Posaconazole Is Effective as Salvage Therapy in Zygomycosis: A Retrospective Summary of 91 Cases

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To evaluate the activity of posaconazole for treatment of zygomycosis, a disease for which therapeutic options are limited, we conducted a retrospective study including 91 patients with zygomycosis (proven zygomycosis, 69 patients; probable zygomycosis, 22 patients). Patients had infection that was refractory to prior antifungal treatment ($n = 81$) or were intolerant of such treatment ($n = 10$) and participated in the compassionate-use posaconazole (800 mg/day) program. The rate of success (i.e., either complete or partial response) at 12 weeks after treatment initiation was 60%, and 21% of patients had stable disease. The overall high success and survival rates reported here provide encouraging data regarding posaconazole as an alternative therapy for zygomycosis.

Zygomycetes are opportunistic filamentous fungal pathogens that are ubiquitous in the environment [1]. Infections are acquired by inhalation or ingestion of Zygomycetes or by trauma-related exposure. Rhinocerebral and pulmonary manifestations are common types of infection [2, 3]. Poorly controlled diabetes mellitus, dysfunction of macrophages-monocytes (as seen following prolonged corticosteroid use), receipt of iron chelation therapy, profound neutropenia, and disruption of the integrity of the integument and mucosal membranes are risk factors for this infection [1–5].

Zygomycetes are highly angioinvasive; infections caused by these organisms, if undetected, rapidly progress to tissue and blood vessel invasion, leading to tissue destruction, thrombosis, infarction, and dissemination [1, 5]. Optimal treatment of zygomycosis has not been defined, owing to the lack of appropriate prospective trials involving this rare opportunistic mycosis. A multimodality approach combining aggressive surgical resection of localized infection, cessation of immunosuppressive therapy (when feasible), correction of metabolic abnormalities, and rapid onset of intense systemic antifungal therapy appear to be important [1, 2, 4–6].

In terms of systemic antifungal therapy, polyenes such as amphotericin B deoxycholate and its lipid derivatives remain the front-line agents, because other licensed antifungal agents lack activity against Zygomycetes [1, 5, 7, 8]. The mechanism for the lack of activity of most azole antifungals against Zygomycetes is unknown. However, preclinical in vitro data have demonstrated that fluconazole and voriconazole may not adequately interact with the target protein (CYP51), thus not functioning to prevent ergosterol synthesis [9]. Posaconazole, conversely, does appear to adequately inhibit ergosterol synthesis in these molds. Unfortunately, amphotericin B–based therapy has important limitations; use of these intravenous agents is limited by infusion-related and dose-related toxicities. Such toxicity, especially renal toxicity, is not uncommon, because therapy must continue to be administered for several months following control of initial Zygomycetes infection.

Therefore, there is an unmet clinical need for an orally administered agent with activity against Zygomycetes. Posaconazole is a novel, extended-spectrum, orally administered triazole that has shown activity against Zygomycetes in vitro [7, 8], in an immunosuppressed mouse model of zygomycosis [10], and in humans with zygomycosis for whom other antifungal therapies have failed [11, 12]. The intent of this case series is to expand our knowledge of the clinical utility of posaconazole given as salvage therapy in an expanded-access program for zygomycosis across a spectrum of host groups with this infection.

Methods. Questionnaires were sent to physicians treating subjects with zygomycosis under the compassionate Schering-Plough protocol P02095 (31 August 2001 through 29 November 2004). Enrolled subjects had disease progression or failure to improve after a 7-day course of standard antifungal therapy (refractory zygomycosis) or had become intolerant to prior antifungal agents, as previously described [13]. Posaconazole was administered as a suspension in divided doses (200 mg given 4 times daily or 400 mg given twice daily) orally with meals or enteral feedings, because these regimens have been shown to produce the greatest posaconazole exposure [14, 15].

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Ninety-nine subject questionnaires were returned from 47 sites in the United States ($n = 33$), Europe ($n = 13$), and Latin America ($n = 1$).

A team of experts was convened to review each returned questionnaire and to evaluate certainty of infection using established European Organization for the Research and Treatment of Cancer/Mycoses Study Group criteria, using methods that have been described previously [4, 16]. Only proven or probable cases of zygomycosis were included in the analysis. Thus, 8 of the 99 returned questionnaires were excluded from this case series (3 subjects were determined not to have zygomycosis, 2 subjects were determined to have possible zygomycosis, and 3 subjects with proven zygomycosis were excluded because they had participated in other posaconazole clinical trials). The outcome of 11 of the 91 subjects included in this analysis was described in an earlier publication [12].

