Isavuconazole Treatment of Cryptococcosis and Dimorphic Mycoses

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Background. Invasive fungal diseases (IFD) caused by Cryptococcus and dimorphic fungi are associated with significant morbidity and mortality. Isavuconazole (ISAV) is a novel, broad-spectrum, triazole antifungal agent (IV and by mouth [PO]) developed for the treatment of IFD. It displays potent activity in vitro against these pathogens and in this report we examine outcomes of patients with cryptococcosis or dimorphic fungal infections treated with ISAV.

Methods. The VITAL study was an open-label nonrandomized phase 3 trial conducted to evaluate the efficacy and safety of ISAV treatment in management of rare IFD. Patients received ISAV 200 mg 3 times daily for 2 days followed by 200 mg once-daily (IV or PO). Proven IFD and overall response at end of treatment (EOT) were determined by an independent, data-review committee. Mortality and safety were also assessed.

Results. Thirty-eight patients received ISAV for IFD caused by Cryptococcus spp. (n = 9), Paracoccidioides spp. (n = 10), Coccioidioides spp. (n = 9), Histoplasma spp. (n = 7) and Blastomyces spp. (n = 3). The median length of therapy was 180 days (range 2–331 days). At EOT 24/38 (63%) patients exhibited a successful overall response. Furthermore, 8 of 38 (21%) had stable IFD at the end of therapy without progression of disease, and 6 (16%) patients had progressive IFD despite this antifungal therapy. Thirty-three (87%) patients experienced adverse events.

Conclusions. ISAV was well tolerated and demonstrated clinical activity against these endemic fungi with a safety profile similar to that observed in larger studies, validating its broad-spectrum in vitro activity and suggesting it may be a valuable alternative to currently available agents.

Clinical Trials Registration. NCT00634049.

Keywords. cryptococcosis; histoplasmosis; coccidioidomycosis; blastomycosis; paracoccidioidomycosis.
approved for use in the treatment of aspergillosis and mucormycosis following the completion of phase 3 trials [15, 16]. Pharmacokinetics are facile because there is no demonstrable food effect with oral administration [17], interpatient pharmacokinetic variability is minimal [18], and the intravenous prodrug formulation does not require the addition of cyclodextrin to achieve solubility and therefore can be used in patients with reduced renal function [19].

We evaluated the results of a phase 3 study performed to determine the safety and efficacy of ISAV as primary or salvage therapy in the treatment of either cryptococcosis or dimorphic mycoses.

METHODS

Study Design

VITAL (ClinicalTrials.gov, NCT00634049) was a phase 3, open-label, nonrandomized trial conducted in 34 medical centers worldwide that evaluated the efficacy, safety, and outcomes of patients treated with ISAV for dimorphic fungi, emerging molds and yeasts, or invasive aspergillosis in the setting of renal impairment. Only patients infected with cryptococcosis and dimorphic fungi are presented in this report.

Inclusion and Exclusion Criteria

All patients enrolled in this subset of the VITAL study had proven infection with *Cryptococcus* or a dimorphic fungus by EORTC/MSG criteria [20]. Eligibility criteria included age ≥18 years, weight ≥40 kg, rate-corrected QTc interval <500 ms, absence of severe liver injury, and no concurrent treatment with strong inhibitors or inducers of cytochrome P450. Patients who were intolerant or refractory to other antifungal agents were also eligible for enrollment in this study. Primary therapy was defined as the receipt of <4 days of other systemic antifungal therapy within the 7 days preceding study enrollment. Dissemination was defined as any extrapulmonary infection (see Supplementary Material).

Administration of Study Drugs

Patients received a loading regimen of ISAV 200 mg (administered as isavuconazonium sulfate 372 mg) every 8 hours for 6 doses, followed by ISAV 200 mg once daily. Patients were treated orally or intravenously at the investigator’s discretion. Patients were evaluated daily for the first 3 days and, thereafter, on treatment days 7, 14, 28, 42, and 84. If therapy was required beyond day 84, patients were assessed monthly. Following discontinuation of ISAV, for any reason, patients underwent end of therapy (EOT) assessment and 2 post-treatment monthly assessments. At days 42, 84, and EOT, investigators documented clinical, radiological, and mycological responses to therapy.

