Clinical Experience with Posaconazole in Patients with Invasive Mucormycosis: a Case Series

MICHELLE M. GONZÁLEZ-RAMOS, MD*; JORGE BERTRÁN-PASARELL, MD, FACP*; HUMBERTO GUIOT, MD*; RUTH SOTO, MD*; JORGE SANTANA, MD†; ROSANA AMADOR, MD‡; ANA CONDE, MD‡

Posaconazole (POS) is approved for prophylaxis of Aspergillus and Candida infections in immunocompromised patients and for the treatment of oropharyngeal candidiasis. Data is limited as step-down therapy after treatment with amphotericin B (AMB). Four cases with refractory mucormycosis who had a favorable response after a change in antifungal therapy to POS are presented. In these four patients, POS demonstrated to be an effective therapeutic option in the management of refractory mucormycosis. Further studies should be conducted to define its role, whether as a single agent or as adjuvant therapy in combination with AMB.

Key words: Mucormycosis, Amphotericin B, Posaconazole

Mucormycosis is an infection caused by fungi within the Zygomycetes class, which includes the genera Rhizopus, Mucor, and Absidia. Most of the previously reported cases involve patients with immunocompromising illnesses, such as uncontrolled diabetes mellitus with ketoacidosis or hematologic malignancies. Different presentations, especially rhinocerebral and pulmonary involvement, have been observed. Despite aggressive medical and surgical treatment, mortality in patients with mucormycosis can be as high as 60 % (1). Amphotericin B (AMB) formulations have remained the mainstay of treatment for mucormycosis in combination with early surgical debridement and reversal of the factors contributing to immunosuppression. Recent studies have demonstrated that posaconazole (POS), a novel triazole agent, has in vitro activity against Zygomycetes and may represent a therapeutic option for patients with serious invasive fungal infections. Clinical data on the use of this medication for mucormycosis is limited. We present data from four patients with mucormycosis who had refractory disease despite treatment with AMB and had a favorable response after a change in antifungal therapy to POS.

*Assistant Professor; †Associate Professor; ‡Infectious Diseases Fellow; Department of Internal Medicine, Infectious Diseases Section, University of Puerto Rico School of Medicine, San Juan, Puerto Rico

Address correspondence to: Michelle M. González-Ramos, MD, Department of Internal Medicine, Infectious Diseases Section, University of Puerto Rico School of Medicine, PO Box 365067, San Juan, PR 00936-5067. Tel: (787) 754-0101 ext. 2421 • E-mail: mgonzalezmd@yahoo.com

Case Series

Case 1

A 63 year-old Hispanic female with a history of diabetes mellitus type 2 and coronary artery disease was admitted in February 2006 due to signs and symptoms compatible with chronic sinusitis that had been present for three months. The patient had been evaluated at another institution with a bone scan, MR, and maxillary biopsy which were all compatible with osteomyelitis. After a course of 42 days of intravenous antibiotics, the patient persisted with left facial pain, edema, and paresthesia. A maxillofacial CT scan revealed extensive osteomyelitis of the base of cranium with a left temporal lobe abscess. The patient underwent debridement and the pathology report was compatible with mucormycosis. She was submitted to prolonged treatment with liposomal amphotericin B (l-AMB) without complete resolution of disease confirmed by MR, which showed persistent left temporal lobe involvement. The patient was then started on POS 200 mg PO four times a day and l-AMB was discontinued. She tolerated the medication well and was then changed to 400 mg PO twice a day. She was also treated with hyperbaric oxygen as adjuvant therapy. Repeated MR of the brain 4 months after initiating therapy with POS showed considerable reduction in size of the cerebral lesion without evidence of maxillary osteomyelitis. Twenty months after being started on POS, therapy was discontinued. At the time of writing (four months after discontinuing medication), the patient is clinically stable without evidence of relapse.

