Real-world Considerations in the Management of Patients With Invasive Aspergillosis or Invasive Mucormycosis: A Pharmacist's Perspective

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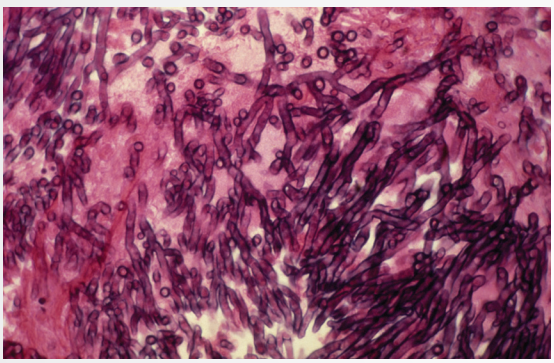
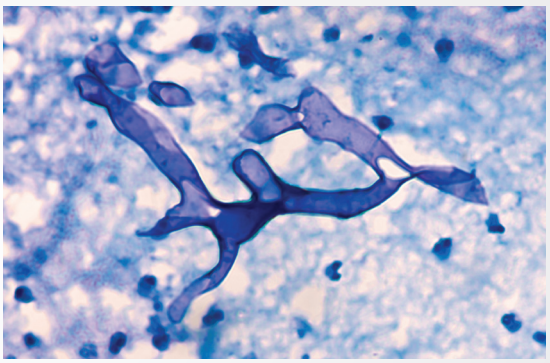
Identifying Potential Life-Threatening Fungal Infections

Figure 1: Invasive aspergillosis (left) and invasive mucormycosis (right)



Source: Stock photo. https://www.medicalimages.com/stock-photo-image-image22422660.html. Accessed February 9, 2019.



Source: Stock photo. https://www.shutterstock.com/image-photo/fungal-infection-mucormycosis-broad-wideangle-nonseptate-734850160. Accessed February 9, 2019.

Invasive aspergillosis (IA) and invasive mucormycosis (IM) (**Figure 1**) are serious fungal infections that can pose a significant threat to immunocompromised or critically ill patients.[1,2] These fungi are normally present in the environment and typically cause no harm to people with healthy immune systems; however, when patients with underlying risk factors such as critical illness or immunosuppression are exposed, severe and life-threatening infections can take hold.

The lungs are the most common site of infection for *Aspergillus* as inhalation is the usual route of exposure.[1] Disease can then spread from the lungs to the brain, skin, heart, bone, or other organs, either through the bloodstream or via extension from the lung. Similarly, mucormycosis is predominantly acquired via inhalation but can also be acquired percutaneously through a wound, or less commonly, through the gastrointestinal tract.[2] Initial clinical presentation varies and may include rhinocerebral, pulmonary, cutaneous, gastrointestinal, or disseminated infection. The site of infection is often related to the patient's underlying medical condition. For example, pulmonary mucormycosis is most closely associated with hematologic malignancy, whereas rhinocerebral mucormycosis is more frequent in people with poorly controlled diabetes.

Immunosuppressive therapy among certain patient populations (e.g., oncology, transplant) and the increasing use of invasive devices such as central venous catheters has increased the number of patients at risk for invasive fungal infection (IFI).[3] Knowledge of the specific risk factors for IA and IM can help to raise suspicion for these diseases and facilitate a timely diagnosis, which remains the key to initiating effective therapy.[4] Neutropenia is one of the most notable risk factors, with the risk of serious infection rising with increasing duration and intensity of neutropenia.[5,6] Neutropenia may be related to a particular disease state or may be drug induced by chemotherapy or other bone marrow toxic agents. Concomitant administration of other drugs that suppress different cells of the immune system may exacerbate the risk for IFI. These may include steroids, purine analogues, newer antineoplastics, T-cell–targeted agents, and tumor necrosis factor blockers.[5] Patients undergoing hematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT) are considered to be at risk as a result of prolonged immunosuppression, although risk may vary based on type of transplant, stem cell source (in HSCT), and time from transplant. In IM, metabolic acidosis associated with poorly controlled diabetes is also considered a risk factor.

In critical care, IFI can occur in patients without underlying hematologic malignancies. Risk factors in this setting may include a diagnosis of chronic obstructive pulmonary disease and liver failure.[5] A retrospective cohort study by Baddley et al identified comorbidities in intensive care unit (ICU) patients diagnosed with IA who did not have the "traditional" risk factors of hematologic cancers, transplant, neutropenia, or human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS).[7] The most common comorbidities are listed in **Table 1**.

