Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis

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Summary

Background Mucormycosis is an uncommon invasive fungal disease with high mortality and few treatment options. Isavuconazole is a triazole active in vitro and in animal models against moulds of the order Mucorales. We assessed the efficacy and safety of isavuconazole for treatment of mucormycosis and compared its efficacy with amphotericin B in a matched case-control analysis.

Methods In a single-arm open-label trial (VITAL study), adult patients (≥18 years) with invasive fungal disease caused by rare fungi, including mucormycosis, were recruited from 34 centres worldwide. Patients were given isavuconazole 200 mg (as its intravenous or oral water-soluble prodrug, isavuconazonium sulfate) three times daily for six doses, followed by 200 mg/day until invasive fungal disease resolution, failure, or for 180 days or more. The primary endpoint was independent data review committee-determined overall response—ie, complete or partial response (treatment success) or stable or progressive disease (treatment failure)—according to prespecified criteria. Mucormycosis cases treated with isavuconazole as primary treatment were matched with controls from the FungiScope Registry, recruited from 17 centres worldwide, who received primary amphotericin B-based treatment, and were analysed for day-42 all-cause mortality. VITAL is registered with ClinicalTrials.gov, number NCT00634049. FungiScope is registered with ClinicalTrials.gov, number NCT01731353.

Findings Within the VITAL study, from April 22, 2008, to June 21, 2013, 37 patients with mucormycosis received isavuconazole for a median of 84 days (IQR 19–179, range 2–882). By day 42, four patients (11%) had a partial response, 16 (43%) had stable invasive fungal disease, one (3%) had invasive fungal disease progression, three (8%) had missing assessments, and 13 (35%) had died. 35 patients (95%) had adverse events (28 [76%] serious). Day-42 crude all-cause mortality in seven (33%) of 21 primary-treatment isavuconazole cases was similar to 13 (39%) of 33 amphotericin B-treated matched controls (weighted all-cause mortality: 33% *vs* 41%; p=0·595).

Interpretation Isavuconazole showed activity against mucormycosis with efficacy similar to amphotericin B. Isavuconazole can be used for treatment of mucormycosis and is well tolerated.

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Introduction

Mucormycosis, an opportunistic invasive fungal disease, which is classically associated with diabetic ketoacidosis and iron overload[1] is increasingly encountered in immunocompromised individuals, especially those receiving treatment for haematological malignancies or undergoing transplantation.[2,3] The outlook in these populations is particularly poor, with fatality rates of 52–91%.[1–4] Present guidelines recommend antifungal treatment, surgical debridement, and correction of underlying predisposing disorders.[5] Although amphotericin B and posaconazole show in-vitro activity against Mucorales moulds, their clinical use is often restricted.[6,7] Nephrotoxicity remains a common adverse effect of amphotericin B,[8] and posaconazole has mainly been studied in the salvage setting.[9,10]

Isavuconazonium sulfate is a water-soluble prodrug, which is rapidly hydrolysed to the triazole isavuconazole after oral or intravenous administration. Isavuconazole has high oral bioavailability, linear pharmacokinetics, and is active against a broad range of clinically important fungi, including moulds of the order Mucorales. Isavuconazole inhibits ergosterol biosynthesis, which results in accumulation of toxic sterols and cell death.[11]

We present the results of a single-arm open-label trial of isavuconazole treatment of mucormycosis, and a case-control analysis. The primary objective of the open-label trial was to assess the efficacy of isavuconazole; the case-control analysis evaluated the mortality outcomes recorded with isavuconazole compared with amphotericin B.

Methods

Patients and study design

VITAL was a single-arm open-label trial done in 34 centres worldwide (appendix) that assessed the efficacy and safety of isavuconazole for the treatment of

Research in context

Evidence before this study

Mucormycosis is a rare invasive fungal disease diagnosed in patients who are immunocompromised, including those affected by diabetes or iron overload, and those who are undergoing treatment for haematological malignancies or transplantation. When mucormycosis is not promptly diagnosed and treated, mortality exceeds 90%. Treatment of this disease has classically consisted of surgical resection of the infected tissue, reversal of predisposing disorders, and antifungal treatment with amphotericin B. The lower nephrotoxicity of lipid formulations of amphotericin B compared with amphotericin B deoxycholate, and earlier recognition of the disease, have reduced mortality to about 40% in the past decade. Posaconazole has been used for salvage treatment and in patients who experience nephrotoxicity from amphotericin B, but no studies have been done to assess the activity of azole treatment for primary treatment of mucormycosis.

Isavuconazole has antifungal activity against a broad range of clinically important fungi, including moulds of the order Mucorales. Isavuconazole has high bioavailability, linear pharmacokinetics, and was well tolerated by healthy volunteers and by patients undergoing chemotherapy for acute leukaemia. In a phase 2 trial, daily or weekly isavuconazole treatment showed similar efficacy to fluconazole in patients with oesophageal candidosis. In the SECURE phase 3 trial, isavuconazole was non-inferior to voriconazole for the primary treatment of invasive mould disease caused by *Aspergillus* spp and other filamentous fungi; isavuconazole was well tolerated compared with voriconazole, with significantly fewer study drug-related adverse events and adverse events of the skin, eye, and hepatobiliary systems.

We searched PubMed for articles containing the search terms "mucormycosis OR zygomycosis AND trial", with no restrictions on publication date or language. We limited the search to papers with primary data from prospective clinical trials. The date of the last search was Jan 19, 2016.

We found no prospective clinical trials in patients with mucormycosis published before April 22, 2008, in our search. In the Deferasirox-AmBisome Therapy for Mucormycosis (DEFEAT Mucor) study, 20 patients with mucormycosis were randomly assigned to receive liposomal amphotericin B plus deferasirox or liposomal amphotericin B plus placebo. This trial showed inferior outcomes with adjunctive deferasirox treatment. In the single arm AmBizygo trial, 34 evaluable patients received 10 mg/kg per day of liposomal amphotericin B for treatment of mucormycosis. In this study, mortality at 12 weeks was 38%; 40% of patients had substantial nephrotoxicity.

