Title

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Journal

Clinical Infectious Diseases, 76(12)

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Publication Date

2023-06-16

DOI

10.1093/cid/ciad146

Peer reviewed

Clinical Infectious Diseases

BRIEF REPORT

Isavuconazole in the Treatment of Chronic Forms of Coccidioidomycosis

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Coccidioidomycosis is a fungal infection with a range of clinical manifestations. Currently used antifungal agents exhibit variable efficacy and toxicity profiles that necessitate evaluation of additional therapeutic options. Improvement was observed in the majority of patients treated with isavuconazole, with clinical failures observed only in those with coccidioidal meningitis.

Keywords. antifungal; treatment; *Coccidioides*; Valley fever; isavuconazonium.

Coccidioidomycosis is a fungal infection caused by *Coccidioides immitis* or *Coccidioides posadasii* [1]. These soil-dwelling dimorphic pathogens reside in the soil of California, Arizona, parts of Washington, Nevada, New Mexico, Texas, throughout Mexico, and Central and South America [2]. Clinically apparent illness typically manifests as a subacute process known as "Valley fever" (primary pulmonary infection) with symptoms of cough, fever, chills, dyspnea, and fatigue [3]. Chronic disease, including chronic pulmonary disease and disseminated infection, may develop in a subset of patients [4].

Isavuconazole offers potential advantages over other triazoles commonly used for coccidioidomycosis (eg, fluconazole, itraconazole). Isavuconazole exhibits low minimum inhibitory concentrations (MICs) against *Coccidioides*, excellent bioavailability, fewer drug–drug interactions, and a lower adverse event rate than comparators [5]. There are limited patient-level data regarding the in vivo efficacy of isavuconazole in the treatment of coccidioidomycosis [6, 7]. We report the experience of 2 high-volume coccidioidomycosis centers in the treatment of patients with coccidioidomycosis who received isavuconazole.

METHODS

Patients with coccidioidomycosis who received isavuconazole were identified by cross-indexing *International Classification of Diseases, Ninth Revision, Clinical Modification*, and *International Classification of Diseases, Tenth Revision, Clinical Modification*, codes from patients at Kern Medical Center (Bakersfield, California) and the University of California–Davis Medical Center (Sacramento, California) with pharmacy databases (2016–2021). Patients were included if they had ≥30 days of isavuconazole therapy with subsequent clinical follow-up. Data related to 9 of the included patients (meningitis only) have been previously published, although their treatment courses and duration of follow-up are expanded here [6]. Abstracted data included demographic and clinical information; laboratory, serologic, and radiographic studies; microbiology, pathology, and serologic results; prior antifungal regimens; durations of therapy; and any adverse events that necessitated a change in therapy.

Responses to isavuconazole therapy were measured using a modified Mycoses Study Group (MSG) coccidioidomycosis scoring system as described previously (Supplementary Table 3) and adjudicated by 3 authors [8]. This scoring system combines clinical, radiographic, and serologic data to evaluate a therapeutic response to antifungal therapy and includes additional variables for those with coccidioidal meningitis. Each patient was assigned a composite score at the time of isavuconazole initiation and the last available follow-up appointment, at the completion of therapy, or when there was a change in therapy.

An improved outcome was defined as 1 of the following: >50% improvement (as reflected by a lower MSG score after isavuconazole therapy), the unequivocal documentation of clinical improvement as recorded in the medical record by the treating physician, or a 25%–49% decrease in the MSG score and a physician's impression of improvement as recorded on the progress note. A stable outcome was defined as an unchanged MSG score or a score that declined by <25% by the end of the follow-up. A worsened outcome was defined as 1 of the following: the MSG score increased (reflecting progressive infection), progress notes reported relapsed or progressing infection, or patients stopped therapy because of intolerance. When retrospective data were unavailable or not completed, the MSG score was modified and included only the sum of points available at the initial and final visits. Simple descriptive statistics were used to summarize the data. Continuous

Received 20 December 2022; editorial decision 27 February 2023; published online 11 March 2023

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Clinical Infectious Diseases® 2023;76(12):2196–9

https://doi.org/10.1093/cid/ciad146

variables were reported as medians and interquartile ranges, and categorical variables were reported as percentages. Changes in ordinal data from the MSG scores were analyzed using the Wilcoxon signed-rank test. $P < .05$ was considered statistically significant. The University of California–Davis Medical Center and Kern Medical Center institutional review boards approved this study.

