

Posaconazole Treatment in Korea: Single-Center Experience Over 5 Years

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Purpose: Posaconazole is a second-generation triazole with a broad spectrum. However, there is a lack of data to support a significant role for posaconazole in the treatment of invasive fungal infection (IFI), especially in Korea. Until recently, posaconazole was available only through the Korean Orphan Drug Center. This study was designed to review the use of posaconazole at a single-center in Korea.

Materials and Methods: Data from patients who received posaconazole treatment at Catholic Blood and Marrow Transplantation Center were retrospectively reviewed between January 2007 and September 2012. **Results:** A total of 11 cases (3 males and 8 females, median age 52 years) received posaconazole. Five patients were given the drug for mucormycosis, two for invasive aspergillosis, and four for unspecified IFI for which galactomannan (GM) assays were negative. The treatment duration ranged from 4-250 days. Three patients received posaconazole for management refractory IFI, two for intolerance of previous antifungal therapy, and six for long-term maintenance treatment. The overall successful response rate to posaconazole was 55% (six of eleven patients). Five of eleven patients died during the study period. However, only one death was attributed to the progression of IFI. None of the patients discontinued posaconazole therapy due to adverse events.

Conclusion: Posaconazole is an attractive oral antifungal agent for salvage treatment of IFI, particularly upon diagnosis of mucormycosis or in cases in which mucormycosis cannot be ruled out due to a negative GM.

Key Words: Immunocompromised host, mucormycosis, posaconazole, salvage therapy

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INTRODUCTION

Posaconazole (Noxafil®, Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA) is a second-generation triazole that exhibits *in vitro* activity against many filamentous fungi and yeasts.¹ It exerts its effects by direct inhibition of the enzyme

lanosterol 14- α demethylase, which is responsible for the development of ergosterol.² Posaconazole is highly lipophilic, orally absorbed, and distributed extensively in tissues.³ It has been approved by Korea Food and Drug Administration for antifungal prophylaxis in high risk patients with acute myeloid leukemia or myelodysplastic syndrome, who are expected to have prolonged neutropenia after cytotoxic chemotherapy, and in immunosuppressed patients with graft-versus-host disease after hematopoietic stem cell transplant. Also, it has received approval from US Food and Drug Administration or European Commission, for treatment of oropharyngeal candidiasis patients who require systemic administration of an antifungal agent, as well as for treatment invasive aspergillosis (IA) patients who have refractory diseases to amphotericin B deoxycholate (AMB) or itraconazole, or who are intolerant to these drugs. Posaconazole has also been proposed as an alternative therapeutic agent for infections caused by some filamentous fungi, including *Mucorales*.^{4,5} However, in Korea, there is a lack of data to support a significant role for posaconazole in the treatment of invasive fungal infection (IFI). Until recently, posaconazole was available through the Korean Orphan Drug Center. Here, we describe the use of posaconazole for the salvage treatment of patients with IFI at a single-center in Korea.

MATERIALS AND METHODS

Study design

Data from patients who received posaconazole at Catholic Blood and Marrow Transplantation Center between January 1, 2007 and September 15, 2012 were retrospectively reviewed. Information from case notes, radiological findings and laboratory results were compiled using a structured case-report form. The endpoint of the study was set to September 15, 2012 or time of death or loss to follow-up. This study was approved by the Institutional Review Board of Seoul St. Mary's hospital at the Catholic University of Korea (No. KC12RISI0411).

Definitions

The classification of proven, probable, and possible IFI was made based on the European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria.⁶

Posaconazole salvage treatment was applied when cases fulfilled at least one of the following criteria: 1) presence of

a refractory IFI (disease progression, or failure to improve clinically after at least 7-day use of other licensed antifungal agents); 2) history of intolerance of standard antifungal therapy due to toxicity; 3) preexisting organ dysfunction that prevented the administration of other licensed antifungal therapies; or 4) need for long-term maintenance treatment of IFI with posaconazole after treatment with any other antifungal agent.¹

Clinical responses were evaluated at the end of treatment using both clinical and radiological data. However, if posaconazole was administered to the subject after the end of the research period, clinical responses were assessed in September 15, 2012, the end of this study. Assessments of IFI treatment responses were made based on EORTC/MSG criteria.⁷ Successful response were defined as either a complete response (CR) or partial response (PR).⁸

Neutropenia was defined as an absolute neutrophil count <500 cells/mm³ or expected to be <500 cells/mm³ within 2-3 days.⁹ Toxicity was recorded and categorized using the National Cancer Institute Common Toxicity Criteria, version 4.0 when possible.¹⁰

