Success of Combination Therapy with Isavuconazole in a Pediatric Patient with Breakthrough Invasive Aspergillosis

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Abstract

The increasing incidence of invasive fungal infections, coupled with the growing population of immunocompromised patients, has led to an increased need for antifungal agents. The newest azole, isavuconazole, plays an important role in the treatment of invasive aspergillosis in adults due to its broad spectrum, tolerability, and no need for therapeutic drug monitoring. This agent, which has not yet been approved for use in children, has significant problems with drug supply in Türkiye. We present the treatment response to isavuconazole combination therapy used in salvage treatment in a patient with breakthrough invasive aspergillosis, who had treatment failure with different antifungal combination treatment options and surgical resection.

Keywords
- aspergillosis
- isavuconazole
- salvage treatment
- pediatric

Introduction

Invasive aspergillosis (IA) has been associated with high morbidity and mortality in immunocompromised patients. Triazoles are the agents of choice for first-line treatment and prophylaxis of IA. Voriconazole pharmacokinetics and dosage have been established for children aged 2 years and older; however, children metabolize voriconazole more rapidly than adults, resulting in difficulties reaching therapeutic troughs. Therapeutic drug monitoring (TDM) is therefore recommended. When voriconazole is not possible, alternative treatments include liposomal amphotericin-B (L-AMB), posaconazole, isavuconazole, and echinocandins. Isavuconazole is the most recently approved triazole for the treatment of IA.[1–4] It is used in combined or salvage therapy in patients with progressive disease or breakthrough fungal infection. Guidelines recommend an individualized treatment approach, taking into account the rapidity, severity, and extent of infection and the patient's comorbidities.[1–3] Isavuconazole is the active component of isavuconazonium sulfate, a water-soluble triazole precursor that can be administered orally or intravenously. The drug has a large volume of distribution and the majority (~98%) binds to a protein.[5] Unlike other antifungals in its group, there is less variability in its pharmacokinetic parameters and routine TDM is not recommended.[6]

We will present the treatment response to isavuconazole combination therapy that we used in salvage treatment in a patient with breakthrough IA, who had treatment failure with different antifungal combination treatment options and surgical resection.

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Case

A 17-year-old girl diagnosed with acute lymphocytic leukemia was accepted during her second relapse after her skin biopsy demonstrated leukemic infiltration after bone marrow transplantation. Antifungal prophylaxis in the form of oral voriconazole (200 mg, twice a day) and FLAG-IDA (fludarabine, cytarabine, idarubicin) chemotherapy protocol was started. In the 3rd week of chemotherapy, imaging was performed due to severe neutropenia and fever for 7 days. The findings on thorax computed tomography (CT) were focal nodular parenchymal infiltrations in the upper lobe of the right lung and ground-glass densities around them. These findings were compatible with invasive fungal infection (►**Fig. 1A**). Antifungal treatment was changed to L-AMB (3 mg/kg/day). Serum galactomannan was positive at 96 pg/mL (< 25 pg/mL). Paranasal sinus CT and abdominal ultrasonography (USG) were normal. On the 16th day of L-AMB treatment, the antifungal treatment was changed to voriconazole (6 mg/kg intravenous every 12 hours on day 1 followed by 4 mg/kg every 12 hours thereafter) as the fever decreased and general condition improved. Posteroanterior chest radiograph after 2 weeks of antifungal treatment, there was an increase in density with clear borders in the upper lobe of the right lung (►**Fig. 2**). Followed by thorax CT revealed focal nodular and patchy parenchymal density increases of 6 cm in the upper lobe of the right lung, and the findings were progressive (►**Fig. 1B**). Caspofungin (70 mg/day, intravenous) was added to the treatment. Absolute neutrophil count (ANC) < 100 cells/mm^3 was refractory and repeated granulocyte transfusions failed to increase ANC. On the 43rd day of severe neutropenia, L-AMB (3 mg/kg/day) was added due to the persistence of fever despite 14 days of voriconazole/caspofungin treatment. Caspofungin was discontinued. Repeat thorax CT angiography showed a 5 × 5.5 cm nodular appearance in the upper lobe of the right lung with thick-walled, focal nodular and patchy parenchymal density increases with cavitation compared with the previous examination. New infiltration areas, close proximity of the lesion to the right pulmonary artery and pulmonary vein branches, and pleural effusion measuring 24 mm on the right and 35 mm on the left were detected in both hemithoraces (►**Fig. 1C–E**). ANC was > 500 cells/mm^3 for 3 days.

