Isavuconazole treatment of a patient with disseminated mucormycosis

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Abstract

We report a patient with relapsed acute myelogenous leukemia after allogeneic stem cell transplantation who developed disseminated mucormycosis due to *Rhizomucor pusillus/miehei* involving lung, brain and skin. After failing posaconazole and being intolerant to amphotericin, he was treated effectively with isavuconazole for over six months despite ongoing treatment for relapsed leukemia.
Case Report

A 59-year-old male construction worker, with a past history of coronary artery disease, was diagnosed with myelodysplastic syndrome (MDS) and underwent reduced-intensity HLA-matched related allogeneic hematopoietic stem cell transplantation (HSCT) in October 2008. In July 2009 (9 months later) a bone marrow biopsy demonstrated MDS relapse and progression to acute myelogenous leukemia (AML), which persisted despite tapering of immunosuppression and donor-lymphocyte infusion.

In August 2009, he presented to the emergency room with left upper quadrant and shoulder pain, diaphoresis, and fevers. Chest X-ray demonstrated a left lower lobe infiltrate. He was admitted to the hospital and started on ceftazidime for suspected bacterial pneumonia. His leukocyte count was 36,000/μL with 14% blasts and an absolute neutrophil count of 11,500/μL.

The patient underwent bronchoalveolar lavage but no bacteria or fungi grew in culture. Serum galactomannan and (1→3)-β-D-glucan were also negative. He was started on hydroxyurea and reinduction chemotherapy with cytarabine and daunorubicin, after bone marrow biopsy confirmed progressive AML.

His hospital course was complicated by neutropenia, mucositis, persistent fevers, pain and redness at his central venous catheter site. The catheter was removed and empirical treatment with vancomycin and micafungin were initiated a week after admission.

Ten days after admission, a chest computed tomography (CT) scan revealed a left-sided pleural effusion, scattered areas of nodular consolidation with adjacent ground-glass in the right lower lobe and bilateral ground-glass abnormalities. The patient developed altered mental status and facial droop 18 days after admission. A head CT was normal. Subsequent brain MRI
demonstrated multiple foci of restricted diffusion compatible with acute ischemia or embolic events.

The patient developed violaceus nodular plaques on his face, scalp, posterior neck and mid upper back two weeks after admission. A skin biopsy was performed and revealed hyphal forms suggestive of mucormycosis within and outside dermal vessels on hematoxylin-eosin stain. Skin biopsy cultures were negative. Three weeks after admission, treatment with liposomal amphotericin (LAmB) 5mg/Kg once daily was started. Improvement was noted with decrease in the size of the skin lesions and partial improvement in mental status.

The patient received treatment with LAmB for four weeks. The infecting species was identified as *Rhizomucor pusillus/miehei* by DNA sequencing performed on formalin-fixed, paraffin-embedded skin biopsy tissue. Extracted DNA was amplified by a semi-nested PCR targeting the 18S rDNA of Mucorales (1, 2). Sequencing demonstrated 100% identity to the 18S rDNA of *Rhizomucor pusillus/miehei*. Given this information, the patient was switched to oral posaconazole solution 200mg four times per day and subsequently discharged to home on posaconazole after five additional days of treatment in hospital.

In October 2009, three days after discharge (after 8 days of posaconazole treatment), patient returned to hospital with new onset seizures and altered mental status. Head CT showed a significant increase in edema surrounding the brain lesions (Figure 1). Due to the clinical deterioration, he resumed LAmB treatment. No posaconazole blood levels were obtained on admission. He stabilized but experienced significant further adverse effects including catheter-associated *Staphylococcus aureus* bacteremia and severe LAmB related renal tubular potassium and magnesium wasting that precluded discharge.
Given these circumstances, we obtained FDA authorization under the Emergency Investigational New Drug program (EIND #107,161) and from our Human Research Committee to treat the patient with oral isavuconazole, which was started in November 2009. The patient received a two-day oral loading dose of 200mg three times per day (600mg/day) followed by a daily dose of 200mg/day, the same dose regimen being studied in the Phase 3 program. The patient was able to go home two days later.

Four days later, the patient returned for a scheduled follow-up appointment. He experienced intermittent nausea. The cutaneous lesions remained stable. He displayed mild aphasia and decreased breath sounds on the right base with occasional crackles in the left base.