Added value of this study

VITAL is the first trial to show the efficacy and safety of isavuconazole for the treatment of mucormycosis, either when given for primary treatment, for refractory disease, or as an alternative in patients intolerant to amphotericin B. A matched case-control analysis using contemporaneous controls from the FungiScope database showed similar efficacy to primary amphotericin B-based treatment.

Implications of all the available evidence

Mucormycosis remains a challenging opportunistic fungal disease in patients who are immunocompromised. Antifungal treatment with amphotericin B-based regimens (in addition to surgical resection and reversal of predisposing disorders, when feasible) remains the most frequently used approach in view of the antifungal susceptibility profiles of most Mucorales moulds. The use of higher doses of lipid formulations of amphotericin B for this infection is associated with a higher risk of nephrotoxicity. Isavuconazole can be used for primary treatment for mucormycosis and is well tolerated. A need remains to develop more precise means for mucormycosis diagnosis than exist at present and to improve understanding of the comparative pharmacodynamics of various treatments.

invasive aspergillosis in patients with renal impairment and for the treatment of rare invasive fungal diseases. The study prespecified a category for mucormycosis primary treatment, defined as 4 days or less of previous systemic antifungals. Patients were also eligible if they were intolerant or refractory to other antifungals. Patients were deemed to have disseminated fungal disease if they had mucormycosis involving more than one non-contiguous anatomical site.

An independent data review committee established the diagnostic certainty of invasive fungal disease using European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria.[12] Mucormycosis was proven by histopathology or growth from sterile body sites. Probable mucormycosis included growth from respiratory specimens in patients with pneumonia and no alternative cause.[12] Eligibility criteria included age 18 years or older, weight 40 kg or more, rate-corrected QT interval (QTc) of less than 500 ms, absence of severe liver injury, and no concurrent treatment with strong inhibitors or inducers of cytochrome P450 enzymes (appendix).

To assess the clinical efficacy of isavuconazole in the treatment of mucormycosis, in accordance with the US Food and Drug Administration's guidance for comparators in studies of rare diseases,[13] we also did a matched case-control analysis using the FungiScope: Global Emerging Fungal Infection Registry, which maintains a global, web-based, anonymised database on rare invasive fungal diseases.[14]

For the open-label study, the institutional review board at each centre approved the study and all patients provided written informed consent. For the matched case-control study, informed consent was obtained if

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See Online for appendix

required by local laws or regulations and the ethics committee at University of Cologne, Germany, confirmed the data protection and privacy policy. The study protocol is included with the appendix.

Procedures

Patients received either an oral or intravenous loading regimen (determined at the discretion of the local investigators) of isavuconazonium sulfate 372 mg, equivalent to isavuconazole 200 mg, every 8 h for six doses, followed by isavuconazole 200 mg daily. Patients were assessed on days 1, 2, 3, 7, 14, 28, 42, and 84, and monthly if treatment was needed after day 84. Patients who discontinued isavuconazole had an end of treatment assessment and two post-treatment monthly assessments. At day 42, day 84, and at the end of treatment, investigators documented clinical, radiological, and mycological responses.

In the matched case-control analysis, patients with isavuconazole primary treatment were matched with up to three contemporaneous FungiScope patients who had received primary amphotericin B-based treatment for proven or probable mucormycosis. Matching was based on three dichotomous covariates: severe disease, defined as CNS or disseminated involvement,[1,15–18] haematological malignancy,[1,4,16] and surgical treatment within 7 days of antifungal treatment initiation.[1,3,16,18] If a case was not matched to a control on all three criteria, a second matching was based on the first two criteria. The algorithm was developed in R 3.0.2 (R Foundation, Vienna, Austria). Coordinating FungiScope investigators, sponsors, and trial statisticians were blinded to patient outcomes until database lock. OAC was a data review committee member in the VITAL study and thus not blinded to the outcome of VITAL patients. OAC was blinded towards FungiScope patient outcomes and to the case-matching and the comparative analysis.

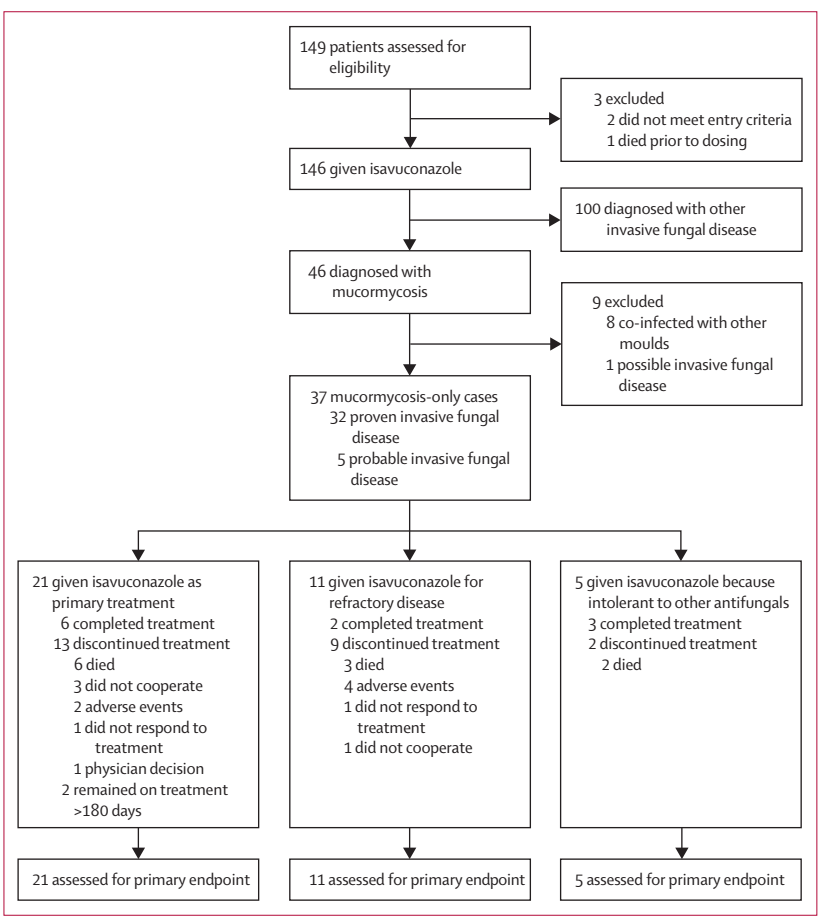

Figure 1: **Enrolment and study flow for VITAL study**
The 21 patients with mucormycosis who were given isavuconazole as primary treatment were used for the matched-case analysis with patients in the FungiScope Registry.