Study Oversight

The sponsors, Basilea Pharmaceutica International Ltd (Basel, Switzerland) and Astellas Pharma Global Development, Inc. (Northbrook, Illinois) designed the study protocol. Individual site investigators and central laboratories provided all study data. Study analysis was performed by the sponsors and they vouch for the integrity and validity of all data. All authors agreed to submit the manuscript for publication. The study was conducted in accordance with the Declaration of Helsinki (2000) and the International Conference on Harmonisation Guidelines for Good Clinical Practice. The institutional review board at each medical center approved the study. All patients provided written informed consent prior to enrollment.

Efficacy and Safety Assessments

An independent data-review committee (DRC) verified the diagnostic certainty of all IFDs and provided a judgment for each assessment component (clinical, radiological, and mycological responses) and for the overall response for each patient. Overall responses were classified as complete or partial responses (both considered a treatment success), stable or progressive disease (both considered treatment failure), based on these assessments and following prespecified criteria (see Supplementary Materials).

The primary study endpoint was DRC-assessed overall response at day 42. Prespecified secondary endpoints included assessments of overall, clinical, radiological and mycological responses at days 42, 84, and EOT, and all-cause mortality through days 42 and 84 of ISAV treatment. The treatment of the endemic mycoses and cryptococcosis is often prolonged and for this reason efficacy at EOT was used for final outcome assessments in this study.

Adverse events (AEs) and findings from the physical examination, laboratory tests, electrocardiograms, and imaging studies were recorded by the investigators at each study visit.

Laboratory procedures are outlined in the Supplementary Materials. Patients had trough ISAV levels measured during study visits. Fungal isolates from study participants underwent central laboratory identification and susceptibility testing.

Antimicrobial Susceptibility Testing

All isolates were tested in accordance with the Clinical and Laboratory Standards Institute M27-A3 methodology [21] at Case Western Reserve University or the Fungus Testing Laboratory (UT-San Antonio).

Plasma Isavuconazole Concentrations

Plasma levels of ISAV were measured on days 7, 14, 28, and presumed steady state (>day 30) 1 hour prior to the next scheduled dose or 24 ± 1 hours after last dose. ISAV and the inactive cleavage product (prodrug moiety) concentrations in plasma samples were measured using a validated liquid chromatography-mass spectrometry/mass spectrometry (LC–MS/MS) method at Pharmaceutical Product Development Inc., Middleton, Wisconsin.

Statistical Analysis

VITAL Study—patient characteristics, antifungal exposure, outcomes, AEs, and mortality were summarized using descriptive
statistics. Deaths were considered failures for all DRC assessments.

RESULTS

A total of 149 patients were enrolled in the VITAL trial, of which 38 were diagnosed with cryptococcosis or a dimorphic mycosis. The patients (age, 20–79 years) were derived from 5 countries and 10 medical centers. Thirty-one of these 38 patients (81.6%) completed the study. Patients with specific mycoses included 9 with cryptococcosis (C. neoformans, n = 4; C. gattii, n = 3; Cryptococcus spp. not otherwise specified, n = 2), 9 with coccidioidomycosis, 3 with blastomycosis, 7 with histoplasmosis, and 10 paracoccidioidomycosis (Table 1). Most patients received ISAV as primary therapy (33/38, 87%) for these mycoses. The most common underlying conditions were diabetes mellitus (n = 5) and chronic obstructive pulmonary disease (COPD) (n = 2).

