

# Posaconazole: A new agent for the prevention and management of severe, refractory or invasive fungal infections

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AV Page, WC Liles. Posaconazole: A new agent for the prevention and management of severe, refractory or invasive fungal infections. *Can J Infect Dis Med Microbiol* 2008;19(4):297-305.

Posaconazole is the newest antifungal agent to be approved for use in Canada. With excellent *in vitro* activity against a broad spectrum of yeasts and filamentous fungi, as well as having a well-tolerated oral formulation, posaconazole offers many potential advantages. Of particular interest are its seemingly lower potential for cross-resistance with other azoles and its activity (unique among oral antifungal agents) against the zygomycetes. As the incidence of both common and uncommon fungal infections increases commensurate with the growing population of immunocompromised individuals, posaconazole may ultimately become an important therapeutic option. The present article reviews the *in vitro* and *in vivo* data describing its activity, and focuses on both the proven and the potential clinical applications of this new triazole agent.

**Key Words:** *Aspergillosis; Candidiasis; Mucormycosis; Posaconazole; Zygomycosis*

Severe and invasive fungal infections (IFIs) are increasing in incidence. Intensive chemotherapeutic regimens, hematopoietic stem cell and solid organ transplantations, corticosteroid and biological therapies, and HIV/AIDS have all contributed to the growing number of at-risk immunosuppressed individuals. In this patient population, serious fungal infections range from recurrent and potentially debilitating infections (refractory oropharyngeal candidiasis [OPC]) to acute and potentially fatal infections (invasive aspergillosis or zygomycosis following transplantation). IFIs portend a particularly poor prognosis in certain high-risk subpopulations; in two large, retrospective studies (1,2) of allogeneic hematopoietic stem cell transplant (HSCT) recipients, attributable mortality rates varied between 20% for those patients with candidemia and 77.2% for those with invasive aspergillosis.

These studies of IFI-associated mortality were conducted either in full or in part during an era in which antifungal therapy was limited to the polyenes, such as amphotericin B, or the early generation triazoles, such as fluconazole or itraconazole. Amphotericin B, whether in the deoxycholate or lipid-based formulation, is an intravenous medication with the most diverse spectrum of activity of any antifungal agent. However, its use is associated with a high rate of infusion reactions and nephrotoxicity; progressive fungal disease has occurred in patients who were unable to complete treatment (3). In addition, fungi

## Le posaconazole : Un nouvel agent pour prévenir et prendre en charge les infections à champignons graves, réfractaires ou envahissantes

Le posaconazole est le dernier antifongique à être approuvé au Canada. Étant donné son excellente activité *in vitro* contre un large spectre de levures et de champignons filamenteux et sa formulation orale bien tolérée, le posaconazole offre de nombreux bienfaits potentiels. Notamment, il a un potentiel en apparence plus faible à l'interrésistance à d'autres azoles et une activité (unique parmi les antifongiques oraux) contre les zygomycètes. Puisque l'incidence des infections à champignons courantes et peu courantes augmente proportionnellement avec la population de personnes immunocompromises, le posaconazole pourrait bien devenir une option thérapeutique importante. Le présent article analyse les données *in vitro* et *in vivo* décrivant son activité et porte à la fois sur les applications cliniques démontrées et potentielles de ce nouveau triazole.

resistant to amphotericin B, such as *Aspergillus terreus*, have emerged as important human pathogens (4).

Although generally better tolerated than amphotericin B, particular characteristics of the early generation triazole agents also limit their use: fluconazole has no activity against certain *Candida* species and most filamentous fungi, while itraconazole has multiple drug-drug interactions and variable bioavailability, particularly in capsule form.

However, in recent years, a spate of new antifungal options, including the expanded-spectrum triazoles (such as voriconazole) and the echinocandins have emerged. Both are well-tolerated and active against most *Candida* and *Aspergillus* species. However, both also lack activity against notable causes of post-transplantation IFIs, including the zygomycetes and *Fusarium* species. Voriconazole prophylaxis in HSCT recipients has been contemporaneously associated with an increase in infections due to these organisms, which hints at the potential clinical relevance of these omissions from the spectrum of activity of any antifungal agent (5,6). In addition, case reports (7-9) have documented the emergence of echinocandin resistance during treatment of candidemia.

