Three Years After the SECURE Trial – Are We Still Feeling Secure with Isavuconazole?

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Learning Objectives
1. Describe pathophysiology and diagnosis of invasive pulmonary aspergillosis (IPA)
2. Review current practices for treatment of IPA
3. Evaluate recent evidence for and against isavuconazole use for IPA
4. Identify preferred agent for primary treatment of IPA
Assessment Questions

1. Which of the following comorbidities confers the highest risk for developing IPA?
   A. HIV-positive
   B. Allogeneic stem cell transplant
   C. Type II diabetes mellitus
   D. Colorectal cancer

2. True or False? Treatment of IPA should be initiated only after a pathogen has been isolated from sterile culture.
   A. True
   B. False

3. Which of the following agents is NOT an appropriate first-line option for treatment of IPA?
   A. Isavuconazole
   B. Liposomal Amphotericin B
   C. Voriconazole
   D. Caspofungin

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Faculty (Speaker) Disclosure: Chase Ayres has indicated he has no relevant financial relationships to disclose relative to the content of his presentation
Background

I. Invasive Aspergillosis (IA)\textsuperscript{1-3}
   a. Potentially life-threatening infection caused by environmental molds, most commonly affecting immunocompromised patients
   b. Epidemiology
      i. Approximately 15,000 hospitalizations in the US attributed to IA yearly
      ii. Annual healthcare cost estimated at $1.2 billion
      iii. Mortality rate >25-90% 
         1. If left untreated, 100% 
      iv. Incidence of 0.5-11% in at-risk populations

II. *Aspergillus* species\textsuperscript{4}
    a. Genus of spore-forming, filamentous fungus found naturally in soil, water, air, decaying vegetation, and other organic debris
    b. Favors warm, damp habitats
    c. Inhaled regularly but not pathogenic in most immunocompetent individuals
    d. Most common species isolated in human infections include *A. fumigatus, A. flavus, A. terreus*, and *A. niger*\textsuperscript{4}

Figure 1. Overview of Fungi\textsuperscript{6}

III. Spectrum of disease
    a. Allergic bronchopulmonary, chronic, and invasive aspergillosis infections\textsuperscript{1-4}
       i. Pulmonary disease is most common due to direct environmental exposure
          1. Conidia small enough (2.5 to 3 microns) to reach alveoli
          2. Spores may eventually germinate into invasive hyphae, causing infection
       ii. Invasive pulmonary aspergillosis (IPA) is the most common manifestation

IV. Invasive pulmonary aspergillosis (IPA)\textsuperscript{1-6}
    a. Accounts for >90% of all IA
    b. Advanced infection may disseminate elsewhere in the body, including the central nervous system
    c. Patients with underlying pulmonary disease or immune compromise are at higher risk (Figure 2)
**d. Pathogenesis**

i. **Immunocompetent**

1. *Aspergillus* conidia regularly inhaled from environment
2. Respiratory epithelial cells provide physical barrier to infection
3. Alveolar macrophages help clear conidia and promote secondary inflammation
   a. Recruit neutrophils and natural killer cells to site of infection

ii. **Immunocompromised**

1. Immune deficiency allows germination from conidia into hyphae, subsequently leading to invasive fungal disease
2. Neutrophils are the main defense against invasive hyphae
   a. Patients with severe, prolonged neutropenia are particularly vulnerable
   i. ANC <500 cells/mcL for > 10 days

**Figure 2. Risk categories for IPA**

<table>
<thead>
<tr>
<th>Highest Risk</th>
<th>Intermediate Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chronic granulomatous disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Allogenic stem cell transplant with graft-versus-host disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lung transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Acute myeloid leukemia/myelodysplastic syndrome with induction therapy or in relapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Allogeneic stem cell transplant without graft-versus-host disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Non-lung, non-kidney solid organ transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Acute lymphoblastic leukemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Acute myeloid leukemia (consolidation phase)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Chronic lymphoblastic leukemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Myelodysplastic syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Multiple myeloma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Chronic obstructive pulmonary disease acute exacerbation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Acquired immunodeficiency syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Non-hodgkin's's lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Autologous stem cell transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Kidney transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Solid tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Autoimmune disorder</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**e. Diagnosis**

i. No gold standard diagnostic test available

ii. Clinical diagnosis based on multiple factors and classified as proven, probable, or possible (Appendix 1)

iii. **Microbiological (Table 1)**

1. Isolation of *Aspergillus* coupled with clinical manifestations of infection
   a. Cultured from respiratory source (e.g. bronchoalveolar lavage)
   b. Risk factors must be accounted for with clinical presentation
2. Visualized via microscopy
   a. Morphology described as septated hyaline hyphae branching at 45 degree angles
   b. Sometimes confused other hyaline molds such as *Fusarium* spp
3. Respiratory culture should be evaluated in conjunction with histopathology or culture from sterile site
   a. Both cultures and tissue microscopy have low sensitivities