RESULTS

Patient characteristics

A total of 11 patients (3 males and 8 females) received posaconazole treatment between January 1, 2007 and September 15, 2012. The characteristics of the patients are shown in Table 1. The median age of the patients was 52 years. All patients had hematologic diseases. Most patients [seven (64%) of eleven] had neutropenia at the diagnosis of IFI. Five of the 11 patients received posaconazole treatment for mucormycosis, two for IA, and four for unspecified IFI for which galactomannan (GM) assays were negative. The six patients had proven, two had probable, and three had possible IFI categories. The most common site of infection was the lungs, which was documented in 6 cases (55%).

Prior antifungal drug exposure and surgical treatment

Antifungal agents administered prior to initiation of posaconazole therapy included either AMB, liposomal amphotericin B deoxycholate (LAMB), caspofungin (CSFG), or voriconazole (Table 2). Surgical resection was performed in six patients. Among them, five patients had mucormycosis and one patient (No. 9) had IA at the paranasal sinus and eye which was distinguished between mucormycosis and aspergillosis.

Table 1. Clinical Characteristics of Patients Who Underwent Posaconazole Treatment

Patient	Age/sex	Underlying disease (disease status)	Neutropenia at IFI diagnosis	Site of infection	Pathology, culture	Suggestive organism	Diagnosis (EORTC/MSG criteria)	GM assay
1	35/F	AML (after reinduction CTx)	Y	Fallopian tube Colon Psoas muscle	Fallopian tube, colon biopsy: wide angled branched, non septated fungal hyphae	Mucormycosis	Mucormycosis (proven)	Negative
2	52/M	MM (during PBSC mobilization)	N	Skull base External ear	Ear abscess culture: <i>Mucor</i> genera Mastoid biopsy: wide angled branched, non septated fungal hyphae	Mucormycosis	Mucormycosis (proven)	Negative
3	55/M	AML (during consolidation CTx)	Y	Paranasal sinus	Paranasal sinus biopsy: septated fungal hyphae	Miscellaneous	IFI (proven)	Negative
4	66/F	MPAL (during reinduction CTx)	Y	Lung CNS	Not done	Miscellaneous	IFI (possible)	Negative
5	47/F	AML (during reinduction CTx)	Y	Lung	Not done	Miscellaneous	IFI (possible)	Negative
6	47/F	SAA (post state of allogeneic SCT)	N	Lung	Bronchial wash fluid culture: <i>Cunninghamella bertholletiae</i> Lung abscess biopsy: sporangioophores in terminal swellings fungal hyphae	Mucormycosis	Mucormycosis (proven)	Negative
7	53/F	AML (during reinduction CTx)	Y	Lung	Not done	Miscellaneous	IFI (possible)	Negative
8	37/F	AML (after consolidation CTx)	N	Lung	Lung biopsy: wide angled branched, non septated fungal hyphae	Mucormycosis	Mucormycosis (probable)	Negative
9	56/F	ALL (during induction CTx)	Y	Eye Paranasal sinus	Paranasal sinus biopsy: acute angled branched, septated fungal hyphae	Aspergillosis	IA (proven)	Positive
10	32/F	AML (after autologous SCT, recur)	Y	Liver Ileum	Liver, ileum biopsy: wide angled branched, non septated fungal hyphae	Mucormycosis	Mucormycosis (proven)	Negative
11	67/M	AML (after consolidation CTx)	N	Lung	Not done	Aspergillosis	IPA (probable)	Positive

IFI, invasive fungal infection; EORTC/MSG, the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group; GM, galactomannan assay; AML, acute myeloid leukemia; CTx, chemotherapy; MM, multiple myeloma; PBSC, peripheral blood stem cell; MPAL, mixed phenotype acute leukemia; CNS, central nervous system; SAA, severe aplastic anemia; SCT, stem cell transplantation; ALL, acute lymphoblastic leukemia; IA, invasive aspergillosis; IPA, invasive pulmonary aspergillosis.

Posaconazole treatment and outcome

Posaconazole was administered for an average of 75 days (range, 4-250 days) (Table 2). The median duration of treatment was 37 days. Of the 11 patients, three met the criteria for infection refractory to other licensed antifungal therapy and two had demonstrated intolerance to standard therapy. Six required long-term maintenance therapy of IFI in which mucormycosis could not be ruled out. The overall successful response rate to posaconazole was 55% (6 of 11 patients). CR was seen in patient No. 2, who had cerebral mucormycosis. Five of the 11 patients died during the study period. However, only one death was attributed to the progression of IFI.