Cryptococcosis

Most patients with cryptococcal infections received ISAV as primary therapy (6/9, 67%) (Table 2). Two patients received ISAV following intolerance to alternative fungal therapy—in 1 patient this followed 11 days of AMB therapy, in the other patient this followed 17 days receiving combined AMB deoxycholate and fluconazole. This latter patient had both disseminated nocardiosis and pulmonary cryptococcosis and died after only 6 days of ISAV treatment. The third patient not receiving ISAV as primary therapy was clinically refractory to AMB deoxycholate and fluconazole after 16 days of therapy. The median duration of ISAV therapy in these patients was 180 days (range 6–182 days). Six patients with cryptococcosis had a successful response (complete success in 2, partial success in 4), whereas stable disease was demonstrated in 2 other patients. Of the 2 patients intolerant to prior therapy, one was a partial responder to ISAV and the other exhibited progression of disease and was considered a failure. Eight of 9 patients survived through EOT (all-cause mortality 1/9 [11%]).

Coccidioidomycosis

All patients with coccidioidomycosis received ISAV as primary therapy for pulmonary infection (9/9, 100%); 1 patient had concomitant involvement of the pleura. All patients received ISAV for a median of 180 days (range 180–183 days). At EOT, complete or partial success was observed in 5/9 (56%) patients with complete success in 2, including the patient with pleuropulmonary disease. Those with partial success exhibited complete clearance of infection radiographically (n = 2) and a solitary pulmonary nodule (n = 1). The remaining 4/9 patients had stable disease at EOT. It is noteworthy that all 4 of these patients had diabetes mellitus and all 4 exhibited persistent radiographic abnormalities at EOT (fibrocavitary disease n = 2, and focal infiltrates n = 2). The DRC determined all 9 patients had a clinical response to therapy at EOT.

Table 1. Response to Isavuconazole at the End of Treatment

| Primary Diagnosis               | No. of Successful Outcomes at EOT (%) |
|---------------------------------|---------------------------------------|
| Cryptococcosis                  |                                       |
| All types                       | 6/9 (67)                              |
| Pulmonary                       | 3/4 (75)                              |
| CNS                             | 4/5 (80)                              |
| Non-CNS dissemination           | 0/1 (0)                               |
| Coccidioidomycosis             |                                       |
| Pulmonary                       | 5/9 (56)                              |
| Blastomycosis                   |                                       |
| All types                       | 1/3 (33)                              |
| Pulmonary                       | 1/1 (100)                             |
| Non-CNS dissemination           | 0/2 (0)                               |
| Histoplasmosis                  |                                       |
| All types                       | 4/7 (57)                              |
| Pulmonary                       | 3/5 (60)                              |
| CNS                             | 1/1 (100)                             |
| Non-CNS dissemination           | 2/3 (66)                              |
| Paracoccidioidomycosis         |                                       |
| All types                       | 8/10 (80)                             |
| Pulmonary                       | 6/8 (75)                              |
| CNS                             | 0/1 (0)                               |
| Non-CNS dissemination           | 6/8 (100)                             |

Abbreviations: CNS, central nervous system; EOT, end of treatment.

Blastomycosis

Three patients were treated with blastomycosis, and 2 of these received very short courses of therapy: 1 patient was intolerant to itraconazole therapy in the treatment of pulmonary and genitourinary blastomycosis and withdrew consent after 6 days of ISAV although no adverse effects of therapy were noted, whereas the other was treated with ISAV as primary therapy for blastomycosis. In this second patient, dissemination was confirmed (on day 2 of ISAV therapy) with lesions in the lung, spleen, and skin; ISAV was subsequently discontinued and liposomal AMB (L-AMB) initiated. This patient died on day 18 (following 16 days of L-AMB). A third patient with pulmonary blastomycosis received ISAV after intolerance to itraconazole (anorexia) and was treated for 331 days with a complete clinical and radiographic response to therapy at EOT.