iv. Radiographic
   1. Computed tomography (CT) scan of chest recommended when IPA suspected
   2. Nodules with surrounding ground-glass opacities (halo-sign) common with early IPA and represent alveolar hemorrhage

v. Additional Laboratory Tests

<table>
<thead>
<tr>
<th>Galactomannan (GM) antigen detection</th>
<th>Beta-D-glucan assay</th>
<th>Nucleic acid detection via polymerase chain reaction (PCR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Polysaccharide found in cell walls of <em>Aspergillus</em></td>
<td>• 1,3-Beta-D-glucan is found in many fungi cell walls</td>
<td>• Evidence lacking to form consensus, should be employed alongside other diagnostic modalities, if at all</td>
</tr>
<tr>
<td>• Presence of GM antigen in serum or bronchoscopy acts as an indirect marker of <em>Aspergillus</em></td>
<td>• May indicate presence of invasive fungal infection</td>
<td></td>
</tr>
<tr>
<td>• Cross-reaction with other fungi may produce false-positive results</td>
<td>• Best utilized early if infection suspected</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Recommended in hematologic malignancy and HSCT, but not specific for <em>Aspergillus</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• May result positive for <em>Candida</em> spp or <em>Pneumocystis jiroveci</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Remains negative for <em>Mucor</em> and <em>Cryptococcus</em></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Mechanism of Action</td>
<td>Dosing and Formulations</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td><strong>PRIMARY THERAPY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole (VRC)</td>
<td>Inhibits ergosterol synthesis</td>
<td>6 mg/kg Q12H IV for 1 d, then 4 mg/kg IV q12h (IV solution); 200-300 mg PO Q12H or 3-4 mg/kg PO Q12H (tablets and PO suspension)</td>
</tr>
<tr>
<td><strong>ALTERNATIVE THERAPY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isavuconazole (ISA)</td>
<td>Inhibits ergosterol synthesis</td>
<td>200 mg Q8H for 6 doses, then 200 mg daily (IV solution, PO capsules)</td>
</tr>
<tr>
<td>Amphotericin B (AmB)</td>
<td>Binds ergosterol</td>
<td>3-5 mg/kg/day (liposomal suspension); 1-1.5 mg/kg/day (conventional solution); 5 mg/kg/day (lipid complex suspension)</td>
</tr>
<tr>
<td><strong>SALVAGE THERAPY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caspofungin</td>
<td>Inhibits 1,3-beta-D-glucan synthesis</td>
<td>70 mg/day x1, then 50 mg/day (IV solution)</td>
</tr>
<tr>
<td>Drug</td>
<td>Mechanism of Action</td>
<td>Dosage</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Micafungin</strong></td>
<td>Inhibits 1,3-beta-D-glucan synthesis</td>
<td>100-150 mg/day (IV solution)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Posaconazole (POS)</strong></td>
<td>Inhibits ergosterol synthesis</td>
<td>300 mg BID on day 1, then 300 mg daily (IV solution, delayed-release tablet)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Itraconazole</strong></td>
<td>Inhibits ergosterol synthesis</td>
<td>200 mg PO Q12H (PO suspension)</td>
</tr>
</tbody>
</table>

IV: 62  PO: 191  IV: 490  PO: 20-64
Treatment of Invasive Pulmonary Aspergillosis

I. Infectious Diseases Society of America (IDSA) 2016 Aspergillosis Guidelines recommend voriconazole for primary treatment of IPA (strong recommendation, high-quality evidence)

II. Isavuconazole, liposomal amphotericin B (L-AmB), and amphotericin B lipid complex (ABLC) recommended as alternatives (ISA, L-AmB: strong recommendation, moderate-quality evidence; ABLC: weak recommendation, low-quality evidence)

Figure 3. History of Treatment

III. Amphotericin B
   a. Polyene antifungal brought to market in 1959
   b. Broad spectrum of activity against molds and yeasts alike
   c. Considered first-line treatment prior to 2000s
      i. Lack of available agents with in vitro activity against Aspergillus
      ii. Significant adverse effect (AE) profile limited use
      iii. Mortality rates with amphotericin B deoxcholate (AmB-D) remained high
   d. Improved liposomal formulations developed in the late 1990s
      i. Widened therapeutic index and enhanced tolerability

IV. Voriconazole
   a. Compared to AmB-D for treatment of IA in randomized controlled trial by Herbrecht and colleagues in 2002 (Table 2)