Table 1: Comorbidities of 412 ICU patients diagnosed with IA without "traditional" risk factors[7]

Comorbidities	(N=412)
Acute steroids	76.5%
Acute respiratory failure	76.0%
Mechanical ventilation	72.3%
Acute renal failure	41.3%
COPD	36.9%
Septicemia/septic shock	35.9%
Congestive heart failure	29.6%
Hypertension	25.7%
Anemia	23.3%
Thrombocytopenia	20.5%
Dialysis	17.5%

COPD=chronic obstructive pulmonary disease.

"On a daily basis, I am confronted with decisions that need to be made with regard to the treatment of IA and IM. In my practice, patients typically at risk for IA are those with a new diagnosis of acute myeloid leukemia (AML). These patients may come in already neutropenic or they may soon become neutropenic following chemotherapy. Standard regimens for AML can induce neutropenia for 21 days or longer.[8] Given this duration of prolonged and profound neutropenia, these patients are at risk of developing IA. In my experience, the risk of IM is relatively low in the first-line AML treatment setting but is certainly possible. I am typically more suspicious in patients who are refractory to multiple lines of therapy and/or have been neutropenic for more than 30 days with signs and symptoms of IM such as sinus pain or pressure.

Older patients with AML and/or those with significant comorbidities receive a lower intensity regimen.[9,10] However, these regimens take longer to induce remission and can be accompanied by an even longer period of profound neutropenia. In my experience, given the older population, comorbidities, and duration of neutropenia, the risk of IM is heightened along with IA. This is especially true when patients develop multiply refractory disease.

In my practice, all neutropenic patients are monitored for neutrophil recovery, fever, changes in oxygen requirement, and, in the aforementioned highest risk patients, sinus pain. Patients who are suspected of IA or IM undergo additional monitoring that may include imaging studies of the chest or sinuses. Depending on the clinical scenario, we may consider a biopsy of the suspicious area. Serological testing can sometimes be helpful in IA but not definitively helpful in IM. That being said, β-D-glucan and galactomannan are sent off for patients with clinical suspicion of an IFI."

-Anthony J. Perissinotti, PharmD, BCOP

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Understanding the Burden: Hospitalizations, Mortality, and Cost

Multiple studies have attempted to quantify the increasing burden of IFI on both the patient and the health care system. A 2017 retrospective study from Vallabhaneni et al examined rates of hospitalizations related to IA and IM and found that between 2000-2013, IA-related and IM-related hospitalizations increased at a rate of approximately 3% and 5% a year, respectively.[11]

Moreover, IA and IM continue to have significant consequences for patients, even in patients with and without hematologic malignancies. For example, the survival rate at 1 year for patients with HSCT who developed invasive infection with the mold *Aspergillus* was 25%.[12] A review of reported cases of patients with IM from 1940-2003 found an overall mortality rate of 54%.[13] A 20-year (1989-2008) study of 1213 autopsies from patients with hematologic malignancies identified an IFI prevalence rate of 31%. While *Aspergillus* spp. accounted for the majority of fungal pathogens over the study period, overall prevalence of *Aspergillus* declined in the last 5 study years. Mucormycosis, while less common, increased in prevalence in the last 5 study years.[14]

In addition to morbidity and mortality, IA and IM can present a significant economic burden to patients and health care systems.[15-18] Retrospective studies have found that IA and IM increased the length of hospital stay, between 6.0 and 8.4 days for patients with IA and between 10.6 and 16.5 days for patients with IM.[15-17] Furthermore, IA was associated with higher rates of 30-day readmission compared to patients without IA.[15] The increased care for patients with IA or IM has resulted in significant increases in costs per patient.[15-17] Retrospective analyses estimate that IA results in additional costs from $15,542 to $25,128 and IM results in additional costs from $31,849 to $64,526. Overall, the treatment of IA and IM in the United States in 2017 was estimated to result in a total economic cost of $1.2 billion and $125 million, respectively.[18]

Azole Antifungals in the Management of IA and IM

The pharmacist is an important part of the multidisciplinary team that manages patients with IFI.[19,20] As medication experts, pharmacists may be involved with antifungal selection, dosing, and monitoring. This necessitates familiarity with azole antifungals as these drugs are an important option in the antifungal class for the treatment of IA in most patients and are also included in treatment recommendations for IM.[4,6] Assessment of drug-drug interactions (DDIs) is an important consideration. Because patients with IFI are critically ill, they may be receiving a considerable number of drugs, including immunosuppressants with narrow therapeutic indices. Interactions between azole antifungals and immunosuppressants may be of particular concern. As a class, azole antifungals are inhibitors and/or substrates of CYP450 enzymes, most notably CYP3A4, but also CYP2C9 and CYP2C19.[21] Some azoles act as inhibitors or substrates of the P-glycoprotein (P-gP) drug transport system. When evaluating drug interactions, pharmacists should review the specific pharmacokinetics (PK) of the prescribed azole as the magnitude of the effect and clinical significance of the resulting drug interactions are unique to each azole. Drug doses and genetic variability may also influence the significance of the potential drug interaction.[19,21]