The treating physician assessed response to posaconazole on the basis of symptoms, signs, and microbiologic, histopathologic, and radiographic findings. Responses included complete response (i.e., resolution), partial response (i.e., clinically meaningful improvement), stable disease (i.e., no improvement but no deterioration), and failure (i.e., deterioration) or were not able to be determined. Death and its relationship to zygomycosis, as judged by the treating physician, was recorded on the questionnaire.

All information gathered for this case series was supported under the consent document signed by each subject for the compassionate-use protocol, which was implemented according to the Declaration of Helsinki and local Institutional Review Board requirements.

No formal statistical analysis was conducted. Data were tabulated by number of subjects and percentages. Tables were created using SAS software, version 8.2 (SAS Institute). Clinical response was evaluated at the test-of-cure time point of $\leqslant$12 weeks after commencing posaconazole therapy. "Success rate" is defined as the sum of the rates of complete response and partial response.

Results. Ninety-one subjects included in this case series had proven ($n = 69$) or probable ($n = 22$) zygomycosis. Infection was documented by culture for 60 of 91 patients, by histopathologic study for 8 of 91 patients, and by both culture and histopathologic study for 23 of 91 patients. The median age was 47 years (range, 1–80 years). Eleven subjects were <18 years old; 8 subjects were $\geqslant$65 years old. Most subjects (71%) were male. The majority of patients (56 [62%] of 91) had 1 site of Zygomycetes infection; however, 35 of 91 subjects had >1 site of infection (table 1). Approximately one-half (49 [54%]) of the 91 subjects had received antifungal prophylaxis; most received azoles (fluconazole, itraconazole, or voriconazole). Specifically, 20% of patients in our study had received voriconazole as prophylaxis.

Protocol enrollment was often based on whether the patient had refractory zygomycosis (48 patients) but was also based on intolerance to prior antifungal therapy ($n = 10$) or both ($n = 33$) (table 1). Reasons for intolerance included renal insufficiency (9 [90%] of 10 patients) and a "high risk" of intolerance associated with medical history (1 patient [10%]). Most subjects (77 [85%]) were treated with lipid formulations of amphotericin B, but some (24 subjects [26%]) also started treatment with amphotericin B deoxycholate. Other prior therapeutic antifungal agents included voriconazole in cases where the clinician believed the patient had aspergillosis on the basis of clinical suspicion (28 subjects [31%]).

Posaconazole was given for at least 30 days (range, 6–1005 days) for 80% of subjects. Overall success (complete and partial response) at 12 weeks following the initiation of posaconazole treatment was 60% (13 [14%] of 91 patients had a complete response, 42 [46%] had a partial response, 19 [21%] had stable disease, 15 [17%] experienced treatment failure, and researchers were unable to determine the outcome for 2 [2%]). Thirteen heavily immunosuppressed subjects (e.g., patients with refractory neutropenia, active leukemia, severe graft-versus-host disease after transplantation, or iatrogenic hypercortisolism) who were treated for >1 week with combined posaconazole and lipid formulations of amphotericin B had an overall response rate similar to that for patients who were treated with posaconazole as monotherapy (6 [46%] of 13 patients had a partial response, 3 [23%] had stable disease, and 4 [31%] had failure).

Success rates were similar regardless of site of infection diagnosed prior to posaconazole treatment, predisposing conditions, reason for enrollment, and infecting Zygomycetes species (table 1). Adjunctive surgical debridement in 64 of 91 subjects occurred prior to (38 of 64), during (9 of 64), or both prior to and during (17 of 64) posaconazole therapy; 26 subjects did not undergo surgery. The success rate was similar for patients who did (39 [61%] of 64) and did not (16 [62%] of 26) undergo adjunctive surgical procedures.

A total of 35 subjects (38%) died while receiving posaconazole therapy or within 1 month of follow-up after study drug discontinuation; 15 (43%) of the 35 deaths were attributed to zygomycosis. Death attributed to zygomycosis was seen primarily in subjects treated with <30 days of posaconazole therapy, reflecting the aggressive nature of this infection rather than the effect of posaconazole therapy.