Table 2. VRC versus AmB-D Design Overview

<table>
<thead>
<tr>
<th>Design</th>
<th>Patient Population</th>
<th>Intervention</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized control trial (RCT) comparing VRC to AmB-D as primary therapy for IA</td>
<td>≥ 12 years of age, immunocompromised, Definite or probable IA</td>
<td>Voriconazole (n=144), Amphotericin B deoxycholate (n=133)</td>
<td>Response rate at Week 12, Complete or partial response</td>
</tr>
</tbody>
</table>

i. VRC patients achieved successful outcome in 52.8% compared to 31.6% of AmB-D patients (95% CI, 10.4-32.9)

ii. VRC patients experienced significantly fewer adverse events
1. Superior safety profile for renal impairment, hypokalemia, systemic events (fever, chills, anaphylaxis, asthenia, or myalgia), dyspnea
2. Fewer treatment discontinuations in VRC arm
   a. VRC 13.4% vs AmB-D 24.3%, p=0.008
iii. Non-inferiority trial showed VRC to be superior to AmB-D
   1. VRC supplanted amphotericin B as drug of choice for IA
   2. Rapid shift in standard of care for IPA
      a. Ease of administration (oral therapy)
      b. Tolerable
      c. Efficacious

V. Isavuconazole
   a. Newest triazole antifungal
      i. Approved in 2015
      ii. Activity against <i>Aspergillus</i> and other molds, including <i>Mucorales</i>
   b. Formulated as prodrug, isavuconazonium sulfate

Table 3. SECURE Trial Design Overview

<table>
<thead>
<tr>
<th>Design</th>
<th>Patient Population</th>
<th>Intervention</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double-blind, RCT conducted in population of primarily IA patients</td>
<td>• ≥ 18 years of age</td>
<td>Isavuconazole (n=258)</td>
<td>• All-cause mortality by day 42</td>
</tr>
<tr>
<td></td>
<td>• Criteria for proven, probable, or possible invasive mold disease</td>
<td>Voriconazole (n=258)</td>
<td></td>
</tr>
</tbody>
</table>

c. Results
   i. All-cause mortality
      1. Day 42: ISA 19%, VRC 20%
         a. Adjusted treatment difference -1.0%, 95% CI -7.8 to 5.7
      2. Day 84: ISA 29%, VRC 31%
         a. Adjusted treatment difference -1.4%, 95% CI -9.2 to 6.3
   ii. Overall response at end of treatment
      1. Complete or partial success: ISA 35%, VRC 36%

d. ISA met noninferiority endpoints compared to VRC

e. ISA patients experienced significantly fewer drug-related AE overall (42% vs 60%, p<0.001)
   i. Treatment-emergent AE: significantly fewer skin and subcutaneous skin disorders (33% vs 42%, p=0.037), eye disorders (15% vs 27%, p=0.002), and hepatobiliary disorders (9% vs 16%, p=0.016)
   ii. Drug discontinuation rates lower in ISA arm (significance not reported)
      1. Discontinuation due to treatment-emergent AE: ISA 14% vs VRC 23%
      2. Discontinuation due to drug-related AE: ISA 8% vs VRC 14%
f. ISA granted FDA approval for treatment of IA
   i. VRC remains primary treatment recommendation in 2016 aspergillosis guidelines
      1. Older option with evidence and experience supporting its use
      2. Therapeutic drug monitoring available and validated
      3. Significant drug-drug interactions and side effect profile
   ii. ISA recommended as alternative therapy based on SECURE
      1. Less evidence outside clinical trials to lend confidence to its use
2. Therapeutic drug monitoring not validated, but also may not be necessary\textsuperscript{23,24}
3. Fewer drug-drug interactions and significantly more favorable safety profile compared to VRC\textsuperscript{25}

**Clinical Question:** Should isavuconazole be preferred therapy in the treatment of IPA?
Table 4. Early Real-World Experience with Isavuconazole

<table>
<thead>
<tr>
<th>Article</th>
<th>Design/Purpose</th>
<th>Population</th>
<th>Drug Regimen</th>
<th>Results (Efficacy/Safety)</th>
</tr>
</thead>
</table>
| Arsiè E, et al. 2018<sup>26</sup> | Case report                     | 58 year old male with history of HBV-cirrhosis (Child Pugh Score class C). Treated for possible IPA. | L-AmB x1 dose, then ISA 200 mg daily post loading regimen x1 week, followed by 200 mg every other day | • ISA concentration after 1 week 200 mg daily = 7.5 mg/L  
• ISA concentration after 1 week 200 mg every other day = 9.5 mg/L  
• Patient eventually died of multiorgan failure in setting of worsening infection                                                                 |
| Dadwal S, et al. 2016<sup>27</sup> | Abstract report                 | HM and HCT patients who received ≥7 days ISA for IFI treatment n=131         | ISA (dosing not reported)                                                      | • 6 patients (4.6%) developed breakthrough IFI  
• 4 with Aspergillus, 1 with Rhizopus spp., and 1 with Candida norvegensis  
• All patients had detectable trough levels (range 1.4-4.8 mg/L)                                                                                     |
| Fung M, et al. 2018<sup>28</sup> | Single-center retrospective observational report | ≥18 years old with HM or solid organ transplant with confirmed breakthrough IFI while on ISA n=5 | ISA 200 mg daily, with or without loading dose, for either prophylaxis or treatment | • All patients presented with pneumonia  
• 2 patients with Aspergillus niger  
• 1 each of Rhizopus spp., Scedosporium apiospermum, Aspergillus fumigatus  
• 3 of 5 patients died                                                                                                                                   |