Safety

Two subjects developed hepatotoxicity (grades II and III), but the clinical pictures were reversed without discontinua-

tion of posaconazole. Anorexia (grade I) and nausea (grade II) were considered possibly related to the drug. All adverse events were mild to moderate in severity. None of the patients discontinued use due to clinical or laboratory adverse events. There was no visual disturbance or QT prolongation. In general, posaconazole appeared to be safe and well tolerated in this study group.

Selected case reports

Patient No. 5

A 47-year-old woman with acute myeloid leukemia developed fever and chills after the reinduction of chemotherapy. Twelve days after the initiation of chemotherapy, she was started on cefepime and isepamicin for neutropenic fever. However, the fever persisted in spite of the administration of broad-spectrum antibiotics. Chest computed tomography

Table 2. Antifungal Treatments and Outcomes

Patient	Prior antifungal therapy (days)	Surgical resection	Posaconazole					Death (cause of death)
			Reason for use	Dose (mg/day)	Duration (days)	Adverse event (grade)	Response	
1	AMB 1 mg/kg/D QD (65) LAMB 3 mg/kg/D QD (103)	Y	Intolerance	800	10	Nausea (II)	SR	Dead (bacterial pneumonia)
2	AMB 1 mg/kg/D QD (4) LAMB 5 mg/kg/D QD (84)	Y	Refractoriness (combination Tx with LAMB)	800	250	Hepatotoxicity (III) Nausea (II)	CR	Alive
3	LAMB 3 mg/kg/D QD (37)	N	Maintenance	800	29	Anorexia (I)	SR	Alive
4	AMB 1 mg/kg/D QD (24) CSFG 50 mg/m ² QD (8) LAMB 5 mg/kg/D QD (21)	N	Intolerance	800	4	None	PD	Dead (fungal brain abscess)
5	AMB 1 mg/kg/D QD (3) CSFG 50 mg/m ² QD (10) LAMB 4 mg/kg/D QD (62)	N	Maintenance	600	217	Hepatotoxicity (II)	PR	Alive
6	AMB 1 mg/kg/D QD (21) LAMB 5 mg/kg/D QD (10)	Y	Refractoriness	800	137	None	PR	Alive
7	AMB 1 mg/kg/D QD (15) LAMB 3 mg/kg/D QD (49)	N	Maintenance	600	20	None	SR	Dead (progression of AML)
8	AMB 1 mg/kg/D QD (15)	Y	Maintenance	800	12	None	SR	Alive
9	AMB 1 mg/kg/D QD (29) LAMB 3 mg/kg/D OD (29)	Y	Maintenance	800	38	None	PR	Dead (progression of ALL)
10	AMB 1 mg/kg/D QD (22) LAMB 5 mg/kg/D OD (76)	Y	Maintenance	800	37	None	PR	Alive
11	AMB 1 mg/kg/D QD (3) CSFG 50 mg/m ² QD (6) VCZ 200 mg BID (59)	N	Refractoriness	800	71	None	PR	Dead (bacterial infection septic shock)

AMB, amphotericin B deoxycholate; QD, every day; LAMB, liposomal amphotericin B deoxycholate; SR, stable response; CR, complete response; CSFG, caspofungin; PD, progression of fungal disease; PR, partial response; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; VCZ, voriconazole; BID, twice a day.

(CT) revealed multiple consolidations with surrounding ground-glass opacities in the right-upper lobe (Fig. 1A). AMB was administered empirically for fungal pneumonia. Three days after starting AMB, she began to experience severe chills, nausea, and headache upon AMB administration. AMB was substituted with CSFG, but 10 days later both the chest CT and clinical status had worsened (Fig. 1B). Instead of CSFG, LAMB therapy was started. On the eighth day of LAMB treatment, follow-up chest CT showed a slight interval decrease in consolidations, and the patient's condition had improved. GM assays were consistently negative, therefore, the patient had the possibility of mucormycosis. Long-term LAMB therapy was required for complete resolution, but the patient wished to be discharged. Therefore, posaconazole was administered for continued treatment of IFI in the outpatient clinic. After 40 days of posaconazole treatment, the patient underwent successful allogeneic stem cell transplantation. Following the initiation of posaconazole, liver enzymes were slightly elevated, but returned to normal without discontinuation of posaconazole. The patient continues to take posaconazole and her IFI has shown a PR, as revealed by 6-month follow-up chest CT (Fig. 1C).

