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Graded isavuconazole introduction in a patient with voriconazole allergy

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Abstract:

Triazole antifungal drugs may rarely cause serious allergic reactions including angioedema. No standardized tests are available to predict cross-reactivity within the azole class and little guiding information on whether to change therapy within the class or to another class after a serious allergic reaction. Herein we report the first successful use, to our knowledge, of graded isavuconazole introduction for treatment of aspergillosis in a liver transplant recipient with severe voriconazole allergy.

Keywords:

angioedema, azole allergy, azole cross-reactivity, isavuconazole challenge, voriconazole allergy

1 INTRODUCTION

Triazole antifungal agents are important tools for treatment of systemic mycoses. Currently marketed agents include fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole (administered as the prodrug isavuconazonium sulfate). While rare, severe allergic reactions, including urticaria, angioedema, anaphylaxis, and Stevens-Johnson syndrome can pose a major problem.¹⁻³ In trial and post-marketing data, skin rashes accounted for approximately 17% of

adverse drug reactions from voriconazole, with the most common forms being erythema and maculopapular exanthema, then urticaria and bullous and blistering eruptions.⁴ It is not clear whether patients in such circumstances should avoid further azoles or be placed on other agents within the class. For fungal infections with limited therapeutic options, use of alternative agents may expose patients to additional toxicity, increased costs, and requirement for intravenous infusion.⁵

Cross-allergenicity within the azole class remains poorly understood, with available information based mostly on case reports (see Table 1^{2,6-19}). Some patients have tolerated a switch to other triazoles,⁶⁻¹⁰ while others have had recurrent allergic reactions with introduction of a new azole.^{6,11} The most commonly reported substitutions after azole allergy have been fluconazole for itraconazole and vice versa, about which we identified seven such reports.^{6-8,10-13} Three of the seven patients demonstrated evidence of cross-allergenicity, with only one of the three able to continue treatment with use of concurrent antihistamines.^{6,11,12} Rather than a change of azoles, others have attempted re-introduction of the same triazole via graded challenge following an allergic reaction.^{2,14-18} Isolated attempts at skin prick testing have not consistently proven to be predictive of immunoglobulin E-mediated allergic response to azoles^{10,13,16,17} and intradermal and patch testing for delayed adverse drug reaction has been inconsistent,^{7,13} leaving no reliable predictors of azole allergy. Skin testing is also complicated by additives in some formulations, which may cause a positive reaction or interfere with preparation of dilutions, such as cellulose or dye in fluconazole tablets, sugar coating on itraconazole, or water in intravenous voriconazole.¹⁸

Desensitization is one option that has facilitated continued use of azole antifungals in patients who have had allergic reactions (Table 1). Use of desensitization protocols has been reported for multiple antifungal agents, but not for isavuconazole. To address this gap in the literature, we report our experience with a liver transplant recipient who had pulmonary aspergillosis and in whom we successfully used increasing graded doses of isavuconazole after she developed voriconazole-induced angioedema.

2 CASE PRESENTATION

A 48-year-old woman with a past medical history of bronchitis, asthma, cigarette use, marijuana use, and hepatitis B cirrhosis for which she underwent orthotopic liver transplantation at age 23, presented with nearly 2 years of weight loss and cough. Computed tomography scan showed pulmonary nodules. Biopsy of one of the nodules showed hyphae consistent with *Aspergillus* species. She was treated with oral voriconazole 300 mg twice daily until, on day 11 of therapy, she woke from sleep with swelling of her tongue, lips, cheeks, and eyes. She denied experiencing pruritus, urticaria, or skin eruptions. She did not have any dyspnea associated with this episode but did find it difficult to speak. Her symptoms resolved within 5 days of discontinuation of voriconazole. Of note, voriconazole has a unique nonlinear pharmacokinetic profile, resulting in variable elimination half-life of 6-24 hours.²⁰ She had not recently introduced other new medications and her long-term home medications were unlikely to account for her new angioedema. No other family members had a history of similar reactions, and serum complement (C4) testing was negative, making hereditary angioedema less likely. Voriconazole trough was 7.5 µg/mL (upper limit of therapeutic range 5.5 µg/mL).