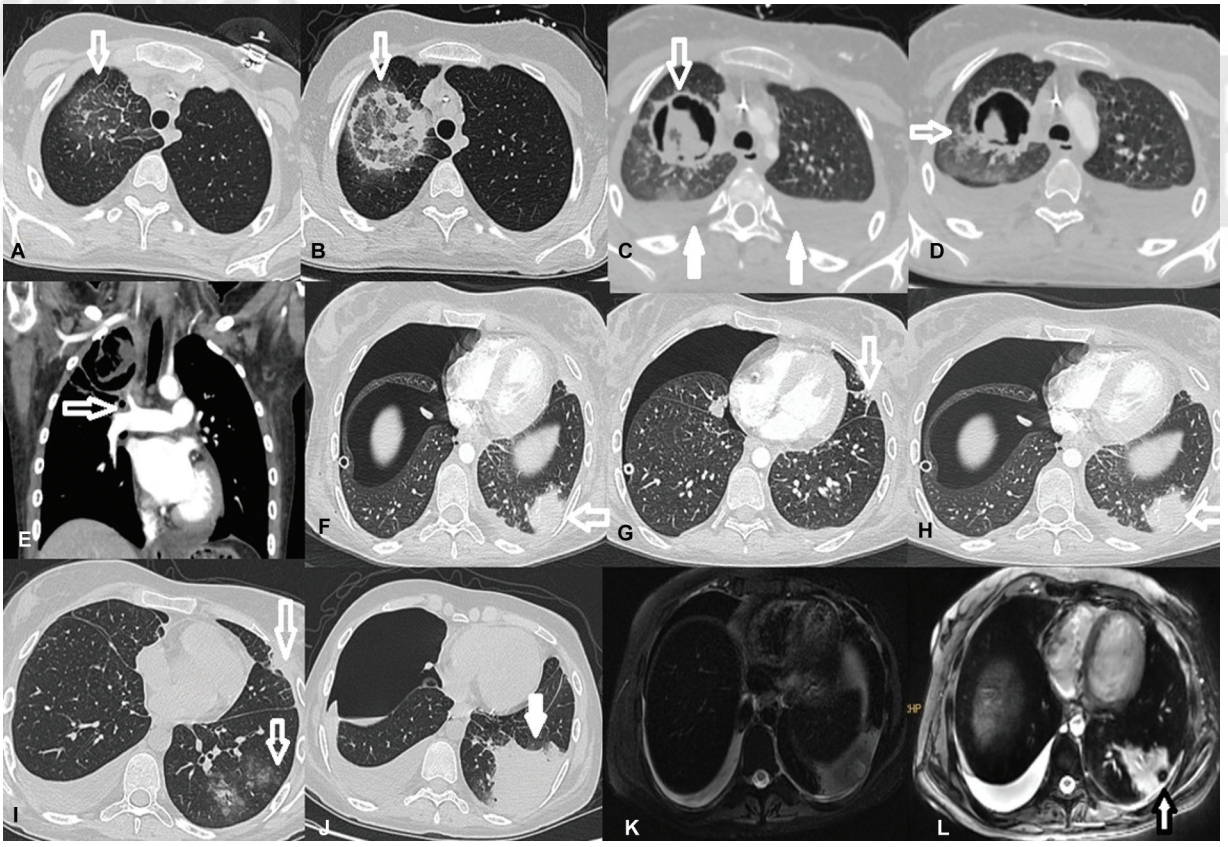


Fig. 1 (**A**) Faintly circumscribed ground-glass infiltration in the right upper lobe on noncontrast thoracic computed tomography (CT) (arrow). (**B**) Thoracic CT obtained 2 weeks later showing a circumscribed area with a consolidated appearance in the periphery and ground-glass infiltration in the center (inverted halo, arrow). (**C** and **D**) Fungus ball inside the cavitated lesion, nodules, and ground-glass infiltration in the periphery and pleural effusion in both hemithoraces (closed arrow) (**D**). Thoracic CT angiogram showing close adjacency of the cavity lesion to the pulmonary artery extending to the upper lobe (**E**). (**G–I**) Contrast-enhanced thoracic CT obtained after right upper lobectomy shows a large pneumothorax on the right. Newly