Outcomes

The primary VITAL study endpoint was overall response at day 42 assessed by a data review committee. Secondary endpoints included assessments of overall, clinical, radiological, and mycological responses at day 42, day 84, and end of treatment, and all-cause mortality at days 42 and 84.

The data review committee provided systematic assessment for clinical, radiological, and mycological responses, and for overall response for each patient. They classified overall responses as complete or partial (deemed treatment success); or stable or progressive disease (deemed treatment failure) according to prespecified criteria (appendix).[19]

Investigators recorded adverse events and findings from physical examination, laboratory tests (appendix), electrocardiograms, and imaging studies at each study visit. Patients had trough isavuconazole plasma concentrations measured during study visits. Fungal isolates underwent central laboratory identification and susceptibility testing.[20]

Statistical analysis

We did not formally calculate sample size for the VITAL study. We kept this single-treatment group, rare disease study open to ensure that at least 20 patients received primary treatment for mucormycosis. We summarised the findings using descriptive statistics. All data review committee assessments regarded deaths as failures. We regarded patients with unknown survival status as deaths in the crude mortality calculations and censored the patients at the last known day alive for the Kaplan-Meier analysis. VITAL is registered with ClinicalTrials.gov, number NCT00634049.

We calculated crude all-cause mortality through day 42; we assessed weighted all-cause mortality on day 42 for the case-control analysis because matching ratios varied per case patient. We applied weights according to the ratio of the number of controls matched to each case. We calculated the hazard ratio and its 95% CI from a Cox model without covariates as summary

statistics for the Kaplan-Meier survival probability through day 84; patients with unknown survival status were censored at the last known day alive. Statistical analyses used SAS 9.1.3. FungiScope is registered with ClinicalTrials.gov, number NCT01731353.

Role of the funding source

The sponsors, Astellas Pharma Global Development (Northbrook, IL, USA) and Basilea Pharmaceutica International (Basel, Switzerland), designed the study protocol. Six protocol amendments were made from 2007 to 2013 (appendix). Notably, the primary efficacy endpoint of overall response was changed from the investigator assessment to the independent data review committee assessment. All investigators and central laboratories provided study data. The sponsors did the study analyses and vouch for their integrity and validity; they affirm that the study was done as specified by the protocol. The first and corresponding authors had full access to all the data and had final responsibility for the decision to submit for publication.

Results

From April 22, 2008, to Oct 6, 2008, six patients consented to participate in the VITAL study. Enrolment was suspended between Jan 23, 2009, and April 3, 2011, to conduct additional non-clinical safety studies and transfer sponsorship from Basilea Pharmaceutica International to Astellas Pharma Global Development. From April 20, 2011, to June 21, 2013, another 143 patients consented to participate in the study (figure 1). Of 37 patients with mucormycosis only, 32 had proven and five had probable disease.[12] 21 patients received isavuconazole for primary treatment, 11 for refractory disease, and five after intolerance to other antifungals. 15 patients had protocol deviations during the study: one patient started isavuconazole treatment on dialysis; one patient had discontinued carbamazepine less than 5 days before starting isavuconazole; 11 patients received protocol-prohibited drugs at some point; three patients had transient isavuconazole dosing errors; and one patient who developed QTc prolongation remained on isavuconazole with subsequent normalisation of QTc (appendix).

Overall, 24 patients discontinued isavuconazole treatment (figure 1). Of 37 patients on isavuconazole treatment, main reasons for discontinuation were death (11 patients [30%]), adverse events (six patients [16%]), non-compliance (four patients [11%]), insufficient treatment response (two patients [5%]), and investigator's decision (one patient [3%]). The six adverse events that led to discontinuation of treatment were relapse or progression of malignant disease (two patients), acute liver injury (two patients), *Escherichia coli* bacteraemia (one patient), and nausea (one patient).

22 (59%) of 37 patients had pulmonary mucormycosis, 12 patients (32%) with and ten patients (27%) without other organ involvement (table 1). Of 21 patients on isavuconazole primary treatment, eight patients (38%) had disseminated, one (5%) had pulmonary only, and 12 (57%) had non-pulmonary disease (table 1); the most common non-pulmonary sites of mucormycosis in these patients were the paranasal sinuses (13 patients [62%]), orbit (seven patients [33%]), and CNS (six patients [29%]; table 2).