Abbreviations: HCT, hematopoietic stem cell transplant; HM, hematologic malignancy; IFI, invasive fungal infection; ISA, isavuconazole; L-AmB, liposomal amphotericin B

- ISA affected by hepatic function  
  o No dosing recommendations currently available  
  o Insufficient data to compare to VRC in hepatic failure
- Early breakthrough data concerning  
  o ISA expected to be equal with VRC based on SECURE results  
  o Requires more thorough investigation
# Breakthrough Fungal Infections in Patients With Leukemia Receiving Isavuconazole


## Objective
Report evidence of breakthrough invasive fungal infections (b-IFI) in patients receiving isavuconazole

## Methods

### Design
Single-center retrospective observational case series

### Patient Population
681 bed academic medical center in Houston, Texas

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult patients in leukemia service</td>
<td>Concomitant antifungal agent for IFI treatment</td>
</tr>
<tr>
<td>Received ISA for prophylaxis or treatment of IFIs ≥ 7 days</td>
<td></td>
</tr>
</tbody>
</table>

## Results

### Demographics (n=100)
- Male gender, 73 (73%)
- Median age, 68 years [range 24-91]
- Neutropenia at time of ISA initiation, 69 (69%); > 14 days, 61 (61%)
- Malignancy types: AML (70%), ALL (10%), CML blast crisis (2%), CLL (6%), other (12%)
- Treatment of aspergillosis, 57 (57%)
- Primary prophylaxis, 27 (27%)
- Secondary prophylaxis, 16 (16%)
- ISA started in 39 patients previously on posaconazole
  - Switched due to intolerance or failure to reach therapeutic levels

### Results
- Total b-IFI rate of 13%
  - Treatment, n=6/13 (46%)
  - Primary prophylaxis, n=5/13 (39%)
  - Secondary prophylaxis, n=2/13 (15%)
- Mold-causing b-IFI, n=6 (46%)
  - Mortality rate, 50%
  - *Aspergillus* spp. rate, 7.7%
- Rate of b-IFIs nonneutropenic at diagnosis, n=4 (31%)
  Additional 7 patients had possible breakthrough fungal pneumonia

## Table 1. Occurrence of proven or probable breakthrough IFIs

<table>
<thead>
<tr>
<th>Patient Age/Sex</th>
<th>ANC, cells/mcL</th>
<th>ISA indication</th>
<th>Duration of ISA, d</th>
<th>b-IFI</th>
<th>Breakthrough pathogen</th>
<th>ISA MIC, mcg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>45/F</td>
<td>&lt;100</td>
<td>Secondary prophylaxis</td>
<td>146</td>
<td>Esophagitis</td>
<td><em>Candida albicans</em></td>
<td>N/A</td>
</tr>
<tr>
<td>71/M</td>
<td>500-1000</td>
<td>Treatment</td>
<td>7</td>
<td>Fungemia</td>
<td><em>Candida parapsilosis</em></td>
<td>N/A</td>
</tr>
<tr>
<td>52/M</td>
<td>&lt;100</td>
<td>Primary prophylaxis</td>
<td>53</td>
<td>Fungemia</td>
<td><em>Trichosporon asahii</em></td>
<td>0.5</td>
</tr>
<tr>
<td>76/M</td>
<td>500-1000</td>
<td>Primary prophylaxis</td>
<td>14</td>
<td>Disseminated</td>
<td><em>Rhizopus spp.</em></td>
<td>2</td>
</tr>
<tr>
<td>61/F</td>
<td>&lt;100</td>
<td>Primary prophylaxis</td>
<td>34</td>
<td>Pneumonia</td>
<td><em>Mucorales spp.</em></td>
<td>N/A</td>
</tr>
</tbody>
</table>
### Breakthrough infections a concern for anti-fungal agents

