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Safety and Outcomes of Open-Label Deferasirox Iron Chelation Therapy for Mucormycosis▽

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We sought to describe the safety profile of open-label, adjunctive deferasirox iron chelation therapy in eight patients with biopsy-proven mucormycosis. Deferasirox was administered for an average of 14 days (range, 7 to 21) at 5 to 20 mg/kg of body weight/day. The only adverse effects attributable to deferasirox were rashes in two patients. Deferasirox treatment was not associated with changes in renal or liver function, complete blood count, or transplant immunosuppressive levels. Thus, deferasirox appears safe as an adjunctive therapy for mucormycosis.

Mucormycosis is a life-threatening infection caused by fungi of the subphylum Mucormycotina, order Mucorales (5, 10, 12). Iron availability is a critical factor in the growth of Mucorales (12). However, the potential therapeutic role of iron chelation therapy for mucormycosis was initially obscured by the paradoxically increased risk of developing mucormycosis during treatment with the iron chelator deferoxamine (2). This paradox was resolved when it was realized that deferoxamine actually enhances iron uptake by the fungi (2). Animal models have shown that other iron chelators do not act as iron siderophores for Mucorales (1, 7). Furthermore, deferasirox, an iron chelator recently approved by the U.S. Food and Drug Administration for the treatment of transfusion-related iron overload (3), had potent in vitro activity and in vivo efficacy in mice against clinical isolates of Mucorales (8).

To date, virtually all of the published clinical data on deferasirox therapy has been accumulated for uninfected patients with transfusion-related iron overload (13). Furthermore, safety concerns regarding potential use in infected patients have been underscored by sporadic postmarketing reports of acute renal failure, hepatic insufficiency, and agranulocytosis in iron-overloaded patients being treated with deferasirox (6). We therefore sought to define the safety of adjunctive deferasirox therapy for mucormycosis.

We reviewed data from eight patients with mucormycosis treated with open-label deferasirox (Table 1). All patients had biopsy-proven mucormycosis, in accordance with Mycosis Study Group-European Organization for the Research and Treatment of Cancer criteria (4). Seven of eight patients had diabetes mellitus, and five were taking corticosteroids at diagnosis. Five patients had received post-solid organ transplantation (two lung transplant patients, two kidney transplant patients, and one liver transplant patient). Active antifungal therapy was initiated a median of 9 days (range, 4 to 93) after symptom onset. Seven of eight patients underwent surgical debridement (all except patient 1) (Table 1), and the patients received their first surgical intervention at a median of 17 days (range, 5 to 86) after the start of symptoms.

In all cases, deferasirox was used in combination with other antifungal therapy (Table 1). In three cases, deferasirox was added as salvage therapy after a failure of initial therapy, and in five cases, the deferasirox was added prior to disease progression on the initial treatment regimen. One patient was treated for 20 days with a dose of 5 mg/kg of body weight/day of deferasirox because he had coexisting hepatic disease; all other patients received 15 to 20 mg/kg/day for a median of 14 days (range, 7 to 21 days).

Five patients showed improvements in signs or symptoms attributable to mucormycosis by the end of deferasirox therapy; of the three patients who did not show improvement in signs or symptoms, two had persistent, irreversible blindness due to orbital exenteration which occurred prior to initiation of deferasirox therapy (Table 1). Five of the six patients with repeat imaging studies after the end of deferasirox therapy had improvement or resolution of lesions. These improvements were not related to surgical management, since the improved lesions were predominantly in the brain or cavernous sinus and hence were not debrided. Seven of the eight patients survived to hospital discharge, all of whom were alive and not in hospice care at 30 days postdischarge. Two of those patients remained on maintenance antifungal therapy as of the last follow-up, and

