

Case Report

An AIDS patient with progressive disseminated histoplasmosis was treated with itraconazole 200 mg twice daily. Progressive increase in alkaline phosphatase and alanine aminotransferase necessitated discontinuation of itraconazole during the third week of treatment.



Which triazoles are effective alternatives to itraconazole for treatment of histoplasmosis?



Answer

Evidence suggests that fluconazole is not adequate. Information about the other triazoles is insufficient to make an evidence-based choice. However, posaconazole appears to be the best alternative.

Itraconazole is the triazole of choice for treatment of histoplasmosis^[1]. A prospective clinical trial of non-immunocompromised patients reported response to therapy in all 10 patients with disseminated and 16 of 20 with chronic pulmonary histoplasmosis^[2].

The first clinical trial evaluating itraconazole in AIDS patients with disseminated histoplasmosis assessed its role for preventing relapse in patients who completed at least 15 mg/kg of amphotericin B. The study duration was 12 months, but the median follow-up was 109 weeks. Two of 42 patients (5%) relapsed, one who was nonadherent and another who withdrew from the study after 18 weeks. One patient withdrew because of hypokalemia attributed to itraconazole.

A subsequent prospective study in AIDS patients reported that 50 of 59 (85%) patients responded to treatment^[1]. Four of the six treatment failures occurred within the first 2 weeks of treatment. Two failures resulted from toxicity and one was lost to follow-up.

Itraconazole was also highly effective as consolidation therapy in AIDS patients with moderately severe or severe disseminated histoplasmosis in a randomized, double blinded prospective trial comparing liposomal amphotericin B and amphotericin B deoxycholate for 2 weeks as “induction” therapy followed by itraconazole 400 mg daily for 12 weeks as “consolidation” therapy^[3]. Two of 57 patients (4%) completing itraconazole consolidation therapy died of histoplasmosis but none discontinued itraconazole because of toxicity.

Fluconazole was evaluated in two clinical trials. The first evaluated non-immunocompromised patients with moderately severe pulmonary or disseminated histoplasmosis and reported successful outcome in 17 of 27 (63%) cases^[4]. The second trial evaluated 59 patients with AIDS who had disseminated histoplasmosis, of which 49% failed treatment

^[5]. Resistance to fluconazole developed in 10 of 17 (59%) patients who failed fluconazole treatment, table 1 ^[6]. Fluconazole is recommended only in patients who cannot take itraconazole ^{[4][7]}.

Voriconazole demonstrated in vitro activity against *Histoplasma capsulatum* superior to that of fluconazole, table 1 ^[5]. Clinical trials evaluating voriconazole for treatment of histoplasmosis have not been reported. A retrospective study reported the experience using voriconazole as “salvage” therapy in patients who were intolerant of (5 patients), failed treatment with other antifungal agents (2 patients) or other reasons (2 patients) ^[8]. Six of the patients were immunocompromised. Three patients showed improvement and six remained stable. Treatment was subsequently changed to itraconazole in one because of persistent antigenuria. It was previously reported that *Histoplasma capsulatum* isolates that developed fluconazole resistance had elevated MICs to voriconazole, table 1 ^[5]. Whether the elevated MICs will cause treatment failure in immunocompromised patients is unknown.

Posaconazole is highly active *in vitro* against *Histoplasma capsulatum* and was very effective in an experimental model of disseminated histoplasmosis in immunocompetent and immunocompromised mice ^[9]. It was also effective in a prospective clinical trial of the salvage treatment in six immunocompromised patients who failed or were intolerant of treatment with amphotericin B alone or amphotericin B followed by itraconazole, fluconazole, or voriconazole ^[10]. ^[11]. All 6 patients were classified as successful outcomes. The five intolerant patients each developed amphotericin B nephrotoxicity. None of the fluconazole resistant isolates were resistant to posaconazole (table 1) ^[5] and resistance has not been reported.

Isavuconazole is highly active in vitro against *Histoplasma capsulatum*, table 1 ^[10]. It was successful in four of seven (57%) patients with histoplasmosis in a clinical trial to evaluate treatment of rare fungal infections ^[12]. There are no reports evaluating isavuconazole in animal models or prospective studies treating humans with histoplasmosis. Structural similarity to fluconazole and voriconazole would imply potential for development of resistance ^[13]. One fluconazole resistant isolate developed a twofold increase in MIC to isavuconazole, figure 1 ^[10, 14]. Whether resistance will develop in immunocompromised patients treated with isavuconazole is unknown.