<table>
<thead>
<tr>
<th>Age</th>
<th>ANC</th>
<th>Type</th>
<th>N</th>
<th>Pathogen</th>
<th>MIC</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>30/M</td>
<td>&lt;100</td>
<td>Secondary prophylaxis</td>
<td>63</td>
<td>Fungemia</td>
<td>Candida guilliermondii</td>
<td>1</td>
</tr>
<tr>
<td>76/F</td>
<td>100-500</td>
<td>Treatment</td>
<td>81</td>
<td>Pneumonia</td>
<td>Fusarium spp.</td>
<td>N/A</td>
</tr>
<tr>
<td>54/F</td>
<td>&lt;100</td>
<td>Treatment</td>
<td>160</td>
<td>Disseminated</td>
<td>Candida krusei</td>
<td>4</td>
</tr>
<tr>
<td>34/M</td>
<td>&lt;10</td>
<td>Primary prophylaxis</td>
<td>24</td>
<td>Fungemia</td>
<td>Candida glabrata</td>
<td>4</td>
</tr>
<tr>
<td>51/F</td>
<td>&gt;1000</td>
<td>Primary prophylaxis</td>
<td>41</td>
<td>Fungemia</td>
<td>Candida glabrata</td>
<td>4</td>
</tr>
<tr>
<td>60/F</td>
<td>500-1000</td>
<td>Treatment</td>
<td>157</td>
<td>Pneumonia, fungemia</td>
<td>Rhizopus spp.; C. glabrata</td>
<td>N/A</td>
</tr>
<tr>
<td>61/M</td>
<td>100-500</td>
<td>Treatment</td>
<td>194</td>
<td>Pneumonia</td>
<td>Rhizomucor spp.</td>
<td>N/A</td>
</tr>
<tr>
<td>78/F</td>
<td>&lt;100</td>
<td>Treatment</td>
<td>26</td>
<td>Disseminated</td>
<td>Aspergillus spp.</td>
<td>N/A</td>
</tr>
</tbody>
</table>

ANC, absolute neutrophil count (at time of b-IFI diagnosis); b-IFI, breakthrough invasive fungal infection; ISA, isavuconazole; MIC, minimum inhibitory concentration; N/A, nonapplicable

### Author's Conclusions
- Single-agent ISA resulted in higher than expected rate of breakthrough infection
- Breakthrough infections occurred primarily in non-Aspergillus spp.

### Reviewer's Critique

#### Strengths
- Most comprehensive report to date for b-IFIs on ISA

#### Limitations
- Retrospective, observational
- Small, single-center
- Previous posaconazole exposure in many patients
- ISA MICs not tested for all patients
- Limited to leukemia patients
- No comorbidities reported

#### Overall Conclusions
- ISA associated with relatively high rates of b-IFI
- *Candida* spp. represent most common b-IFI pathogens on ISA

- Real-world data necessary to evaluate ISA’s place in therapy
- Breakthrough infections a concern for anti-fungal agents
  - Isavuconazole b-IFI rates ranged 4.6-13%
  - Previously reported b-IFI rates across retrospective studies\(^{30-35}\)
    - Posaconazole: 7.5%
    - Voriconazole: 2.4-14%
- ISA and VRC are likely equally efficacious for IPA
  - What other evidence has emerged since ISA approved?
Studies conducted with isavuconazole since SECURE

Lack of Toxicity With Long-term Isavuconazole Use in Patients With Hematologic Malignancy

DiPippo A, Kontoyiannis D. Clin Infect Dis. 2019

Objective

Present real-world tolerability data in hematologic malignancy patients on long-term isavuconazole

Methods

Design

Single-center retrospective report

Patient Population

681 bed academic medical center in Houston, Texas

Inclusion Criteria

• Consecutive patients receiving isavuconazole continuously for ≥6 months
• Diagnosed with hematologic malignancy

Exclusion Criteria

• N/A

Results

Demographics (n=50)

• Male gender, n=35/50 (70%)
• Median age, 61 years (range, 23-91)
• Malignancy types: AML/MDS (60%), ALL (12%), B-cell lymphomas (8%), CLL (6%), CML (6%), MM (4%), aplastic anemia (4%)
• Median ISA duration, 356 days (range, 180-832)
• Indication for ISA
  o Possible or presumed infection (66%)
  o Mold-active prophylaxis (34%)

Results

Table 1. Toxicity Indicators of Chronic (≥6 Months) ISA Use

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Baseline</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months(a)</th>
<th>24 Months(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTc</td>
<td>421 (324-531)(^b)</td>
<td>405 (371-473)(^d)</td>
<td>400 (372-476)(^f)</td>
<td>425.5 (371-471)(^h)</td>
<td>391 (362-399)(^k)</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>124.5 (94-171)</td>
<td>126 (96-155)</td>
<td>122.5 (88-163)</td>
<td>125.5 (90-149)(^j)</td>
<td>119.5 (102-154)(^l)</td>
</tr>
<tr>
<td>Serum potassium, mg/dL</td>
<td>3.8 (2.7-5.7)</td>
<td>4.1 (3-5.3)</td>
<td>4.25 (3.1-5.2)</td>
<td>4.2 (3.1-5.9)(^i)</td>
<td>3.9 (3.3-5.1)(^j)</td>
</tr>
<tr>
<td>Liver function tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>37 (12-426)(^c)</td>
<td>33 (12-155)</td>
<td>33.5 (14-224)</td>
<td>33 (16-460)(^j)</td>
<td>26 (6-63)(^l)</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>31 (12-245)(^c)</td>
<td>29.5 (15-185)(^e)</td>
<td>29 (17-184)(^g)</td>
<td>29 (13-325)(^j)</td>
<td>26 (11-83)(^m)</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>103 (38-570)</td>
<td>86 (52-357)</td>
<td>90.5 (43-240)</td>
<td>97.5 (48-434)(^j)</td>
<td>83.5 (58-330)(^j)</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>0.8 (0.2–3.7)</td>
<td>0.7 (0.3–4.2)</td>
<td>0.6 (0.2–5.9)</td>
<td>0.6 (0.2–14.1)</td>
<td>0.5 (0.2–1.4)</td>
</tr>
<tr>
<td>-----------------------</td>
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</tr>
</tbody>
</table>