Isavuconazole (BAL4815) plasma levels were measured during the loading dose and on subsequent clinic visits (Table 1), using analytical methods based on liquid chromatography-mass spectrometry with a lower limit of quantification of 5ng/mL (Inovalab AG, Switzerland). The trough levels were initially below the 1000-2000 ng/mL selected target range. As a result a re-loading protocol of 6 doses over 48 hours was prescribed, while maintenance dose was increased from 200 to 400 mg/day. Despite mild nausea and minimal elevations of alanine transaminase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase, no other adverse effects were noted. Since the patient had reached an isavuconazole level within the target range (1322 ng/mL) before the re-loading doses, the maintenance dose was reduced back to 200mg/day after drug level results became available. No electrocardiogram abnormalities were noted; QTc remained less than 450msec throughout treatment.

On his one-month follow up, neurological deficits and cutaneous lesions had resolved clinically. The patient had increased appetite and gained weight. AST and ALT values had normalized but his blood work demonstrated evidence of relapsed AML. His leukemia now had
a FLT-3 mutation, so he started treatment with sorafenib and hydroxyurea. Given that isavuconazole is a moderate CYP3A4 inhibitor and sorafenib a 3A4 substrate the dose of sorafenib was adjusted.

A chest CT scan 19 weeks on isavuconazole treatment (March 2010), showed reduction of the dominant mass with an air crescent sign apparent and areas of low attenuation, as well as significant improvement of the pleural effusions (Figure 2). A head CT scan at the same time interval showed that the brain lesions had decreased in size and had no surrounding edema (Figure 1). Trough isavuconazole levels remained between 1851-3968 ng/mL during treatment. The patient received further treatment with azacitidine for relapsed AML. He was able to celebrate his 60th birthday at home. He received 29 weeks of isavuconazole until he expired from refractory leukemia. No autopsy was performed.

Mucormycosis is a life-threatening and emerging disease in immunocompromised hosts in which patients usually develop relatively rapid angioinvasive fungal disease. Treatment options are limited. Only amphotericin formulations are reliably active to treat this disease. Mucorales are usually resistant to antifungal agents commonly used to treat presumed fungal disease, such as voriconazole and the echinocandins (3). The response of mucormycosis to antifungal agents is host- and site-dependent and is particularly problematic in patients with hematological disorders or who have undergone HSCT (4). Although less common than other invasive fungal diseases, such as those caused by Aspergillus species, mucormycosis is associated with higher mortality. A comprehensive review of patients with mucormycosis showed that dissemination developed in 23% of cases and was associated with 96% mortality.
Thus, early recognition of this disease along with aggressive management and appropriate antifungal treatment is critical for optimal outcomes (3, 5).

In the present case, the patient presented with disseminated mucormycosis involving lung, brain and skin and was successfully treated with isavuconazole in the setting of relapsed leukemia after allogeneic HSCT after failing posaconazole and being intolerant to amphotericin. The diagnosis was established by skin biopsy, and imaging was consistent with lung and brain involvement. Even though respiratory and skin biopsy cultures were negative, tissue PCR and sequencing confirmed *Rhizomucor pusillus/miehei* as the causative agent (1, 2).

To our knowledge this is the first report of isavuconazole treatment of mucormycosis in the United States. Ervens and colleagues recently reported a patient in Germany with ulcerative colitis on prednisolone treatment that developed sinoorbital mucormycosis caused by *Rhizopus oryzae* in whom isavuconazole was used for further treatment after extensive surgical resection and histopathological findings suggestive of persistent infection after nearly two months of treatment with amphotericin and posaconazole (6).

Our patient was initially treated with and responded to LAmB and then switched to oral posaconazole for further treatment. He did not undergo surgical resection of his multiple brain and lung lesions. His brain disease subsequently progressed possibly due to low posaconazole levels which can be associated with poor oral intake due to mucositis (7), reduced central nervous system penetration of posaconazole as suggested in prior reported cases with very low to undetectable posaconazole levels in cerebrospinal fluid (8, 9), or antifungal resistance. Ervens and colleagues also found very low levels of posaconazole in plasma and in sampled soft tissue of their patient after 24 days of posaconazole treatment (6). Although our patient’s disease
stabilized again after resuming LAmB, the patient was unable to go home due to profound amphotericin-related potassium and magnesium wasting.

