

Safety of Long-Term Oral Posaconazole Use in the Treatment of Refractory Invasive Fungal Infections

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Background. Invasive fungal infections are found most frequently in immunosuppressed and critically ill hospitalized patients. Antifungal therapy is often required for long periods. Safety data from the clinical development program of the triazole antifungal agent, posaconazole, were analyzed.

Methods. A total of 428 patients with refractory invasive fungal infections ($n = 362$) or febrile neutropenia ($n = 66$) received posaconazole in 2 phase II/III open-label clinical trials. Also, 109 of these patients received posaconazole therapy for ≥ 6 months. Incidences of treatment-emergent, treatment-related, and serious adverse events and abnormal laboratory parameters were recorded during these studies.

Results. Treatment-emergent, treatment-related adverse events were reported in 38% of the overall patient population. The most common treatment-related adverse events were nausea (8%) and vomiting (6%). Treatment-related serious adverse events occurred in 8% of patients. Low rates of treatment-related corrected QT interval and/or QT interval prolongation (1%) and elevation of hepatic enzymes (2%) were reported as adverse events. Treatment-emergent, treatment-related adverse events occurred at similar rates in patients who received posaconazole therapy for < 6 months and ≥ 6 months.

Conclusions. Prolonged posaconazole treatment was associated with a generally favorable safety profile in seriously ill patients with refractory invasive fungal infections. Long-term therapy did not increase the risk of any individual adverse event, and no unique adverse event was observed with longer exposure to posaconazole.

Posaconazole (SCH56592) is an orally administered, extended-spectrum triazole antifungal agent. Activity of posaconazole against the most common fungal pathogens, as well as emerging, hard-to-treat, and endemic infections, has been demonstrated in in vitro studies and clinical trials [1–9]. The need for new treatment options for invasive fungal infections (IFIs) is indicated by increasing rates of opportunistic fungal pathogens in hospitalized patients [10] and reports of toxicities

and emerging resistance to existing antifungal therapies [11, 12], suggesting that posaconazole will be an important treatment option for many patients [13].

Initial clinical studies indicated that oral posaconazole was well tolerated and associated with minimal cardiac and hepatic effects in healthy volunteers [14, 15]. In addition, posaconazole may be associated with a low potential for drug interactions caused by inhibitory activity against a narrow spectrum of cytochrome P450 (CYP) isozymes. Posaconazole is a potential inhibitor of CYP 3A4 only and is not significantly metabolized by any CYP isozyme [16, 17]. Favorable safety and tolerability results have also been presented in patients with IFIs [7, 18–20], including patients > 65 years of age [21] and patients with chronic renal disease [22].

This article presents integrated safety data from a pooled set of patients ($n = 428$) who had febrile neu-

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tropenia (66 patients) or refractory IFIs (362 patients) in 2 phase II/III clinical trials of posaconazole. A significant proportion of these patients (108 patients; 25%) received posaconazole for ≥ 6 months. Because few data on long-term safety of newer antifungal agents are available, safety data were analyzed separately for patients who received posaconazole treatment for < 6 months and for those who received therapy for ≥ 6 months.

METHODS

Patient population and treatment. Analyses of safety were performed for a set of 428 patients who received posaconazole treatment in 2 phase II/III open-label studies. One trial was a pharmacokinetic dose-finding study, in which 98 patients with IFIs (32 patients) or febrile neutropenia (66 patients) were randomized to treatment with posaconazole (either 400 mg twice per day, 600 mg twice per day, or 800 mg once per day) for a maximum period of 6 months. The second study was a pivotal, phase III, nonrandomized trial, in which 330 patients with refractory IFIs were treated with 800 mg of posaconazole per day. The overall population of 428 patients included 397 patients who were assigned to receive 800 mg per day and 31 patients who were assigned to receive 1200 mg per day after an initial dose of 1600 mg per day for 2 days. Posaconazole was administered as an oral suspension in divided doses. Duration of therapy was based on the severity of underlying disease, the extent of recovery from immunosuppression, and the degree of clinical response for each patient.