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TABLE 1. Summary of cases

Gender (age [yr])	Risks	Site(s) of infection	Antifungal treatment history[a,b]	Clinical response	Radiographic response	Clinical outcome[b]
M (57)	Renal transplant, corticosteroid, diabetes mellitus, polycystic kidney disease	Pulmonary	ABLC + posa + deferasirox × 21 days, cured	Resolution (cough and SOB[d])	No repeat imaging	Cured, off therapy at 4 mo of follow-up
M (67)	Lung transplant, corticosteroids, diabetes mellitus, sarcoidosis, acute renal failure	Rhino-orbital-cerebral and pulmonary	LAmB + posa × 24 days, failed (progression of infection resulting in intractable epistaxis from intracranial arterial ulceration); LAmB + posa + deferasirox × 17 days, completed deferasirox course; LAmB + posa × 60 days; died	No change (pain, vision changes, chemosis)	Improved: persistent sinus disease but resolved right cerebellar lesion	Death
F (26)	Diabetes mellitus, corticosteroids, lung transplant, cystic fibrosis	Rhino-orbital-cerebral	LAmB + posa + caspo × 15 days, change of venue; LAmB + posa + caspo + deferasirox × 14 days, completed course; LAmB + posa + caspo × 11 days, step-down therapy; Posa × 80 days, cured	Resolution (headache)	No change: dural and cavernous sinus enhancement	Cured, off therapy at 1 year of follow-up
M (73)	Liver transplant; Crohn's disease; primary sclerosing cholangitis; corticosteroids	Gastric	Posa + deferasirox × 7 days; Posa × 4 mo, cured	Resolution (abdominal pain, melena)	No imaging	Signs and symptoms resolved but still on maintenance therapy
M (31)	Renal transplant; Goodpasture's disease, primary red cell aplasia, transfusion-related iron overload treated with deferoxamine, corticosteroids	Sinus	LAmB × 10 days; LAmB + deferasirox × 20 days; LAmB × 4 mo, cured	Improved (facial swelling, pain, diplopia)	Improved: diminished pansinusitis	Cured, off therapy at 5 mo of follow-up
M (40)[c]	Diabetes mellitus, chronic renal failure	Rhino-orbital-cerebral	LAmB × 13 days, change of venue; LAmB + caspo × 50 days, step-down therapy; LAmB × 206 days, failed (new flare of disease in cerebellum and brainstem); LAmB + deferasirox × 7 days, cured	No change (blind from exenteration)	Improved: marked regression of cerebellar and brainstem enhancement	Cured, off therapy at 2 yr of follow-up
M (27)	Diabetes mellitus	Rhino-orbital-cerebral	LAmB + caspo × 28 days, step-down therapy; LAmB × 122 days, step-down therapy; Posa × 400 days, failed (persistent enhancing lesion in brain with no change in size or intensity after >1 yr of therapy); Posa + deferasirox × 11 days, cured	No change (blind from exenteration)	Improved: significant regression of brainstem lesion	Cured, off therapy at 1.5 yr of follow-up
F (51)	Diabetes mellitus	Rhino-orbital-cerebral	LAmB + mica × 10 days change of venue; LAmB + mica + deferasirox × 17 days, change of venue; LAmB + mica × 10 days, step-down; LAmB + posa, ongoing	Improved (blurry vision)	Improved: persistent sinus disease but resolution of dural and cavernous sinus enhancement	Signs or symptoms improved but still on maintenance therapy

[a] ABLC, amphotericin B lipid complex; posa, posaconazole; caspo, caspofungin; mica, micafungin.
[b] "Change in venue" was defined as a transfer of a patient's care to a new facility (including transitioning from inpatient to outpatient care) or a change in the physician responsible for making treatment decisions for the patient. "Cure" was defined as a live patient with no clinical or radiographic evidence of active infection and off all antifungal therapy during follow-up.
[c] Case previously published (9).
[d] SOB, shortness of breath.

five were considered cured (i.e., alive and well and off all antifungal therapy) at a median of 365 days (range, 60 to 730 days) of follow-up.