Patient No. 6

A 47-year-old woman was admitted to the hospital because of cough, sputum, and fever. Allogeneic stem cell transplantation for severe aplastic anemia was performed 1 month previously. Chest CT revealed necrotizing pneumonia with

abscesses in the right peribronchial area and subpleural portion of the right lower lobe (RLL) (Fig. 2A and B). Serum GM assay was negative. AMB was administered in addition to meropenem. After 21 days, AMB was changed to LAMB to increase treatment efficiency. Bronchoscopic biopsy of the lung tissue showed sporangioophores in terminal swellings with positive Gomori methenamine-silver and periodic acid-Schiff stains. Cultures from bronchial-wash fluid were positive for *Cunninghamella bertholletiae*. Follow-up chest CT revealed little interval change in pneumonia. After 10 days, LAMB was discontinued and posaconazole was started for the treatment of refractory IFI. After posaconazole administration, her clinical status improved. About six months later, chest imaging (Fig. 2C) showed a PR in the right peribronchial region. However, abscess in the subpleural portion of the RLL remained with little interval decrease. The patient subsequently underwent a video-assisted thoracoscopic wedge resection of the RLL abscess. The pathologic results of the RLL lung abscess were consistent with *Cunninghamella bertholletiae*. Posaconazole was discontinued after the resection, and the patient showed no relapse.

DISCUSSION

Posaconazole has been proposed as an option for salvage treatment of IFI. Because posaconazole is not readily available in Korea, there are few clinical reports of its use.^{11,12}

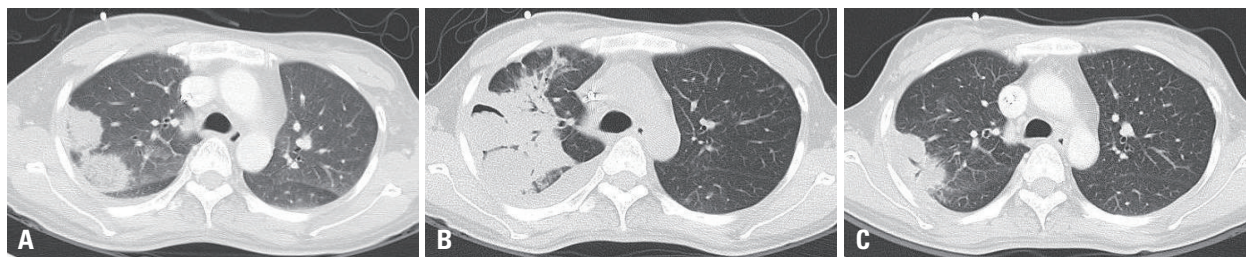


Fig. 1. The chest computed tomography of patient No. 5 shows two, round consolidations with surrounding grounding glass opacities in the right upper lobe: (A) at the time of diagnosis of fungal pneumonia, (B) 2 weeks later, (C) 6 months later.

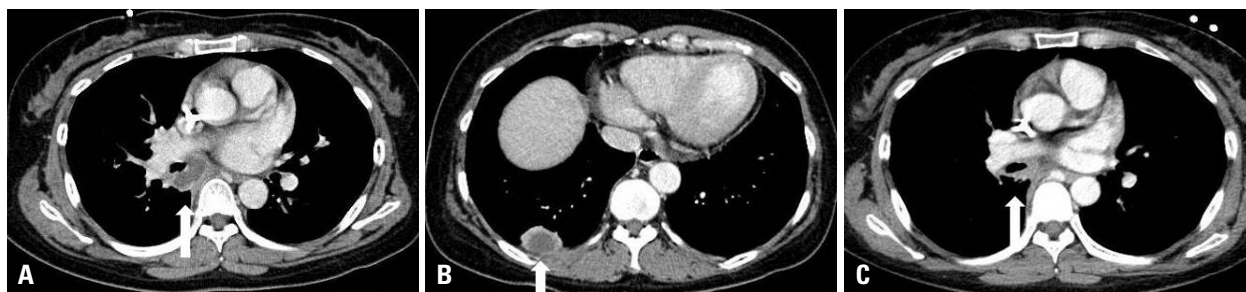


Fig. 2. The chest computed tomography of patient No. 6 shows necrotizing pneumonia: (A) superior segment of the right lower lobe at the time of diagnosis of pulmonary mucormycosis, (B) subpleural portion of the right lower lobe at the time of diagnosis of pulmonary mucormycosis, (C) 6 months later.