Safety data were analyzed to compare 2 groups. The first group consisted of 319 patients who received all doses of posaconazole for < 6 months. The second group consisted of 109 patients who received all doses of posaconazole treatment for ≥ 6 months. Rates of follow-up monitoring and laboratory tests were the same in the short-term and long-term groups throughout the studies.

Adverse events. Treatment-emergent, treatment-related adverse events were defined as any physical or clinical change or disease experienced by the patient at any time during the study, including onset of new illness and exacerbation of preexisting conditions, which were defined as possibly or probably related to posaconazole treatment by the investigator or as events for which no relationship was specified. Serious adverse events were defined as those that were fatal, were life-threatening, were disabling, required hospitalization, or were considered medically significant by the investigator.

Electrocardiogram and laboratory data. In the pharmacokinetic dose-finding study, findings from electrocardiograms were recorded at baseline, at 10 h or 24 h after the first dose, and monthly thereafter or as clinically indicated. Hematologic testing and serum chemistry studies were performed weekly for 12 weeks and then performed monthly throughout the study

or as clinically indicated. In the phase III trial, findings from electrocardiograms were recorded at baseline, at week 4 and as clinically indicated thereafter. Results of hematologic tests and serum chemistry studies were recorded at every visit (at weeks 2 and 4 and then monthly thereafter or as clinically indicated). Hematologic test and blood chemistry results were classified using Common Toxicity Criteria (CTC) grading, version 2.0 (National Cancer Institute) [23]. Potentially clinically significant shifts in these parameters were defined as shifts from CTC grade 0, 1, or 2 at baseline to grade 3 or 4 as the worst value that occurred at any time during treatment.

RESULTS

Baseline demographic and disease characteristics. Characteristics of the overall population of patients with refractory IFIs who received all doses of posaconazole ($n = 428$) are shown in table 1. As expected for patients with IFIs, most were severely immunocompromised. Patients who received treatment with posaconazole for < 6 months and for ≥ 6 months had similar baseline demographic and disease characteristics.

Course of posaconazole treatment. The mean duration of posaconazole treatment among the overall population was 115 days (range, 1–609 days), with a median duration of 54 days. The actual exposure to treatment (treatment duration minus any missed doses or gaps in treatment) was very similar (mean duration of exposure to treatment, 113 days), suggesting a high level of compliance with the treatment regimen. A total of 109 patients received posaconazole for ≥ 6 months, including 27 (25%) who received treatment for ≥ 12 months. The maximum duration of treatment was 609 days (~ 20 months).

Treatment-related adverse events and discontinuation due to adverse events. Among the overall population of patients, 164 (38%) of 428 reported adverse events were judged to be possibly or probably related to posaconazole treatment. In the dose-finding study, patients who received 400 mg of posaconazole twice a day, which was the regimen involving the greatest exposure to drug, reported more treatment-related adverse events than those who received 600 mg of posaconazole twice a day or 800 mg once a day (11 [31%] of 31, 6 [19%] of 31, and 7 [22%] of 32 patients, respectively), but the differences were not statistically significant. The most common treatment-related adverse events were gastrointestinal in nature (e.g., nausea, vomiting, diarrhea, and abdominal pain) (table 2).

Treatment-related adverse events that led to discontinuation of therapy, discontinuation of the study, or death were reported in 25 (6%) of 428 patients. Table 3 compares these events in patients who received posaconazole for < 6 months and those who received posaconazole for ≥ 6 months. Overall, more patients (8 [32%] of 25) discontinued treatment because of treatment-related gastrointestinal events than because of any other class of events.

Table 1. Baseline demographic characteristics and disease characteristics of patients with refractory invasive fungal infections who received posaconazole.