Requirements for therapeutic drug monitoring (TDM) differ by azole antifungal agent. Regardless of the recommendation for TDM, monitoring of the patient for clinical response, drug side effects, and laboratory parameters are important tools for assessing antifungal appropriateness.[19]

"From a pharmacist's perspective, patients who develop IA and/or IM can be challenging to manage due to numerous, and oftentimes competing, comorbidities. In hematology/oncology, treatments for the underlying malignancy pose unique challenges. I find that the treatment landscape in oncology is constantly changing. The introduction of novel oncology agents creates new obstacles and uncertainties in the management of IFI that are best tackled with a team-based approach.

A key role for all pharmacists is the identification and management of DDIs. For patients receiving antifungals, as with all drugs, this may involve assessing potential interactions, suggesting medication regimen changes to avoid interactions, or making dose adjustments when appropriate. Similarly, close monitoring of drug levels for some antifungals is required to prevent overlapping toxicities (i.e., hepatotoxicity, neurotoxicity, and QTc prolongation) between chemotherapy and antifungals.

In addition to monitoring drug interactions, pharmacists must understand how different antineoplastic agents affect the immune system and which types of opportunistic infections to look out for. Pharmacists are uniquely positioned to educate other team members about the risk of IFI associated with newly approved chemotherapeutic agents and immunosuppressants. Similarly, pharmacists are often asked about the appropriate time to resume chemotherapy while treating the underlying IFI.

A pharmacist may contribute to patient care by critically appraising literature to aid in the diagnosis (including understanding drug levels, interpreting susceptibility testing, and knowing the risk/likelihood of an IFI), management, and monitoring of patients with breakthrough IFI."

-Anthony J. Perissinotti, PharmD, BCOP

In conclusion, the clinical pharmacist should have access to comprehensive, up-to-date information about DDIs that includes antifungal drugs such as triazoles.[20] They should also have a full understanding of the underlying mechanisms of action and extensive knowledge of a drug's PK profile to provide suitable advice on how to manage DDIs.

CRESEMBA® (isavuconazonium sulfate) as a Treatment Option for Adult Patients With IA or IM

INDICATIONS AND USAGE

CRESEMBA is an azole antifungal indicated for patients 18 years of age and older for the treatment of **invasive aspergillosis and invasive mucormycosis**.[22]

Specimens for fungal culture and other relevant laboratory studies (including histopathology) to isolate and identify causative organism(s) should be obtained prior to initiating antifungal therapy.[22] Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

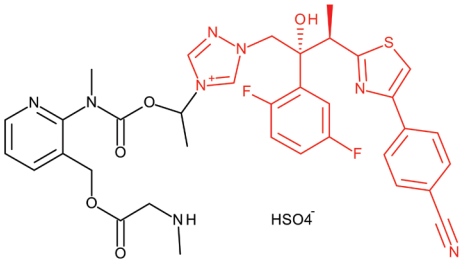
- CRESEMBA is contraindicated in persons with known hypersensitivity to isavuconazole[22]
- Coadministration of strong CYP3A4 inhibitors, such as ketoconazole or high-dose ritonavir (400 mg every 12 hours), with CRESEMBA is contraindicated because strong CYP3A4 inhibitors can significantly increase the plasma concentration of isavuconazole
- Coadministration of strong CYP3A4 inducers, such as rifampin, carbamazepine, St. John's wort, or long acting barbiturates with CRESEMBA is contraindicated because strong CYP3A4 inducers can significantly decrease the plasma concentration of isavuconazole
- CRESEMBA shortened the QTc interval in a concentration-related manner. CRESEMBA is contraindicated in patients with familial short QT syndrome

PLEASE SEE ADDITIONAL IMPORTANT SAFETY INFORMATION THROUGHOUT THIS SUPPLEMENT. PLEASE CLICK HERE FOR FULL PRESCRIBING INFORMATION FOR CRESEMBA.

PK profile of CRESEMBA

CRESEMBA contains isavuconazonium sulfate, which is the prodrug of isavuconazole, an azole antifungal drug[22] (**Figure 2**). Isavuconazole has activity against most strains of the following microorganisms, both *in vitro* and in clinical infections: *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger*, and Mucorales such as *Rhizopus oryzae* and Mucormycetes species.