Here, we present our experience with posaconazole as an IFI salvage treatment.

In this study, a total of 11 patients received posaconazole over the last 5 years; among them, five (45%) exhibited mucormycosis. In the rest of the subjects, however, among whom GM assays were negative in 4 IFI patients, mucormycosis could not be ruled out. It is well-known that only AMB formulations and posaconazole have shown activity against Mucorales.¹³ Even though AMB formulations have been recommended as first-line therapies for mucormycosis treatment, posaconazole has been shown to be effective as a salvage therapy of refractory mucormycosis.³ Posaconazole may represent an alternative option for patients intolerant of AMB formulations.¹⁴ Among the subjects of the present study, two received posaconazole due to AMB and LAMB intolerance. Two cases received posaconazole for treatment-refractory mucormycosis. Cornely, et al.¹⁴ suggested that if impaired kidney function is overt or expected, posaconazole could be a reasonable option for the primary treatment of mucormycosis. However, it should be noted that posaconazole has a lower efficacy than AMB against some Mucorales species, as suggested by an *in vitro* study.¹⁵ In our study, posaconazole was used only for salvage treatment.

Posaconazole can be also applied for refractory IA.^{16,17} Previously, an externally controlled trial was conducted to determine the efficacy and safety of posaconazole salvage treatment in patients with IA.¹⁸ The overall success rate was 42% in posaconazole recipients and 26% in controls. Our study comprised one refractory invasive pulmonary aspergillosis patient who received posaconazole treatment, after the use of AMB, CSFG and voriconazole. The outcome of posaconazole for the patient was PR. Voriconazole has been recommended as a first-line treatment for IA; however, posaconazole may be an attractive option for salvage therapy of IA.¹⁹

The efficacy of posaconazole salvage therapy in 91 cases of mucormycosis infection was examined retrospectively.²⁰ The rate of success (CR and PR) was 60%, and 21% of the patients had stable response. In our report, the overall success rate was 55%, and only one death was attributed to IFI. Furthermore, CR was seen in a patient with lethal cerebral mucormycosis. Thus, posaconazole may be an effective modality for salvage therapy of IFI, especially mucormycosis.

In this study, 6 patients received posaconazole as maintenance therapy after using an intravenous antifungal agent. Krishnan-Natesan, et al.²¹ examined the fungicidal activity of AMB and posaconazole against Mucorales *in vitro*. They reported that the fungicidal activity of AMB was more rapid

than that of posaconazole. The authors pointed out that using AMB in the early phase, followed by a later switch to posaconazole, may have had a clinical benefit. The findings of our study are consistent with Kontoyiannis' strategy.²² The author suggested AMB use (with or without an echinocandin) for the first 2-3 weeks in patients with mucormycosis as an induction therapy, and a subsequent step-down to oral posaconazole as maintenance/secondary prophylaxis. This is a useful clinical modality because few drugs are effective against mucormycosis. In addition, no oral drug is currently available for mucormycosis outpatients. Posaconazole may thus facilitate a reduction in the hospitalization period.

In terms of safety, 11 patients had no evidence of nephrotoxicity after using posaconazole. Thus, posaconazole can be safely given to patients who are intolerant to AMB because of nephrotoxicity. The most common side effects of posaconazole are gastrointestinal disturbances [nausea (5%), vomiting (4%), and diarrhea (3%)].²³ The safety of posaconazole was previously examined, and treatment-related adverse effects were reported in 38%.²⁴ The authors concluded that long-term posaconazole treatment is associated with a generally favorable safety profile. In our study, three patients (No. 2, 5, and 6) received posaconazole treatment for more than 3 months. Although two patients (No. 2 and 5) had hepatotoxicity and nausea, these adverse events were transient and did not warrant withholding of the medication.

To our knowledge, our results are the first report of the current status of posaconazole treatment in Korea. There were two case reports of posaconazole treatment in rhinocerebral mucormycosis in 2010.^{11,12} Our findings suggest that posaconazole is an effective and safe oral antifungal agent for salvage treatment of IFI, particularly when mucormycosis is diagnosed or when it cannot be ruled out due to a negative GM result. Limitations of this study include its retrospective design and use of a small sample size from a single-center. In addition, we were unable to obtain information regarding serum levels of the drug.

Further investigations should evaluate posaconazole treatment in Koreans, including its role in the prevention of IFIs and its pharmacokinetic properties.

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