An appraisal of the properties of these existing agents suggests that a well-tolerated oral medication with a broad spectrum of activity against both yeasts and filamentous fungi, as well as a high barrier to the development of resistance, may

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Received for publication January 8, 2008. Accepted June 2, 2008

**TABLE 1**  
**Comparative in vitro spectra of activity of antifungal agents currently approved for use in Canada**

Pathogen	Amphotericin B	Echinocandins	FLU	ITR	VOR	POS
<i>Candida</i> species	+	+	+	+	+	+
<i>Candida glabrata</i>	+	+	-	-	+	+
<i>Candida krusei</i>	+	+	-	-	+	+
<i>Candida lusitanae</i>	+*	+	+	+	+	+
<i>Candida parapsilosis</i>	+	+/-†	+	+	+	+
<i>Cryptococcus neoformans</i>	+	-	+	+	+	+
<i>Trichosporon</i> species	+/-	-	+	+	+	+
<i>Rhodotorula</i> species	+	-	-	+	+	+
<i>Geotrichum capitatum</i>	+	+/-	+/-	+	+	+
Dimorphic fungi	+	Mould forms only	+	+	+	+
<i>Aspergillus</i> species	+	+	-	+	+	+
<i>Aspergillus terreus</i>	+/-	+	-	+	+	+
<i>Fusarium</i> species	+/-	-	-	-	+/-	+/-
<i>Scedosporium apiospermum</i>	-	-	-	-	+	+
<i>Scedosporium prolificans</i>	-	-	-	-	-	-
Zygomycetes	+	-	-	-	-	+
Dematiaceous Fungi	+/-	-	-	+	+	+

\*Resistance may develop during treatment; †The minimum concentration of posaconazole (POS) required to inhibit the growth of 90% of isolates was greater than 16 mg/L in some studies. FLU Fluconazole; ITR Itraconazole; VOR Voriconazole. Data from references 63 to 67

provide a useful therapeutic option. Approved for use in Canada in 2007, posaconazole possesses an in vitro spectrum of activity comparable with amphotericin B (Table 1), an oral formulation and a low risk of adverse events. It has been granted Health Canada approval for the treatment of OPC and refractory invasive aspergillosis, as well as for the prophylaxis of invasive aspergillosis and candidiasis in certain high-risk patient populations (10). In Europe, however, its indications for use are broader, and include refractory fusariosis, chromoblastomycosis, mycetoma and coccidioidomycosis (11). The present article reviews the evidence in support of the current Canadian indications for use of posaconazole and explores its potential clinical applications for the treatment of a wide variety of other opportunistic mycoses.

### MECHANISM OF ACTION

Similar to all triazoles, posaconazole inhibits the fungal lanosterol 14 alpha-demethylase enzyme (CYP51), a member of the cytochrome P450 family (12). In doing so, posaconazole blocks the synthesis of ergosterol, the primary sterol in the fungal cell membrane, and an important determinant of cell membrane integrity, membrane-associated protein function and progression through the cell cycle.

### PHARMACOKINETICS

Posaconazole is administered as an oral suspension at a dose of 800 mg per day; no parenteral formulation is currently available. Serum drug concentrations increase in a dose-proportional manner up to the recommended daily dose, with no further increases thereafter (13). Because high-fat meals, nutritional supplements and frequent administration all promote the absorption of posaconazole, the 800 mg dose is divided twice daily if the patient is taking enteral nutrition, and four times daily if not (14,15). In fasting individuals, the average steady-state plasma concentration is 0.5 mg/L based on four times daily dosing; it is slightly higher at 0.72 mg/L when administered twice daily with

a high-fat meal or nutritional supplement (10,15). In contrast, voriconazole administered at the recommended treatment dose of 200 mg twice daily achieves average plasma concentrations of 2.5 mg/L (16). When posaconazole was studied for antifungal prophylaxis in patients with chemotherapy-induced neutropenia or severe graft-versus-host disease, the recommended dose of 200 mg three times daily achieved a mean steady-state plasma concentration of 0.58 mg/L, albeit with a wide range of concentrations up to a maximum of 1.47 mg/L (17,18). Notably, an association between lower average plasma concentrations of posaconazole and treatment failures has been reported (19).

As a liquid suspension, posaconazole has significantly greater bioavailability than as a tablet and reaches its peak plasma concentration in 10 h (20). The volume of distribution of posaconazole, at least 10-fold greater than the total body water content, suggests a wide distribution throughout peripheral tissues. In particular, posaconazole has been shown to be at least as effective as amphotericin B in murine and human treatment trials for IFIs of the central nervous system, providing indirect evidence for drug delivery across the blood-brain barrier (21-23). Case reports (24) have also shown drug penetration into the vitreous fluid during the treatment of ocular fungal infections.

Posaconazole has a half-life of 35 h, and is eliminated unchanged through the gastrointestinal tract. Because the kidneys play a minor role in the excretion of posaconazole, no dose adjustment is necessary, even in cases of severe renal impairment (creatinine clearance lower than 20 mL/min). Consistent with the high degree of protein binding (98%), the drug is not removed by hemodialysis (25). Dose adjustments due to hepatic dysfunction have not been well studied, and many clinical trials have excluded patients with baseline elevations in serum hepatic aminotransferases.

Posaconazole's pharmacokinetic characteristics are not affected by sex, ethnicity or age (26). As with most other triazole

agents, posaconazole is categorized as pregnancy risk class C, because skeletal malformations were detected in the fetuses of pregnant rats administered 1.4 times the usual adult dose of the drug (10). In a small study (27) of children younger than 18 years of age, all of whom received 800 mg per day of posaconazole as salvage therapy for IFIs, pharmacokinetic parameters, adverse events and treatment outcomes among the children approximated those reported in adults.