All values presented as median (range)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; SBP, systolic blood pressure.

\(a\)Or last date of isavuconazole (ISA) as appropriate.

\(b\) \(n = 33.\)
\(c\) \(n = 34.\)
\(d\) \(n = 24.\)
\(e\) \(n = 44.\)
\(f\) \(n = 27.\)
\(g\) \(n = 38.\)
\(h\) \(n = 46.\)
\(i\) \(n = 38.\)
\(j\) \(n = 21.\)
\(k\) \(n = 44.\)
\(l\) \(n = 18.\)
\(m\) \(n = 15.\)

- Sixteen occurrences of toxicity possibly related to ISA use
  - Hepatotoxicity: 4 (8%)
  - Skin rash: 6 (12%)
  - Blurry vision: 3 (6%)
  - Squamous cell carcinoma: 2 (4%)
  - Neurologic toxicity: 1 (2%)

### Author's Conclusions
- First real-world data assessing long-term tolerability of ISA
- ISA was well tolerated overall

### Reviewer's Critique

#### Strengths
- First real-world report of effects of chronic ISA use
- Spectra of ISA-attributed toxicity largely consistent with SECURE
  - Primarily hepatobiliary, skin, ophthalmic events

#### Limitations
- No comparator group
- Retrospective, single-center
  - Incidence of adverse events lower than reported in clinical trials
- Small sample size
- Comorbidities not reported

### Overall Conclusions
- Practical evidence of successful long-term use of ISA

---

**Comparative evaluation of isavuconazonium sulfate, voriconazole, and posaconazole for the management of invasive fungal infections in an academic medical center**


**Objective**

Compare safety end points between triazole antifungals in the treatment of IFIs

**Methods**

**Design**
Single-center retrospective matched cohort study

**Patient Population**

<table>
<thead>
<tr>
<th>678-bed academic hospital in Aurora, Colorado</th>
</tr>
</thead>
</table>

**Inclusion Criteria**

- Adult patients > 18 years of age
- Receipt of isavuconazole (ISA), voriconazole (VRC), or posaconazole (POS) for active treatment of confirmed

**Exclusion Criteria**

- Patients in vulnerable category such as pregnancy, prisoners
or suspected fungal infection

Intervention Compared patients who received ISA vs VRC vs PSC

Outcome Primary: Composite safety outcome
- QTc prolongation (>470 ms for females, >450 ms for males)
- Liver function tests five times the upper limit of normal (ALT > 260 units/L, AST > 195 units/L)
- Any documented antifungal treatment related adverse event based on primary team documentation

Secondary:
- Individual components of composite outcome (percent change in QTc length from baseline, percent change in calcineurin inhibitor serum concentration)
- Total cost of inpatient antifungal therapy per day
- All-cause in-hospital mortality
- In hospital and ICU LOS

Statistics
- 30 patients needed in each group to detect 30% difference in primary outcome between groups with 80% power and 5% alpha
- Categorical data compared using chi-squared test, with pairwise comparisons if statistical significance was found
- Continuous, normally distributed data compared with analysis of variance t-test followed by pairwise t-test
- Non-normally distributed data with Kruskal-Wallis test, then Mann-Whitney U tests