Of the 37 mucormycosis-only cases, the three most often identified Mucorales (table 1) were *Rhizopus oryzae* (seven cases [19%]), *Mucor* spp (six [16%]), and

	Primary treatment group (N=21)	Refractory group (N=11)	Intolerant to other antifungals group (N=5)	Total (N=37)
Median age, years (IQR)	51 (46–57)	50 (28–54)	42 (25–51)	50 (41–57)
Sex				
Men	17 (81%)	8 (73%)	5 (100%)	30 (81%)
Women	4 (19%)	3 (27%)	0	7 (19%)
Race				
White	12 (57%)	10 (91%)	3 (60%)	25 (68%)
Black	1 (5%)	1 (9%)	2 (40%)	4 (11%)
Asian	8 (38%)	0	0	8 (22%)
Risk factors at baseline*				
Haematological malignancy	11 (52%)	7 (64%)	4 (80%)	22 (59%)
Allogeneic HSCT	4 (19%)	4 (36%)	5 (100%)	13 (35%)
Solid organ transplantation	1 (5%)	2 (18%)	0	3 (8%)
Diabetes	4 (19%)	0	0	4 (11%)
Active malignant disease	11 (52%)	6 (55%)	1 (20%)	18 (49%)
Neutropenia at diagnosis	4 (19%)	5 (45%)	1 (20%)	10 (27%)
Glucocorticoid use	5 (24%)	3 (27%)	2 (40%)	10 (27%)
T-cell immunosuppressant use	7 (33%)	6 (55%)	5 (100%)	18 (49%)
Renal dysfunction†	6 (29%)	3 (27%)	2 (40%)	11 (30%)
Baseline pathogen				
Mucorales moulds‡	6 (29%)	5 (45%)	2 (40%)	13 (35%)
Rhizopus oryzae	4 (19%)	3 (27%)	0	7 (19%)
Mucor spp	6 (29%)	0	0	6 (16%)
Rhizomucor spp	2 (10%)	2 (18%)	1 (20%)	5 (14%)
Rhizopus spp	0	1 (9%)	1 (20%)	2 (5%)
Lichtheimia corymbifera	2 (10%)	0	0	2 (5%)
Actinomucor elegans	1 (5%)	0	0	1 (3%)
Cunninghamella spp	0	0	1 (20%)	1 (3%)
Mucormycosis location				
Pulmonary only	1 (5%)	5 (45%)	4 (80%)	10 (27%)
Pulmonary and other organs	8 (38%)	3 (27%)	1 (20%)	12 (32%)
Non-pulmonary disease	12 (57%)	3 (27%)	0	15 (41%)
Disseminated disease§	8 (38%)	2 (18%)	1 (20%)	11 (30%)
Median days on treatment (IQR)	102 (27–180)	33 (18–87)	85 (28–132)	84 (19–179)

Data are n (%) unless stated otherwise. HSCT=haemopoietic stem-cell transplantation. MDRD=Modification of Diet in Renal Disease. *Patients could have more than one risk factor. †Renal dysfunction was defined at baseline as an estimated glomerular filtration rate less than 60 mL/min per 1·73 m² by the MDRD formula. ‡No species differentiation available. §Disseminated disease was defined as mucormycosis involving more than one non-contiguous anatomical site, as confirmed by the data review committee.

Table 1: **Demographics and baseline characteristics by treatment status of patients with mucormycosis in VITAL study**

	Isavuconazole	Amphotericin B
Number of patients	21	33
Year of diagnosis	2008–13	2005–13
Median age, years (IQR)	51 (46–57)	57 (49–65)
Sex		
Men	17 (81%)	22 (67%)
Women	4 (19%)	11 (33%)
Race		
White	12 (57%)	31 (94%)
Asian	8 (38%)	2 (6%)
Black	1 (5%)	0
Median weight, kg (IQR)	81 (53–91)	70 (58–80)
Underlying disorder		
Immunosuppressant use	9 (43%)	9 (27%)
Baseline neutropenia	4 (19%)	8 (24%)
Diabetes	4 (19%)	6 (18%)
HSCT	4 (19%)	5 (15%)
GVHD treatment	4 (19%)	3 (9%)
Solid organ transplant	1 (5%)	3 (9%)
Diagnostic certainty		
Proven	18 (86%)	20 (61%)
Probable	3 (14%)	13 (39%)
Pathogen		
Actinomucor spp	1 (5%)	0
Lichtheimia spp	2 (10%)	6 (18%)
Mucor spp	6 (29%)	5 (15%)
Mucorales moulds	6 (29%)	7 (21%)
Rhizomucor spp	2 (10%)	2 (6%)
Rhizopus spp	4 (19%)	13 (39%)
Disease location		
Pulmonary only	1 (5%)	10 (30%)
Pulmonary and other organ	8 (38%)	7 (21%)
Non-pulmonary only	12 (57%)	16 (48%)
Non-pulmonary locations		
Paranasal sinuses	13 (62%)	11 (33%)
CNS	6 (29%)	8 (24%)
Orbit	7 (33%)	4 (12%)
Bone	4 (19%)	5 (15%)
Deep soft tissues	1 (5%)	6 (18%)
Gastrointestinal tract	2 (10%)	5 (15%)
Skin	2 (10%)	5 (15%)
Other*	7 (33%)	9 (27%)

Table 2 continues in next column

	Isavuconazole	Amphotericin B
(Continued from previous column)		
Disseminated disease	8 (38%)	8 (24%)
Matching covariate†		
Haematological malignancy	11 (52%)	18 (55%)
Severe disease‡	12 (57%)	13 (39%)
Surgical treatment§	9 (43%)	13 (39%)
Primary treatment¶		
Isavuconazole	21 (100%)	0
Deoxycholate amphotericin B	0	7 (21%)
Liposomal amphotericin B	0	22 (67%)
Amphotericin B lipid complex	0	4 (12%)
Median daily dose, mg (range)		
Isavuconazole	200‖	..
Deoxycholate amphotericin B	..	70 (50–80)
Liposomal amphotericin B	..	350 (20–1000)
Amphotericin B lipid complex	..	325 (250–350)
Median treatment duration, days (IQR)		
Isavuconazole	102 (27–180)**	..
Amphotericin B	..	18 (13–34)
Amphotericin B followed by posaconazole‡	..	34 (14–111)

Data are n (%) unless stated otherwise. Primary treatment with isavuconazole-treated cases (VITAL) versus amphotericin B-treated controls (FungiScope). HSCT=haemopoietic stem-cell transplantation. GVHD=graft-versus-host disease. *Other locations include liver, spleen, kidneys, biliary system, and other organs. †Proportions for matching covariates varied between the cases and controls because the matching ratio varied per case. ‡CNS involvement or disseminated disease (defined as disease involving >1 non-contiguous organ), or both. §Resection or debridement at the site of infection at treatment start (SD 7 days). ¶12 FungiScope controls received posaconazole after amphotericin B as continuing treatment; seven patients started posaconazole treatment before day 42. ‖No range reported because all patients were given the same dose per protocol. **Four patients had an isavuconazole treatment duration that exceeded 180 days.

