Fungus, fungus, on the (bronchiole) wall, which is the best triazole of them all?
Antifungal prophylaxis in lung transplant recipients

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Learning Objectives:
I. Discuss the prevalence and clinical impact of fungal infections in lung transplant recipients
II. Review guideline recommendations and current antifungal prophylaxis practices post-lung transplantation
III. Evaluate the pharmacology, safety, and efficacy of triazoles for antifungal prophylaxis in lung transplant recipients
Assessment Questions

1. **What is the most frequent causative pathogen of invasive fungal infections in lung transplant recipients?**
   b. Endemic mycoses
   c. *Aspergillus* spp.
   d. *Cryptococcus* spp.

2. **Which triazole antifungal is not recommended as a first-line option by the American Society of Transplantation Infectious Diseases Community of Practice guidelines?**
   a. Itraconazole
   b. Isavuconazole
   c. Posaconazole
   d. Voriconazole

3. **Which triazole antifungal has the most evidence of its use in lung transplantation?**
   a. Itraconazole
   b. Isavuconazole
   c. Posaconazole
   d. Voriconazole
Antifungal Prophylaxis in Lung Transplant

I. Introduction to lung transplant
   a. In 2017, 2478 lung transplants were performed in the US\(^1\)
   b. Organ Procurement Transplant Network (OPTN) & Registry of the International Society for Heart and Lung Transplantation (ISHLT)\(^1\)–\(^5\)
      i. Patient survival is highest for kidney transplant recipients and lowest for lung transplant recipients (Table 1)
      ii. Patient survival rates in lung transplant at 1-year, 3-year, and 5-year were 85%, 68%, and 58%, respectively
      iii. Infection is primary cause of death (37.3%) among adult lung transplant recipients (LuTR) at 12 months\(^1\)

<table>
<thead>
<tr>
<th>Table 1. Patient survival in solid organ transplantation(^1)–(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number Transplants 2017</td>
</tr>
<tr>
<td>Kidney</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Lung</td>
</tr>
<tr>
<td>Pancreas</td>
</tr>
</tbody>
</table>

II. Focus on fungal infections in lung transplant
   a. Increase risk of acute rejection and chronic lung allograft dysfunction\(^6\)–\(^7\)
   b. Pathogenic sources of IFI after lung transplant
      i. *Aspergillus* species (spp.) is most frequent causative pathogen of IFIs in LuTRs\(^6\)–\(^8\)
   c. Mortality rate of invasive aspergillosis (IA) in LuTR may exceed 50%\(^8\)
   d. Airway anastomotic complications, specifically tracheobronchial aspergillosis, may occur from 0 to 3 months post-transplant\(^5\)–\(^7\)
      i. Airway anastomosis typically performed between bronchus of donor lung and that of recipient
      ii. Causative pathogen is most commonly *Aspergillus* spp.
      iii. Mortality rate of tracheobronchial aspergillosis in LuTR ranges from 67-82%\(^9\)
   e. Risk of fungal colonization and invasive fungal infections (IFI) highest from 0 to 6 months post-transplant\(^5\)–\(^6\),\(^10\)
      i. Fungal colonization
         1. Absence of symptoms, radiologic, and endobronchial changes
         2. Presence of fungus in respiratory secretions detected by culture or biomarker (galactomannan)
         3. One-year incidence & prevalence in LuTR: 20-50%
      ii. IFI
         1. Presence of symptoms, radiologic, and endobronchial changes
         2. Presence of fungus in secretions detected by culture
         3. One-year incidence & prevalence in LuTR: 3-14%
         4. *Aspergillus* spp. most common pathogen
5. Lung transplant is second most common organ for IFI’s following small bowel transplant recipients.

III. Risk factors for IFI

a. Cystic fibrosis diagnosis
b. Fungal colonization or infection
c. Cytomegalovirus (CMV) infection or viremia
d. Advanced donor age > 50 years
e. Lymphocyte-depleting induction therapy
   i. Thymoglobulin
   ii. Alemtuzumab
   iii. Murine anti-CD3 monoclonal antibody (OKT3)
f. Use of tacrolimus, cyclosporine, or sirolimus
g. Single lung transplant
h. Surgical factors
   i. Airway ischemia, airway stenting, anastomotic complications