Posaconazole inhibits the hepatic CYP3A4 enzyme, a member of the cytochrome P450 enzyme system; therefore, it may raise the serum concentrations of drugs with which it is coadministered, including tacrolimus and cyclosporine (28). Seizures have occasionally occurred when these drugs have been used in combination, underlining the importance of therapeutic drug monitoring (29). Likewise, the concentrations of phenytoin, rifabutin and midazolam may be increased by coadministration with posaconazole (10). Although not yet studied in vitro or in vivo, the concentrations of other CYP3A4 substrates, such as the ergot and vinca alkaloids, sirolimus, the HMG-CoA reductase inhibitors and some calcium channel blockers, may be affected by concomitant administration of posaconazole, and may therefore require dose adjustment and careful monitoring. Coadministration of posaconazole and the ergot alkaloids, or posaconazole and medications which prolong the QT interval, is not recommended (10). Posaconazole has not been found to inhibit the other P450 isoforms studied (30). Although posaconazole is both an inhibitor of and a substrate for P-glycoprotein in vitro, polymorphisms of P-glycoprotein have no effect on posaconazole disposition in vivo (10,26).

#### ANTIFUNGAL ACTIVITY IN EXPERIMENTAL MODELS, IN VITRO AND IN VIVO

Posaconazole possesses antifungal activity that is greater than, or within one dilution of, the other triazole agents and amphotericin B against yeasts, dimorphic fungi and most genera of filamentous fungi when examined in vitro (31). The minimum concentration of posaconazole required to inhibit the growth of 90% of isolates ( $MIC_{90}$ ) was 1 mg/L when tested against 18,351 yeasts and 4499 hyaline moulds. In comparison, the mean  $MIC_{90}$  values for voriconazole were 0.5 mg/L and 2.0 mg/L, respectively, when tested against the same isolates.

Posaconazole is potentially fungicidal in vitro against some species of *Candida*, *Cryptococcus neoformans*, *Trichosporon* species, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Aspergillus* species and selected dermatophytes (21,32-37). It is particularly active against yeasts. Posaconazole inhibited 97% of all *Candida* species and 98% of all *C. neoformans* isolates at a concentration of 1 mg/L in a large study (38) of over 4000 clinical specimens. The major exception occurred among isolates of *Candida glabrata*, of which 80% were inhibited at a concentration of 1 mg/L. By comparison, voriconazole inhibited 92% of *C. glabrata* isolates at the same concentration. For all other isolates tested, posaconazole was equivalent to voriconazole, inhibiting the same percentage of isolates at concentrations of 1 mg/L. In comparison with fluconazole, posaconazole inhibited a greater percentage of isolates of *C. glabrata*, *Candida parapsilosis*, *Candida tropicalis* and *Candida krusei* at a concentration of 1 mg/L (38). However, because the mean steady-state plasma concentration of posaconazole achievable in humans was below 1 mg/L, albeit with wide individual variation, these in vitro results suggest

that voriconazole may be a more reliable choice for the treatment of confirmed invasive candidiasis; the  $MIC_{90}$  value of voriconazole for most *Candida* species lies well within the average steady-state plasma concentration achieved with the recommended dosing regimen.

In contrast, posaconazole is more active in vitro against a wide variety of filamentous fungi than is voriconazole. At a concentration of 1 mg/L, posaconazole inhibited 95% of all 448 isolates of filamentous fungi tested, including the agents of chromoblastomycosis, mycetoma and phaeohyphomycosis, while voriconazole inhibited 90% of these isolates at the same concentration (39). Although approximately equivalent to voriconazole against most *Aspergillus* species, particularly the relatively amphotericin-resistant *A. terreus*, posaconazole displayed greater activity against *Aspergillus niger* (40). In addition, posaconazole was more active than voriconazole against the zygomycetes, more active than amphotericin B against *A. terreus*, and more active than both against *Penicillium* species and *Paecilomyces* species (31,39).

Despite these promising in vitro results, there are some notable gaps in the antifungal activity of posaconazole. Although it is the only triazole agent with consistent activity against the zygomycetes, posaconazole displays higher  $MIC_{90}$  values than amphotericin B for *Rhizopus*, *Mucor* and *Cokeromyces* species. In addition, posaconazole has an  $MIC_{90}$  of 16 mg/L against *Cladosporium* species, compared with 4 mg/L for amphotericin B (31). The in vitro activity of posaconazole against all *Fusarium* species is comparable with that of amphotericin B (both have mean  $MIC_{90}$  values of 32 mg/L), but the activity of both is highly species dependent. Similarly, no existing antifungal agent had an  $MIC_{90}$  value less than that of posaconazole, at 32 mg/L, for *Scedosporium prolificans*.