Figure 2: Isavuconazonium sulfate[22]



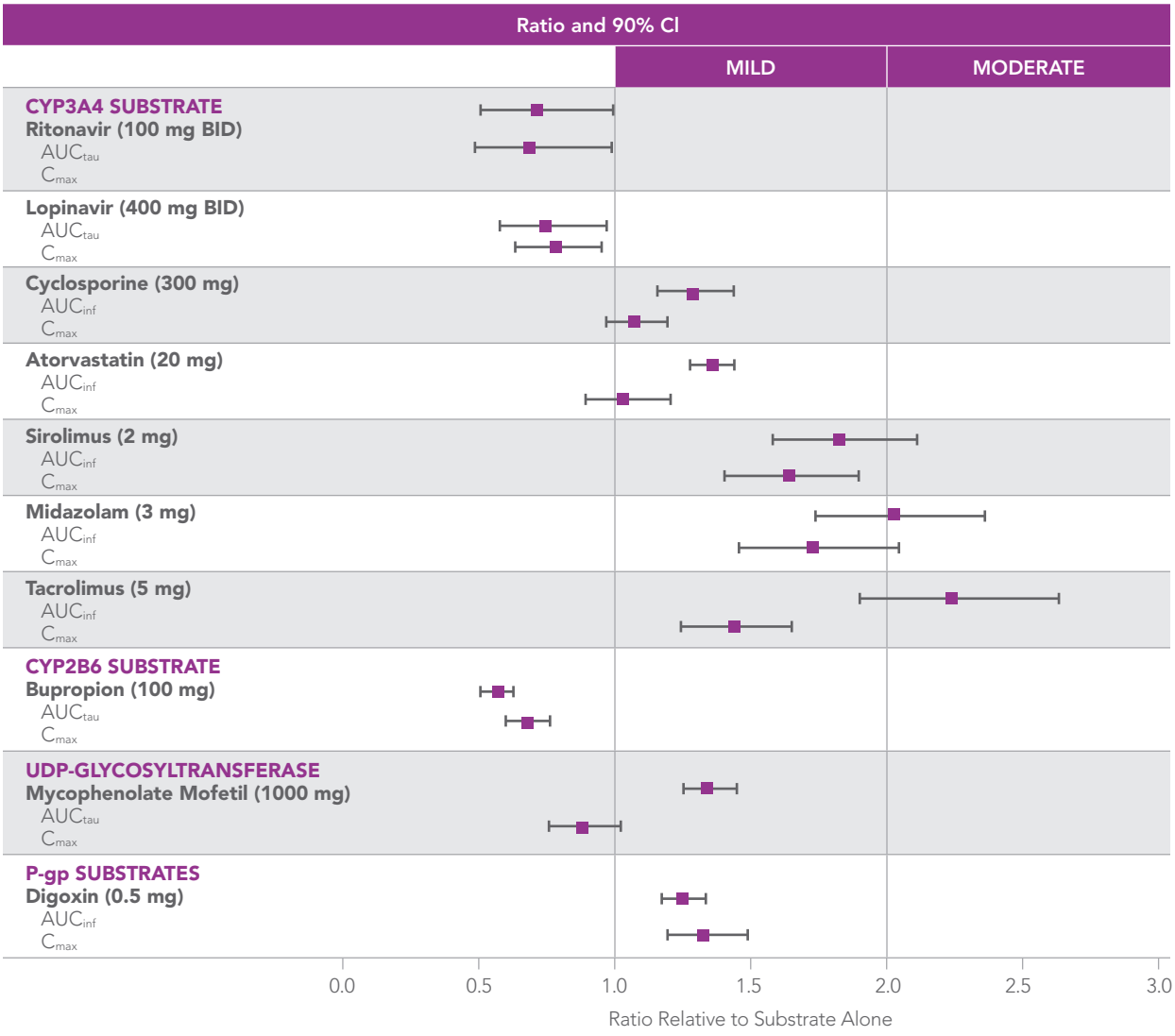
CRESEMBA has a predictable and consistent PK profile with both IV and PO formulations.[22] In patients treated with CRESEMBA for IA in a controlled trial, there was no significant association between plasma area under the curve (AUC) or plasma isavuconazole concentration and efficacy. CRESEMBA is water soluble and in *in vitro* studies, isavuconazonium sulfate is rapidly hydrolyzed in blood to isavuconazole by esterases, predominately by butyrylcholinesterase. CRESEMBA is extensively distributed with a mean steady-state volume of distribution of approximately 450 L and is highly protein bound with greater than 99% predominantly to albumin.

Following intravenous (IV) administration of CRESEMBA, maximal plasma concentrations of the prodrug and inactive cleavage product were detectable during infusion and declined rapidly at end of administration.[22] After oral administration, no significant concentrations of the prodrug or inactive cleavage product were seen in plasma.