Case 2

A 54 year-old black female with history of diabetes mellitus type 2, hypertension, and pacemaker placement

developed a clinical picture of chronic left maxillary sinusitis with left facial swelling in May 2006. Endoscopic sinus drainage was performed and the pathology report was compatible with mucormycosis. Despite treatment with AMB, her clinical status worsened, developing left facial paralysis. A repeated biopsy revealed a suppurative granulomatous process consistent with unresolved mucormycosis. The patient was then transferred to our institution and underwent multiple extensive surgical debridements of involved facial bones and sinuses. In view of the presence of residual disease, despite surgical procedures and completing almost 4 grams of AMB, the patient was started on POS 200 mg PO four times a day in August 2006, and AMB was discontinued. The patient tolerated POS well for which it was then changed to 400 mg PO twice a day. She also received hyperbaric oxygen as adjuvant therapy. Repeated endoscopic procedure done 6 months after being started on POS demonstrated healthy nasal mucosa without evidence of residual disease. The patient has also undergone physical therapy with partial recovery of function of the affected facial structures. More than one year after being started on POS, she is still on treatment and has been clinically stable without relapse.

Case 3

A 25 year-old Hispanic male without history of systemic illness presented himself to our institution in March 2007 with a one month history of general malaise, non-quantified fever, chills, diaphoresis, headache, and dark urine. He had been evaluated at the emergency department on several occasions and had been treated with levofloxacin for urinary tract infection without resolution of symptoms. Further reevaluation revealed severe leukocytosis, anemia, and thrombocytopenia, for which bone marrow biopsy was performed. The patient was diagnosed with AML and was started on chemotherapy. Five days after initiation of treatment, the patient was started on cefepime for neutropenic fever. However, the fever persisted despite broad spectrum antibiotics and antifungal therapy with caspofungin. The patient then developed right periorbital swelling with tenderness and erythema of the corresponding side of the face, which progressed up to a point in which he was unable to open his eye. Yellowish ocular secretions were also noted. Maxillary CT scan revealed a right small tonsillar abscess and right pansinusitis with severe soft tissue swelling. Caspofungin was discontinued and l-AMB was started to cover the possibility of filamentous fungal infection. Nasal endoscopy revealed soft tissue and bone necrosis consistent with invasive fungal infection. Necrosis of the right hard palate, nasal septum, inferior and middle turbinates, pterygoid plate, and maxillary walls was also reported. Initially, tracheotomy, subtotal right maxillectomy, and septectomy were performed with preservation of the right eye as residual vision was present. The patient underwent several surgical interventions with extensive debridement of necrotic tissue. He required a gastrostomy to provide enteral feeding. The patient continued receiving chemotherapy and l-AMB, but the development of electrolyte imbalances thought to be secondary to this medication brought the need of considering other treatment alternatives. On the 46th day of l-AMB, POS was added to therapy. Twenty-one days after receiving combination antifungal treatment, his clinical improvement had been such that l-AMB was discontinued. The patient underwent a final debridement and was discharged on POS. He has been readmitted twice for consolidation chemotherapy and remains taking POS 400 mg PO twice a day without evidence of recurrent infection.

Case 4

A 50 year-old Hispanic female without history of systemic illness presented herself to our institution in November 2007 complaining of occasional headache, retro-orbital pain, arthralgia, non-quantified fever, and chills that had been present for five months. Initial test results revealed pancytopenia and a diagnosis of dengue fever was considered. Later, the patient developed severe anemia. After a bone marrow aspiration was performed, AML was diagnosed. Low grade fever was documented after starting chemotherapy and broad spectrum antibiotics were started. Several days after, she developed diarrhea, and oral metronidazole was added to therapy for suspected Clostridium difficile colitis. After 72 hours of optimization of antibiotic treatment, fever spikes persisted and antibiotic coverage was broadened in view of the presence of multilobar pneumonia. Famciclovir and caspofungin were also added to therapy by the hematology-oncology service. On day 12 of hospitalization and just after completion of induction chemotherapy, the infectious diseases service was consulted for evaluation of persistent fever. Upon physical examination, a black eschar was noticed in the hard palate, suggesting the possibility of invasive mucormycosis. Caspofungin and metronidazole were discontinued and l-AMB was started. Nasal endoscopy revealed a right middle turbinate lesion and right septal lesion with surrounding erythema and central brownish discoloration. Biopsies of the lesions were consistent with mucormycosis. Antibacterial therapy was gradually simplified as fever improved. She could not undergo surgical debridement due to persistent thrombocytopenia. Follow up nasal endoscopy performed 14 days after l-AMB had been initiated revealed resolution of the

infectious process, eliminating the need for surgical intervention. POS 200 mg four times a day was added to antifungal treatment and l-AMB was discontinued after one week of combination therapy. The patient has been re-admitted once for consolidation chemotherapy and continues taking POS 400 mg PO twice a day without evidence of recurrence.