Results

<table>
<thead>
<tr>
<th>Demographics n = 100</th>
<th>Characteristic</th>
<th>Total (n=100)</th>
<th>ISA (n=33)</th>
<th>VRC (n=34)</th>
<th>POS (n=33)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years ± SD</td>
<td>55.9 ± 13.7</td>
<td>58.8 ± 14.0</td>
<td>56.9 ± 11.4</td>
<td>52.1 ± 15.1</td>
<td>0.124</td>
<td></td>
</tr>
<tr>
<td>Primary diagnosis of oncology, n (%)</td>
<td>62 (62)</td>
<td>17 (51.5)</td>
<td>23 (67.6)</td>
<td>22 (66.7)</td>
<td>0.097</td>
<td></td>
</tr>
<tr>
<td>Hematologic malignancy, n (%)</td>
<td>58 (93.6)</td>
<td>16 (94.1)</td>
<td>22 (95.6)</td>
<td>20 (90.9)</td>
<td>0.806</td>
<td></td>
</tr>
<tr>
<td>Primary diagnosis of solid organ transplant, n (%)</td>
<td>26 (26)</td>
<td>14 (42.4)</td>
<td>5 (14.7)</td>
<td>7 (21.2)</td>
<td>0.097</td>
<td></td>
</tr>
<tr>
<td>Baseline AST, units/L ± SD</td>
<td>27.3 ± 36.0</td>
<td>22.0 ± 17.7</td>
<td>21.9 ± 15.5</td>
<td>36.4 ± 41.8</td>
<td>0.053</td>
<td></td>
</tr>
<tr>
<td>Baseline ALT, units/L ± SD</td>
<td>26.8 ± 28.2</td>
<td>22.2 ± 22.0</td>
<td>22.5 ± 22.1</td>
<td>37.1 ± 53.3</td>
<td>0.160</td>
<td></td>
</tr>
<tr>
<td>Baseline QTc, ms ± SD</td>
<td>457 ± 40</td>
<td>478 ± 46</td>
<td>445 ± 29</td>
<td>450 ± 35</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Concurrent echinocandin therapy, n(%)</td>
<td>23 (23)</td>
<td>8 (24.2)</td>
<td>5 (14.7)</td>
<td>10 (30.3)</td>
<td>0.298</td>
<td></td>
</tr>
<tr>
<td>Concurrent QTc prolonging medications, n (%)</td>
<td>83 (83)</td>
<td>24 (72.7)</td>
<td>28 (82.35)</td>
<td>31 (93.9)</td>
<td>0.057</td>
<td></td>
</tr>
<tr>
<td>Characteristic</td>
<td>Total (n=100)</td>
<td>ISA (n=33)</td>
<td>VRC (n=34)</td>
<td>POS (n=33)</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td><strong>Primary outcome:</strong> Composite safety, n (%)</td>
<td>40 (40)</td>
<td>8 (24.2)</td>
<td>19 (55.9)</td>
<td>13 (39.4)</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>QTc prolongation following drug initiation, n (%)</td>
<td>28 (28)</td>
<td>4 (12.1)</td>
<td>13 (38.2)</td>
<td>11 (33.3)</td>
<td>0.037</td>
<td></td>
</tr>
<tr>
<td>LFT elevation, n (%)</td>
<td>8 (8.0)</td>
<td>2 (6.1)</td>
<td>3 (8.8)</td>
<td>3 (9.1)</td>
<td>0.876</td>
<td></td>
</tr>
<tr>
<td>Adverse reaction, n (%)</td>
<td>9 (9)</td>
<td>2 (6.1)</td>
<td>5 (15.2)</td>
<td>2 (6.1)</td>
<td>0.356</td>
<td></td>
</tr>
<tr>
<td>Change in QTc, ms ± SD</td>
<td>7.5 ± 42.0</td>
<td>-18.0 ± 37.6</td>
<td>20.5 ± 37.8</td>
<td>22.6 ± 38.6</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Max QTc, ms ± SD</td>
<td>464.2 ± 35.1</td>
<td>460.0 ± 29.5</td>
<td>465.4 ± 33.8</td>
<td>467.4 ± 42.2</td>
<td>0.739</td>
<td></td>
</tr>
<tr>
<td>Change in ALT, units/L ± SD</td>
<td>93.2 ± 393.6</td>
<td>95.1 ± 440.3</td>
<td>105.6 ± 448.5</td>
<td>78.5 ± 281.2</td>
<td>0.964</td>
<td></td>
</tr>
<tr>
<td>Change in AST, units/L ± SD</td>
<td>192.4 ± 894.7</td>
<td>159.5 ± 717.3</td>
<td>259.2 ± 1226.2</td>
<td>155.4 ± 629.8</td>
<td>0.875</td>
<td></td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>48 (48)</td>
<td>15 (45.5)</td>
<td>16 (47.1)</td>
<td>17 (51.5)</td>
<td>0.878</td>
<td></td>
</tr>
<tr>
<td>Hospital LOS, days ± SD</td>
<td>32.9 ± 37.4</td>
<td>31.8 ± 25.9</td>
<td>28.2 ± 19.5</td>
<td>38.7 ± 56.7</td>
<td>0.515</td>
<td></td>
</tr>
<tr>
<td>30 day readmission, n (%)</td>
<td>29 (42)</td>
<td>8 (34.78)</td>
<td>7 (30.4)</td>
<td>14 (60.9)</td>
<td>0.077</td>
<td></td>
</tr>
<tr>
<td>Recurrent infection, n (%)</td>
<td>9 (14.1)</td>
<td>1 (4.5)</td>
<td>4 (19.1)</td>
<td>4 (19.1)</td>
<td>0.230</td>
<td></td>
</tr>
</tbody>
</table>