Table 2: **Demographics and baseline characteristics for a matched case-control analysis of patients with mucormycosis**

Rhizomucor spp (five [14%]). No species differentiation was available for 13 cases (35%) of Mucorales. Antifungal susceptibilities of VITAL isolates are presented in the appendix.

37 patients received isavuconazole treatment for a median of 84 days (IQR 19–179, range 2–882), 21 of whom received primary treatment for a median of 102 days (IQRx7–180, range 2–882; table 1). Some patients switched between oral and intravenous isavuconazole and vice versa; 30 patients received intravenous isavuconazole for a median of 10 days (IQR 6–21, range 2–77) and 29 patients received oral isavuconazole for a median of 80 days (IQR 25–176, range 7–882). Eight of 37 patients initiated treatment with oral isavuconazole. Seven patients (19%) received study treatment for more than 180 days. The median isavuconazole trough plasma concentration was 3·32 μg/mL (IQR 1·95–4·10, n=13) on day 7, 3·47 μg/mL (IQR 0·84–5·65, n=11) on day 14, and 4·19 μg/mL (IQR 3·04–5·70, n=18) on day 28 (appendix).

By treatment day 42, four (11%) of 37 patients had a partial response to isavuconazole treatment, including three patients who received isavuconazole primary treatment and one patient who had refractory disease (table 3). Mucormycosis had stabilised in 16 (43%) of 37 patients (table 3). One (3%) of 37 patients had invasive fungal disease progression (the patient had received isavuconazole primary treatment). Clinical assessment data were missing for three (8%) of 37 patients (one patient in the primary treatment group and two in the refractory disease group), including one who was lost to follow-up. 13 (35%) of 37 patients had

died (table 3). Day 42 all-cause mortality, including the patient lost to follow-up, was 14 (38%) of 37 patients (table 3). The data review committee attributed eight deaths (22%) to progressive invasive fungal disease. Isavuconazole treatment was discontinued before day 42 in two patients with stable disease, one due to elevated liver function tests and another because of cancer progression; one of these patients switched treatment to posaconazole.

By day 84, of 37 patients, the data review committee noted complete responses in two patients (5%), partial responses in five patients (14%), and stable disease in 11 patients (30%). By end of treatment, five (14%) of 35 patients were considered to have had a complete response (table 3; appendix); two patients continued treatment beyond day 180 and did not have an end of treatment assessment by the data review committee. All-cause mortality was 43% (16 of 37 patients) by day 84. Notably, in eight additional patients with mixed invasive fungal diseases that included a Mucorales infection, all-cause mortality was 25% (two of eight patients) by day 42, and 38% (three of eight patients) by day 84.

A relation between trough isavuconazole plasma concentrations, fungal isolate minimum inhibitory concentrations, and key outcomes could not be identified, possibly because of the small number of patients with data available. Clinical responses occurred across the range of isavuconazole minimum inhibitory concentrations and trough concentrations recorded (appendix).

Of 37 patients receiving isavuconazole treatment, 35 patients (95%) had one or more adverse events during treatment (table 4); 28 (76%) patients had serious adverse events (appendix). The most common adverse events reported (≥10% of patients) are summarised in the appendix. Gastrointestinal complaints were most commonly reported; however, increases in alanine transaminase, aspartate aminotransferase, or other hepatic enzymes were seen in less than 10% of patients each.

Overall, the adverse events reported in patients with mucormycosis were similar in distribution to those reported in the SECURE invasive aspergillosis trial (appendix).[21] No organ-specific pattern of serious adverse events was seen (appendix). 34 patients (25%) had an increase in QTc of more than 30 ms, whereas 57 patients (42%) had a decrease in QTc of more than 30 ms during isavuconazole treatment (appendix). The percentages are calculated from a total of 135 patients whom have both baseline and at least one post-baseline value. Moreover, no sustained ventricular arrhythmias were seen (appendix).

In the matched case-control analysis, of 144 amphotericin B-treated FungiScope patients with mucormycosis assessed for eligibility, 62 fulfilled the inclusion criteria and 33 patients from 17 centres were matched as controls to 21 VITAL study patients who received isavuconazole for primary treatment (appendix). 14 cases were matched with one control (n=14), two cases were matched to two controls each (n=4), and five cases were matched to three controls each (n=15). 19 of 21 cases matched on all three matching criteria; in two instances surgical debridement was regarded as mismatched as it occurred 2 days outside of the prespecified 7 day window. A similar proportion of cases and controls had surgical treatment and underlying haematological malignancies. An increased proportion of cases had severe disease (12 [57%] of 21 patients; table 2) compared with the control group (13 [39%] of 33 patients). Immunosuppressant use and treatment for graft-versus-host disease were more frequent in cases than controls. A higher proportion of cases had proven invasive fungal disease (18 [86%] of 21 cases) compared with matched controls (20 [61%] of 33 controls). Although the proportion of CNS involvement was similar in both groups, a higher proportion of cases had disseminated