In vivo experimental animal models of IFIs have uniformly corroborated these in vitro findings. Posaconazole has been shown to improve survival, reduce fungal burden, or both, in disseminated candidiasis; cerebral and disseminated cryptococcosis; cerebral, pulmonary and disseminated aspergillosis; pulmonary blastomycosis; disseminated coccidioidomycosis; disseminated histoplasmosis; cerebral and disseminated phaeohyphomycosis; and disseminated pseudallescheriasis (40). Gaps in the in vivo antifungal activity of posaconazole are the same as those identified by in vitro susceptibility testing; posaconazole demonstrates dose-dependent activity in murine models of disseminated fusariosis and zygomycosis, but no activity in murine models of disseminated infection due to *S. prolificans* (40).

#### CLINICAL EFFICACY – TREATMENT TRIALS Mucosal and invasive candidiasis

Posaconazole has been most extensively studied for the treatment of mucosal candidiasis in the setting of advanced HIV disease. As primary therapy, posaconazole was compared with fluconazole (200 mg on the first day, followed by 100 mg for the next 13 days for both drugs) in a randomized, evaluator-blinded study (41) of 350 patients with OPC, most of whom were infected with fluconazole-susceptible strains of *Candida albicans*. By day 14, an equal number of patients in each group had achieved a satisfactory clinical response (cure or symptomatic improvement in 92%) or mycological cure (68%). Although more patients in the posaconazole group had a sustained mycological cure four weeks after the end of treatment, the rate of clinical relapse was not significantly different

between the two groups (31.5% in the posaconazole arm and 38.2% in the fluconazole arm).

As salvage therapy, posaconazole was evaluated in an observational study (42) of 199 patients with advanced HIV disease and OPC or esophageal candidiasis that had failed to respond to a standard duration of fluconazole or itraconazole therapy (10 days for OPC and three weeks for esophageal candidiasis). Relapsing mucosal candidiasis was a common occurrence in patients with advanced HIV disease before the advent of highly active antiretroviral therapy. With the widespread use of antiretroviral therapy, treatment-refractory mucosal candidiasis is now observed much less frequently, occurring in approximately 4% of patients with a history of OPC and with CD4 counts less than 150 cells/ $\mu$ L (43). Fluconazole-resistant *Candida* species colonize the oropharynx in 8% of fluconazole-naive patients with HIV and in 45% of fluconazole-experienced patients with HIV (43,44). In the present study of posaconazole salvage therapy, the infecting species of *Candida* was resistant to fluconazole and/or itraconazole in the majority of patients. Eligible patients received posaconazole according to a schedule of either 800 mg per day for three days followed by 400 mg per day for 25 days or 800 mg per day for 28 days. The primary end point of cure or improvement after 28 days of therapy was met in 75% of participants. Furthermore, the same degree of success was observed in the subset of patients infected with fluconazole- and/or itraconazole-resistant *Candida* species. These results are comparable with those achieved with caspofungin, the other agent approved for use in the treatment of refractory mucosal candidiasis (45). Notably, 74% of patients overall (80% receiving the low-dose posaconazole regimen and 68% receiving the standard-dose regimen) had recurrent signs and/or symptoms four weeks after the end of treatment.

To combat the high relapse rate following discontinuation of treatment, Vazquez et al (46) investigated the suitability of posaconazole (800 mg/day) for use as chronic suppressive therapy for azole-refractory mucosal candidiasis in patients with HIV. In this open-label, noncomparative study, 77 of 90 patients (85.6%) in the modified intention-to-treat population were considered to have had a complete or partial clinical response after receiving posaconazole for up to three months. Fifteen patients continued therapy for a full 12 months. Of the 28 patients who discontinued treatment at or before the three-month evaluation, 13 (46.4%) experienced a relapse within one month after discontinuing therapy. No posaconazole susceptibility data were reported on isolates from those patients who failed therapy or relapsed after discontinuation of therapy. Of those who continued treatment beyond three months, 25% experienced a treatment-related adverse event. Eight patients discontinued therapy as a result of adverse events. While the present study suggests that posaconazole is effective as chronic suppressive therapy for refractory mucosal candidiasis in the select subpopulation of patients who can tolerate long-term treatment, almost one-third of the modified intention-to-treat population discontinued therapy within three months, and almost 50% of these patients had a clinical relapse within one month of treatment discontinuation. Longer post-treatment follow-up is required to determine the true benefit, if any, of extended courses of therapy.

Nonetheless, based on the data from the primary and salvage therapy studies, posaconazole has been approved in Canada for the treatment of OPC in patients 13 years of age

and older. Posaconazole is unlikely to find immediate use as first-line therapy, however, given that fluconazole is well tolerated, inexpensive and effective for most patients. On the other hand, posaconazole's oral formulation does offer significant benefit over intravenous caspofungin for the treatment of azole-refractory mucosal candidiasis.