Discussion

Zygomycetes are fungi that can be commonly found in the soil and in a variety of foods such as fruits or bread, or decomposing plant and animal organic matter (2, 3). The risk of acquiring a serious invasive fungal infection by aerosolization depends on what degree the patient is immunocompromised due predisposing factors, such as diabetes mellitus, malnutrition, acidosis, steroid therapy, or severe neutropenia (2, 4). Other means of acquisition include exposure through disrupted cutaneous barriers, especially in trauma and burn victims, intravenous catheters, or subcutaneous injections (3, 4). The estimated incidence of mucormycosis in the United States is 1.7 cases per million people per year, or 500 cases annually (5). This incidence has been increasing during the past two decades, especially in immunocompromised patients such as those with a diagnosis of hematologic malignancy or transplant recipients.

Rhino-orbital mucormycosis is an uncommon devastating infection that can be rapidly fatal due to angioinvasion, tissue necrosis, central nervous system involvement, and/or vascular thrombosis (4, 6-7). The initial presentation frequently consists of nasal sinusitis, which can progress to involve facial structures including the palate and orbits. Patients may present with eye or facial pain and facial numbness, which can be followed by conjunctival suffusion, blurred vision, and soft tissue edema, resulting in extraocular muscle involvement and proptosis (4). The onset of bilateral facial signs strongly suggests cavernous sinus thrombosis (4). Progressive tissue invasion eventually presents as a black eschar secondary to tissue infarction. Rhino-orbital mucormycosis requires aggressive management with a combination of surgical resection, control of predisposing factors, and prolonged therapy with antifungal agents (1, 4). Patients in which urgent surgical debridement is performed have a better clinical outcome compared to those managed with antifungal therapy alone. Unfortunately, there are no tests available for the early diagnosis of this serious fungal infection. Mortality rate remains high despite treatment with high doses of AMB and debridement. It is believed that one of the contributing factors to such mortality rate is the nonspecificity of radiographic findings on imaging studies, which sometimes reveal only sinus thickening or opacification (1, 4). Patients with hematologic malignancies who experience prolonged neutropenia after chemotherapy are prone to develop mucormycosis with a possible dissemination rate of 40% and a very poor prognosis (8). Some studies have suggested that the increased use of voriconazole in hematologic malignancy patients has negatively selected Zygomycetes as agents causing opportunistic fungal infections. Exposures to voriconazole along with a history of diabetes mellitus or malnutrition were the only risk factors identified in a study conducted to evaluate the association between prophylactic or preemptive antifungal therapy and zygomycosis (9).

A high level of suspicion in high-risk patients is critical in the early initiation of empiric antifungal therapy. The lack of activity of newer antifungal agents, such as the echinocandins and voriconazole, has been well established (8). Despite the risk of renal toxicity, which can be as high as 80%, high doses (1-1.5mg/kg/day) of AMB has remained the gold standard antifungal agent against mucormycosis (2, 10). Recent reports have postulated the use of l-AMB as a better therapeutic agent in view of improved penetration into the blood brain barrier than the conventional formulation. Liposomal formulations facilitate deposition of this drug into the reticuloendothelial system with higher dose concentrations in the central nervous system (8). A markedly improved survival rate of 67% with l-AMB was observed when compared to 39% in those treated with regular AMB formulation (11). Liposomal formulations have also been shown to bind preferentially to fungal cell membranes, which might explain its reduced toxicity in vivo (10).

POS is an extended-spectrum triazole indicated in the prophylaxis of invasive Aspergillus and Candida infections in immunocompromised patients, 13 years or older, and for treatment of oropharyngeal candidiasis. It has demonstrated activity against Zygomycetes, both in vitro and in animal models (1, 12-13). Microbiologic studies have confirmed in vitro activity comparable to AMB against Rhizopus and Mucor (1, 14). Several reports have documented a good clinical response when used as salvage therapy in patients with refractory disease, such as the cases discussed above. A retrospective study performed to evaluate the activity of POS in the treatment of zygomycosis in 91 cases revealed an overall success of 60% at 12 weeks following the initiation of treatment (15). Some of these patients had an overall response similar to those who were treated with POS as monotherapy (15). The high success rate in the

subpopulation of patients with cerebral involvement suggests that this medication has the ability to penetrate brain parenchyma (15). Our experience in the resolution of the cerebral infection in Case 1, which was evidenced by MR after conservative management with POS without the need of neurosurgical intervention, supports its role in the management of rhinocerebral involvement. These findings place POS as an attractive alternative in patients intolerant to AMB or in whom its use has been limited by nephrotoxicity.

