all consecutive CPA patients started on isavuconazole and voriconazole during an observation period of 12 and 6 months respectively were analysed.

Results: During this study period, 20 patients were started on isavuconazole and 21 patients on voriconazole. Adverse events were seen in 18 of 21 (86%) the patients in the voriconazole group and 12 of 20 (60%) in the isavuconazole group ($P = 0.02$). For those who developed adverse events to these agents, the rates of discontinuation of therapy were comparable (ie 10/18 [56%], voriconazole vs 8/12 [67%], isavuconazole; $P = 0.54$). Five (25%) patients in the isavuconazole group who were intolerant to other triazoles tolerated the standard dose of isavuconazole.

Conclusions: Compared with isavuconazole, adverse events were significantly higher in CPA patients commenced on voriconazole. Isavuconazole may be an option for those patients who are intolerant to other triazoles.

KEYWORDS

adverse events, chronic pulmonary aspergillosis, isavuconazole, voriconazole

1 | INTRODUCTION

Chronic pulmonary aspergillosis (CPA) is a debilitating pulmonary condition estimated to affect approximately 3 million people worldwide.[1] CPA is caused by an *Aspergillus* species, typically *Aspergillus fumigatus*, and occurs in ostensibly immunocompetent or subtly immunocompromised patients with current or prior lung diseases.[2] Patients with CPA commonly present with pulmonary symptoms such as a persistent and/or productive cough, breathlessness,

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chest discomfort and haemoptysis, as well as constitutional symptoms such as weight loss and fatigue.[3]

Long-term oral triazole antifungal therapy is the cornerstone of management for patients with CPA.[2] Itraconazole is generally considered the most appropriate first-line choice of treatment due to its efficacy in controlling symptoms and progression of CPA, a relatively favourable safety profile and low cost.[2,4] Voriconazole or posaconazole can be used as alternative treatments in cases of clinical or microbiological antifungal resistance, or treatment intolerance. At our Centre, voriconazole is used as the second-line agent after itraconazole. In patients with pan-azole resistance, treatment intolerance or where oral triazole therapy is unsuitable, either an intravenous echinocandin or amphotericin B may be effective.[3,5] In patients with limited disease, surgical intervention may be an option.[3]

Isavuconazole is a new triazole antifungal agent licensed for the treatment of invasive pulmonary aspergillosis and mucormycosis.[6] Development of isavuconazole as a new antifungal was an important breakthrough in the treatment of *Aspergillus* infections due to the steady rise in azole resistance and unfavourable side effects seen with use of previous azoles.[7] The oral formulation has a high bioavailability of 98% and does not require food to be taken at the time of dosage, unlike certain itraconazole and posaconazole formulations.[7] Isavuconazole shows extensive tissue distribution and protein binding.[8] Isavuconazole has also been shown to have a higher or equivalent fungicidal activity against *A fumigatus* compared with posaconazole and voriconazole, and can often show activity against isolates resistant to itraconazole, caspofungin and amphotericin B.[8] Isavuconazole has a favourable toxicity profile and fewer drug-drug interactions compared to the other triazoles. There is no requirement for isavuconazole dosage adjustment based on age or renal function impairment.[6,9]

Careful and regular monitoring of serum drug concentrations is recommended during triazole antifungal therapy to assure therapeutic levels and to avoid toxicity, complications associated with drug-drug or drug-food interactions and the development of antifungal resistance.[10,11] Triazole cross-intolerance is common for patients who are on long-term therapy for CPA.[12] Therapeutic drug monitoring (TDM) is usually required for itraconazole, voriconazole and posaconazole.[11] However, there is insufficient evidence from "real-world" data to recommend routine TDM of isavuconazole in patients on long-term therapy. The aim of this study was to evaluate how patients with CPA tolerate isavuconazole compared with voriconazole and what the role of TDM is in this.