Characteristic	Patients who received posaconazole, by duration of therapy		
	Overall population (n = 428) ^a	<6 Months (n = 319)	≥6 Months (n = 109)
Age, years			
Mean ± SD	45 ± 16.0	44 ± 16.4	45 ± 14.9
Median (range)	45 (8–84)	45 (8–84)	45 (12–76)
<18	16 (4)	12 (4)	4 (4)
≥18 to <65	364 (85)	272 (85)	91 (84)
≥65	48 (11)	35 (11)	13 (12)
Sex			
Male	277 (65)	205 (64)	72 (67)
Female	151 (35)	114 (36)	36 (33)
Race			
Caucasian	289 (68)	222 (70)	66 (61)
Black	27 (6)	16 (5)	11 (10)
Asian	27 (6)	26 (8)	1 (1)
Hispanic	84 (20)	54 (17)	30 (28)
Other	1 (<1)	1 (<1)	0
Underlying disease characteristics^b			
Malignancy	271 (63)	224 (70)	46 (43)
Solid tumor	36 (8)	26 (8)	9 (8)
Hematologic	247 (58)	206 (65)	41 (38)
Transplant	149 (35)	122 (38)	27 (25)
Autologous bone marrow	22 (5)	18 (6)	4 (4)
Allogenic bone marrow	102 (24)	84 (26)	18 (17)
Solid organ	25 (6)	20 (6)	5 (5)
Acquired immunocompromising conditions	128 (30)	95 (30)	33 (31)
No known underlying immunocompromising disease	33 (8)	8 (3)	25 (23)
Primary pathogen^c			
<i>Aspergillus</i> species	157 (37)	...	43 (39)
<i>Candida</i> species	39 (9)	...	8 (7)
<i>Fusarium</i> species	27 (6)	...	5 (5)
<i>Cryptococcus</i> species	46 (11)	...	6 (6)
<i>Coccidioides</i> species	21 (5)	...	17 (16)
<i>Zygomycetes</i> species	16 (4)	...	4 (4)
Chromoblastomycosis/mycetoma	12 (3)	...	9 (8)
<i>Histoplasma</i> species	7 (2)	...	3 (3)
Other fungi	35 (8)	...	14 (13)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

^a The overall population with invasive fungal infection (n = 428) included 66 patients with febrile neutropenia.

^b Subjects may have had >1 underlying disease characteristic.

^c Subjects with multiple primary pathogens are counted more than once.

Serious adverse events. Overall, 35 (8%) of 428 patients reported any treatment-related serious adverse event. Most individual events occurred in <1% of patients and involved the cardiac, neurologic, or hepatic systems or were associated with potential drug reactions. Serious adverse events that occurred in ≥1% of patients were altered drug level (digitalis in 1 patient, cyclosporine in 1 patient, and tacrolimus in 2 patients), increased hepatic enzymes (4 patients), nausea (3 patients), rash

(3 patients), and vomiting (3 patients). Tacrolimus toxicity was reported in 1 patient, and cyclosporine toxicity was reported in 1 patient. No treatment-related serious adverse events were observed in any group in the dose-finding study.

Of particular note, convulsions were considered to be related to posaconazole treatment for 2 patients (<0.5%). One patient had a prior history of convulsions and had received concomitant cyclosporine (see below), and the other patient with con-

Table 2. Treatment-related adverse events reported in $\geq 2\%$ of patients with refractory invasive fungal infections who were assigned to receive posaconazole.

Adverse event	No. (%) of patients who received posaconazole, by duration of therapy	
	<6 Months (n = 319)	≥ 6 Months (n = 109)
Patients reporting any adverse event ^a	113 (35)	51 (47)
General body disorders		
Anorexia	3 (1)	5 (5)
Asthenia	2 (1)	2 (2)
Dizziness	6 (2)	1 (1)
Drug level altered	2 (1)	5 (5)
Fatigue	5 (2)	2 (2)
Headache	10 (3)	10 (9)
Central and peripheral nervous system disorders		
Hyperreflexia	0	2 (2)
Paresthesia	4 (1)	2 (2)
Somnolence	1 (<1)	2 (2)
Tremor	0	2 (2)
Blood and lymphatic system disorders		
Anemia	2 (1)	2 (2)
Disorders of reproductive system and breast		
Menstrual disorder ^b	0	2 (5)
Gastrointestinal system disorders		
Abdominal pain	13 (4)	5 (5)
Diarrhea	11 (3)	4 (4)
Mouth dry	4 (1)	2 (2)
Nausea	27 (8)	8 (7)
Vomiting	21 (7)	4 (4)
Heart rate and rhythm disorders		
QTc interval and/or QT interval prolongation	4 (1)	2 (2)
Liver and biliary system disorders		
Increased hepatic enzyme levels	7 (2)	2 (2)
Increased SGOT levels	8 (3)	1 (1)
Increased SGPT levels	6 (2)	5 (5)
Metabolic and nutritional disorders		
Increased phosphatase alkaline levels	4 (1)	2 (2)
Platelet, bleeding, and clotting disorders		
Thrombocytopenia	0	2 (2)
Renal and urinary system disorders		
Increased blood creatinine levels	5 (2)	0
Renal failure	0	2 (2)
Skin and subcutaneous tissue disorders		
Alopecia	2 (1)	2 (2)
Dry skin	0	3 (3)
Rash	9 (3)	1 (1)