CRESEMBA® (isavuconazonium sulfate) has 98% absolute bioavailability following oral administration.[22] CRESEMBA reaches maximum plasma concentrations (C_{max}) 2 to 3 hours after single and multiple oral dosing and has dose-proportional PK following oral administration at doses of up to 6 capsules/day (the equivalent of 600 mg of isavuconazole).

Drug interaction studies were conducted to investigate the effect of coadministered drugs on the PK of isavuconazole as well as the effect of isavuconazole on the PK of coadministered drugs.[22] CRESEMBA is contraindicated with all potent CYP3A4 inhibitors such as ketoconazole (which led to a >5-fold increase in exposure in clinical studies) and rifampin (which led to a 97% decrease in exposure in clinical studies).[22,23] CRESEMBA is a sensitive substrate of CYP3A4, a moderate inhibitor of CYP3A4, and a mild inhibitor of P-gp and organic cation transporter 2 (OCT2).[22] **Figure 3** demonstrates the effect of CRESEMBA on coadministered CYP3A4 substrate medications, OCT2, and P-gp substrates. The majority of CYP3A4, OCT2, and P-gp substrates have a mild increase in AUC and C_{max}. No dose adjustment for CRESEMBA is necessary when coadministered with the drugs listed in **Table 2**. However, TDM and dose adjustment of immunosuppressants (i.e., tacrolimus, sirolimus, and cyclosporine) may be necessary when coadministered with CRESEMBA.

Figure 3: DDIs and recommended drug monitoring and/or dose adjustments for concomitant medications[22]



AUC_{tau}=area under the curve over dosing interval; C_{max}=maximum plasma concentration; AUC_{inf}=area under the curve from time 0 to infinity; CI=confidence interval; P-gp=P-glycoprotein.

PLEASE CLICK HERE FOR FULL PRESCRIBING INFORMATION FOR CRESEMBA.

CRESEMBA® (isavuconazonium sulfate) 372 mg for injection • 186 mg capsules

Table 2: Concomitant medications that do not require a dose adjustment[22-26]

Esomeprazole	Omeprazole	Norethindrone	Methadone	Warfarin	Dextromethorphan
Ethinyl estradiol	Prednisone	Caffeine	Repaglinide	Methotrexate	Metformin

Following oral administration in healthy volunteers, the mean total radioactive dose of radiolabeled CRESEMBA® (isavuconazonium sulfate) recovered in feces and urine was 46.1% and 45.5%, respectively.[22] Renal excretion of isavuconazole was less than 1% of the dose administered.

Efficacy of CRESEMBA in the Treatment of IA and IM

CRESEMBA for IA pivotal clinical trial

The IA trial was a Phase 3, randomized, double-blind, non-inferiority trial to evaluate the safety and efficacy of CRESEMBA versus voriconazole for primary treatment of invasive fungal disease caused by *Aspergillus* species or other filamentous fungi.[22] Eligible patients included men and women age 18 years or older (mean age was 51), with proven, probable, or possible IFI per the European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria. The majority of patients were male (60%), Caucasian (78%), and had fungal disease involving the lungs (95%).[22,27] Patients with moderate to severe renal impairment (creatinine clearance <50 mL/min, or currently on or likely to require dialysis) were excluded per labeling restrictions associated with the active comparator.[27,28] Patients in the IA trial had baseline risk factors presented in **Table 3**.

Table 3: Baseline risk factors in the ITT* population[22]

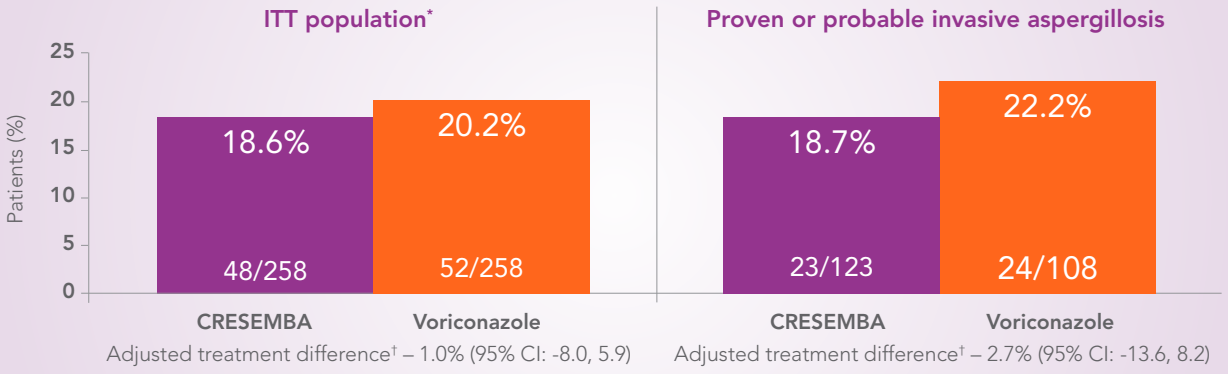
Risk Factors	CRESEMBA n=258 n (%)	Voriconazole n=258 n (%)
Hematologic malignancy	211 (82)	222 (86)
Allogeneic hematopoietic stem cell transplant	54 (21)	51 (20)
Neutropenia (defined as <500 cells/mm^3)	163 (63)	175 (68)
Corticosteroid use	48 (19)	39 (15)
T-cell immunosuppressant use	111 (43)	109 (42)