Histoplasmosis

Seven patients were treated for histoplasmosis. All received ISAV as primary therapy – 3 with primary pulmonary infection and 4 with dissemination including 1 with central nervous system (CNS) involvement. Patients were treated for a median of 180 days (range 85–327 days). Complete clinical and radiographic success was observed in the patient with CNS involvement after 178 days of treatment. Partial success was found in 3 patients: 2 with disseminated disease, and 1 with lung disease alone. Stable disease was documented in a heart transplant patient with isolated pulmonary infection, and progression (failure) was seen in 1 patient with dissemination and another with
lung disease despite 185 days of ISAV. All patients were alive at EOT.

Paracoccidioidomycosis
All 10 patients with *Paracoccidioides* infections received ISAV as primary therapy. Treatment was administered for a median of 180 days (range 27–182 days). Complete success was found in 1 patient with widespread dissemination after 180 days of treatment, and partial success was determined in 7/10 (70%), with 5 of these 7 presenting with disseminated paracoccidioidomycosis including 1 with AIDS (CD4 count = 144 cell/mm³). Progressive disease was observed in 2 patients, both of whom died on days 27 and 91 after starting ISAV.

Safety Results
Thirty-three (87%) patients experienced AEs. The most common AEs were vomiting (n = 8), nausea (n = 6), back pain (n = 5), and headache (n = 5). Twelve (32%) patients had a serious adverse event (SAE) reported. Three events (septic shock, pneumonia, and vomiting) were reported in 2 patients each. Other SAEs were reported in a single patient. Fourteen (36.8%) patients had a treatment-related AE (Table 3). No patients were discontinued from the study primarily due to an AE.

In vitro Susceptibility Testing (MICs)
CLSI MIC data for ISAV were available for 22 isolates (Table 4): *Coccidioides*, 0.06–0.12 µg/mL (n = 6); *Cryptococcus gattii*, 0.008–0.12 µg/mL (n = 7); *C. neoformans*, 0.008–1.2 µg/mL (n = 6); *Histoplasma*, 0.03 µg/mL (n = 2); *Paracoccidioides*, 0.001 µg/mL (n = 1). *Blastomyces* isolates were not available for susceptibility testing.

| Table 2. Treatment of Cryptococcosis |
|--------------------------------------|
| Patient | Age | Sex | Comorbidity | Site of Infection | Species | Primary or Salvage Therapy | Duration of ISAV (days) | Mycologic Response | Overall DRC Assessment at EOT |
|---------|-----|-----|-------------|-------------------|--------|---------------------------|------------------------|-----------------|-------------------------------|
| 1       | 45  | M   | None        | Pulmonary         | NOS    | Primary therapy           | 180                    | Presumed persistence | Stable Failure               |
| 2       | 43  | M   | Polycythemia vera | Meningitis        | C. neoformans | Intolerance to 11 days of AMB-d | 180                    | Sterile CSF day 11   | Partial success              |
| 3       | 54  | F   | None        | Pulmonary and meningitis | C. gattii | Primary therapy           | 181                    | Sterile CSF day 14   | Partial success              |
| 4       | 69  | F   | Bladder CA  | Pulmonary         | C. neoformans | Primary therapy           | 182                    | Presumed eradication | Partial success              |
| 5       | 34  | F   | None        | Pulmonary and meningitis | C. gattii | Primary therapy           | 176                    | Sterile CSF day 165  | Complete success              |
| 6       | 20  | F   | None        | Pulmonary, meningitis and blood | C. gattii | Refractory to 16 days of AMB | 181                    | Presumed eradication | Partial success              |
| 7       | 66  | M   | Heart transplant pulmonary/ CNS nocardiosis | Bone, skin and soft tissue | C. neoformans | Intolerance to 17 days AMB | 6                      | Presumed persistence | Death – progression (Day 7)               |
| 8       | 79  | M   | NSCLC       | Pulmonary         | NOS    | Primary therapy           | 75                     | Presumed eradication | Complete success              |
| 9       | 68  | M   | Interstitial lung disease | Meningitis        | C. neoformans | Primary therapy           | 25                     | CSF sterile day 24   | Stable failure              |