NOTE. The overall population with invasive fungal infection (n = 428) included 66 patients with febrile neutropenia. QTc, corrected QT; SGOT, serum glutamic-oxaloacetic transaminase (also known as aspartate transaminase); SGPT, serum glutamic pyruvic transaminase (also known as alanine transaminase).

^a No. of patients who reported treatment-related adverse events at least once during the studies. Some patients may have reported >1 treatment-related event.

^b Denominator includes female patients only.

convulsions received concomitant tacrolimus. Serum levels of tacrolimus for the second patient (on day 5 of posaconazole treatment) were 5.6 ng/mL. Posaconazole and tacrolimus were discontinued, and no additional convulsions were reported.

Four patients (<1%) also had treatment-related serious adverse events of the renal and/or urinary system, including acute renal failure with increased blood creatinine concurrent with tacrolimus toxicity, renal failure concurrent with grade 4 pancreatitis in a patient with a history of renal dysfunction, renal failure and nephrotoxicity concurrent with cyclosporine elevation, and abnormal urine (choloria) in conjunction with hepatic failure.

Deaths. A total of 157 patients (37%) among the overall population of patients died. The most common causes of death were adverse events that were considered to be unrelated to the study treatment (75 patients). In most instances, these adverse events were attributable either to complications of the patient's underlying disease or to progression of the disease under investigation. Seventy-seven deaths were directly attributed to the disease under investigation or progression of the disease under investigation, and 3 deaths were attributed to other causes (complications due to AIDS, unknown cause after the patient was discharged to hospice, and end-stage chronic obstructive pulmonary disease).

Two deaths were considered to be possibly related to posaconazole treatment because of temporal relationships between administration of drug and the adverse events that led to death. One death occurred in a 16-year-old female recipient of a bone marrow transplant who died of respiratory failure after a seizure that occurred 1 day after the last dose of posaconazole, on day 95. This patient had a history of seizures and had a prolonged seizure at home that resulted in hospitalization with coma, followed by multiple organ failure and death. This event was considered likely to be a recurrence of seizures that occurred during posaconazole therapy. The other death involved a 38-year-old male patient, who was found to be unresponsive while sleeping at home after day 119 of posaconazole treatment. This patient had a previous history of type I diabetes, hypoglycemic episodes, end-stage renal disease, and renal transplant 4 months before study entry. No autopsy or laboratory studies were performed. Although the respective investigators could not rule out posaconazole as a possible cause, these events are considered more likely to be related to preexisting medical conditions or intercurrent infections.

Adverse events associated with long-term posaconazole treatment. As shown in table 2, many common treatment-related adverse events (such as anorexia, headache, menstrual disorder, and increased serum glutamic pyruvic transaminase levels) occurred at slightly higher rates among the population receiving long-term posaconazole treatment than they did among the population receiving short-term treatment. How-

Table 3. Treatment-related adverse events in patients with refractory invasive fungal infections that resulted in the discontinuation of treatment, discontinuation of the study, or death.