In contrast, posaconazole is neither approved nor well studied for the treatment of invasive candidiasis. In the largest trial (29) of posaconazole therapy involving 362 patients, of whom the majority had an underlying malignancy or had undergone hematopoietic stem cell or solid organ transplantation, 39 patients had refractory invasive candidiasis. However, details of the indications for treatment and treatment outcomes are lacking. There are two case reports (47,48) of posaconazole salvage therapy in patients with acute myelogenous leukemia – one patient had disseminated *C albicans* infection and the other had *C krusei* vertebral osteomyelitis. Both infections were successfully eradicated after prolonged posaconazole therapy (10 and 12 months, respectively). Although these reports suggest that posaconazole may also be effective as salvage therapy for invasive candidiasis, more data are needed before posaconazole gains widespread use for this indication.

#### Invasive aspergillosis

Posaconazole has also been evaluated as salvage therapy in a study of 107 patients with invasive aspergillosis, most of whom had an underlying hematologic malignancy or had undergone HSCT (19). Eighty-eight per cent of patients were considered to be refractory to conventional antifungal therapy; the majority having received either amphotericin B or itraconazole for a minimum of seven days without clinical improvement. The remainder were unable to tolerate standard therapy. Pulmonary aspergillosis was the primary diagnosis in 74% of patients. When compared with 86 matched control subjects with invasive aspergillosis who had been treated with either amphotericin B or itraconazole as salvage therapy, significantly more patients receiving posaconazole had a complete or partial response than those receiving standard salvage therapy (42% versus 26%, adjusted OR 4.06). This response was consistent regardless of the site of infection or the infecting *Aspergillus* species, but was significantly greater in the subgroup of patients who achieved average plasma drug concentrations higher than 1 mg/L as a result of coadministration of posaconazole with food or a nutritional supplement. Survival rates at both 30 days and the end of therapy also differed between the two treatment arms, being 74% and 38% in the posaconazole-treated patients, and 49% and 22% in the patients receiving standard salvage therapy, respectively.

Posaconazole was also compared directly with high-dose lipid formulation amphotericin B (greater than or equal to 7.5 mg/kg per day), as well as with a combination of high-dose lipid formulation amphotericin B and caspofungin in a retrospective study (49) of salvage therapy for proven or probable invasive aspergillosis in HSCT recipients and patients with hematologic malignancies. Primary antifungal therapy consisted of lipid formulation amphotericin B monotherapy in more than 50% of the patients, while only four of 143 patients overall, and none in the posaconazole group, received primary therapy with voriconazole. Significantly more patients in the posaconazole arm demonstrated a complete or partial response to treatment than

patients in either of the amphotericin arms when assessed at the end of therapy or after 12 weeks, whichever came first (40% versus 8% and 11% for amphotericin B alone and in combination with caspofungin, respectively;  $P < 0.01$ ). Importantly, patients in both amphotericin arms had significantly fewer days of therapy (mean duration 16 to 18 days in the amphotericin arms versus 70 days in the posaconazole arm;  $P < 0.001$ ). In addition, 15% of patients in the amphotericin monotherapy arm, and 42.1% of patients in the amphotericin and caspofungin combination arm, were infected with amphotericin-resistant *A terreus*. Any or all of these factors may have contributed to the observed superiority of posaconazole over the comparator regimens.

Nonetheless, whether secondary to greater antifungal activity or greater tolerability, these data support a role for posaconazole as second-line therapy in the treatment of immunocompromised patients with invasive aspergillosis. The results are comparable with those obtained when caspofungin monotherapy is used for this indication (50). Notably, however, few patients in either posaconazole trial had received voriconazole as primary therapy. Therefore, the role of posaconazole as a second triazole for salvage therapy in this group of patients is still unclear. In addition, there have been no human treatment trials investigating posaconazole as primary therapy for invasive aspergillosis, nor comparing it directly to voriconazole. Posaconazole, therefore, has a very specific indication for the treatment of invasive aspergillosis that is refractory to amphotericin B or itraconazole (progression or failure to improve after seven days), or that occurs in patients intolerant of these agents. It is not approved for use as first-line therapy for invasive aspergillosis.

### Other IFIs

Multiple small observational studies have been conducted to investigate the use of posaconazole as salvage therapy in less common mycoses (Table 2). As second-line therapy, posaconazole has been used successfully to treat mucormycosis, fusariosis, phaeoohyphomycosis, eumycetoma and chromoblastomycosis, histoplasmosis and coccidioidomycosis. Although the rates of clinical success, usually defined as either a partial or complete clinical response, were comparable in all studies with those achieved with accepted standard therapy, it should be noted that no study directly compared posaconazole with another antifungal agent. However, given the relative rarity of these infections, randomized trials are likely to be difficult to perform and may not be forthcoming.

There is a single published case report (51) of successful posaconazole salvage therapy for paecilomycosis in a 60-year-old man with multiple myeloma in whom chronic suppressive therapy with posaconazole facilitated successful allogeneic HSCT. Posaconazole use for the treatment of other agents of hyalohyphomycosis has not been reported.