2 | PATIENTS AND METHODS

2.1 | Study setting and design

We performed a retrospective observational study to investigate adverse events related to isavuconazole and voriconazole in patients with CPA receiving treatment at the National Aspergillosis Centre (NAC) based at Wythenshawe Hospital, Manchester University NHS Foundation Trust (MFT), Manchester, UK. Consecutive patients with CPA who had been prescribed either isavuconazole or voriconazole were identified and observed for a period of 12 and 6 months, respectively, prior to December 2016.

2.2 | Patients

Suitable patients were identified from the hospital's electronic prescribing and medicines administration system database (JAC Computer Services Ltd., Essex, UK). Patients were included in this study if they had (a) a clinical diagnosis of CPA[2,3] and (b) were prescribed either isavuconazole or voriconazole.

2.3 | Clinical and laboratory data

Demographic characteristics, underlying pulmonary disorders, past and present antifungal drug and dose, all serum drug levels and liver function tests measured over a 6-month (for voriconazole group) and 12-month (for isavuconazole) study period were collected from case notes. To compare similar number of patients, a longer study period was required for the isavuconazole group as it is less commonly prescribed. All adverse events during therapy and reasons for discontinuation of therapy were also collected. Adverse drug reactions were summarised according to the organ system affected: neurological, visual, cardiac, pulmonary, gastrointestinal tract, hepatic, skin, musculoskeletal and connective tissue, or other. An increase in serum alanine aminotransferase (ALT) more than three times the upper limit of normal (55 IU/L) was used as a marker of hepatotoxicity. Clinical failure was defined as radiological, serological, mycological or symptomatic worsening of disease despite antifungal therapy.[4] The antifungal dose was adjusted with respect to the serum predose drug levels as per local protocols.

2.4 | Statistical analyses

Data were analysed using GRAPHPAD PRISM version 7.0d (GraphPad Software, La Jolla, CA, USA). Categorical data are presented as frequencies and percentages, and continuous data as means and standard deviations or as medians and ranges. Chi-square or Fisher's exact tests were used to compare categorical variables. For normally distributed continuous variables, we used independent sample *t* tests, and for non-normally distributed variables, we used Mann-Whitney *U* tests to compare tolerability of voriconazole with that of isavuconazole. Statistical significance was at the 5% level for all analyses.

3 | RESULTS

3.1 | Patient demographics

During the study period, 20 patients were commenced on isavuconazole and 21 patients were initiated on voriconazole. Patients commenced on isavuconazole had a median age of 65 (range: 53-84) years, and 14 (70%) of these were males. Patients starting voriconazole had a median age of 66 (range: 37-78) years, and 12 (57%) of

TABLE 1 Demographic characteristics and underlying pulmonary disorders in both groups of patients

Characteristics	Isavuconazole (n = 20) Number (%)	Voriconazole (n = 21) Number (%)	*P*-value
Demographics			
Age; median (range)	65 (53-84)	66 (37-78)	0.401
Male	14 (70)	12 (57)	0.166
Underlying condition leading to CPA			
Chronic obstructive pulmonary diseases	8 (40)	6 (29)	0.441
Tuberculosis (healed)	4 (20)	3 (14)	0.626
Pulmonary sarcoidosis	1 (5)	—	—
Lung cancer survivor	1 (5)	—	—
Community-acquired pneumonia	1 (5)	1 (5)	0.972
Bronchiectasis	1 (5)	3 (14)	0.317
Asthma	1 (5)	1 (5)	0.972
Asbestosis	1 (5)	—	—
Allergic bronchopulmonary aspergillosis	—	2 (10)	—
None	2 (10)	5 (24)	0.240

these were males. There were no significant differences in the demographic characteristics or the underlying conditions between the two groups (Table 1).