Median serum creatinine levels increased significantly between the time of mucormycosis diagnosis and the time of initiation of deferasirox therapy, consistent with polyene-mediated alterations in glomerular function (Table 2). However, neither serum creatinine nor blood urea nitrogen levels significantly changed during deferasirox therapy, including results for three patients with markedly elevated serum creatinines at

TABLE 2. Median (interquartile range) laboratory values[a]

Measurement	Creatinine (mg/dl)	BUN (mg/dl)	AST (U/liter)	ALT (U/liter)	Alkaline phosphatase (U/liter)	Total bilirubin (mg/dl)	WBC count (1,000 cells/μl)	Absolute neutrophil count (1,000 cells/μl)	Hemoglobin (mg/dl)	Platelets (1,000 cells/μl)	Glucose (mg/dl)
At diagnosis	1.2 (0.9, 1.7)	35 (20, 40)	20 (17, 35)	30 (17, 45)	116 (70, 198)	0.9 (0.5, 1.0)	9.6 (6.0, 11.4)	5.4 (5.3, 7.4)	8.9 (8.7, 10.0)	176 (134, 321)	196 (145, 254)
At start of deferasirox	1.6 (1.4, 3)*	34 (24, 57)	27 (22, 30)	21 (17, 40)	126 (103, 134)	0.8 (0.7, 0.9)	8.1 (6.0, 10.7)	5.2 (3.9, 6.8)	9.0 (8.9, 12.2)	217 (187, 296)	131 (115, 142)*
At end of deferasirox	1.9 (1.8, 2.5)	43 (29, 66)	28 (26, 92)	49 (20, 114)	314 (126, 567)	0.6 (0.5, 0.8)	10.8 (8.0, 14.0)	5.4 (5, 10.7)	9 (8.2, 9.4)	199 (179, 347)	104 (98, 126)*
Final	2 (1.7, 2.6)	33 (28, 41)	30 (25, 36)	24 (16, 75)	133 (126, 411)	0.8 (0.6, 1.0)	8.2 (7.4, 10.2)	4.8 (3.9, 5.9)	9.3 (9, 10.3)	173 (89, 212)	126 (117, 159)*

[a] BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine aminotransferase; WBC, white blood cell. *, $P < 0.05$ versus value at diagnosis.

the time deferasirox therapy began. Liver function tests, glucose, white blood cell count, absolute neutrophil count, hemoglobin, and platelet counts were not significantly altered during the course of therapy. In three patients, mean tacrolimus levels declined from 18 ng/ml at the time of diagnosis of mucormycosis to 9 ng/ml at the time of initiation of deferasirox therapy to 4 ng/ml at the end of deferasirox therapy.

Iron was measured for only two patients, one of whom developed massive hemolysis which artificially increased iron levels during deferasirox therapy. That hemolytic reaction occurred during a blood transfusion, and the patient was subsequently found to have a positive cross-match to the donor blood; hence the reaction was felt to be independent of the use of deferasirox. For five patients, ferritin levels were so variable that meaningful changes could not be defined.

Two patients developed rashes during deferasirox therapy, the first on day 7 of therapy and the second on day 11 of therapy. Both rashes were erythematous, generalized maculopapular eruptions which spared the mucosa and were considered mild to moderate in severity. Both rashes resolved off therapy. No other adverse events from deferasirox therapy were noted.

We are aware of at least three other cases of deferasirox therapy for mucormycosis which are not included in this series because data could not be abstracted. One of the cases was previously reported (11), and failure of deferasirox salvage therapy was described for a leukemic patient with widespread disseminated disease, including bowel involvement postcolectomy. Because deferasirox is available only in an enteral formulation, it is likely that malabsorption of the drug contributed to its failure in that case. One of the authors (T. J. Walsh) was involved with the care of the other two patients, both of whom received salvage deferasirox therapy after failing previous regimens and both of whom were subsequently cured of their infection.

A double-blinded, randomized, placebo-controlled phase II clinical trial of the safety and exploratory efficacy of adjunctive deferasirox therapy for patients with mucormycosis treated with liposomal amphotericin B (LAmB) is ongoing (the deferasirox-AmBisome therapy for mucormycosis [DEFEAT Mucor] study [NCT00419770]), and results are anticipated in late 2009. The purpose of the phase II study is to lay the groundwork for a future, definitive phase III efficacy study. The drug's promising safety profile in the current series supports the need for additional study of deferasirox efficacy for this disease.

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