Discussion. This retrospective review of experience with posaconazole for salvage treatment of zygomycosis presents a unique opportunity to assess the efficacy of an oral triazole in the treatment of this complex infection. Our patient population had typical risk factors for zygomycosis, such as underlying hematologic malignancy, transplantation, and/or diabetes [1–6].

The success rate of posaconazole among subjects with proven and probable zygomycosis who had refractory disease and/or

Table 1. Success rate of posaconazole treatment 12 weeks after initiation of therapy, by baseline characteristic.

Baseline characteristic	No. of patients[a]	No. (%) of patients with success[b]
Infection site		
Cutaneous	13	8 (61.5)
Palate	7	2 (28.6)
Sinuses	42	23 (53.5)
Pulmonary	37	24 (64.9)
Gastrointestinal	2	2 (100.0)
Brain	11	8 (72.7)
Liver	1	1 (100.0)
Orbital	11	5 (45.5)
Other	13	7 (53.8)
No. of sites of infection[c]		
1 site	56	37 (66.1)
>1 site	35	19 (54.3)
Predisposing condition at diagnosis		
Diabetes mellitus[d]	30	18 (60.0)
Hematologic malignancy[e]	48	28 (58.3)
Lymphoma	5	1 (20.0)
Neutropenia[f]	29	18 (62.1)
Receipt of stem cell transplant	27	14 (52.8)
Graft-versus-host disease	30	18 (60.0)
Receipt of solid organ transplant	10	6 (60.0)
Receipt of chronic steroid treatment	31	16 (52.6)
Serum albumin level <3 mg/dL	22	10 (45.5)
Enrollment reason		
Refractory infection only	48	30 (62.5)
Intolerant to treatment only	10	6 (60.0)
Refractory infection and treatment intolerance	33	19 (57.7)
Primary pathogen		
Absidia species	2	2 (100.0)
Cunninghamella species	8	6 (75.0)
Mucor species	17	13 (76.5)
Rhizomucor species	7	2 (28.6)
Rhizopus species	25	13 (52.0)

[a] Total number of subjects with indicated characteristic and with proven or probable zygomycosis.
[b] Success was defined as complete or partial clinical response 12 weeks after the initiation of posaconazole treatment.
[c] No. of sites of infection was assessed on the basis of premortem diagnosis.
[d] Includes type 1, type 2, and nonspecified type diabetes.
[e] Includes leukemia (43 subjects, 27 of whom had treatment success) and lymphoma (5 subjects, 1 of whom had treatment success).
[f] Defined as a neutrophil count of <500 cells/mm^3.

were intolerant of prior amphotericin B–based therapy was high (60%). Furthermore, an additional 21% of subjects had stable disease at week 12. Although the subset of patients with zygomycosis who received posaconazole in combination with other drugs had prognostic indicators for poor outcome, responses were reassuringly equivalent to posaconazole monotherapy. These data compare favorably with data for patients who have received amphotericin B products, among whom the survival rate has been reported to be 61% for recipients of amphotericin B deoxycholate and 69% for recipients of lipid formulations [2]. Importantly, success was seen for 72.7% of patients with zygomycosis in the brain, indicating the ability of oral posaconazole to penetrate the brain parenchyma.

Because 20% of the patients in our cohort had received voriconazole as prophylaxis, this study supports the growing evidence that the current increase in the number of reported

zygomycosis cases is likely to be associated with the intensive use of immunosuppressive therapies, coupled with the use of antifungal therapies that do not have activity against these fungi [6]. Furthermore, the frequent use of voriconazole for the presumptive diagnosis of aspergillosis in our series indicates that the development of clinical and radiologic criteria to differentiate aspergillosis from zygomycosis would be helpful [17].

For patients who require additional immunosuppression after treatment of zygomycosis infection, secondary chemoprophylaxis is often desired. Although our study did not specifically address the value of posaconazole as secondary antifungal prophylaxis, it seems that this oral agent fulfills an unmet medical need for patients with zygomycosis who need continuous long-term antifungal therapy because they remain at high risk for relapse of infection.

This retrospective study had several limitations. Clinical decisions regarding the time to switch from amphotericin B–based treatment to posaconazole and the duration of therapy were not controlled but were made according to each treating physician's discretion. Furthermore, owing to the small sample size, we did not evaluate treatment success in relation to the level of immunosuppression, number or duration of previously unsuccessful antifungal therapies, timing and extent of surgery, or effect of combined antifungal therapy. However, it would be difficult, in this patient subset, to dissect the relative contribution of each individual component of the antifungal combination to outcome [18]. Finally, our study did not evaluate long-term follow-up findings, so no data are available to estimate risk of relapse in subjects who experience subsequent intensive immunosuppression.