Abbreviations: AMB, amphotericin B; AMB-d, amphotericin B deoxcholate; CA, cancer; CNS, central nervous system; CSF, cerebrospinal fluid; DRC, data-review committee; EOT, end of therapy; ISAV, isavuconazole; NOS, not otherwise specified (species identification not performed); NSCLC, non-small cell lung cancer.

| Plasma Isavuconazole Concentrations |
|-------------------------------------|
| On day 7 median levels were 3.2 µg/mL (range 0.61–5.05 µg/mL), day 14 median levels were 3.86 µg/mL (range 0.88–5.98 µg/mL), day 28 median levels were 4.01 µg/mL (range 0.78–7.80 µg/mL), and assumed steady-state median levels were 4.05 µg/mL (range 1.09–8.96 µg/mL). |

DISCUSSION
This study demonstrates that ISAV has antifungal activity as both primary and salvage therapy in patients with cryptococcosis and dimorphic fungal infections. A successful response to therapy

| Table 3. Number and Percentage of Patients With Treatment-related Adverse Events |
|----------------------------------------|
| Adverse Event | Total (N = 38) N (%) |
|-------------|---------------------|
| Overall     | 14 (36.8)          |
| Vomiting    | 3 (7.9)             |
| Phlebitis   | 4 (10.5)            |
| Diarrhea    | 2 (5.3)             |
| Nausea      | 2 (5.3)             |
| Chest pain  | 2 (5.3)             |
| GGT elevation | 2 (5.3)         |
| Paresthesia | 2 (5.3)             |
| Somnolence  | 2 (5.3)             |

Alopecia, headache, dizziness, dyspnea, abdominal pain, palpitations, xerosis, seizure, insomnia, dyspnea, asthenia, epistaxis, injection site hemorrhage, injection site pain, back pain, musculoskeletal pain, liver disorder, hepatomegaly, schistosomiasis, depression each occurred once.

Abbreviation: GGT, gamma-glutamyl transferase.

* a Patients may have experienced >1 of each type of treatment-related adverse event.
* b No patients required treatment discontinuation or alteration due to adverse events.
was seen in 24/38 (63%) of all patients at the end of therapy and an overall 89% (34/38) survival rate. The majority of patients treated in this study received ISAV as primary therapy and a successful response was observed in patients with pulmonary, non-CNS dissemination, and CNS infections. Although patient numbers were small, this study found that both *C. neoformans* and *C. gattii* responded similarly to ISAV, and this agent was successfully used in the management of cryptococcal meningitis. In patients refractory to or unable to tolerate prior antifungal therapy, 60% (3/5) exhibited a successful response to ISAV suggesting a potential role for this antifungal agent in the salvage setting as well.

ISAV concentrations in the cerebrospinal fluid (CSF) and brain have been evaluated in animal models and as compassionate-use therapy during the *Exserohilum* fungal meningitis outbreak [22]. Data from these patients showed CSF levels of 29–131 ng/mL with CSF/bloodstream ratios similar to those observed with posaconazole and itraconazole [23, 24]. Despite CSF levels lower than those seen in the blood, efficacy in the treatment of CNS infections has been observed in several murine models of infection and brain/plasma ratios of 1.96 have been found in a rat model, suggesting ISAV may be concentrated in brain tissue [25]. Additionally, ISAV is equivalent to voriconazole in the reduction of brain fungal burden during the treatment of *Candida* infections [26], equivalent to L-AMB in a model of pulmonary and CNS *Rhizopus* infection [11], and as effective as fluconazole in a model of cryptococcal meningitis [27]. Cumulatively, these findings and our early results from human cryptococcal infections suggest a potential role for ISAV in the treatment of CNS mycoses.