Isavuconazole is an investigational broad-spectrum antifungal drug with \textit{in vitro} and \textit{in vivo} activity against a broad range of yeasts and molds as well as \textit{in vitro} activity against Mucorales (10-12). Although our patient was treated with oral isavuconazole, the drug is also being developed for intravenous administration. Both formulations of isavuconazole consist of a water-soluble pro-drug (isavuconazonium, BAL-8557) that is rapidly converted to isavuconazole (BAL-4815) in plasma. Similar to other triazoles, it acts by inhibiting the fungal CYP system. Isavuconazole has favorable, linear pharmacokinetics and a long half-life that allows for once-daily administration. Intravenous isavuconazole does not require potentially-nephrotoxic coadministration of cyclodextrin, which allows isavuconazole to be dosed in patients with renal impairment. Furthermore, isavuconazole can be administered orally with minimal variability in its bioavailability that is not influenced by food intake (13). Our patient’s isavuconazole levels were lower than initially targeted on the first week of treatment. This led us to reload the patient and use higher isavuconazole doses transiently, but 200mg/day of isavuconazole maintenance treatment was sufficient to keep plasma levels above 1000 ng/mL, which remained stable over several months of periodic monitoring, similarly as to what Ervens and colleagues observed (6).

The use of isavuconazole allowed the patient to go home with oral treatment. Remarkably, his mucormycosis disease improved steadily with a decrease in the size of lung (50%) and brain (25%) lesions, and resolution of skin lesions and brain edema, despite ongoing AML relapse requiring further treatment with hydroxyurea, sorafenib and azacitidine.

The patient experienced minimal adverse effects during isavuconazole treatment consisting of transient mild nausea and transient liver enzyme elevations that were less than two
times the upper limit of normal that occurred during a brief period the patient was dosed at 400mg/day of isavuconazole. No other clinical or laboratory abnormalities were noted. Isavuconazole is under investigation in phase 3 studies on the safety and efficacy in treatment of fungal infections caused by Candida spp., Aspergillus spp., other filamentous fungi, rare molds, yeasts, and dimorphic fungi (ClinicalTrials.gov NCT00413218, NCT00634049, and NCT00412893). Our report suggests that isavuconazole can become an option to treat patients with mucormycosis, especially those that cannot tolerate amphotericin-based therapy.
Acknowledgments

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References


**Figures:**

Figure 1: A – Non-contrast head CT demonstrating bilateral scattered lesions with isodense rim and central low attenuation at the grey-white junction. B – Follow up contrast enhanced head CT showing multiple ring-enhancing abscesses. Some of these have increased in size, while edema has improved; C – Late follow up contrast enhanced head CT demonstrates that the ring-enhancing lesions have improved. There is no evidence of new disease.
**Figure 2**: Sequential non-contrast enhanced chest CT images.

A- Opacity in the left lower lobe with small effusion at the hospital admission.

B- Large left pleural effusion with left lower lobe consolidation, and new nodular consolidation with adjacent ground-glass in the right lower lobe (red arrow).

C- Large ground-glass opacities surrounded by soft tissue opacity in the right lung.

D- The right lower lobe lesion progressed to a necrotic mass.

E- Reverse halo sign is now noted on the right lower lobe lesion (red arrow).

F- Late follow up image demonstrates significant decrease of the right lower lobe lesion.
Table 1: Isavuconazole (BAL-4815) plasma levels during the treatment

<table>
<thead>
<tr>
<th>Sample day/ Oral dosing information</th>
<th>Concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial 200mg/day dosing</strong></td>
<td></td>
</tr>
<tr>
<td>Day1, baseline</td>
<td>&lt; 5</td>
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<tr>
<td>Day 2, trough prior to 6\textsuperscript{th} 200mg loading dose</td>
<td>394.6</td>
</tr>
<tr>
<td>Day 2, peak after 6\textsuperscript{th} 200mg loading dose</td>
<td>569.4</td>
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<tr>
<td>Day 7, trough, 200mg/day</td>
<td>455.9</td>
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<td>Day 15, trough, 200mg/day</td>
<td>1,322.0</td>
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<tr>
<td><strong>400mg/day dosing</strong></td>
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<tr>
<td>Day 16, trough after the 3\textsuperscript{rd} 200mg reload</td>
<td>5,436.0</td>
</tr>
<tr>
<td>Day 17, trough after the 6\textsuperscript{th} 200mg reload</td>
<td>8,809.0</td>
</tr>
<tr>
<td>Day 18, trough, 400mg/day</td>
<td>6,810.0</td>
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<tr>
<td>Day 21, trough, 400mg/day</td>
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<td><strong>Doses back to 200mg/day dosing</strong></td>
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<tr>
<td>Day 45, trough, 200mg/day</td>
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<td>Day 51, trough, 200mg/day</td>
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<td>Day 89, trough, 200mg/day</td>
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