Posaconazole is of particular interest in the treatment of mucormycosis, for which amphotericin B remains the only other therapeutic option. Although posaconazole has never been compared directly with amphotericin B in vivo, it has been evaluated as salvage therapy for mucormycosis in 91 patients, the majority of whom had an underlying hematologic malignancy or had undergone hematopoietic stem cell transplantation (52). Almost one-half of the studied patients had received prior antifungal prophylaxis with an azole, and in particular, 20% had received voriconazole.

Eighty per cent of patients received posaconazole for at least 30 days (range six to 1005 days), and 64 of 90 patients also underwent surgical debridement. Twelve weeks after initiation of posaconazole, 60% of patients had either a complete or partial response to therapy. Notably, however, only 14% of patients were considered to have had a complete response, and at least some patients were still receiving posaconazole at the time of evaluation. Nonetheless, the low risk of adverse events makes posaconazole an attractive option in the management of mucormycosis, particularly when compared with amphotericin B.

As primary therapy, posaconazole has been investigated for use in the treatment of pulmonary and disseminated (non-meningeal) coccidioidomycosis (53). While considered successful in 85% of patients at the end of treatment, chronic posaconazole therapy was often required to prevent relapse. As is frequently the case with less common IFIs, the necessary duration of treatment with posaconazole is unclear and has varied widely among published reports.

As a result of these studies, posaconazole has received approval from the European Medicines Agency for the treatment of refractory fusariosis, chromoblastomycosis, mycetoma and coccidioidomycosis (11). It is not approved in Canada or the United States for these indications.

### CLINICAL EFFICACY – PROPHYLAXIS TRIALS

Given the increasing incidence of IFIs in immunocompromised patients, the role of posaconazole as preventive therapy has also been investigated. In a randomized trial (17) of 602 patients receiving chemotherapy for either acute myelogenous leukemia or myelodysplastic syndrome, prophylaxis with either posaconazole (200 mg three times daily in 304 patients), fluconazole (400 mg once daily in 240 patients) or itraconazole (200 mg twice daily in 58 patients) was given with each cycle of chemotherapy, until either recovery from neutropenia and complete remission, or until 12 weeks following randomization. At the end of treatment, IFIs, as adjudicated by an independent review committee, had occurred in 2% of patients receiving posaconazole and 8% of patients receiving either fluconazole or itraconazole ( $P < 0.001$ ). Twenty patients receiving either fluconazole or itraconazole developed invasive aspergillosis, compared with two patients receiving posaconazole. The number needed to treat with posaconazole as compared with either fluconazole or itraconazole to prevent one IFI was 16. Patients in the fluconazole or itraconazole arms also received longer courses of systemic antifungal therapy for suspected, but not proven, IFIs. Furthermore, a 33% relative reduction in mortality 100 days after randomization was noted among patients receiving posaconazole compared with those receiving alternative prophylactic regimens. Note, however, that serious adverse events possibly related to treatment were experienced by 6% of patients in the posaconazole arm, and by only 2% in the fluconazole or itraconazole arms ( $P = 0.01$ ).

In a randomized, double-blind trial (18) of 600 patients receiving intensive immunosuppressive therapy for severe graft-versus-host disease following HSCT, four-month prophylactic regimens of posaconazole and fluconazole were found to be equivalent for the prevention of IFIs and death. However, posaconazole was superior for the prevention of invasive aspergillosis (OR=0.31) and for a reduction in deaths attributable to IFIs (1% versus 4%;  $P = 0.046$ ).