Some studies suggest that early institution of therapy with POS may be critical in the management and outcome of mucormycosis (1). Other advantages of this medication are its oral formulation, a favorable safety profile, an adequate oral bioavailability, and good tolerance, which make much easier the management of patients on an ambulatory basis once they are clinically stable. Our experience also suggests that POS has an important role in the management of immunosuppressed patients who require continuous treatment for their underlying illnesses, such as hematologic malignancies, and who may be at high risk of mucormycosis relapse. POS should be taken with meals or nutritional supplements to increase its gastric absorption. A seven-day period treatment is required prior to reaching plasma steady state levels, and combination therapy during the first week with AMB has been recommended (1). The initial dose of 200 mg four times a day can be changed to 400 mg twice a day once the patient is clinically stable and is tolerating the medication. Because only a few patients have been managed with POS on a long-term basis, there are no specific recommendations about length of therapy, which has varied from 23 to 156 weeks (1). One of our patients was on therapy during 88 weeks with resolution of disease and no apparent recurrence after discontinuation. Some investigators have suggested extending treatment for 12 months after adequate surgical debridement.

The role of hyperbaric oxygen as adjuvant therapy is still controversial in patients with mucormycosis. It is difficult to specifically determine if hyperbaric oxygen therapy was a determining factor in the management of our patients. It is believed that higher oxygen pressures improve the ability of neutrophils to fight the infectious process (4). In vitro studies have confirmed the inhibition of germination of fungal spores and growth of mycelia (16).

Conclusion

The increasing frequency of invasive mucormycosis in immunocompromised patients during the past decade suggests the importance of evaluating new treatment strategies for the management of such a devastating opportunistic infection. In our four patients, POS has demonstrated to be an effective and safe therapeutic option for refractory disease and can be a long-term treatment alternative in patients with residual infection. Further studies should be conducted to define its role in the management of mucormycosis, whether as a single agent or as adjuvant therapy in combination with AMB. The use of hyperbaric oxygen therapy may be an important contributing factor in the favorable outcome of patients with mucormycosis and could be an alternative to consider when studying treatment options.

Resumen

Mucormicosis es una infección causada por un hongo que afecta a pacientes inmunocomprometidos, como aquellos que padecen de diabetes descontrolada con cetoacidosis o malignidades hematológicas. La incidencia estimada de mucormicosis en los Estados Unidos es de 500 casos anuales. La presentación rino-orbital de esta enfermedad puede ser devastadora y rápidamente fatal mediante la invasión de vasos sanguíneos, necrosis del tejido y afección del sistema nervioso central. El cuadro clínico usualmente consiste en sinusitis que progresa afectando otras estructuras faciales, como el paladar y las órbitas. La mortalidad de esta enfermedad puede ser de un 60% a pesar de un manejo médico-quirúrgico agresivo. La anfotericina B actualmente es la droga de elección para tratar esta afección. Los estudios recientes han sugerido que el posaconazol, un agente antifungal indicado en la profilaxis de infecciones por Candida y Aspergillus en pacientes mayores de 13 años y en el tratamiento de candidiasis orofaríngea, pudiese tener un rol importante en el manejo de pacientes con mucormicosis. En este artículo se presentan cuatro casos de pacientes con un diagnóstico de mucormicosis que tuvieron una respuesta clínica adecuada al cambiarles la terapia de anfotericina B, ya fuese en su preparación convencional o liposomal, a posaconazol. Múltiples factores colaboraron en el tratamiento exitoso de estos cuatro pacientes y en el manejo de éstos a nivel ambulatorio. Entre estos factores se encuentran la preparación oral del posaconazol, su buena biodisponibilidad, un perfil de seguridad favorable y una tolerancia adecuada. La duración de la terapia sugerida por varios investigadores luego del tratamiento quirúrgico adecuado es de 12 meses. Se deben llevar a cabo estudios futuros para definir el rol del posaconazol en el manejo de pacientes con mucormicosis, ya sea como agente principal o como adyuvante en combinación con anfotericina B.