*Intent-to-treat (ITT) includes all randomized patients who recived at least 1 dose of study drug.

All patients were treated with CRESEMBA IV at a loading dose of 372 mg isavuconazole every 8 hours for the first 48 hours, and a maintenance dose of 372 mg isavuconazole daily thereafter from Day 3 onward.[22] Patients treated with voriconazole received 6 mg/kg IV every 12 hours for the first 24 hours, followed by 4 mg/kg IV every 12 hours for 24 hours. Maintenance therapy can then be switched to an oral formulation of 200 mg every 12 hours from Day 3 forward. The intent-to-treat (ITT) population included all randomized patients who received at least 1 dose of study drug, and the endpoint was all-cause mortality through Day 42.

The endpoint of all-cause mortality through Day 42 in the ITT population was 18.6% in the CRESEMBA® (isavuconazonium sulfate) treatment group and 20.2% in the voriconazole treatment group, for an adjusted treatment difference of -1.0% with a 95% confidence interval (CI) of -8.0% to 5.9%.[22] Similar results were seen in the population with proven or probable IA confirmed by serology, culture, or histology: 18.7% with CRESEMBA and 22.2% with voriconazole (adjusted treatment difference of -2.7%; 95% CI -13.6% to 8.2% (**Figure 4**). The protocol-defined maximum treatment duration in this trial was 84 days, and mean treatment duration was 47 days for both treatment groups, of which 8 to 9 days was by IV route of administration. In total, the treatment duration ranged from 1 to 102 days.[28]

Figure 4: All-cause mortality through Day 42[22,28]



ITT=intent-to-treat; CI=confidence interval.
*ITT includes all randomized patients who received at least 1 dose of study drug.
†Adjusted treatment difference (CRESEMBA-voriconazole) by Cochran-Mantel-Haenszel method stratified by the randomization factors.

CRESEMBA for IM pivotal clinical trial

This trial was a phase 3, open-label, noncomparative trial to evaluate the safety and efficacy of CRESEMBA in a subset of patients with IM.[22] A total of 37 patients were assessed by the Data Review Committee (DRC) as having proven or probable IM. The mean age of these 37 patients was 49 years (range 22-79); 68% were Caucasian, 81% were male, and 59% had pulmonary disease involvement, half of whom had other organ involvement. The most common nonpulmonary disease locations were sinus (43%), eye (19%), central nervous system (16%), and bone (14%). *Rhizopus oryzae* and Mucormycetes were the most common pathogens identified. There were a few patients with other Mucorales: *Lichtheimia corymbifera*, *Mucor amphibiorum*, *Mucor circinelloides*, *Rhizomucor pusillus*, *Rhizopus azygosporus*, and *Rhizopus microsporus*. All patients were treated with CRESEMBA IV or via oral administration at a loading dose of 200 mg isavuconazole every 8 hours for 6 doses for the first 48 hours, and a maintenance dose of 200 mg isavuconazole daily thereafter (starting 12-24 hours after last loading dose).

Patients had a variety of risk factors for IFI, the most common being hematologic malignancy (60%) and use of T-cell immunosuppressive therapy (49%).[22] Other baseline risk factors included allogeneic HSCT (35%), neutropenia (defined as <500 cells/mm^3) and corticosteroid use (each 27%), and diabetes (11%). Baseline risk factors can be seen in **Table 4**.