	Primary treatment group (N=21)	Refractory group (N=11)	Intolerant to other antifungals group (N=5)	Total (N=37)
DRC-assessed overall response at day 42				
Complete response	0	0	0	0
Partial response	3 (14%)	1 (9%)	0	4 (11%)
Stable disease	9 (43%)	4 (36%)	3 (60%)	16 (43%)
Progression of disease	1 (5%)	0	0	1 (3%)
Death	7 (33%)	4 (36%)	2 (40%)	13 (35%)
Missing data	1 (5%)	2 (18%)	0	3 (8%)
DRC-assessed overall response at day 84				
Complete response	1 (5%)	1 (9%)	0	2 (5%)
Partial response	1 (5%)	3 (27%)	1 (20%)	5 (14%)
Stable disease	9 (43%)	0	2 (40%)	11 (30%)
Progression of disease	0	1 (9%)	0	1 (3%)
Death	9 (43%)	4 (36%)	2 (40%)	15 (41%)
Missing	1 (5%)	2 (18%)	0	3 (8%)
DRC-assessed overall response at EOT†				
Complete response	3/19 (16%)	2 (18%)	0	5/35 (14%)
Partial response	3/19 (16%)	2 (18%)	1 (20%)	6/35 (17%)
Stable disease	6/19 (32%)	2 (18%)	2 (40%)	10/35 (29%)
Progression of disease	7/19 (37%)	5 (45%)	2 (40%)	14/35 (40%)
DRC-assessed success rate at EOT				
Clinical response	10/18 (56%)	2/9 (22%)	2/4 (50%)	14/31 (45%)
Mycological response	6/19 (32%)	4/11 (36%)	2/5 (40%)	12/35 (34%)
Radiological response	3/18 (17%)	2/10 (20%)	1/5 (20%)	6/33 (18%)
All-cause mortality through day 42‡	7 (33%)	5 (45%)	2 (40%)	14 (38%)
All-cause mortality through day 84‡	9 (43%)	5 (45%)	2 (40%)	16 (43%)

Data are n (%) or n/N (%). DRC=data review committee. EOT=end of treatment.*DRC-assessed overall response was based on individual clinical, mycological, and radiological response assessments; details of terms and definitions are presented in the appendix. †Two patients continued to receive isavuconazole treatment beyond day 180 and did not have an EOT assessment by the DRC; however, both patients were deemed to have stable disease and clinical response at day 84 per the DRC assessment. ‡One patient with refractory disease had an unknown survival status and was counted as a death in summary.

Table 3: **Efficacy outcomes by treatment status in VITAL patients with mucormycosis***

	Primary treatment group (N=21)	Refractory group (N=11)	Intolerant to other antifungals group (N=5)	Total (N=37)
Overall	20 (95%)	10 (91%)	5 (100%)	35 (95%)
Vomiting	6 (29%)	5 (45%)	1 (20%)	12 (32%)
Diarrhoea	5 (24%)	3 (27%)	2 (40%)	10 (27%)
Nausea	4 (19%)	6 (55%)	0	10 (27%)
Pyrexia	6 (29%)	2 (18%)	2 (40%)	10 (27%)
Constipation	4 (19%)	3 (27%)	1 (20%)	8 (22%)
Decreased appetite	3 (14%)	2 (18%)	1 (20%)	6 (16%)
Headache	3 (14%)	2 (18%)	1 (20%)	6 (16%)
Oedema, peripheral	2 (10%)	4 (36%)	0	6 (16%)
Abdominal pain	3 (14%)	1 (9%)	1 (20%)	5 (14%)
Dyspnoea	3 (14%)	1 (9%)	1 (20%)	5 (14%)
Pneumonia	3 (14%)	1 (9%)	1 (20%)	5 (14%)
Back pain	2 (10%)	2 (18%)	0	4 (11%)
Cough	2 (10%)	1 (9%)	1 (20%)	4 (11%)
Hypoglycaemia	3 (14%)	1 (9%)	0	4 (11%)
Insomnia	2 (10%)	2 (18%)	0	4 (11%)
Restlessness	1 (5%)	3 (27%)	0	4 (11%)

Data are n (%). *Reported in 10% or more of patients.

Table 4: **Frequently reported* treatment-emergent adverse events**

	Isavuconazole	Amphotericin B	p value
Crude all-cause mortality, n/N (%; 95% CI)*	7/21 (33%; 14·6–57·0)	13/33 (39%; 22·9–57·9)	p=0·775†
Weighted all-cause mortality (%;‡ 95% CI)*	33%; 13·2–53·5	41%; 20·2–62·3	p=0·595§
Crude mortality by matching covariates, n/N (%)			
Haematological malignancy	5/11 (45%)	7/18 (39%)	NA
Severe disease¶	6/12 (50%)	8/13 (62%)	NA
Surgical treatment‖	4/9 (44%)	3/13 (23%)	NA

Primary treatment with isavuconazole-treated cases (VITAL) versus amphotericin B-treated controls (FungiScope). *95% CI are based on an exact binomial distribution (crude) or normal approximation (weighted). †Calculated from Fisher's exact test. ‡Weights were applied according to the ratio of the number of controls matched to each case. §Calculated from a χ^2 test. ¶CNS involvement or disseminated disease (defined as disease involving >1 non-contiguous organ). ‖Resection or debridement at the site of infection at treatment start (SD 7 days).

Table 5: **All-cause mortality through day 42 for a matched case-control analysis of patients with mucormycosis**

mucormycosis in the isavuconazole-treated group of patients (eight [38%] of 21 patients) than in the group treated with amphotericin B (eight [24%] of 33 patients). Conversely, pulmonary disease without other organ disease occurred less frequently for cases versus controls (one [5%] of 21 cases *vs* ten [30%] of 33 controls). Non-pulmonary locations were similar in both groups (table 2). Liposomal amphotericin B was the most commonly used treatment among controls. 12 (36%) of 33 controls switched to posaconazole for further treatment after amphotericin B. The median duration of amphotericin B treatment was 18 days (IQR 13–34); the overall median duration of treatment with amphotericin B followed by posaconazole was 34 days (IQR 14–111; table 2).

Crude all-cause mortality through day 42 was similar between cases (seven [33%] of 21 cases) and controls (13 [39%] of 33 controls); weighted all-cause mortality was also similar between cases and controls (33% *vs* 41%; table 5). Crude all-cause mortality was similar between patients with severe disease and with haematological malignancy, but higher in patients given isavuconazole who underwent surgery (table 5). Survival probability through day 84 was similar between VITAL cases (57%) and FungiScope controls (50%, p=0·653; figure 2).