3.2 | Adverse events

3.2.1 | Isavuconazole

All 20 patients receiving isavuconazole were commenced on a standard regimen (200 mg once daily by mouth). Twelve patients (60%) administered isavuconazole developed an adverse event during the 12-month follow-up period. Of these 12 patients, eight patients (35%) discontinued isavuconazole while four (20%) patients had their dose adjusted. A total of 11 patients (55%) had their therapy discontinued, of these, eight patients (40%) experienced adverse events and one patient (5%) had a pan-azole-resistant isolate of *A fumigatus* (Table 2). The median duration of therapy before discontinuation was 6.0 (range: 2-11) months. The final two patients (10%) met the criteria for clinical failure, defined as radiological, serological, mycological or symptomatic worsening of disease despite antifungal therapy (Table 2). Five (25%) patients in the isavuconazole group who were intolerant to other triazoles tolerated the standard dose of isavuconazole (Table 2). For the nine patients who continued therapy, four patients (44%) had their maintenance dose reduced (halved, 100 mg OD) due to adverse events, three patients (33%) remained on the standard 200 mg once daily maintenance dose and two patients (22%) were on alternate day dosing (100 mg/200 mg; Figure 1A). In relation to serum isavuconazole levels, only one patient (Isavu2, Table 2) experienced serious liver toxicity that was assumed to be due to the patient's high serum drug level.

3.2.2 | Voriconazole

Of the 21 patients commenced on voriconazole, 18 patients (86%) developed adverse events. None of the patients receiving voriconazole experienced clinical failure. Ten (48%) patients discontinued voriconazole therapy, all of whom had adverse events (Figure 1B). Eight patients who reported adverse events continued voriconazole at a reduced dose. Six of the patients who discontinued voriconazole had previously received an azole, while four were treatment naïve (Table 2). The median duration of therapy before discontinuation was 2.5 (range: 2-3) months. Three patients had more than one adverse event leading to discontinuation of voriconazole, and none of the patients had liver toxicity (Table 2). Eleven patients (52%) who received voriconazole had previously been on itraconazole for CPA, and 10 were treatment naive. The median dose of voriconazole prescribed at the time of commencement of therapy was 400 mg (range: 300-500 mg) per day. Eleven (52%) patients remained on voriconazole for the whole 6-month period, 5 (45%) of whom remained on the same dose as originally, and doses were reduced in 3 (27%) and increased in 3 (27%) patients.

3.2.3 | Isavuconazole compared to voriconazole

The rate of adverse drug reactions was significantly higher among patients who received voriconazole compared to those who were on isavuconazole (12/20 [60%], isavuconazole vs 18/21 [86%], voriconazole; $P = 0.02$). Overall, a similar proportion of patients discontinued treatment in both groups (10/20 [50%], isavuconazole vs 11/21 [52%], voriconazole; $P = 0.64$). For those who developed adverse events to these agents, the rates of discontinuation of therapy were comparable (ie 10/18 [56%], voriconazole vs 8/12 [67%],

TABLE 2 Adverse events and treatment outcomes for chronic pulmonary aspergillosis patients commenced on voriconazole and isavuconazole therapy