RESULTS

Eighty-two patients met the criteria for inclusion (Table 1). The median age was 52.5 years (range, 22–86). The majority of patients were male (58 of 82, 71%), and diabetes was the most frequent comorbid condition (30 of 82, 37%), while no comorbidity was seen in 49 of 82 (60%) patients. More than half of the patients exhibited isolated pulmonary involvement (31 of 82, 38%; chronic pulmonary disease and/or cavitary disease). Dissemination with bone and joint disease (11 of 82, 13%), skin/abscess/soft tissue infection (3 of 82, 4%), noncentral nervous system (CNS) multisite dissemination (3 of 82, 4%), CNS dissemination alone (28 of 82, 34%), and CNS with multisite dissemination (6 of 82, 7%) were also seen. Prior antifungal treatment included liposomal amphotericin B, fluconazole, itraconazole, voriconazole, and posaconazole. Reasons for a therapeutic change to isavuconazole included (some patients changed for more than 1 reason) medication intolerance (76 of 82, 93%), coccidioidomycosis refractory to prior antifungal therapy (52 of 82, 63%), and other (24 of 82, 29%; Supplementary Tables 1 and 2).

Table 1. Clinical Characteristics of Patients Who Received Isavuconazole for the Treatment of Refractory or Intolerant Coccidioidomycosis

Characteristic	Isavuconazole (n = 82)	Percent
Median age, y	52.5 (22–86)	…
Male	58	71
Female	24	29
Comorbidity		
None	49	60
HIV with CD4 count >200 cells/microliter	3	4
HIV with CD4 count <200	0	0
Diabetes	30	37
Immunosuppressive medications	0	0
Transplant	0	0
Coccidioidomycosis site[a]		
Lung	45	55
Joint/Bone	14	17
Meningitis	32	39
Skin/Soft tissue	7	9
Prior antifungal treatment[b]		
Amphotericin	23	28
Amphotericin (intrathecal)	1	1
Fluconazole	73	89
Voriconazole	31	38
Itraconazole	10	12
Posaconazole	13	16
Prior antifungal discontinuation reason		
Medication intolerance	76	93
Refractory	52	63
Other[c]	24	29
Outcome[d]		
Improved	57	70
≥50% decrease in MSG score	45	55
25%–49% decrease in MSG score	12	15
Stable/No change	17	21
Worsened	8	10[e]

Abbreviations: HIV, human immunodeficiency virus; MSG, Mycoses Study Group.

[a]Some patients had more than 1 site of infection.

[b]Some patients received more than 1 type of antifungal therapy in combination or as sequential therapy before initiation of treatment.

[c]See Supplementary Table 1 for events of interest.

[d]No patients died during the follow-up period.

[e]Five patients with meningitis worsened on isavuconazole therapy, and 3 patients experienced drug toxicity despite clinical stability or improvement.

The majority of patients experienced a decrease in their MSG score following the initiation of isavuconazole therapy (median MSG score change across all patient groups, 7 → 2, $P < .0001$). The treating physicians' assessments were 100% concordant with MSG score changes over time, likely due to the long duration of longitudinal care for these patients where responses to therapeutic changes could easily be observed. Overall improvement was noted in 57 of 82 (70%) patients, while no change was observed in 17 of 82 (21%) and in 8 of 82 (10%) with worsening coccidioidomycosis following a change to isavuconazole.

Prior antifungal therapy courses were extensive with the median course of therapy over 6 months for all patient groups (Table 2). The duration of follow-up available for isavuconazole therapy was also prolonged with a median treatment duration for all patients of 897 days (interquartile range, 416–1308). Responses to isavuconazole therapy were observed across all patient groups including those with meningitis. Improvement response was most frequently observed in those with skin/soft tissue disease (3 of 3, 100%), followed by those with isolated pulmonary infection (24 of 31, 77%). Isavuconazole was discontinued due to cost/insurance issues in 6 patients (5 had improved and 1 had worsened at the time of discontinuation) and in 3 secondary to possible adverse events (1 each: palpitations, transaminitis, and hot flashes; 2 of these patients had no change in their MSG score, while 1 had improved). All other failures (n = 5) occurred solely in patients with meningitis.

DISCUSSION

Coccidioidomycosis represents a spectrum of diseases that range from asymptomatic acquisition with resultant immunity to widely disseminated and life-threatening diseases. The associated mortality of coccidioidomycosis in the pre-antifungal era was significant, with mortality rates >95% in those with infection of the CNS, approximately 30% in those with non-CNS

Table 2. Treatment of Patients With Salvage Isavuconazole Treatment for Coccidioidomycosis

	Duration of Treatment, Median (IQR), d		Mycoses Study Group Score, Median (IQR)		Response		
Location of Infection	Prior Treatment	Salvage Treatment With Isavuconazole[a]	Baseline for Salvage Treatment	Last Evaluation of Salvage Treatment	Overall Improved Response, No. (%)	No Change, No. (%)	Worsened, No. (%)
Pulmonary (n = 31)	730 (300–1129)	773 (403–1174)	5 (2–9)	0 (0–2)	24 (77)	5 (16)	2 (6)
Bone/Joint (n = 11)	180 (127–618)	716 (213–1426)	6 (2–13)	3 (0–6)	6 (55)	5 (45)	…
Skin/Soft tissue (n = 3)	240	549	10	1	3 (100)	…	…
Non-CNS multisite dissemination (n = 3)	180	1249	12	4	2 (67)	1 (33)	…
CNS (n = 28)	397 (75–848)	1042 (632–1504)	8 (5–11)	4 (2–6)	20 (71)	3 (11)	5 (18)
CNS multisite dissemination (n = 6)	1242 (210–2759)	1124 (409–2086)	6 (1–9)	3 (1–6)	2 (33)	3(50)	1 (17)

Abbreviations: CNS, central nervous system; IQR, interquartile range.