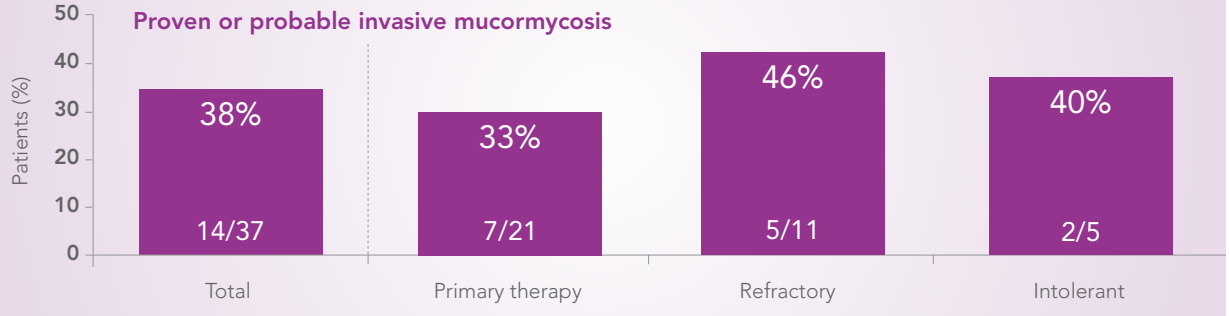
Table 4: Baseline risk factors of Mucorales patients[22]

Risk Factors	Primary (n=21) n (%)	Refactory (n=11) n (%)	Intolerant (n=5) n (%)	Total (N=37) n (%)
Hematologic malignancy	11 (52)	7 (64)	4 (80)	22 (60)
Allogeneic hematopoietic stem cell transplant	4 (19)	4 (36)	5 (100)	13 (35)
Neutropenia (defined as <500 cells/mm^3)	4 (19)	5 (46)	1 (20)	10 (27)
Corticosteroid use	5 (24)	3 (27)	2 (40)	10 (27)
T-cell immunosuppressant use	7 (33)	6 (55)	5 (100)	18 (49)
Diabetic	4 (19)	0	0	4 (11)

Therapy status assessed by the Data Review Committee:
Primary – Received CRESEMBA® (isavuconazonium sulfate) as primary treatment
Refactory – Underlying infection not adequately treated by prior therapy
Intolerant – Unable to tolerate prior therapy

In the IM trial, CRESEMBA was shown to be effective for the treatment for mucormycosis, in light of the natural history of untreated mucormycosis.[22] However, the efficacy of CRESEMBA for the treatment of IM has not been evaluated in concurrent, controlled clinical trials. For patients with proven or probable IM, the endpoint of all-cause mortality through Day 42 as assessed by the DRC in the open-label study was 38% for the total population. All-cause mortality ranged from 33% to 46% within the different subsets of patients in this open-label, noncomparative trial (**Figure 5**). Median treatment duration was 102 days for patients classified as primary, 33 days for refractory, and 85 days for intolerant. Treatment duration was reported to range from 27 to 180 days, however, 4 patients were treated for longer than 180 days.[29]

Figure 5: All-cause mortality through Day 42[22]



Safety Profile of CRESEMBA® (isavuconazonium sulfate) in the Pivotal Clinical Trials

The most frequently reported adverse reactions among CRESEMBA-treated patients were nausea (26%), vomiting (25%), diarrhea (22%), headache (17%), elevated liver chemistry tests (16%), hypokalemia (14%), constipation (13%), dyspnea (12%), cough (12%), peripheral edema (11%), and back pain (10%).[22] The frequencies and types of adverse reactions observed in CRESEMBA-treated patients were similar in the IA and IM trials. CRESEMBA has no warning for visual disturbances.

In the IA trial, adverse reactions resulting in permanent discontinuation were reported in 14% (37/257) of patients treated with CRESEMBA and 23% (59/259) of voriconazole-treated patients.[22] In the IM trial, adverse reactions resulting in permanent discontinuation were reported in 13% (19/146) of patients treated with CRESEMBA. In the IA and IM trials, the adverse reactions which most often led to permanent discontinuation of CRESEMBA therapy during the clinical trials were: confusional state (0.7%), acute renal failure (0.7%), increased blood bilirubin (0.5%), convulsion (0.5%), dyspnea (0.5%), epilepsy (0.5%), respiratory failure (0.5%), and vomiting (0.5%).

CRESEMBA Dosing Information

CRESEMBA dosing information can be seen in **Table 5**. Switching between IV and oral formulations of CRESEMBA is acceptable and does not require a loading dose because CRESEMBA has demonstrated bioequivalence.[22]

Table 5: CRESEMBA dosage regimen[22]

Formulation	Loading Dose	Maintenance Dose‡
CRESEMBA for Injection 372 mg* of isavuconazonium sulfate per vial	1 vial q8h for 6 doses (48 h)	1 vial once daily
CRESEMBA Capsules 186 mg† of isavuconazonium sulfate per capsule	2 capsules q8h for 6 doses (48 h)	2 capsules once daily

*372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole.
†186 mg of isavuconazonium sulfate is equivalent to 100 mg of isavuconazole.
‡Start maintenance doses 12 to 24 hours after the last loading dose.