IV. Invasive aspergillosis (IA) infection

a. Serious infection that usually affects immunocompromised patients
b. Portals of entry include skin, sinuses, lungs
   i. Tracheobronchial aspergillosis may result in dissemination
c. Diagnosis
   i. Role of biomarkers
      1. Serum galactomannan
         1. Sensitivity and specificity in general population in Table 2
         2. Lower sensitivity for IA diagnosis in solid organ transplant
         3. Approximately 30% sensitivity in cardiothoracic recipients
      2. 1,3-B-d-glucan test
         1. Component of fungal cell wall
         2. Not specific for IA
   ii. Three levels of certainty of IA defined in Table 3 as proven, probable, possible

<table>
<thead>
<tr>
<th>Table 2: Characteristics of fungal biomarkers for indirect tests of probable invasive fungal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fungal Biomarker</strong></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Galactomannan</td>
</tr>
<tr>
<td>1,3-β-d-glucan</td>
</tr>
</tbody>
</table>

IA: invasive aspergillosis; BAL: bronchoalveolar lavage; CSF: cerebrospinal fluid
**Table 3. Invasive aspergillosis criteria**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proven</strong></td>
<td>Microscopic analysis: histopathologic, cytopathologic, or direct microscopic examination of a specimen in which hyphae are seen accompanied by evidence of associated tissue damage.</td>
</tr>
<tr>
<td><strong>Probable</strong></td>
<td>One of each of the following: 1. Host factors  a. Recent history of neutropenia (500 neutrophils/mm³) for 110 days  b. Receipt of an allogeneic stem cell transplant  c. Prolonged use of corticosteroids at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for 13 weeks  d. Treatment with other recognized T-cell immunosuppressants  e. Inherited severe immunodeficiency 2. Clinical features (one of the following three signs on computed tomography  a. Dense, well-circumscribed lesion(s) with or without a halo sign  b. Air-crescent sign  c. Cavity 3. Mycological criteria (one of the following)  a. Direct test (cytology, direct microscopy, or culture)  i. Sputum, bronchealverolar fluid, bronchial brush indicating presence of fungal elements or culture recovery <em>Aspergillus</em> spp.  b. Indirect tests  i. Galactomannan antigen detected in plasma, serum, or BAL fluid  ii. 1,3-β-d-glucan detected in serum</td>
</tr>
<tr>
<td><strong>Possible</strong></td>
<td>Presence of host factors and clinical features (see above) but in the absence of or negative mycological findings</td>
</tr>
</tbody>
</table>

V. **Guideline recommendations on antifungal prophylaxis in lung transplant**

a. Types of prophylaxis  
   i. Universal  
      1. Administration of empiric antifungal agents without isolated pathogens  
   ii. Pre-emptive  
      1. Administration of antifungal agents for mold isolated during surveillance post-transplant bronchoscopy without evidence of invasive disease (ie. colonization)  

b. Universal prophylaxis with agents with systemic activity against both *Aspergillus* and *Candida* spp. should be used in the immediate post-transplant period (ie. first 2-4 weeks)  

c. Tracheobronchial aspergillosis prophylaxis for months 0-3 post-transplant  
   i. Amphotericin B (AmB) decreased incidence of IA as vs. no prophylaxis\(^{13-15}\)  
   ii. Nebulized formulation allows  
      1. High local concentration in the lungs  
      2. Good distribution throughout lung airway  
      3. Avoids systemic effects and drug interactions  

d. Many centers utilize combination therapy of triazole plus inhaled amphotericin\(^{16}\)  

e. ISHLT recommendations (Table 4)\(^{5}\)  
   i. Mold-active therapy should be used in immediate post-transplant period  
   ii. Most effective strategy for anti-fungal prophylaxis is unknown\(^{5,8}\)  
   iii. Factors to influence choice
1. Local epidemiology, time post-transplant, susceptibility profile on institutional antibiogram, drug efficacy, toxicity profile, drug-drug interactions, available formulations, degree of need, access to therapeutic drug monitoring (TDM), cost/insurance coverage\(^5\)

f. Infectious Diseases Society of America (IDSA) 2016 Aspergillus guidelines recommend voriconazole or itraconazole in lung transplant\(^17\)

g. American Society of Transplantation (AST) Infectious Diseases (ID) Community of Practice (COP) guidelines\(^19\)
   i. Recommend **voriconazole, itraconazole, or posaconazole** as first-line options
   ii. Isavuconazole recommended as alternative

VI. Controversy of fungal prophylaxis in lung transplant
   a. Universal prophylaxis more common than preemptive therapy, with the most common regimen being nebulized amphotericin and a systemic triazole\(^5,19\)
   b. Guidelines recommend use of triazoles without identifying an optimal triazole for antifungal prophylaxis in LuTR\(^18\)
   c. Limited data comparing efficacy of the various triazole antifungal agents\(^5\)

Clinical Question

Which triazole should be used for antifungal prophylaxis in lung transplant?