**TABLE 2**  
**Posaconazole (800 mg/day) therapy for uncommon invasive filamentous fungal infections**

Indication	Study design	Inclusion criteria	Treatment	Results
Proven mucormycosis; 46% with rhinocerebral disease (68)	Observational study of 24 patients; 11 post-HSCT	Refractory to or intolerant of standard therapy*	Posaconazole for a median duration of 182 days (range eight to 1004 days)	Complete or partial response in 79%†
Proven or probable mucormycosis (52)	Retrospective study of 91 patients, 48 with a hematologic malignancy; 11 patients also described in the study by Greenberg et al (68)	Refractory to or intolerant of standard therapy‡	Posaconazole therapy for six to 1005 days, with 80% of patients receiving at least 30 days of therapy	Complete or partial response 12 weeks after initiation of therapy in 60%, regardless of adjunctive surgical debridement†
Proven or probable invasive fusariosis (24)	Retrospective analysis of 21 patients enrolled in three open-label clinical trials; 76% with a hematologic malignancy	Refractory to or intolerant of standard therapy§	Posaconazole for up to 12 months	Complete or partial response in 48%, although less so in the subset of patients with disseminated infection, persistent neutropenia, or prior HSCT¶
Culture-proven phaeohyphomycosis (69,70)	Case reports: patient 1 – disseminated <i>Exophiala spinifera</i> infection; patient 2 – <i>Alternaria</i> species maxillary osteomyelitis	Patient 1 – refractory to months of therapy with amphotericin B and itraconazole over several years; patient 2 – refractory to voriconazole, caspofungin, amphotericin B, ketoconazole, fluconazole and terbinafine over a 12-year period	Patient 1 – posaconazole for planned duration of 24 months; patient 2 – posaconazole indefinitely	Clinical and mycological suppression in both cases; ongoing posaconazole administration required to prevent the re-emergence of active lesions in both patients**
Proven eumycetoma or chromoblastomycosis (71)	Open-label, observational study of 12 patients	Refractory to standard therapy††	Posaconazole for 168 to 1015 days	Complete or partial response in 10 patients at treatment end
Disseminated/pulmonary histoplasmosis (72)	Observational study of six patients, three with HIV disease, two receiving chronic corticosteroid therapy and one with no identifiable immunosuppression	Refractory to or intolerant of standard therapy‡‡	Posaconazole for six to 34 weeks	Complete or partial response in all six patients by treatment end; no no long-term follow-up provided
Chronic pulmonary or nonmeningeal disseminated coccidioidomycosis (53)	Open-label, phase II study of 20 patients, four with diabetes mellitus and three receiving corticosteroid therapy	Primary therapy in 70% of patients; 30% had relapsing disease but were not receiving other antifungal therapy at study entry	Posaconazole (400 mg/day) for a median duration 173 days (range 15 to 199 days)	Satisfactory response in 85% at week 24; relapse in three of nine patients after treatment end§§
Chronic pulmonary or disseminated coccidioidomycosis (73)	Open-label study of 15 patients, two with diabetes mellitus and one each post-HSCT and receiving corticosteroid therapy	Refractory to amphotericin B and/or an azole for a minimum duration of 40 days and a median duration of 306 days	Posaconazole for 34 to 365 days; 12 patients received the drug for longer than six months	Complete or partial response in 73%

\*For the majority of patients, standard therapy included amphotericin B, with or without itraconazole or caspofungin. Two patients received monotherapy with other agents (itraconazole and voriconazole); †The partial and complete response rate following amphotericin B therapy was documented at 60% (74); ‡Eighty-five per cent received lipid formulations of amphotericin B, 26% amphotericin B deoxycholate and 31% voriconazole. Patients may have received more than one antifungal agent; §Twenty patients were initially treated with amphotericin B, with or without itraconazole and/or caspofungin, for a median of eight days (range two to 38 days). One had not received any prior antifungal therapy; ¶A complete or partial response was noted in five of 11 patients (45%) with fusariosis treated with voriconazole, although details regarding dose and duration of treatment, as well as neutrophil recovery, are lacking (75); \*\*Five cases of phaeohyphomycosis due to *Alternaria*, *Bipolaris* and *Exophiala* species were reported to be successfully treated with voriconazole, although duration of therapy and adjunctive surgical procedures were not documented (75); ††Standard therapy included itraconazole, ketoconazole, terbinafine or flucytosine for a cumulative duration of two months to eight years; ‡‡Patients had received antifungal therapy with either fluconazole, itraconazole, voriconazole or amphotericin B for a variable duration (range eight days to 3.5 years) before study entry; §§Satisfactory response was defined as a 50% reduction from baseline in the Mycoses Study Group score, a composite evaluation of symptoms, physical examination findings and laboratory investigations. HSCT Hematopoietic stem cell transplant. Data from references 24, 52, 53, 68 to 73

In both studies, breakthrough infections during posaconazole therapy were most commonly caused by *Candida* and *Aspergillus* species. The effect of posaconazole prophylaxis on the susceptibility patterns of these fungi is not yet known. Furthermore, there have been no studies comparing posaconazole with voriconazole, which has a similar spectrum of activity,

in terms of primary prophylaxis in this patient population. Nonetheless, recent guidelines from the Infectious Diseases Society of America (54) recommend posaconazole for the prevention of invasive aspergillosis in both populations; posaconazole has been approved for use in Canada for the prophylaxis of *Aspergillus* and *Candida* species infections in patients 13 years of

age and older who are at high-risk for these infections, either from prolonged neutropenia or following HSCT (10).

### RESISTANCE MECHANISMS

Resistance to the triazoles arises either from mutations in the gene (*ERG11*) encoding the target enzyme (CYP51) or from the overexpression of efflux pumps. The long side chain of posaconazole is thought to reduce the development of resistance by either mechanism. Mutations in the active site of CYP51, sufficient to render *C albicans* resistant to fluconazole and voriconazole, do not alone create posaconazole resistance. Instead, numerous mutations outside of the active site are required to disrupt multiple secondary interactions between the posaconazole side chain and CYP51 (55, 56). Furthermore, posaconazole is not a substrate for the MDR1 or FLU1 efflux pumps, and is a poor substrate for the CDR1 and CDR2 efflux pumps. In one study, *C albicans* isolates remained susceptible to posaconazole despite a 30-fold increase in the expression of the CDR2 pump. As a result, of 24 fluconazole-resistant clinical isolates of *C albicans*, 17 had MICs greater than 1 mg/L for voriconazole, seven for itraconazole and only one for posaconazole. Overexpression of *ERG11*, which has been shown to confer resistance to fluconazole, is another possible contributor to posaconazole resistance, although this has yet to be demonstrated in vitro (57).