Discussion

The VITAL study showed that isavuconazole was active as primary or salvage (refractory or intolerant to other antifungals) treatment for mucormycosis, with overall end-of-treatment complete and partial response of 32% for primary treatment and 36% for treatment of mucormycosis refractory to other antifungals (table 3). These response rates are similar to those reported for liposomal amphotericin B.[22] The stringent response criteria used in the VITAL study might underestimate the relevant clinical treatment success at the bedside. However, unlike isavuconazole, amphotericin B formulations have dose-limiting nephrotoxicity.[23] Isavuconazole was well tolerated and toxic effects were an uncommon cause for discontinuation. The improved tolerability of isavuconazole is supported by the finding that investigators obtained permission for seven (19%) of 37 patients to continue treatment beyond 6 months. This is corroborated by the results of the SECURE isavuconazole trial, in which isavuconazole showed favourable tolerability compared with voriconazole for treatment of invasive aspergillosis.[21]

All-cause mortality was a prespecified secondary endpoint in this trial because mucormycosis can rapidly be fatal and brief treatment delays can increase mortality rates to more than 80%.[4] In the VITAL study, all-cause mortality was 43% for isavuconazole-treated patients through day 84 (table 3), which is similar to rates reported for amphotericin B and posaconazole.[9,10,22]

We did a supportive case-control analysis in which patients with mucormycosis who received primary isavuconazole treatment were compared with contemporary controls from the FungiScope registry to further assess the clinical efficacy of isavuconazole. We found that crude and weighted all-cause mortality at day 42 (table 5) and survival through day 84 (figure 2) did not differ for patients primarily treated with either isavuconazole or amphotericin B formulations.

A typical limitation of studies on rare diseases, such as the VITAL study, is the non-randomised single-arm design. By contrast with large randomised clinical trials, the interpretation of VITAL's results relied on external comparisons to support the efficacy of isavuconazole. However, in these rare diseases, case-control comparisons are an acceptable means of

estimating efficacy and toxic effects, but they are limited in their ability to eliminate confounding factors between the treatment groups. In fact, a higher frequency of immunosuppressant use, graft-versus-host disease, and disseminated disease among isavuconazole-treated patients could have predicted a higher baseline mortality risk compared with the amphotericin B-treated controls (table 2).[1,15–18] Similarly, treatment exposure was different between the matched groups. Whereas median isavuconazole primary treatment was 102 days, contemporary controls received amphotericin B treatment for a median of 18 days, followed by posaconazole in several cases (table 2). Interpretation of any differences is constrained by the shorter follow-up period in the FungiScope Registry (minimum 30 days) than in the VITAL study. Favourable tolerability of isavuconazole compared with amphotericin B might have also added to the differences in treatment duration, as was noted with voriconazole in a randomised study[24] involving invasive aspergillosis.

Mucormycosis is composed of a heterogeneous group of difficult to diagnose pathogens and infrequent disease presentations.[5] Therefore, we cannot exclude a differential treatment effect of either isavuconazole or amphotericin B on the specific fungal species being treated. Furthermore, in most patients in the VITAL study and FungiScope registry, mucormycosis was proven by histopathology, rather than by culture. Therefore, the disease-causing species remained elusive in many patients and the numbers of cases infected with Mucorales moulds were underpowered for more refined analyses. Although susceptibility testing of all study isolates was done, the absence of microbiological breakpoints for antifungal minimum inhibitory concentrations prevents robust treatment guidance.[5] Furthermore, animal models of mucormycosis represent the bridge between in-vitro susceptibility and human disease. These models have mixed results on mucormycosis treatment outcomes depending on model, comparative regimen, Mucorales moulds, and outcome measurements.[25–27] However, despite their inadequate precision, treatments with some extended-spectrum azoles have some measurable anti-Mucorales activity and in some models this activity is similar to liposomal amphotericin B. Although posaconazole has been recommended as an alternative to amphotericin B,[5] its use in mucormycosis has not been lent support by a comparative study.[9,10] Researchers clearly need to develop more precise means for diagnosis of mucormycosis than those that exist at present,[28–30] and to improve understanding of the comparative pharmacodynamics of various treatments in human beings with animal models as a guide.

The VITAL trial combined with the FungiScope registry results lend support to the use of isavuconazole as a primary treatment option for mucormycosis or its use in patients refractory or intolerant to amphotericin B. Patients who develop this rare invasive fungal disease usually have several comorbidities, including renal and other organ dysfunction, and often require surgical treatment and management of underlying immunosuppressive disorders. An effective and well tolerated antifungal that can be safely given orally or intravenously is a welcome addition to the complex management of mucormycosis.

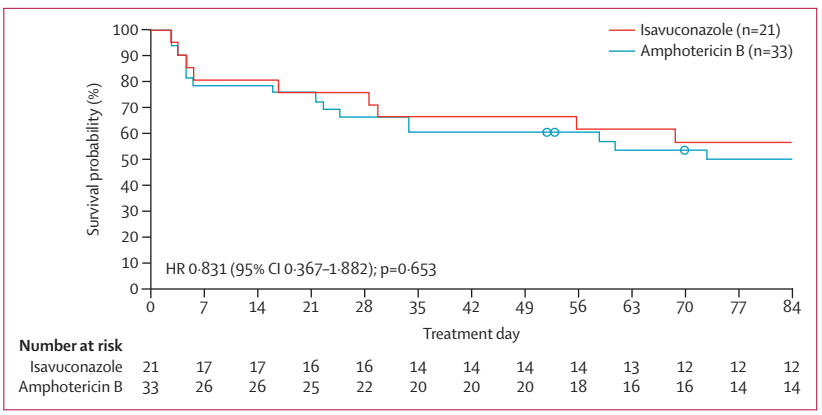

Figure 2: **Kaplan-Meier analysis of patients who received isavuconazole as primary treatment (VITAL) compared with amphotericin B-treated matched controls (FungiScope)**
Hazard ratio (HR) and 95% CI are calculated from a Cox model without covariates. Patients were censored on the day of their last known survival status, represented by the circles.