In summary, itraconazole is the preferred triazole for treatment of histoplasmosis. Treatment failure is rare in patients documented to have therapeutic blood levels. But intolerance is not uncommon and usually is associated with

elevated blood levels: dose reduction may allow continued treatment with itraconazole in some patients.

The IDSA guideline indicates that fluconazole is an alternative in patients who cannot tolerate itraconazole. However, the effectiveness of fluconazole in AIDS patients is poor: 50% relapsed.

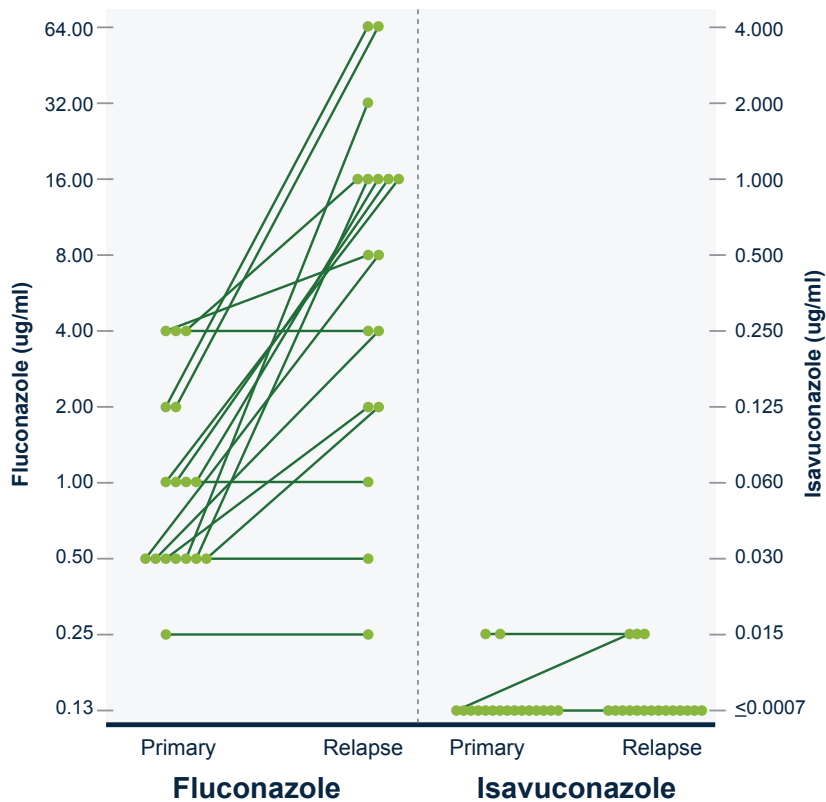
Posaconazole appears to be the best alternative to itraconazole in immunocompromised patients although clinical trials have not been conducted. But, posaconazole was highly effective in experimental models of histoplasmosis in immunocompetent and immunocompromised mice and in a small number of patients who failed treatment or were intolerant of amphotericin B.

Evidence supporting voriconazole as an alternative to itraconazole is unavailable and the increase in MIC in fluconazole resistant isolates raises concern about the potential for development of resistance to voriconazole in immunocompromised patients. Similarly, data is lacking supporting isavuconazole as an alternative to itraconazole in immunocompromised patients although the fluconazole resistant isolates did not exhibit significant increases in MIC.

Table 1. Development of resistance to fluconazole in AIDS patients treated for disseminated histoplasmosis

Primary isolate (n=17)	Percent 4-fold increase	Median MIC
Fluconazole	Not applicable	1.0 ug/ml
Posaconazole	Not applicable	≤ 0.007 µg/mL
Voriconazole	Not applicable	0.015 µg/mL
Isavuconazole	Not applicable	≤ 0.007 µg/mL
Relapse isolate (n=17)	Percent 4-fold increase	Median MIC
Fluconazole	12/17 (70.5%)	8.0 ug/ml
Posaconazole	0/17 (0%)	≤ 0.007 µg/mL
Voriconazole	8/17 (47.0%)	0.023 ug/ml
Isavuconazole	0/17 (0%)	≤ 0.007 µg/mL

Figure 1. Isavuconazole susceptibility in fluconazole susceptible and relapse isolates



MICs for the pre-treatment and relapse isolates are connected by a line for each patient. Of note, due to much lower MICs to isavuconazole, the scales for fluconazole and isavuconazole are different ^[14].

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