Patient	Age	Sex	Itraconazole	Voriconazole	Posaconazole	Isavuconazole	Outcome
Isavu1	65	M	Not used	Heart + GIT	Not used	Liver	Continued
Isavu2	60	M	Low levels	Low levels	Low levels	Liver	Discontinued
Isavu3	74	M	Clinical failure	Liver + skin	Clinical failure	None	Continued
Isavu4	61	M	Neurological	Skin + Neurological	GIT	Neurological	Continued
Isavu5	75	M	Heart	Pulmonary	GIT	Neurological + GIT	Continued
Isavu6	84	M	GIT, neurological, ankle swelling	GIT + neurological	Clinical failure	Clinical failure	Discontinued
Isavu7	66	F	Resistance	Resistance	Resistance	Resistance	Discontinued
Isavu8	66	M	Clinical failure	Clinical failure	Neurological	Skin	Discontinued
Isavu9	60	M	Clinical failure	Skin + eye	Eye + pulmonary	Eye + skin	Discontinued
Isavu10	53	M	Neurological	Neurological + eye	Neurological + GIT	None	Continued
Isavu11	54	M	Not used	Not used	Not used	Liver	Discontinued
Isavu12	59	M	Clinical failure	Skin	Skin	Skin	Continued
Isavu13	73	F	Not used	Not used	Not used	Neurological	Discontinued
Isavu14	63	F	Resistance	GIT	Skin	Neurological	Discontinued
Isavu15	60	F	Resistance	Not used	Not used	None	Continued
Isavu16	57	F	Resistance	Resistance	Resistance	None	Continued
Isavu17	70	F	Musculoskeletal	Neurological	Resistance	Pulmonary	Discontinued
Isavu18	66	M	Neurological	Neurological	Neurological	None	Continued
Isavu19	71	M	Clinical failure	Skin + liver	GIT	Clinical failure	Discontinued
Isavu20	82	M	GIT	Musculoskeletal	Clinical failure	Neurological	Discontinued
Vori1	78	F	Not used	Weight loss			Discontinued
Vori2	66	M	Not used	Neurological			Continued
Vori3	63	F	Neurological	GIT			Continued
Vori4	59	F	Ankle swelling	Eye + Neurological			Discontinued
Vori5	57	F	Not used	Eye			Discontinued
Vori6	74	M	Clinical failure	Skin			Discontinued
Vori7	73	M	Not used	Heart			Discontinued
Vori8	70	M	Not used	None			Continued
Vori9	70	F	Clinical failure	GIT			Continued
Vori10	69	F	Not used	Skin			Discontinued
Vori11	66	F	Skin, pulmonary, GIT, musculoskeletal	None			Continued
Vori12	66	M	Not used	Eye			Continued
Vori13	66	M	Not used	None			Continued
Vori14	65	M	Ankle swelling	Skin + eye			Continued
Vori15	63	M	Clinical failure	Skin + Neurological			Continued
Vori16	51	F	Resistance	Neurological			Discontinued
Vori17	51	M	Clinical failure	GIT, skin + eye			Discontinued
Vori18	44	F	Low levels	GIT + eye			Continued
Vori19	39	M	Clinical failure	Eye			Continued
Vori20	37	M	Not used	Skin + eye			Discontinued
Vori21	66	M	Not used	Skin			Discontinued

GIT, gastrointestinal tract; Isavu, isavuconazole; Vori, voriconazole.

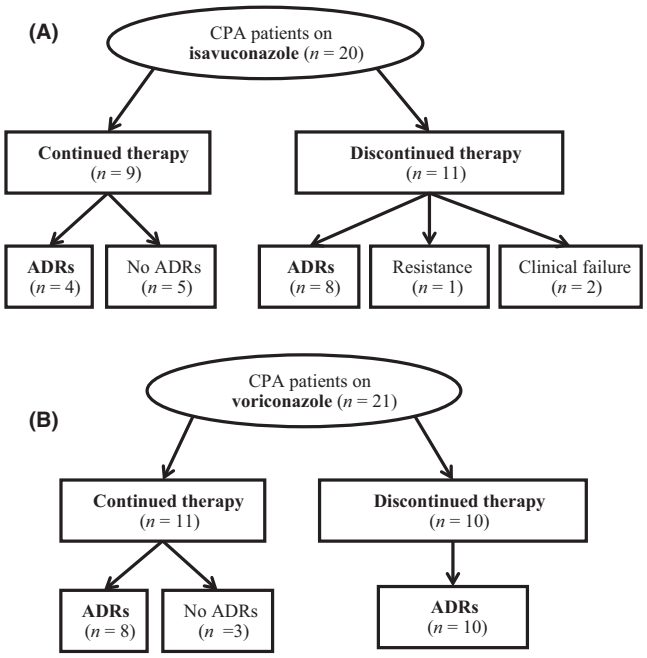

FIGURE 1 Course of isavuconazole and voriconazole therapy. ADR, adverse drug reaction; CPA, chronic pulmonary aspergillosis

isavuconazole; $P = 0.54$). Also, a similar proportion of patients did not develop any adverse drug reaction to either isavuconazole (5/20, [25%]) or voriconazole (3/21, [14%]), $P = 0.48$).