After a washout period of approximately 3 weeks, she was hospitalized to resume treatment. She briefly received liposomal amphotericin B, then began a graded drug challenge with isavuconazole. No recommended desensitization regimens had yet been reported for this drug, so a 5-day protocol was designed based on a voriconazole desensitization first reported by Pinto and Chan¹⁹ and utilized successfully by others⁶ (Table 2).

The patient had cardiac telemetry monitoring and subcutaneous epinephrine available at the bedside throughout her graded challenge. She tolerated the 5-day graded challenge without tachycardia or hemodynamic changes, rash or angioedema, to reach the usual adult loading dose of isavuconazonium sulfate 372 mg (equivalent to 200 mg of isavuconazole) by mouth every 8 hours for 6 doses, then has since been maintained on 372 mg by mouth daily.

At 2 months after isavuconazole challenge, she continues to tolerate full oral doses without adverse reactions. Although serum isavuconazole level monitoring is available, there are no current recommendations for monitoring or dose titration based on levels, and levels have not been checked in our patient.

3 SUMMARY AND CONCLUSIONS

Allergic reactions to azole antifungal agents pose serious dilemmas for treating clinicians. Alternative therapeutic options can be limited, carry significant toxicity, and may be available only by intravenous infusion. In addition, guidance from the literature is scant regarding whether to avoid drugs from that class altogether or try another azole.

In this report, we describe our experience using a graded isavuconazole challenge in a patient who had an allergic reaction to voriconazole. To our knowledge, this is the first reported case of challenge with isavuconazole in a patient with azole allergy. This patient had angioedema, which has previously been reported with voriconazole.³ In that report, the patient responded to antihistamines and was maintained on voriconazole. Out of concern for the potentially life-threatening nature of this reaction in our patient, we stopped voriconazole in favor of alternative therapy. We opted to use isavuconazole, which is administered as the pro-drug isavuconazonium sulfate. Like voriconazole, this drug is approved for treatment of invasive aspergillosis.²¹ With increasing doses of isavuconazole administered over a 5-day period, the patient has been able to tolerate the drug long term, without recurrence of allergic symptoms.

This report is limited by being a single case report. In addition, no reliable allergy testing is available for any azole agent, so the diagnosis of allergy is based solely on reported clinical symptoms and nonspecific laboratory markers such as eosinophilia. Nonetheless, voriconazole allergy is a rare and challenging situation and this is, to our best knowledge,

the first report of isavuconazole introduction in a voriconazole-allergic patient. Successful introduction and maintenance of isavuconazole in this patient suggests that even patients with severe allergic reaction to voriconazole may be considered for alternative therapy with isavuconazole, provided that a desensitization protocol is used.

AUTHOR CONTRIBUTIONS:

M.K.M.: Concept, patient care, chart review, literature review, drafting article; C.H.: Patient care, chart review, literature review, drafting article; S.S.: Patient care, literature review, drafting article, critical revision of article.

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TABLE 1 Literature review: Reported cases of azole desensitization or challenge

Case synopsis and azole indication	Initial azole allergy	Allergy testing	Full-dose challenge or graded-dose challenge (desensitization)	Reintroduction of azole	Outcome	Concluded cross-reactivity	Author (Reference)
41-year-old immunocompetent man with coccidioidomycosis	Fluconazole: At 17 days into therapy, developed rash, abdominal pain, nausea, and vomiting	Not reported	Full-dose challenge (Fluconazole to voriconazole, voriconazole to itraconazole) Graded-dose challenge (desensitization) (voriconazole)	Voriconazole for 4 doses (tolerated), then itraconazole used because of insurance coverage issue	Itraconazole stopped after 2 days because of worsening rash. Treated with AmB for 5 months, then, received graded voriconazole challenge of (Pinto protocol ¹⁹). Tolerated voriconazole long term.	Fluconazole and itraconazole Lack of cross-reactivity between itraconazole and voriconazole	Benjamin Lash et al. (6)