Contributors

FMM, OAC, KMM, GRT, and MJGTV wrote the initial manuscript draft. All authors provided direction for content of the manuscript, contributed intellectual content, participated in reviews, approved the final version of the publication, and are accountable for all aspects of the study in ensuring that questions related to the accuracy or integrity of any part of the Article are appropriately investigated and resolved.

VITAL contributors

LO-Z, OAC, JRP, GRT, JMB, SS, SJ, AK, ML, CS, and BZ proposed the key elements of the study design. FMM, LO-Z, OAC, GRT, JMB, SS, PC, SJ, ME, AK, and BZ provided critical review of the draft protocol and made significant contributions to the design. FMM, LO-Z, OAC, JRP, GRT, GJA, JMB, PC, SJ, AK, MI, RMM, and BZ had an advisory role on the study and provided significant direction to the study development and conduct. LO-Z was chair of the data review committee. FMM was the principal coordinating investigator. DNF was a local principal investigator, enrolled participants, and collected and verified data. RMM was sponsor project lead. Other investigators were OAC, KMM, GRT, GJA, JMB, WJH, GK, JAM, SRM, IO, PGP, GR, RS, J-AHY, PC, SJ, and SSK. FMM, LO-Z, OAC, GRT, JMB, PC, SJ, ME, AK, MI, ML, CS, RMM, and BZ established the methodology used for the analysis. FMM, LO-Z, OAC, KMM, JRP, GRT, GJA, JMB, WJH, JAM, J-AHY, PC, SJ, SSK, AK, MI, ML, CS, RMM, and BZ participated in evaluation and assessment of data.

FungiScope contributors

OAC is the inventor and lead investigator for FungiScope. JJV and MJGTV proposed the key elements of the study design and provided critical review of the draft protocol, making substantial contributions to the protocol design. JJV and MJGTV had an advisory role on the study and provided direction to the study development and conduct. JJV provided a substantial contribution to the FungiScope database and epidemiology. Other investigators were RH, NK, ZR, and MJGTV. JJV, MJGTV, RH, ML, and BZ established the methodology used for the case-control analysis. JJV, MJGTV, and ML participated in evaluation and assessment of data.

Declaration of interests

FMM reports grants, personal fees, and non-financial support from Astellas and Merck, and grants and personal fees from WHISCON, during the conduct of the study. Additionally, FMM has a patent (Diagnosis and Treatment of Invasive Aspergillosis, Application 61/698,155) pending from Brigham and Women's Hospital. LO-Z reports personal fees from Astellas during the conduct of the study, personal fees from Merck, and grants and personal fees from Astellas and Pfizer, outside the submitted work. OAC reports grants from 3M, Bayer, Celgene, Genzyme, GSK, Miltenyi, Quintiles, and Viropharma; personal fees from Da Volterra, Daiichi Sankyo, F2G, Sanofi Pasteur, Summit, Vical, and Vifor; and grants and personal fees from Actelion, Astellas, Basilea, Cubist, Gilead Sciences, Merck/MSD, Optimer, and Pfizer, outside the submitted work. KMM reports grants and personal fees from Astellas, outside the submitted work. JRP reports support from Astellas at the time of the study, and grants and consulting fees from Amplyx, Arno, Astellas, Cidara, F2G, Merck, Scynexis, Viamet, Vical, and Tokoyama, outside of the submitted work. GRT was a member of the data review committee for the SECURE study (Astellas) and reports grants from Astellas and Merck, outside the submitted work. WJH reports personal fees from Astellas, Basilea, and Gilead Sciences; and grants and personal fees from Merck/MSD and Pfizer, outside the submitted work. RH reports personal fees from Astellas, Basilea, Gilead Sciences, MSD, and Schering-Plough; and grants and personal fees from Pfizer during the conduct of the study. NK reports personal fees from Astellas and Pfizer, and grants and personal fees from Merck, outside the submitted work. GK reports lectures fees from Astellas Russian Federation, and lectures fees and travel grants from Pfizer Russian Federation, and MSD Russian Federation, outside the submitted work. JAM reports personal fees and non-financial support from Basilea, and grants, personal fees, and non-financial support from Astellas, Gilead Sciences, Merck Sharpe and Dohme, and Pfizer. PGP reports grants and personal fees from Astellas, during the conduct of the study; grants from Gilead, Merck, Scynexis, and T2 Biosystems; and personal fees from Viamet, outside the submitted work. ZR reports grants and personal fees from Astellas, outside the submitted work. SS reports personal fees from MSD Sharp and Dohme, Pfizer, and Gilead Sciences and grants and personal fees from Astellas, during the conduct of the study; and personal fees from Amgen and BTG International, outside the submitted work. JJV reports grants from Astellas during the conduct of the study; grants, personal fees, and non-financial support from Astellas, Gilead Sciences, Merck/MSD, and Pfizer, outside the submitted work. J-AHY reports that the University of Minnesota was paid by Astellas on a per participant basis for the participants that were enrolled on this clinical trial, during the conduct of the study. PC reports grants from Astellas during the conduct of the study. SSK received principal investigator fees for enrolling patients, and received honorarium for talks for Pfizer and MSD outside the submitted work. MJGTV reports grants from Astellas, Gilead Sciences, Merck/MSD, and Pfizer during the conduct of the study; grants from 3M; personal fees from Merck/MSD, Berlin Chemie, and Pfizer; and grants and personal fees from Astellas, DaVolterra, and Gilead Sciences, outside the submitted work. ME and AK are employees of Basilea Pharmaceutica International. MI, ML, CS, RMM, and BZ are employees of Astellas Pharma Global Development. GJA, JMB, DNF, SRM, IO, GR, RS, and SJ declare no competing interests.

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