developed irregularly circumscribed areas of consolidation (arrows) are seen in the left lower lobe posterobasal segment and lingula. (**J**) Contrast-enhanced CT obtained 3 months later shows decreasing continuity of the pneumothorax on the right. Ground-glass infiltrations in the left lower lobe (arrow) and an area of consolidation in the diaphragmatic area (closed arrow). (**K** and **L**) Contrast-enhanced thoracic magnetic resonance imaging obtained 4 months later shows a small amount of pleural fluid on the right and a limited lesion in the basal left lung with cavitation (arrow).

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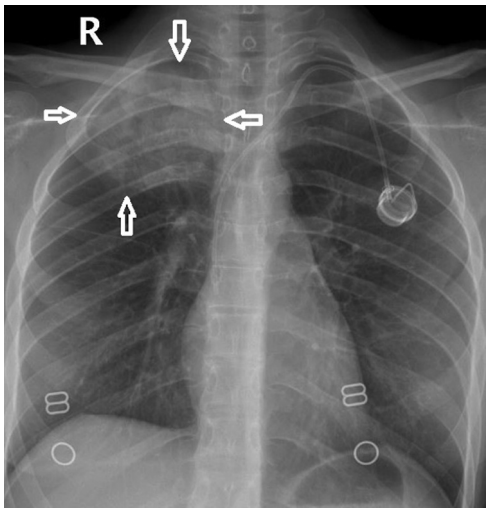


Fig. 2 In the upper zone of the right lung, there is a lesion with increased density that can be limited to the apex (arrows).