13-year-old male with pre-B-cell acute lymphoblastic leukemia and prolonged neutropenic fever	Voriconazole: Administered in a graded challenge beginning with 1/200 th of the total dose, developed anaphylaxis at 1 mg dose.	Skin prick testing was positive with a 5-mm wheal and 10-mm flare elicited from a 1/10 dilution of intravenous concentration (5 mg/mL), despite recent corticosteroid and antihistamine administration. Test results in two controls were negative at this dilution.	Graded-dose challenge (desensitization)	Intravenous voriconazole desensitization performed over 3.5 hours with two mild skin reactions, for which he received diphenhydramine but no systemic symptoms developed.	Tolerated full dose voriconazole for a 10-day course.	n/a	Jean & Kwong (2)
30-year-old woman with recurrent vaginal candidiasis	Fluconazole: Vesicular and blistering lesions, patchy erythematous eruption	Patch tests with fluconazole 2%, ketoconazole 1%, itraconazole 2%, and voriconazole 2%, with negative results at 48 and 96 hours. Intradermal tests with fluconazole 0.002 and 0.02 mg/mL negative at 30 minutes and 24 hours.	Full-dose challenge	Oral fluconazole challenge resulted in pruritic, patchy erythema followed by confluent blistering eruptions. Oral challenge with itraconazole provoked no reaction.	Future treatment courses not reported	No cross-reactivity between fluconazole and itraconazole	González-Fernández et al. (7)

39-year-old immunocompetent woman with pulmonary cryptococcosis	Itraconazole: Urticaria and pruritus. Had previously tolerated fluconazole.	Skin testing not performed because of unknown positive and negative predictive values	Graded-dose challenge (desensitization)	Oral fluconazole desensitization, 24-hour protocol	Successful desensitization, although after her third dose at home had a pruritic, fine, nonurticarial rash that responded to a temporary increase in diphenhydramine. She remained on cetirizine and diphenhydramine during several months of fluconazole.	Fluconazole and itraconazole	Rankin & Jariwala (12)
29-year-old HIV-positive woman with cryptococcal meningitis	Fluconazole: Developed a rash within 3 minutes of first dose when treated for candidiasis 1 year prior. Now stopped AmB and flucytosine because of rash.	Not done because of recent antihistamine use and lack of standardized testing method	Graded dose challenge (desensitization)	Oral fluconazole desensitization, 48-hour protocol	Successful desensitization	n/a	Jariwala et al. (14)

Patient demographics not reported. Infection with refractory Zygomycete sinusitis and pneumonia.	Posaconazole: Hypersensitivity reaction	Not reported	Graded-dose challenge (desensitization)	Graded oral posaconazole challenge, 8-hour protocol.	Successful desensitization	n/a	Reed et al. (15)
65-year-old immunocompetent man with cerebral cryptococcosis	Fluconazole: Pruritic rash Rash improved after stopping phenytoin, then recurred 2 weeks later along with periorbital edema and right arm edema. Also had eosinophilia and an asymptomatic rise in liver enzyme tests.	Not reported	Graded-dose challenge (desensitization)	Graded oral voriconazole challenge, 5-day protocol.	Tolerated for 8 months at time of publication.	Lack of cross-sensitivity between fluconazole and voriconazole	Pinto & Chan (19)

42-year-old female with vulvovaginal candidiasis.	Fluconazole: Pruritic rash after 4 hours. Had tolerated fluconazole 1 year prior.	Skin prick test with three fluconazole dilutions was negative. Histamine skin prick was reactive as a positive control and normal saline as a negative control. Intradermal test with the same preparations gave a positive response. Patch test was negative. Oral challenge test with 1/10th standard dose was positive (rash after 12 hours).	Graded-dose challenge (desensitization)	Oral challenge test to cumulative full dose itraconazole	Tolerated itraconazole at therapeutic dose	Lack of cross-reactivity between itraconazole and fluconazole	Di Leo et al. (13)
36-year-old woman with acute lymphoblastic leukemia and pulmonary fungal infection	Itraconazole: On day 17 developed anaphylaxis (hypotension, hypoxemic shock). This recurred on days 18 and 19 after additional doses.	Not reported	Full-dose challenge	Change to full-dose intravenous voriconazole	Tolerated voriconazole	Lack of cross-reactivity between itraconazole and voriconazole.	Chen et al. (9)