Results Clinical Outcomes
### Percent change in immunosuppression dose [IQR]

<table>
<thead>
<tr>
<th></th>
<th>ISA (n=33)</th>
<th>VRC (n=34)</th>
<th>POS (n=33)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent change in immunosuppression dose [IQR]</td>
<td>-46.1 [-27.8, -57.8]</td>
<td>-48.4 [-35.1, -65.9]</td>
<td>-46.4 [-35.1, -65.9]</td>
<td>0.029</td>
</tr>
</tbody>
</table>

- Primary outcome pairwise comparison
  - ISA < VRC, p=0.008

### Cost Outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=100)</th>
<th>ISA (n=33)</th>
<th>VRC (n=34)</th>
<th>POS (n=33)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic drug monitoring n (%)</td>
<td>22 (22)</td>
<td>0 (0)</td>
<td>14 (41.2)</td>
<td>8 (24.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Author's Conclusions

- Primary outcome difference was driven by ISA's lower incidence of QTc prolongation
- Increase in transaminases with ISA numerically lower than VRC, although not compared 1:1 for significance
- ISA required less immunosuppressive dose reduction than other triazoles
- Drug cost and overall total cost were similar across drug groups, but cost per day was lowest with voriconazole

### Reviewer’s Critique

**Strengths**
- Cohort mostly well-matched at baseline
- Representation of patients outside of hematologic malignancy

**Limitations**
- Retrospective single-center study
  - Inherent bias in baseline drug selection
  - Limited external validity
- Small population
- Adverse effects not well-characterized
- Reliance on biomarkers as surrogates for safety outcomes
- Potential confounders with echinocandin therapy
- Unable to follow up with patients past 30 days from discharge

**Overall Conclusions**
- Evidence from a practical setting that generally validates previous data regarding outcomes with ISA compared to other triazoles for treatment of invasive fungal infections
Conclusions
I. Efficacy data outside of clinical trials for ISA are limited
   a. Evidence suggests ISA is similarly effective to its comparators
II. Therapeutic drug monitoring may be warranted in select populations (e.g. hepatic failure)
III. Role of prophylaxis in settings outside IPA remain unclear
IV. Breakthrough rates appear consistent with VRC and POS
V. Safety data continue to favor ISA over VRC

Summary
I. Recent evidence upholds the conclusions of SECURE
II. ISA has comparable efficacy and a clearly favorable adverse effect profile relative to VRC
III. ISA is a compelling first line option for treatment of IPA

Recommendations
I. Recommend ISA for primary IPA
II. Recommend VRC for extrapulmonary IA
References

27. Dadwal S, Kriengkauykij T, Tegtmeier D, Breakthrough Invasive Fungal Infections in Patients With Hematologic Malignancy (HM) and Hematopoietic Cell Transplantation (HCT) Receiving Isavuconazole for Empiric or Directed Antifungal Therapy. Mycology abstract
Appendix 1. Invasive fungal disease (IFD) criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proven IFD</strong></td>
<td><strong>One of the following:</strong></td>
</tr>
<tr>
<td></td>
<td><strong>1) Microscopic analysis:</strong> Histopathologic, cytopathologic, or direct microscopic examination obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage**</td>
</tr>
<tr>
<td></td>
<td><strong>2) Culture:</strong> recovery of a mold or &quot;black yeast&quot; from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding bronchoalveolar lavage fluid, cranial sinus cavity specimen, and urine</td>
</tr>
<tr>
<td><strong>Probable IFD</strong></td>
<td><strong>One from EACH of the following three categories:</strong></td>
</tr>
<tr>
<td></td>
<td><strong>1) Host Factors:</strong> Recent history of neutropenia temporally related to the onset of fungal disease, receipt of an allogeneic stem cell transplant, prolonged use of corticosteroids at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for &gt;3 weeks, treatment with other recognized T-cell immunosuppressants in the past 90 days, or inherited severe immunodeficiency**</td>
</tr>
<tr>
<td></td>
<td><strong>2) Clinical Criteria:</strong> Dense well-circumcised lesions with or without a halo sign, air-crescent sign, or cavity**</td>
</tr>
<tr>
<td></td>
<td><strong>3) Mycologic Criteria:</strong> Mold in sputum, bronchoalveolar lavage (BAL) fluid, bronchial brush, or aspirate samples indicated by presence of fungal elements indicating a mold or recovery by culture of a mold, galactomannan antigen detected in plasma, serum, BAL fluid, or cerebrospinal fluid**</td>
</tr>
<tr>
<td>Possible IFD</td>
<td><strong>One Host Factor and one Clinical Criteria as defined above</strong></td>
</tr>
</tbody>
</table>