Adverse event	No. (%) of patients who received posaconazole, by duration of therapy	
	<6 Months (n = 319)	≥6 Months (n = 109)
Events resulting in discontinuation		
Any ^a	22 (7)	3 (3)
Body as a whole	3 (1)	0
Cardiovascular disorders	1 (<1)	0
Nervous system disorders	5 (2)	0
Blood and lymphatic system disorders	2 (1)	0
Immune system disorders	1 (<1)	0
Gastrointestinal system disorders	7 (2)	1 (1)
Infections	0	1 (1)
Injury and poisoning	1 (<1)	0
Liver and biliary system disorders	6 (2)	0
Metabolic and nutritional disorders	2 (1)	0
Musculoskeletal system disorders	2 (1)	0
Renal and urinary system disorders	3 (1)	0
Respiratory system disorders	1 (<1)	0
Skin and subcutaneous tissue disorders	4 (1)	1 (1)
Other special senses disorders	1 (<1)	0
Events resulting in death		
Any ^a	3 (1)	0
Body as a whole (death)	1 (<1)	0
Cardiovascular disorders (cardiorespiratory arrest)	1 (<1)	0
Disorders of blood and lymphatic system (pancytopenia)	1 (<1)	0
Liver and biliary system disorders (hepatic failure)	1 (<1)	0

NOTE. The overall population with invasive fungal infection (n = 428) included 66 patients with febrile neutropenia.

^a Some patients may have reported >1 event that led to treatment or study discontinuation or death.

ever, rates of certain grade 3 or 4 adverse events, such as respiratory insufficiency, multiple organ failure, cardiorespiratory arrest, hypotension, and coma, were lower in patients who received longer treatment. No trend in treatment-related adverse events suggested increasing risk of any adverse event with longer treatment.

Hematologic data. Most patients among the overall population had abnormal baseline values (CTC grade 1 or higher) for hematocrit, hemoglobin, and platelet levels and slightly more than one-half had abnormal baseline values for neutrophil counts or leukocyte counts. Changes from grades 0, 1, or 2 to grades 3 or 4 at any time during treatment are shown in table 4.

Blood chemistry data. Potentially clinically important shifts in blood chemistry values for patients with baseline measurements and at least 1 post-baseline measurement are also reported in table 4. Approximately 25% of patients had abnormal values for liver parameters at baseline, and 40% had increased creatinine

values at baseline. No trends suggested adverse laboratory effects were associated with longer exposure to posaconazole.

Cardiac safety data. A total of 265 patients had electrocardiogram findings recorded at baseline and at least 1 electrocardiogram finding recorded during posaconazole therapy, and 288 patients had at least 1 electrocardiogram finding recorded during treatment. Treatment-related adverse events included prolongation of the corrected QT (QTc) interval and/or the QT interval (among 1% of the overall population) and atrial fibrillation (among 1% of the overall population) that were generally mild to moderate in nature and did not lead to study discontinuation. Treatment-related QTc interval and/or QT interval prolongations occurred after 28–64 days of treatment and led to interruption of treatment (in accordance with protocol) for 2 patients. One instance of serious QTc interval and/or QT interval prolongation was considered to be related to either posaconazole, systemic lupus erythematosus, or renal

Table 4. Shifts in hematologic and blood chemistry values from Common Toxicity Criteria grades 0, 1, or 2 at baseline to grades 3 or 4 as the worst value during posaconazole treatment in patients with refractory invasive fungal infections.

Laboratory parameter	No. (%) of patients who received posaconazole, by duration of therapy	
	<6 Months (n = 319)	≥6 Months (n = 109)
Hematocrit	69/281 (25)	20/100 (20)
Hemoglobin level	68/281 (24)	18/101 (18)
Neutrophil count	23/256 (9)	16/94 (17)
Platelet count	41/279 (15)	14/101 (14)
Leukocyte count	25/280 (9)	16/101 (16)
SGOT level	13/266 (5)	4/87 (5)
SGPT level	21/266 (5)	8/98 (8)
Total bilirubin level	13/267 (5)	2/94 (2)
Alkaline phosphatase level	13/267 (5)	3/95 (3)
Creatinine level	4/283 (1)	4/101 (4)

NOTE. Data are the no. of patients who had the specified shift in values divided by the no. of patients with a baseline measurement and at least 1 post-baseline measurement. The overall population with invasive fungal infection (n = 428) included 66 patients with febrile neutropenia. Laboratory Common Toxicity Criteria grades are defined in Methods. SGOT, serum glutamic-oxaloacetic transaminase (also known as aspartate transaminase); SGPT, serum glutamic pyruvic transaminase (also known as alanine transaminase).

failure. No increased risk of cardiac events was observed with posaconazole treatment for ≥6 months.