Triazole Agent Review

I. Mechanism of action\(^20\)
   a. Inhibit C-14a demethylation of lanosterol in fungi by binding to one of the cytochrome P450 enzymes (lanosterol 14a-demethylase), which leads to the accumulation of C-14a methylsterols and reduced concentrations of ergosterol
      i. Ergosterol: essential for normal fungal cytoplasmic membrane structure
      ii. Triazoles differ in affinities to their target, accounting for differences in spectrum of activity

Fluconazole lacks coverage of Aspergillus, the most common causative pathogen in LuTRs, and is therefore not used for fungal prophylaxis post-lung transplant\(^21\)
II. **Review of triazole antifungal pharmacology**<sup>20</sup>
   a. Pharmacology of triazole antifungal provided in Table 4 and Appendix A
   b. Formulation pitfalls<sup>20-24</sup>
      i. Difficulty with achieving adequate levels exists with itraconazole capsule and solution and posaconazole suspension
      ii. Stelzer et al. compared prophylactic triazole serum concentrations
         1. Itraconazole solution and posaconazole suspension showed lowest percentage of achievement of prophylactic serum concentrations (itraconazole solution 62%, voriconazole 85%, posaconazole suspension 49%, and posaconazole delayed release tab 76%)
      iii. Brett, et al. conducted retrospective audit of heart and LuTR
         1. Demonstrated considerable inter- and intra-patient variability in itraconazole capsule concentrations and sub-therapeutic concentrations

### Table 4. Triazole antifungal pharmacology review<sup>20,22</sup>

<table>
<thead>
<tr>
<th></th>
<th>Voriconazole</th>
<th>Itraconazole</th>
<th>Posaconazole</th>
<th>Isavuconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA indications</td>
<td>IA, candidemia, esophageal candidiasis, <em>Scedosporium apiospermum</em> infections</td>
<td>Salvage therapy of IA, blastomycosis, candidiasis, histoplasmosis, onychomycosis</td>
<td>Prophylaxis of IA and candidiasis in immunocompromised host</td>
<td>IA, Mucormycosis</td>
</tr>
<tr>
<td>Formulations</td>
<td>Tablets, IV</td>
<td>Capsule, Solution, XR capsule</td>
<td>Capsule, IV, Suspension</td>
<td>Capsule, IV</td>
</tr>
<tr>
<td>IA dosing</td>
<td>6 mg/kg q 12 hrs x 2 doses, then 4 mg/kg q 12 hrs (IV/PO)</td>
<td>Sporonox® capsules: 200 mg PO once or BID</td>
<td>IV or DR tablets: 300 mg q 12 hrs x 2 doses, then 300 mg daily Suspension: 200 mg TID - QID</td>
<td>372 mg IV/PO q 8 hours x 6 doses, then 372 mg daily</td>
</tr>
<tr>
<td>Oral bioavailability</td>
<td>96%</td>
<td>Sporonox® capsule: 55% Solution: 70-78%</td>
<td>DR Capsule: 54% (AUC ↑ with high fat)</td>
<td>&gt;95 %</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hydrolysis in blood, metabolized hepatically</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal</td>
<td>Hepatobiliary</td>
<td>Fecal</td>
<td>Fecal/Renal</td>
</tr>
<tr>
<td>Half-life</td>
<td>8 hrs</td>
<td>Solution: 39.7 hrs Active metabolite: 20 hrs</td>
<td>DR: 30 hrs, Susp: 20-66 hrs IV: 27 hrs</td>
<td>~130 hrs</td>
</tr>
</tbody>
</table>

III. **Adverse effects**<sup>20</sup>
   a. Summary of adverse effect profile provided in Table 5
   b. Voriconazole
      i. Transplant patients have higher frequency and shorter time to development of squamous cell carcinoma than non-transplant recipients<sup>25,26</sup>
Table 5. Adverse effects