The heterogeneity of these mycoses, including differences in the host severity of illness, site of infection, concurrent medications, antifungal drug costs, and comorbidities plays a major role in the selection of an antifungal agent for treatment. AMB formulations are frequently prescribed for patients with severe manifestations of endemic mycoses while fluconazole, posaconazole, or voriconazole are reserved for those with mild-to-moderate disease or as “step-down” therapy following a response or intolerance from induction AMB [1, 4–7]. Significant differences do exist between the triazoles with regard to efficacy, pharmacokinetics and pharmacodynamics, drug–drug interactions, and toxicity [28] and balancing these concerns, particularly for patients necessitating prolonged therapy, can be difficult.

Fluconazole, with limited potency, has a minor role in the treatment of blastomycosis, paracoccidioidomycosis, and histoplasmosis, and higher doses are frequently necessary for effectiveness against coccidioidomycosis [5–8]. It is generally used in cryptococcosis during either low burden infections or in non-CNS infections. There are patient tolerability and absorption concerns with itraconazole [9], and there are limited data on the efficacy of posaconazole in the treatment of blastomycosis and paracoccidioidomycosis. Voriconazole has been demonstrated to be effective in the treatment of these endemic fungi [29–31]. However, drug-drug interactions and concerns with long-term use are common during treatment [32, 33] and combined with limited clinical experience make this triazole an uncertain choice.

ISAV offers potential advantages over these agents. Lower MICs have been described with ISAV compared to fluconazole against a number of these pathogens [13]. Additionally, ISAV can be taken with or without food [17], interpatient pharmacokinetic differences appear minimal [18], and fewer side-effects have been found compared to voriconazole in a recently completed phase 3 study of invasive aspergillosis [15]. Further evaluation of ISAV in the treatment of these mycoses is needed, however, the potential advantages over existing agents is encouraging and this study supports further evaluation of this new triazole.

None of the patients reported here were discontinued from the study drug primarily due to an AE. Thirty of the patients received ISAV for >175 days suggesting long-term therapy, which is often indicated in the treatment of these mycoses, is tolerable.

The nonrandomized nature of this study limits the ability to precisely compare the efficacy and safety of ISAV directly to other triazoles used during treatment of these mycoses. However, the response rate observed in this study is similar to those previously reported for fluconazole, itraconazole, posaconazole, and voriconazole in the treatment of endemic mycoses [30, 31, 34–38]. The low number of patients enrolled with blastomycosis also merits future evaluation in the treatment of this infection. Other groups not included in this study, such as patients with coccidioidal meningitis, sporotrichosis, and infection with *Talaromyces marneffei* (formerly *Penicillium marneffei*) could be examined in future studies.

In summary, ISAV was effective in the treatment of this cohort of patients with cryptococcosis and dimorphic fungal infections and the observed outcomes in these patients suggest

### Table 4. Susceptibility of Endemic Fungi Infecting Patients With Primary Disease, Refractory or Intolerant to Treatment per Clinical and Laboratory Standards Institute Standards

| Species                              | MIC Range (µg/mL) |
|--------------------------------------|-------------------|
| Cryptococcus spp.                     | ISAV   | VRC    | POS    | AMB    |
| C. neoformans (n = 6)                | 0.008–0.12 | 0.03–0.25 | 0.03–0.25 | 0.06–1.0 |
| C. gattii (n = 7)                    | 0.008–0.12 | 0.03–0.06 | 0.03–0.12 | 0.5–1.0  |
| Coccioididetes immitis (n = 8)       | 0.06–0.12  | 0.06–0.06 | 0.06–0.25 | 0.5–0.5  |
| Histoplasma capsulatum (n = 2)       | 0.03–0.03  | 0.06–0.25 | 0.06–0.12 | 0.12–0.12 |
| Paracoccidioides brasiliensis (n = 1)| 0.001–0.001 | 0.03–0.03 | 0.03–0.03 | 0.25–0.25 |

Abbreviations: AMB, amphotericin B; ISAV, isavuconazole; MIC, minimum inhibitory concentration; POS, posaconazole; VRC, voriconazole.