Patients with mild, moderate, or severe renal impairment, including end-stage renal disease do not require a dose adjustment to take CRESEMBA,[22] and CRESEMBA is not removed by hemodialysis. Patients with mild to moderate hepatic impairment do not require a dose adjustment. When treating patients with severe hepatic impairment, it is recommended to monitor for CRESEMBA-related adverse reactions because CRESEMBA has not been studied in these patients.

Capsules not actual size.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS

Hepatic Adverse Drug Reactions (e.g., elevations in ALT, AST, alkaline phosphatase, total bilirubin) have been reported in clinical trials and were generally reversible and did not require discontinuation of CRESEMBA. Cases of severe hepatic adverse drug reactions including hepatitis, cholestasis or hepatic failure including death have been reported in patients with serious underlying medical conditions (e.g., hematologic malignancy) during treatment with azole antifungal agents, including CRESEMBA. Evaluate liver tests at the start and during therapy. Monitor patients who develop liver abnormalities during CRESEMBA therapy for severe hepatic injury. Discontinue if clinical signs and symptoms consistent with liver disease develop that may be attributable to CRESEMBA.

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CRESEMBA®
(isavuconazonium sulfate)
372 mg for injection • 186 mg capsules

Expert Commentary on a Hypothetical Critical Care Patient

Anthony J. Perissinotti, PharmD, BCOP

A 23-year-old male with Hodgkin lymphoma presented to a hematology service following his last cycle of dose-adjusted chemotherapy with febrile neutropenia and cellulitis of the leg. He was initially treated with antibiotic therapy but over a 48-hour period rapidly deteriorated. The patient was transferred to the ICU and the infectious diseases service was consulted. The recommendations were to perform a biopsy of the leg. The microbiology pathology report preliminarily revealed a mold with nonseptated hyphae. A diagnosis of IM was made, and treatment was initiated. The infectious diseases service instructed the surgical team to debride the tissue and debridement led to negative margins. The patient clinically improved, neutropenia resolved, susceptibility testing was finalized, and he was eventually discharged home on isavuconazole.

A positron emission tomography scan to assess his underlying malignancy revealed no active disease. Isavuconazole was continued for approximately 1 year and during this time he tolerated therapy well without any need for modifications.

This hypothetical case highlights the importance of a quick diagnosis and the quick initiation of treatment for IM even in hosts that may not be considered at high risk for IM. This patient had only one risk factor, neutropenia, and despite the relatively short duration of neutropenia still developed a rare mold infection.

IMPORTANT SAFETY INFORMATION FOR CRESEMBA® (isavuconazonium sulfate) (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

Infusion-Related Reactions including hypotension, dyspnea, chills, dizziness, paresthesia, and hypoesthesia were reported during intravenous administration of CRESEMBA. Discontinue the infusion if these reactions occur.

Serious Hypersensitivity and Severe Skin Reactions, such as anaphylaxis or Stevens Johnson syndrome, have been reported during treatment with other azole antifungal agents. Discontinue CRESEMBA if a patient develops a severe cutaneous adverse reaction. Caution should be used when prescribing CRESEMBA to patients with hypersensitivity to other azoles.

Embryo-Fetal Toxicity: During pregnancy, CRESEMBA may cause fetal harm when administered, and CRESEMBA should only be used if the potential benefit to the patient outweighs the risk to the fetus. Women who become pregnant while receiving CRESEMBA are encouraged to contact their physician.

Drug Interactions: Coadministration of CRESEMBA with strong CYP3A4 inhibitors such as ketoconazole or high-dose ritonavir and strong CYP3A4 inducers such as rifampin, carbamazepine, St. John's wort, or long acting barbiturates is contraindicated.

Drug Particulates: Following dilution, CRESEMBA intravenous formulation may form precipitate from the insoluble isavuconazole. Administer CRESEMBA through an in-line filter.

ADVERSE REACTIONS

The most frequently reported adverse reactions among CRESEMBA-treated patients were nausea (26%), vomiting (25%), diarrhea (22%), headache (17%), elevated liver chemistry tests (16%), hypokalemia (14%), constipation (13%), dyspnea (12%), cough (12%), peripheral edema (11%), and back pain (10%).

The adverse reactions which most often led to permanent discontinuation of CRESEMBA therapy during the clinical trials were: confusional state (0.7%), acute renal failure (0.7%), increased blood bilirubin (0.5%), convulsion (0.5%), dyspnea (0.5%), epilepsy (0.5%), respiratory failure (0.5%), and vomiting (0.5%).

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