<table>
<thead>
<tr>
<th></th>
<th>Voriconazole</th>
<th>Itraconazole</th>
<th>Posaconazole</th>
<th>Isavuconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Discomfort</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>↑ Hepatic Transaminases</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Rash or Photosensitivity</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Skin Malignancy</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>CNS &amp; Visual Disturbances</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Cardiomyopathy, ↑QT</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

IV. Drug interactions

a. Summary of drug interactions in Table 6
b. Inhibition of metabolism of co-administered drug by triazole antifungal leads to increased serum concentrations of co-administered drug
c. Induction of azole metabolism leads to decreased triazole antifungal serum concentration
   i. Examples: rifampin, enzyme-inducing anti-epileptic drugs, St. John’s wort

Table 6. Drug Interactions

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Voriconazole</th>
<th>Itraconazole</th>
<th>Posaconazole</th>
<th>Isavuconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>2C19</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2C9</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3A4</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Pgp</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Voriconazole</th>
<th>Itraconazole</th>
<th>Posaconazole</th>
<th>Isavuconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>2C19</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2C9</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3A4</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Table 7. Dose reductions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tacrolimus Dose Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole</td>
<td>66%</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>50-60%</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>50-75%</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>0-50%</td>
</tr>
</tbody>
</table>

V. Therapeutic drug monitoring (Table 8)

a. Isavuconazole
   i. Data does not support therapeutic drug monitoring

Table 8. Therapeutic drug monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>Timing of Trough</th>
<th>Goal Trough</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole</td>
<td>7 days after initiation</td>
<td>&gt;1 mg/L *</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>5-7 days after initiation</td>
<td>Parent: 0.5 ug/mL + active metabolite: 1 ug/mL</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>7 days after initiation</td>
<td>&gt;0.7 mg/L</td>
</tr>
</tbody>
</table>

*Trough >6 mg/L associated with toxicity
Efficacy of Triazole Antifungals

I. Voriconazole\textsuperscript{30-32}
   a. Triazole most frequently studied for anti-fungal prophylaxis in LuTRs
      i. Summary of evidence in Table 9
   b. Supporting data has lead to its guideline recommendations as a first-line option for antifungal prophylaxis
   c. However, this agent’s side effect profile has created many issues regarding its use

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen/Duratio</th>
<th>Follow-up</th>
<th>Results</th>
<th>Adverse events</th>
</tr>
</thead>
</table>
| Mitsani et al. 2012    | Voriconazole 6 mg/kg IV q12h x 2 doses, then 200 mg PO BID for at least 3 months | Equal duration to prophylaxis | IFI: 10/93 (10%)                       | Discontinuation 27%
|                        |                       |                  |                               | Nausea/vomiting 14%
|                        |                       |                  |                               | Hepatotoxicity 11%
|                        |                       |                  |                               | CNS events 3%|
| Tofte et al. 2012      | Voriconazole 200 mg PO BID for 3 months (n=57) | Not consistently defined | IA: 11/57 (19%)                  | Not reported |
|                        | No prophylaxis (n=82) |                  | IA: 8/82 (10%)                 |                                         |
| Neoh et al. 2013       | Preemptive voriconazole 200mg PO BID in 87% of patients for a median of 85 days (range 4-455) | 6 mo                   | Proven/probable IA: 1/62 (1.6%)     | Hepatotoxicity 16%
|                        |                       |                  |                               | Discontinuation 12.9%|

d. Comparative efficacy
   i. Voriconazole versus itraconazole for antifungal prophylaxis in LuTR
      1. Both agents have data supporting use as anti-fungal prophylactic agents
      2. Long term use of both agents is not optimal due to unpredictable pharmacokinetics, drug interactions, and adverse effects\textsuperscript{19}

e. Cadena, et al. attempted to evaluate the safety and efficacy profile of both voriconazole and itraconazole in LuTR (Table 10)\textsuperscript{33}

<table>
<thead>
<tr>
<th>Table 10. Cadena, et al. 2009\textsuperscript{33}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose</td>
</tr>
<tr>
<td>Study Design</td>
</tr>
<tr>
<td>Patient Population</td>
</tr>
<tr>
<td></td>
</tr>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Interventions</td>
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</tr>
</tbody>
</table>
### Primary & Secondary Endpoints

**Primary Endpoint**
- Incidence of hepatotoxicity related to antifungal prophylaxis

**Secondary Endpoints**
- Time to development of hepatotoxicity
- Incidence of IFI during study period
- Effect of antifungal prophylaxis on death (overall mortality and fungal-related mortality)
- Clinical success of treatment for IFI