Acknowledgements

Two of the patients described above participated in a non-funded protocol conducted by Schering Plough Pharmaceuticals regarding the use of POS in the management of invasive fungal infections. At the time of writing, one of the patients is enrolled in the Commitment to Care Program from this pharmaceutical company. Four authors have participated in POS speaker programs offered by Schering Plough del Caribe.

References

1. Kok J, N Gilroy, C Halliday, OC Lee, D Novakovic, P Kevin, S Chen. Early use of posaconazole in the successful treatment of rhino-orbital mucormycosis caused by Rhizopus oryzae. J Infect 2007;55:33-36.
2. Nosari A, P Oreste, M Montillo, G Carrafiello, M Draisci, G Muti, A Molteni, E Morra. Mucormycosis in hematologic malignancies: an emerging fungal infection. Haematologica 2000;85:1068-1071.
3. Kauffman CA. Zygomycosis: reemergence of an old pathogen. Clin Infect Dis 2004;39:588-590.
4. Spellberg B, J Edwards Jr, A Ibrahim. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev 2005;18:556-569.
5. Rees JR, RW Pinner, RA Hajjeh, ME Brandt, AL Reingold. The epidemiologic features of invasive mycotic infections in the San Francisco Bay area, 1992-1993: results of population-based laboratory active surveillance. Clin Infect Dis 1998;27:1138-1147.
6. Gelston C, V Durairaj, E Simoes. Rhino-orbital mucormycosis causing cavernous sinus and internal carotid thrombosis treated with posaconazole. Arch Ophthalmol 2007;125:848-849.
7. Barchiesi F, E Spreghini, A Santinelli, A Fothergill, E Pisa, D Giannini, MG Rinaldi, G Scalise. Posaconazole prophylaxis in experimental systemic zygomycosis. Antimicrob Agents Chemother 2007;51:73-77.
8. Pagano L, M Offidani, L Fianchi, A Nosari, A Candoni, M Piccardi, L Corvatta, D D'Antonio, C Girmenia, P Martino, A Del Favero. Mucormycosis in hematologic patients. Haematologica 2004;89:207-214.
9. Kontoyiannis DP, M Lionakis, RE Lewis, G Chamilos, M Healy, C Perego, A Safdar, H Kantarjian, R Champlin, TJ Walsh, II Raad. Zygomycosis in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis 2005;191:1350-1360.
10. Walsh TJ, JW Hiemenz, NL Seibel, JR Perfect, G Horwith, L Lee, JL Silber, MJ DiNubile, A Reboli, E Bow, J Lister, EJ Anaissie. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. Clin Infect Dis 1998;26:1383-1396.
11. Gleissner BA, A Schilling, I Anagnostopopous, I Siehl, E Thiel. Improved outcome of zygomycosis in patients with hematological diseases? Leuk Lymphoma 2004;45:1351-1360.
12. Sun Q, LK Najvar, R Bocanegra, D Loebenberg, JR Graybill. In vivo activity of posaconazole against mucor ssp. In an immunosuppressed-mouse model. Antimicrob Agents Chemother 2002;46:2310-2312.
13. Almyroudis, NG, DA Sutton, AW Fothergill, MG Rinaldi, S Kusne. In vitro susceptibilities of 217 clinical isolates of zygomycetes to conventional and new antifungal agents. Antibiob Agents Chemother 2007;51:2587-2590.
14. Tobón A, M Arango, D Fernández, A Restrepo. Mucormycosis (zygomycosis) in a heart-kidney transplant recipient: recovery after posaconazole therapy. Clin Infect Dis 2003;36:1488-1491.
15. Van Burik J, RS Hare, HF Solomon, ML Corrado, DP Kontoyiannis. Posaconazole is effective as salvage therapy in Zygomycosis: a retrospective summary of 91 cases. CID 2006:42:61-65.
16. Robb SM. Reactions of fungi to exposure to 10 atmospheres pressure of oxygen. J Gen Microbiol 1966:45:17-29.