DISCUSSION

Posaconazole was found to have a favorable safety profile during treatment of seriously ill patients with IFIs. In these phase II/III trials, the most common adverse events considered possibly or probably related to treatment were gastrointestinal in nature. Other treatment-related adverse events that are known to be associated with the azole class occurred at low rates, including increased serum glutamic pyruvic transaminase levels (11 [3%] of 428 patients), altered drug levels (7 [2%] of 428 patients), QTc interval and/or QT interval prolongations (6 [1%] of 428 patients), and convulsions (2 [$<0.5\%$] of 428 patients). Both patients with convulsions received concomitant cyclosporine or tacrolimus, and blood levels of these drugs are known to increase when they are coadministered with azoles [24–26]. Similar drug interactions have been reported with posaconazole [27].

In one of the most extensive evaluations of long-term therapy with an azole in a clinical development program, posaconazole safety was analyzed in 109 patients who received treatment for ≥6 months. Of those, 27 patients received posaconazole treatment for >1 year. There are only a few reports of treatment for comparable durations with other agents in the azole class [28,

29]. These assessments are especially relevant for agents used to treat patients with IFIs, who may require weeks or months of prophylaxis or therapy to achieve prevention, improvement, or cure. Our investigation did not suggest increased risk of any adverse event, and no unique treatment-related adverse event was observed with longer exposure to posaconazole.

A total of 157 (37%) of 428 patients died during the course of the 2 studies. Adverse events leading to death were reported as possibly related to posaconazole treatment for 2 patients because of temporal association with therapy, but were more likely to be related to preexisting medical conditions. The risk of death and discontinuation was not different for those patients who received short-term posaconazole versus long-term posaconazole. The high death and discontinuation rates are not unexpected among this very ill patient population, who were considered for salvage therapy because previous antifungal therapies had failed or because they could not tolerate the therapy. Many received posaconazole therapy until death, because there were no alternative treatments.

The polyene antifungal agents, amphotericin B and its lipid formulations, are still a mainstay of therapy for serious fungal infections, but their use is associated with considerable renal toxicity and infusion-related adverse events [30].

Voriconazole was introduced in 2002 and has proven efficacy for many fungal infections [31, 32], but possible development of serum level–related hepatic toxicity is a safety concern [31, 33], and transient visual disturbances are reported in as many as 45% of patients in clinical studies [30]. A new class of antifungal agents, the echinocandins, is represented by caspofungin, micafungin, and anidulafungin. The spectrum of activity of echinocandins is limited to infection with *Aspergillus* species and *Candida* species [34]. Echinocandins have limited activity against the newly emerging molds, such as *Fusarium* species, *Scedosporium* species, and zygomycetes [35, 36]. In addition, several yeasts, such as *Cryptococcus neoformans*, *Trichosporon* species, and *Rhodothorula* species are relatively resistant to echinocandins [37–39].

Posaconazole has been shown to have broad-spectrum in vitro and clinical activity against various yeasts and molds causing IFI [3]. In this study, the long-term use of posaconazole had a safety profile comparable to that of its short-term use. In a recent study, posaconazole had a similar safety profile and tolerability, compared with fluconazole, during treatment for oropharyngeal candidiasis in patients with HIV/AIDS [40]. This is of paramount importance, because the safety, tolerability, and oral bioavailability of this drug are all factors that contribute to its long-term successful use in the prolonged outpatient prophylaxis or treatment of IFIs [1, 12, 14, 21, 22].

We conclude that the safety profile of posaconazole justifies its use in salvage treatment for critically ill patients with IFI.

Also, the safety and tolerability of long-term posaconazole use suggest that evaluation of this active drug for prophylactic and/or primary antifungal treatment is warranted.

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