Clinically, posaconazole has been used successfully to treat infections resulting from fluconazole- or itraconazole-resistant *Candida* species (42). Its high barrier to resistance is also apparent in studies (58) of azole-resistant *Aspergillus* species, in which itraconazole- or voriconazole-resistant isolates exhibited only low-level cross-resistance to posaconazole, and amphotericin-resistant isolates exhibited no cross-resistance.

As a consequence of increasing resistance to antifungal agents and the attendant possibility of resulting clinical failures, interest in antifungal drug combinations has grown. No antagonism was observed between posaconazole and caspofungin against *C glabrata* in in vitro studies, nor between posaconazole and amphotericin B against *C albicans* and *C neoformans* in in vivo or in vitro studies, respectively (59-61). With the latter combination, either additive or synergistic effects were observed for the majority of *C neoformans* isolates tested. Moreover, no antagonism was observed between posaconazole and caspofungin in a murine model of invasive aspergillosis (62). Although there have been no prospective clinical trials reported to date of posaconazole use in combination with other antifungal agents, these studies suggest that no deleterious effects would be expected by coadministration of agents from two different classes. Notably, however, in the presence of a fully susceptible organism, no additional therapeutic benefit would necessarily be derived from the combination.

### SAFETY AND TOLERABILITY

The commonly reported adverse effects of posaconazole are similar to those of other triazoles. Adverse events were reported in 38% of 428 patients, 109 of whom received posaconazole for longer than six months, and 27 of whom received it for longer than 12 months (29). Adverse events lead to discontinuation of therapy in only 6% of patients, and there was no difference in the type or incidence of adverse events reported among patients receiving therapy for longer or

shorter than six months. The most commonly reported adverse events were nausea, which occurred in 8% of patients, and vomiting, which occurred in 6% of patients. Abdominal pain, diarrhea, headache, fatigue, dizziness and rash were also each reported in 2% to 4% of patients. Serious adverse events occurred in 8% of patients, and included elevations in serum hepatic aminotransferases and serum creatinine in 2% of patients, and prolongation of the corrected QT interval in 1%. QT prolongation occurred between 28 and 64 days of therapy. A similar rate and spectrum of adverse events has been reported with the three times daily dosing regimen (18). In total, the safety of posaconazole has been evaluated in 1844 patients and was found to be similar to fluconazole in comparative studies (10). Monitoring of serum aminotransferases and markers of liver function is recommended before the initiation of therapy, and intermittently throughout, because there have been rare reports of fatal cholestasis and hepatic failure associated with posaconazole use (10).

### CONCLUSIONS

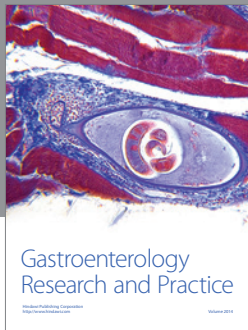
Despite the diverse spectrum of activity indicated by in vitro and in vivo experimental data, posaconazole has received Canadian approval only for the treatment of OPC and refractory invasive aspergillosis, as well as for the prophylaxis of invasive aspergillosis and candidiasis in high-risk patients (10). Given that fluconazole is an inexpensive, well-tolerated, long-used option for most patients with HIV-associated OPC, posaconazole will most likely be used only in those patients with azole-refractory disease. In this setting, its oral formulation provides benefit over intravenous caspofungin, the other approved treatment option for these patients. Likewise, in patients with refractory invasive aspergillosis, oral posaconazole may be of benefit over intravenous caspofungin. Posaconazole may be of use even in those patients who have failed therapy with voriconazole or who are infected with voriconazole-resistant isolates, because the risk of cross-resistance appears to be low. Nonetheless, close monitoring of susceptibility patterns is indicated. In high-risk patients with hematological malignancies, including those undergoing induction chemotherapy for acute leukemia, hematopoietic stem cell transplantation and treatment for severe graft-versus-host disease, posaconazole demonstrated a reduction in all-cause mortality compared with fluconazole, primarily on the basis of its activity against *Aspergillus* species. Posaconazole is now the recommended prophylactic regimen for use in these high-risk patients, but its cost may limit its use. As recommended in the Infectious Diseases Society of America guidelines, further studies may be helpful to better define the precise population at highest risk. In addition, increasing use requires close laboratory monitoring for the development of resistance, as well as for an increased incidence of those IFIs against which posaconazole is less effective, including fusariosis and scedosporiosis. In terms of other IFIs, with its well-tolerated oral formulation and few drug interactions, posaconazole may become the agent of choice for long-term treatment of the opportunistic mycoses against which voriconazole has little or no activity, including mucormycosis. Again, the impact of this projected increase in posaconazole use on fungal susceptibility patterns needs to be monitored closely. However, the high barrier to resistance created by posaconazole's unique structure may secure its niche in treating polyene-, echinocandin- and even triazole-resistant IFIs.

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