In summary, this case series supports the use of posaconazole as a broad-spectrum azole with activity against Zygomycetes. This drug offers an attractive oral treatment alternative for patients with zygomycosis who cannot tolerate or do not respond to intravenous amphotericin B products. These encouraging data invite a prospective comparative study to evaluate posaconazole versus amphotericin B–based therapies as primary therapy for zygomycosis.

Investigators who returned questionnaires included in this case series. Richard Neil Greenberg, University of Kentucky Medical Center, Lexington, KY; Karlene Reid, Texas Tech University Health Sciences Center, Odessa, TX; Amelia A. Langston, Emory University Hospital BMT Center, Atlanta, GA; John Perfect, Duke Hospital South, Durham, NC; Dimitrios P. Kontoyiannis, M. D. Anderson Cancer Center, Houston, TX; John Wingard, University of Florida Health Sciences Center, Gainesville, FL; Angela Restrepo, Corporación Para Investigaciones Biológicas, Medellin, Colombia; Eliane Gluckman, Hôpital Saint Louis, Paris, France; Raoul Herbrecht, Hôpital de Hautepierre, Strasbourg, France; Jo-Anne van Burik, University of Minnesota Medical Center, Minneapolis, MN; Kathleen Mullane, Loyola University Medical Center, Maywood, IL; Stephen Threlkeld, Infectious Diseases Associates, Memphis, TN; Glenn Neel, Lucedale, MS; John Edwards, Harbor–University of California, Los Angeles, Research and Education Institute, Torrance, CA; Susan Seo, Memorial Sloan-Kettering Cancer Center, New York, NY; Andrew J. Ullmann, III. Medisinizche Klinik und Poliklinik Der Johannes Gutenberg–Universitat Mainz, Mainz, Germany; William Lau, Kuakini Medical Center, Honolulu, HI; Lindsey Baden, Brigham and Women's Hospital, Boston, MA; Eric Sandler, Nemours Children's Clinic, Jacksonville, FL; Joseph Solomkin, University of Cincinnati, OH; Scott Ostdiek, Phoenix, AZ; Albert Kheradpour, Loma Linda University Medical Center, Loma Linda, CA; Ann Falsey, Rochester General Hospital, Rochester, NY; Mark Abzug, The Children's Hospital, Denver, CO; Brahm Segal, Roswell Park Cancer Institute, Buffalo, NY; Katherine Knapp, St. Jude Children's Research Hospital, Memphis, TN; Rachel Miller, University of Iowa, Iowa City, IA; Mickael Aoun, Institut Jules Bordet, Brussels, Belgium; Peter Pappas, University of Alabama at Birmingham; N. P. M. Schaap, University Medical Center Nijmegen, The Netherlands; Carol Kauffman, Ann Arbor Veteran's Affairs Healthcare System, Ann Arbor, MI; Mindy Schuster, University of Pennsylvania, Philadelphia, PA; Lawrence Eron, Kaiser Foundation Hospital, Honolulu, HI; Pranatharthi Chandrasekar, Harper University Hospital, Detroit, MI; Roman Tuma, Memorial Sloan-Kettering Cancer Center, New York, NY; Aimee Wilkin, Wake Forest University Health Sciences, Winston-Salem, NC; Aleksandra Simic, Oregon Health and Science University, Portland, OR; Xaver Schiel, Klinikum Der Ludwig-Maximillians, Munich, Germany; Jorge Garbino, University of Geneva Hospital, Switzerland; Thomas Bregenzer, Kantonsspital Aarau, Aarau, Switzerland; Dan Garganera, Regional Care Association, Joliet, IL; Volker Richerts, Klinikum Der J. W. von Goethe-Universitat, Frankfurt, Germany; Bertrand Dupont, A. P. H. Paris, Hôpital Necker Enfants, Paris, France; Jutte van der Werff ten Bosch, AZ VUB, Brussels, Belgium; Helen Giamarellou, Attikon University Hospital, Athens, Greece; and C. M. Zwaan, Vrije Universiteit Medisch Centrum, Amsterdam, The Netherlands.

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