63-year-old asthmatic female on inhaled and oral steroids with recurrent oral candidiasis, refractory to nystatin and clotrimazole	Fluconazole: After multiple previously tolerated courses, developed urticaria. Reintroduction caused oropharyngeal and lower airway symptoms.	Intradermal skin test was positive with 5-mm wheal/10-mm flare with a 1/1000 concentration. Intradermal skin test in an unaffected volunteer was negative.	Graded-dose challenge (desensitization)	Desensitization protocol done in an office over 3-4 hours, done on 6 occasions.	After her second desensitization, developed urticaria after 2 hours. After her fifth desensitization, developed a generalized pruritic rash after 4 hours, including a single blistered lesion. After the sixth desensitization, stopped oral prednisone and then developed a transient rash with a single blistered vesicle beginning after 4 hours. Completed a 14-day course of fluconazole after each desensitization.	n/a	Randolph et al. (16)
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65-year-old man with candidiasis	Itraconazole: Angioedema and generalized urticaria. Had previously tolerated the drug 2 years prior.	Skin prick test with itraconazole concentration of 10 mg/mL was negative.	Full-dose challenge	Double-blinded oral itraconazole administration resulted in immediate maculopapular eruption and angioedema. Double-blind oral challenge test with fluconazole and ketoconazole caused no reaction.	Not described.	No cross-reactivity between fluconazole and itraconazole, or ketoconazole and itraconazole.	Martinez-Alonso et al. (10)
53-year-old HIV-positive man with pulmonary cryptococcosis	Fluconazole: Fever and rash. Of note, had tolerated fluconazole previously for esophageal candidiasis.	Not reported	Full-dose challenge (itraconazole) Graded-dose challenge (desensitization) (fluconazole)	After resolution of rash, itraconazole introduced, led to rash and fever. Oral fluconazole desensitization, 7-day protocol	Successful desensitization. Tolerated fluconazole for 3 months at time of publication.	Fluconazole and itraconazole	Takahashi et al. (11)

30-year-old woman with asthma, eczema, persistent sinusitis who underwent ethmoidectomy with fungal balls excised and culture growth of <i>Aspergillus</i> and <i>Curvularia</i> species.	Itraconazole: Rash after 1 week Rash recurred with reintroduction of itraconazole.	Skin prick test with itraconazole 10 mg/mL was negative	Graded-dose challenge (desensitization)	Oral desensitization using the Bittleman protocol ¹⁸ with diluted solutions rather than crushed tablets.	Tolerated a 6-week course of itraconazole.	n/a	Douglas et al. (17)
36-year-old HIV-positive man with cryptococcal meningitis	Fluconazole: Rash and eosinophilia, with progression to urticaria, dyspnea and tachycardia.	Not done owing to lack of testing protocol	Full-dose challenge (fluconazole to itraconazole) Graded-dose challenge (desensitization) (fluconazole)	Tolerated itraconazole as prophylaxis for 6 months. After recurrence of cryptococcal meningitis treated with AmB induction, then did a 15-day graded fluconazole desensitization	Transient pruritic rash from days 4-6 of the desensitization that resolved despite increasing doses. Tolerated fluconazole for 4 months at time of publication.	No cross-reactivity between fluconazole and itraconazole	Craig et al. (8)
67-year-old immunocompetent woman with tenosynovitis of the left wrist caused by <i>Coccidioides immitis</i> .	Itraconazole: Pruritic rash after 6 days.	Not done because drug is coated in sugar spheres and insoluble in water (not able to prepare a suspension for test administration)	Graded-dose challenge (desensitization)	Graded oral desensitization over 270 minutes	Tolerated itraconazole for 10 months at the time of publication.	n/a	Bittleman et al. (18)

AmB, amphotericin B; n/a, not available; HIV, human immunodeficiency virus.

TABLE 2 Isavuconazole¹ graded dose challenge

Day	Dosage, route, and frequency	Ratio of dose administered to recommended adult dose
1	3.72 mg in 250 mL normal saline IV once ²	1:100
2	37.2 mg in 250 mL normal saline IV once	1:10
3	186 mg PO once	1:2
4	372 mg PO once	1:1
5	372 mg PO every 8 hours	Usual loading dose

¹ After administration as isavuconazonium sulfate via 372 mg vials or 186 mg capsules, the drug undergoes metabolism to the active form of isavuconazole at the equivalent of 200mg (per 372 mg vial) or 100mg (per 186 mg capsule).

² To prepare, reconstitute 372 mg (1 vial) with 5 mL SWFI (sterile water for injection). Then add to 250 mL normal saline bag (Bag A). For the final dose, take 2.5 mL of Bag A and add to 250 mL normal saline bag (Bag B). Bag B is then dispensed to the patient.

IV, intravenous, PO, by mouth.