The patient underwent lobectomy. In the pathology report, fungal hyphae and spores forming necrotic granulomatous inflammation were observed. The fungal hyphae were thick, showing wide-angled branching, without prominent septa. It was stated that mucormycosis may be possible but hyphae may become dysmorphic while receiving antifungal treatment and this may make histological confirmation difficult. Aspergillosis could not be ruled out. Microbiologic culture of the sample could not be performed due to technical difficulties. Considering the pathology result, the treatment was changed to L-AMB (5 mg/kg/day) and intravenous posaconazole (800 mg/day, all divided into 4 doses). On the 40th day of L-AMB and 25th day of posaconazole, the patient experienced left-sided chest pain and there was left basal consolidation on chest radiography and the left costophrenic sinus was closed. Thorax CT angiography revealed a 13-mm pleural effusion in the left hemithorax and an infiltrating parenchymal area with ground-glass densities around the left lower basal segments with a size of 4 × 2.5 cm. It was stated that the findings could be primarily evaluated in favor of fungal infection (►**Fig. 1G–I**). Refractory or breakthrough invasive fungal infection was diagnosed and the dose of L-AMB (10 mg/kg/day) was increased and caspofungin was added. Off-label drug application was made for isavuconazole. Isavuconazole was obtained 2 weeks later. The duration of antifungal treatment when isavuconazole was received was 55 days of L-AMB, 40 days of posaconazole, and 15 days of caspofungin. Posaconazole was discontinued. Isavuconazole (200 mg, every 8 hours for 6 doses, then 200 mg, once a day, oral) was started. Two weeks later, thorax CT showed ground-glass infiltrations in the left lower lobe and consolidation in the diaphragmatic area (►**Fig. 1J**). Bronchoscopy was performed and USG-guided biopsy was taken in the same session. However, since the pathology report did not show any specific findings for the causative agent of fungal infection, Aspergillus polymerase chain reaction (PCR) test was performed. *Aspergillus flavus* was detected by real-time PCR (Qiagen, Germany). L-AMB treatment was discontinued on day 95, isavuconazole and caspofungin were continued. Thorax magnetic resonance imaging revealed a cavity appearance in the left lung with a 7-mm air signal located close to the pleura, and the findings tended to regress significantly (►**Fig. 1K, L**). While receiving isavuconazole and caspofungin treatment, caspofungin was discontinued on day 80 upon clinical and radiological response. The patient was discharged on the 70th day of isavuconazole treatment. Tolerable hepatic dysfunction and metabolic imbalance (hypomagnesemia, hypokalemia) were observed during antifungal treatment. Vomiting and nausea were the most common adverse events when isavuconazole was added. The patient received chimeric antigen receptor-T (CAR-T) cell therapy in a clinic (►**Table 1**). The patient received isavuconazole treatment for a total of 100 days. The chest radiograph of the patient at the end of the treatment is shown in ►**Fig. 3**. The patient continues secondary prophylaxis with oral voriconazole due to drug supply shortage.

Discussion

Treatment options for IA are limited and standard drugs used in treatment have toxicities and drug interactions. Isavuconazole is increasingly being used because of its efficacy against molds, tolerability, and no need for TDM.[5] To confirm in vitro data on the efficacy of isavuconazole against *Aspergillus* species, the SECURE study was designed to compare the treatment outcomes of isavuconazole and voriconazole.[7] In this study, a total of 527 patients were randomized to voriconazole ($n = 264$) and isavuconazole ($n = 263$).[7] In total, 65 (13%) patients were proven, 207 (40%) were probable, 196 (38%) were possible, and 48 (9%) had no evidence of disease.[7] At day 42, all-cause mortality was 19% with isavuconazole and 20% with voriconazole. Response to treatment was similar for isavuconazole and voriconazole (35% vs. 36%). The incidence of hepatobiliary disorders, ocular disorders, and skin or subcutaneous tissue disorders was significantly lower in patients treated with isavuconazole (2% vs. 10%).[7] In another study conducted on patients diagnosed with IA, 87% of patients receiving isavuconazole treatment had a complete or partial response, and disease progression led to death in 9% of patients.[8] Another study analyzed the use of isavuconazole in the treatment and prophylaxis of invasive fungal disease in children with hemato-oncological disease. The majority of patients in the study (20/24) had aspergillosis. The study emphasizes that isavuconazole may be an effective salvage therapy for patients with aspergillosis and those treated with azoles or combination therapy. They emphasized that it may also be useful as first-line treatment when other antifungal therapies are contraindicated.[9] The Infectious Diseases Society of America and the European Society for Clinical Microbiology and Infectious Diseases/European Confederation of Medical Mycology guidelines emphasize the importance of microbiological confirmation in cases of refractory or progressive disease.[1,2] Therefore, in this case, surgical resection was performed for confirmation of the pathogen, exclusion/confirmation of potential differential diagnosis or coinfections (e.g., mucormycosis), and treatment failure. The pathologic diagnosis

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Table 1 Relationship with treatment-radiology-absolute neutrophil count