### RESULTS

**Baseline characteristics**
- No significant differences in baseline characteristics between groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ITR Group (n=32)</th>
<th>VORI Group (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>25 (78.1)</td>
<td>25 (71.4)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (21.9)</td>
<td>10 (28.6)</td>
</tr>
<tr>
<td>Age, years (Mean ± SD)</td>
<td>53 ± 11.1</td>
<td>53 ± 12.4</td>
</tr>
<tr>
<td>Indication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>9 (28.1)</td>
<td>8 (22.9)</td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td>13 (40.6)</td>
<td>14 (40)</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>2 (6.3)</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>25 (78.1)</td>
<td>24 (68.6)</td>
</tr>
<tr>
<td>Double</td>
<td>7 (21.9)</td>
<td>11 (31.4)</td>
</tr>
<tr>
<td>APACHE (Mean ± SD)</td>
<td>14.7 ± 3.3</td>
<td>14.5 ± 5.3</td>
</tr>
</tbody>
</table>

**Outcomes**

- **Incidence of hepatotoxicity related to antifungal prophylaxis**
  - VORI Group: 12/35, ITR Group: 0/32 (p<0.001)

- **Time to development of hepatotoxicity**
  - Average time (days) to hepatotoxicity from transplant: 36.8 (± 33) with median (range) of 24 (0 to 91)
  - No significant difference in hepatotoxicity within first week post-transplant (ITR Group: 11 (34%), VORI Group: 14 (40%), p=1.0)

- **Incidence of IFI during study period**
  - All IFI occurrences were tracheobronchial anastomotic infections and occurred within first 60 days

<table>
<thead>
<tr>
<th>Number of IFIs</th>
<th>ITR Group (n = 32)*</th>
<th>VORI Group (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. fumigatus</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>A. niger</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Rhizopus spp.</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

* ITR Group: IFI occurred on days 8, 18, and 64 after starting prophylaxis

**Overall mortality and fungal-related mortality**
- 11 deaths at 1 year follow-up (4 in ITR group, 7 in VORI group)
- No deaths related to fungal infections in prophylaxis period
- Fungal-related mortality within 1 year similar (1 in ITR group, 2 n VORI group)

### AUTHOR CONCLUSION & DISCUSSION

**Author Conclusions**
- Voriconazole prophylaxis after lung transplant was associated with higher incidence of hepatotoxicity and similar clinical effectiveness when compared to itraconazole

**Critique**

**Strengths:**
- First study to evaluate universal prophylaxis effectiveness of two different triazoles

**Limitations:**

– Small sample size
– Majority of patients were single lung transplants, limiting external validity
– Average duration of prophylaxis not provided
– VORI levels not assessed to determine dose-dependent hepatotoxic effect
– VORI group received dual prophylaxis with inhaled amphotericin B
– No discussion of management to another agent if hepatotoxicity occurred
– Other common adverse effects not addressed (ie. QT prolongation)

Reviewer’s Conclusions
– Hepatotoxicity was higher with VORI group
– Although more IFI’s were seen in the ITR Group, ITR cannot be ruled out as an option for fungal prophylaxis given that the ITR group did not receive additional antifungal coverage with amphotericin B during highest risk period of time to acquire IFI post-transplant

II. Itraconazole
a. AST ID COP discusses itraconazole as option for anti-fungal prophylaxis in LuTRs
b. Most common reason for discontinuation of itraconazole was malabsorption
   i. Greater issues with malabsorption with non-SUBA formulation of itraconazole
   ii. Hayes, et al. evaluated itraconazole on fungal infection rates in heart and lung transplant patients (Table 11)

Table 11. Hayes, et al. 2011

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Evaluate the effect of single-agent anti-fungal prophylaxis with itraconazole on the rate of fungal infections after heart or lung transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Observational, retrospective study performed at University of Kentucky Medical Center (UKMC) in Lexington, KY between January 2001 and May 2005</td>
</tr>
</tbody>
</table>
| Patient population | **Inclusion Criteria**
| | Lung and heart transplant recipients with single agent antifungal prophylaxis with itraconazole |
| | **Exclusion Criteria**
| | <18 years of age at time of transplant |
| Intervention | Single-agent antifungal prophylaxis with itraconazole 200 mg orally daily given to patients undergoing heart or lung transplant during study period |
| Primary & secondary endpoints | Incidence of IFIs
| | Time of IFI from transplant
| | Mean rejection episodes per patient year
| | 1-month, 1-year, and 3-year survival |
| Infection definition | EORTC/Mycoses Study Group Definitions of invasive fungal infections
| | Proven, probable IFI, possible IFI |