[a]There were 58 of 82 patients who remained on isavuconazole with plans for continuation of therapy at the time of data review.

disseminated coccidioidomycosis, and 6.5% in those with cavitary disease [4, 9].

Advances in antifungal therapy have significantly improved outcomes for patients with severe or chronic forms of coccidioidomycosis. The development of amphotericin B in the 1950s was life-saving for many, followed by miconazole and ketoconazole, although these suffered from low efficacy and adverse reactions that limited their utility in treatment and have since been supplanted by other antifungal agents [10, 11]. The development of fluconazole was a significant advance and revolutionized the treatment of coccidioidomycosis, particularly meningeal disease. More recently, the mold-active triazoles (itraconazole, posaconazole, and voriconazole) have been developed and demonstrated activity in clinical coccidioidomycosis cases; however, therapeutic failure and toxicity concerns remain [11].

Fluconazole and itraconazole are the agents most frequently prescribed for the various manifestations of coccidioidomycosis. However, elevated *Coccidioides* fluconazole MICs [12] are common, suggesting alternative agents may be more efficacious. Tolerability concerns with the long courses of therapy often required in chronic coccidioidomycosis are also frequently encountered with more than 50% of patients undergoing treatment with fluconazole for coccidioidomycosis experiencing adverse effects (eg, xerosis, 16%; alopecia, 16%; fatigue, 11%) and a therapeutic intervention in 65% of patients [13]. Itraconazole exhibits variable absorption, and food/acidity requirements are problematic for patients to maintain long term. Voriconazole has been associated with cutaneous photosensitivity, fluorosis, malignancy [14], hepatotoxicity, and interpatient pharmacokinetic variability. Posaconazole solution similarly exhibits dietary requirements and absorption concerns that limit patient compliance and bioavailability, while the delayed-release formulation has been associated with pseudohyperaldosteronism [15].

Isavuconazole exhibits several attributes that make it an attractive choice in the treatment of invasive fungal infections including coccidioidomycosis. Isavuconazole offers a long half-life and shortens the QTc interval (compared with the QTc prolonging effects of other triazoles). It is available in both intravenous and oral formulations. Therapeutic drug monitoring during treatment with isavuconazole may not be indicated given the excellent bioavailability (approximately 98%) that is unchanged by food intake. However, in cases of severe infection, in cases when compliance is questioned, or when patient symptoms suggest isavuconazole-associated adverse events are present, assessment of plasma drug concentrations may be useful [5].

Prior experience with isavuconazole in the treatment of coccidioidomycosis is limited. In vitro susceptibility testing of *Coccidioides* isolates has shown low isavuconazole MICs (range, 0.125–1 μg/mL; MIC_{50}, 0.25 μg/mL; MIC_{90}, 0.5 μg/mL) [16]. These in vitro results have translated into in vivo efficacy in a murine model of disseminated coccidioidomycosis where improved survival and reduced fungal burdens were observed with isavuconazole treatment [17]. A phase 3 open-label study evaluating isavuconazole in the treatment of cryptococcosis and endemic mycoses enrolled 9 patients with primary pulmonary coccidioidomycosis of whom all exhibited a clinical response at the end of therapy adjudicated by the data review committee [7].

These results are promising and extend the number of antifungals with potential activity in chronic coccidioidomycosis. Patients treated with isavuconazole salvage therapy were highly treatment-experienced. Although their MSG scores before isavuconazole therapy suggest they had evidence of active coccidioidal infection, the potential for survivor bias and the retrospective nature of the study are potential limitations. Failures were noted only in the patients with the meningeal disease, further reiterating the need for new therapeutic options in these patients with the most morbid form of coccidioidomycosis.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The funders had no role in the manuscript's design, data acquisition, or preparation.

Financial support. This work was supported by Astellas. Partial support was provided by the Burden Family Gift Fund for Coccidioidomycosis Research at the University of California–Davis Medical Center and the National Institutes of Health (NIH; 5U19AI166798).

Potential conflicts of interest. G. R. T. has served as a consultant and received research support from Astellas, Amplyx, Cidara, F2G, Mayne, and Scynexis. R. S. has received research support from Astellas. The Valley Fever Institute received research support from Astellas, F2G, and NIH. All remaining authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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