Treatment	VOR	L-AMB	VOR + Caspo	L-AMB (3 mg/kg) + VOR	L-AMB (5 mg/kg) + POS	L-AMB (10 mg/kg) + POS + Caspo	L-AMB (10 mg/kg) + ISA + Caspo	ISA + Caspo	ISA
Duration of treatment (d)	20	16	14	15	25	15	40	25	5
Radiology/ clinical status		►**Fig. 1A**	►**Fig. 1B**	►**Fig. 1C, D**	Lobectomy/ Mucormycosis?	►**Fig. 1G–I**	Biopsy/*Aspergillus flavus* PCR+	►**Fig. 1L**	CAR-T
ANC (cells/mm^3)	< 100 cells/mm^3	< 100 cells/mm^3	< 100 cells/mm^3	> 500 cells/mm^3	> 500 cells/mm^3	> 500 cells/mm^3	> 500 cells/mm^3	> 500 cells/mm^3	> 500 cells/mm^3

Abbreviations: ANC, absolute neutrophil count; CAR-T, chimeric antigen receptor-T; Caspo, caspofungin; ISA, isavuconazole; L-AMB, liposomal amphotericin-B; PCR, polymerase chain reaction; POS, posaconazole; VOR, voriconazole.

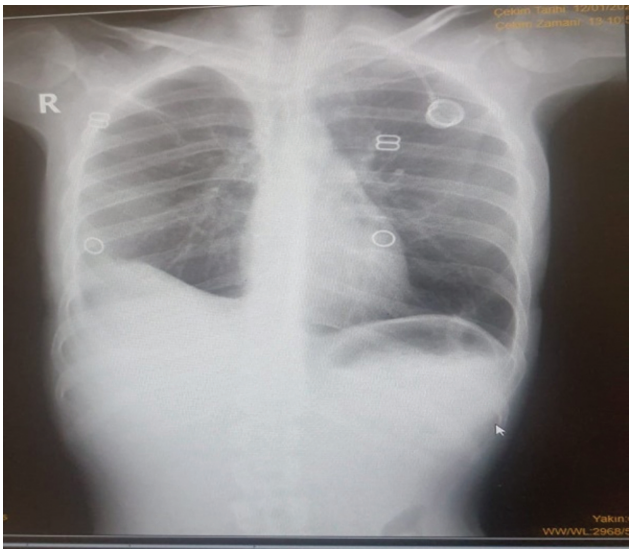


Fig. 3 Chest radiograph at the end of treatment.

was mucormycosis according to the morphologic structure of the hyphae, but the antifungal treatment the patient was receiving may have caused structural changes in the hyphae. Microbiological diagnosis was not available. Treatment was organized to cover both agents. USG-guided biopsy was performed due to breakthrough infection under antifungal treatment. PCR result was *A. flavus*. *A. flavus* is the second most common *Aspergillus spp*. The use of voriconazole in prophylaxis may increase the dominance of voriconazole-resistant clinical isolates of *A. flavus* and reduce the efficacy of this antifungal drug against *A. flavus* infection.[10] In addition, TDM is recommended when using voriconazole in treatment.[1] The treatment failure during voriconazole use in our patient may be due to the fact that they received voriconazole prophylaxis before treatment or that the therapeutic level could not be reached because TDM could not be performed. The availability of only three antifungal drug classes for the treatment of IA greatly limits salvage treatment options and recommended drug class switching. Regression was observed with salvage therapy including isavuconazole from the triazole class, which we had not used before, and L-AMB and caspofungin. CAR-T cell therapy was performed in a clinic.

In general, isavuconazole is well tolerated compared with other agents in the azole class. The most commonly reported adverse events include nausea, vomiting, and diarrhea.[11] Nausea and vomiting were the most common adverse events during the period when we received isavuconazole.

In conclusion, in clinical cases of treatment failure/progression of IA with antifungal therapy, efforts should be made to identify the causative pathogen and, if necessary, more than one diagnostic test should be used. Organizing treatment in patients with progressive or breakthrough IA remains challenging. Current guidelines provide only limited recommendations and emphasize individual approaches. We achieved treatment success with isavuconazole in our case, but prospective pediatric studies are warranted.

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Conflict of Interest
None declared.

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