4 | DISCUSSION

In this retrospective observational study on the tolerability of isavuconazole and voriconazole in CPA patients, more patients tolerated isavuconazole compared to voriconazole. However, the proportions of patients who discontinued both agents were similar. In contrast, in the SECURE trial,[6] permanent drug discontinuation due to drug-related adverse events was less common with isavuconazole than with voriconazole (21 [8%] vs 35 [14%]). However, adverse event rate of 60% in the isavuconazole group is high and the reasons for this observation could be a subject for future studies. A greater proportion of patients receiving voriconazole experienced skin- and/or eye-related side effects compared to patients receiving isavuconazole (52% vs 10%). Skin and eye adverse effects are well characterised in voriconazole use.[13] The most common side effects seen with isavuconazole use were neurologically related (25%), liver toxicity (15%) and skin-related (15%).

One patient on isavuconazole had high serum levels (>7.5 mg/L) which lead to discontinuation of therapy due to liver toxicity. Three patients (15%) receiving isavuconazole experienced liver toxicity, compared to none of the voriconazole patients. Previous studies suggest that isavuconazole would not require serum drug level monitoring.[13] However, the results of this study show that some groups of patients may benefit from TDM, especially those with adverse drug reactions and those with poor response to treatment.

Adverse events experienced by patients following prior triazole therapy did not predict the adverse reaction that developed while on voriconazole. None of the voriconazole patients who had previously received itraconazole presented the same adverse events with voriconazole as they had with itraconazole. However, six (30%) of the 20 patients who received isavuconazole presented with similar adverse events to those experienced on previous azoles, across all classes of adverse events except liver, and 25% of patients who were intolerant to other azoles tolerated the standard dose of isavuconazole.

The SECURE study found the most common adverse events to both drugs to be gastrointestinal-related (68% of isavuconazole patients vs 69% of voriconazole patients). This is in contrast with the findings of the present study where gastrointestinal adverse events were only seen in 5% of isavuconazole patients and 19% of voriconazole patients. Interestingly, the SECURE study found a much greater number of voriconazole patients with liver toxicity (16%) compared to isavuconazole patients (9%), contradictory to the 15% of isavuconazole patients and no voriconazole patients in this study with liver toxicity.[6] This difference could be due to the SECURE trial only using the standard dose of voriconazole without monitoring of serum drug levels, whereas in this study, dose changes were made in response to aberrant serum drug levels.

The main weaknesses of this study are the small sample size and retrospective nature of the design. However, this is the first study to compare the clinical use of isavuconazole and voriconazole in the long-term management of patients with CPA. In addition, most patients observed had previously discontinued one or more other azoles, particularly in the isavuconazole group, which could mean this group of patients are particularly vulnerable to triazole side effects. Future studies characterising the nature and predictors of adverse drug reactions among CPA patients are called for, especially in triazole-experienced individuals.

In conclusion, we saw a similar proportion of patients discontinuing isavuconazole or voriconazole treatment due to adverse events. Less than a third of the patients experienced similar adverse events with isavuconazole as with the prior azoles, with neurologically related adverse effects being the most common. A quarter of patients who were intolerant to other azoles tolerated the standard dose of isavuconazole and a third were able to continue therapy on a reduced dose. Isavuconazole adds to the treatment armamentarium for the long-term management of patients with CPA and may be an option for those patients who are intolerant to other triazoles, but further study of isavuconazole adverse effects in CPA patients would be welcomed.

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CONFLICT OF INTEREST

FB, NM, CBM, TF and RRR: None.

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