*a* Thirteen Cryptococcus isolates were collected from 9 patients. Blastomyces isolates were not available for susceptibility testing.
that it is a welcome addition to the limited antifungal armamentarium for clinicians dealing with these mycoses.

**Supplementary Data**

**Supplementary materials** are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the author, so questions or comments should be addressed to the author.

**Notes**

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**References**

1. Kaufman CA. Endemic mycoses: blastomycosis, histoplasmosis, and sporotrichosis. Infect Dis Clin North Am 2006;20:645–62.
2. Sabitti W, May RC. Mechanisms of infection by the human fungal pathogen Cryptococcus neoformans. Future Microbiol 2012;7:1297–313.
3. Lortholary O, Denning DW, Dupont B. Endemic mycoses: a treatment update. J Antimicrob Chemother 1999;43:321–31.
4. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2010;50:291–322.
5. Galgiani JN, Ampel NM, Blair JE, et al. Coccidioidomycosis. Clin Infect Dis 2005;41:1217–23.
6. Chapman SW, Dismukes WE, Proia LA, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis 2008;46:1801–12.
7. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis 2007;45:807–25.
8. Shikani-Yasuda MA, Telles Filho Fde Q, Mendes RP, Colombo AL, Moretti ML. Cryptococcosis in paracoccidioidomycosis. Rev Soc Bras Med Trop 2006;39:297–310.
9. Andes D, Pascual A, Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. Antimicrob Agents Chemother 2009;53:24–34.
10. Lepak AJ, Marchillo K, VanHecker J, Andes DR. Isavuconazole (BAL41815) pharmacodynamic target determination in an in vivo murine model of invasive pulmonary aspergillosis against wild-type and cyp51 mutant isolates of Aspergillus fumigatus. Antimicrob Agents Chemother 2013;57:5284–9.
11. Luo G, Gebremariam T, Lee H, Edwards JE Jr, Kovanda I, Ibrahim AS. Isavuconazole therapy protects immunosuppressed mice from mucormycosis. Antimicrob Agents Chemother 2014;58:2450–3.
12. Lepak AJ, Marchillo K, VanHecker J, Diekema D, Andes DR. Isavuconazole pharmacodynamic target determination for Candida species in an in vivo murine disseminated candidiasis model. Antimicrob Agents Chemother 2013;57:5642–8.
13. Thompson GR III, Wiederhold NP. Isavuconazole: a comprehensive review of the spectrum of activity of a new triazole. Mycospathologia 2010;170:291–313.
14. Thompson GR III, Wiederhold NP, Fothergill AW, Valler AO, Wicke BL, Patterson TF. Antifungal susceptibilities among different serotypes of Cryptococcus gattii and Cryptococcus neoformans. Antimicrob Agents Chemother 2009;53:309–11.
15. Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mold disease caused by Aspergillus and other filamentous fungi (SUREC): a phase 3, randomised-controlled, non-inferiority trial. Lancet 2016;387:760–9.
16. Marty FM, Ostrosky-Zeichner L, Corneley OA, et al. Isavuconazole treatment for mucormycosis: open-label trial and contemporaneous case-control analysis. Lancet Infect Dis 2016; doi.org/10.1016/S1473-3099(16)00071-2.
17. Schmitt-Hoffmann A, Desai A, Kowalski D, Pearlan H, Yamazaki T, Townsend R. Isavuconazole absorption following oral administration in healthy subjects is comparable to intravenous dosing, and is not affected by food, or drugs that alter stomach pH. Int J Clin Pharmacol Ther 2016; In press.
18. Desai A, Kowalski L, Kowalski D, Lu Q, Townsend RW. Isavuconazole (ISA) population pharmacokinetic modeling from phase 1 and phase 3 clinical trials and target attainment analysis. Washington, DC: Inter society Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 5–9 September 2014. Poster A-697.
19. Isavuconazole [package insert]. Northbrook, IL: Astellas Pharma US, Inc. revised 2015.
20. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008;46:1813–21.
21. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard—Third Edition. CLSI document M27-A3. Wayne, PA: Clinical and Laboratory Standards Institute.
22. Everson N, Smith J, Garner D. Successful treatment of contaminated epidural steroid associated fungal meningitis with isavuconazole. Copenhagen, Denmark: European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), 25–28 April 2015. Poster P0231.
23. Wiederhold NP, Pennick GJ, Dorsey SA, et al. A reference laboratory experience of clinically achievable voriconazole, posaconazole, and itraconazole concentrations within the bloodstream and cerebral spinal fluid. Antimicrob Agents Chemother 2014;58:424–31.
24. Ketheriddy S, Andes D. CNS pharmacokinetics of antifungal agents. Expert Opin Drug Metab Toxicol 2007;3:573–81.
25. Schmitt-Hoffmann AF, Richter WF. Isavuconazole is widely distributed in rat tissue. London, UK: ECCMID, 31 March–3 April 2012. Poster F063.
26. Majithya J, Sharp A, Parmar A, Denning DW, Warn PA. Efficacy of isavuconazole, voriconazole and fluconazole in temporarily neutropenic murine models of disseminated Candida tropicalis and Candida krusei. J Antimicrob Chemother 2009;63:161–6.
27. Najvar LK, Wiederhold NP, Bocanegra R, Olivo M, Kirkpatrick WR, Patterson TF. Isavuconazole is effective for the treatment of experimental cryptococcal menigitis. ICAAC, 5–9 September 2014. Poster M-427.
28. Dodd SL, Ashley ES, Lewis R, Lewis JS, Martin C, Andes D. Pharmacology of systemic antifungal agents. Clin Infect Dis 2006;43:528–39.
29. Freifeld A, Proia L, Andes D, et al. Voriconazole use for endemic fungal infections. Antimicrob Agents Chemother 2009;53:1648–51.
30. Queiroz-Telles F, Goldani LZ, Schlamm HT, Goodrich JM, Espinel-Ingroff A, Shikanai-Yasuda MA. An open-label comparative pilot study of oral voriconazole.
and itraconazole for long-term treatment of paracoccidioidomycosis. Clin Infect Dis 2007; 45:1462–9.

31. Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. Clin Infect Dis 2003; 36:1122–31.

32. Moon WJ, Scheller EL, Suneja A, et al. Plasma fluoride level as a predictor of voriconazole-induced periostitis in patients with skeletal pain. Clin Infect Dis 2014; 59:1237–45.

33. Williams K, Manoh M, Chin-Hong P, Singer J, Arron ST. Voriconazole-associated cutaneous malignancy: a literature review on photocarcinogenesis in organ transplant recipients. Clin Infect Dis 2014; 58:997–1002.

34. Galgiani JN, Catanzaro A, Cloud GA, et al. Comparison of oral fluconazole and itraconazole for progressive, nonmeningeal coccidioidomycosis. A randomized, double-blind trial. Mycoses Study Group. Ann Intern Med 2000; 133:676–86.

35. Kim MM, Vikram HR, Kusne S, Seville MT, Blair JE. Treatment of refractory coccidioidomycosis with voriconazole or posaconazole. Clin Infect Dis 2011; 53:1060–6.

36. Pitisuttithum P, Negroni R, Graybill JR, et al. Activity of posaconazole in the treatment of central nervous system fungal infections. J Antimicrob Chemother 2003; 56:745–55.

37. Dismukes WE, Bradsher RW Jr, Cloud GC, et al. Itraconazole therapy for blastomycosis and histoplasmosis. NIAID Mycoses Study Group. Am J Med 1992; 93:489–97.

38. Naranjo MS, Trujillo M, Munera MI, Restrepo P, Gomez I, Restrepo A. Treatment of paracoccidioidomycosis with itraconazole. J Med Vet Mycol 1990; 28:67–76.