RESULTS

Baseline characteristics
| Induction: muromonab-CD3 for 5-7 days (heart transplants only)
| Lung transplants did not receive induction
| Post-op day 1: tacrolimus 1 mg daily, mycophenolate mofetil 1 gram every 12 hours, and methylprednisolone 125mg every 8 hours
| Post-op day 2: methylprednisolone dose reduced to 30 mg daily after 3 doses
| Median (range) duration of anti-fungal prophylaxis: 12 months (6-39.5)
| Heart transplant (n=42), lung transplant (n=41)
| Indication for lung transplant (%): COPD (60.9), pulmonary fibrosis (26.8), pulmonary hypertension (9.9), cystic fibrosis (2.4)
| Time to initiation from transplant: 3.2 days ± 3.8 days (range, <24 hours and 25 days) |

Outcomes
| Fungal infection incidence of entire cohort: 14/83 (16.9%) |
- Heart: 5/42 (11.9%)
- Lung: 9/41 (22%)
- Causative pathogens of fungal infection:

<table>
<thead>
<tr>
<th>Causative pathogen</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Aspergillus</em> spp.</td>
<td>10/14 (71.4)</td>
</tr>
<tr>
<td><em>Candida</em> spp.</td>
<td>3/14 (21.4)</td>
</tr>
<tr>
<td><em>Mucor</em> spp.</td>
<td>1/14 (7.1)</td>
</tr>
</tbody>
</table>

- 8/14 (57.1%) patients had concomitant bacterial infections
- 50% had fungal infection occur at more than 6 months after transplant
- 6/9 (67%) occurred at more than 6 months in LuTRs
- 1-month, 1-year, and 3-year survival: 95%, 85%, 68%, respectively
- Mean rejection of 0.7 episodes/patient year in LuTRs
- 6/6 LuTRs who developed an IFI > 6 months out from transplant were treated for acute rejection
- 2/3 LuTR with an IFI less than 6 months out from transplant were treated for acute rejection
- 32(78%) of lung transplants did not develop IFI

**AUTHOR DISCUSSION & CONCLUSION**

<table>
<thead>
<tr>
<th>Author conclusions</th>
<th>Incidence of fungal infections significantly increased within 3 months after escalation of immunosuppressant for treatment of acute rejection</th>
</tr>
</thead>
</table>
| Critique           | **Strengths:**
|                    | High risk population of cystic fibrosis patients only accounted for 2.4% of the population
|                    | Utilized EORTC/Mycoses Study Group Definitions for IA
|                    | **Limitations:**
|                    | Small sample size
|                    | Wide range of time to initiation of anti-fungal agent
|                    | Itraconazole levels were not monitored, therefore, adequate fungal prophylaxis was not assessed
|                    | No specification of formulation used for prophylaxis, or if proton-pump inhibitor used
|                    | Difficult to evaluate survival of LuTRs given many risk factors unassessed
| Reviewer’s conclusions | Monitoring levels to ensure optimized levels of itraconazole levels were utilized
|                    | Outlines need for reliable prophylaxis when immunosuppression is increased
|                    | Itraconazole can be used for IFI prophylaxis, and consideration of optimization of fungal prophylaxis should be reassessed when immunosuppression is increased
|                    | Utilize TDM
|                    | Switch to a more reliable agent

   c. Kato, et al. utilized combination therapy of itraconazole and micafungin until itraconazole levels were achieved to assess rates of proven and probable IA

      i. Efficacy:
         1. Proven IA occurred in 2/30 patients (6.7%)
         2. Probable IA occurred in 3/30 (10%)

      ii. Safety: No adverse effects were noted

IV. **Posaconazole**

   a. Limited data exists on efficacy and safety in this population

      i. May be better tolerated with lower incidence of resistance, but further data on safety and efficacy are required

      ii. Pennington, et al. found that posaconazole was discontinued significantly less often than voriconazole and itraconazole (18.3%, 11 out of 60, p<0.05)
b. Hematologic malignancy population
   i. National Comprehensive Cancer Network recommends posaconazole as first line
      agent for antifungal prophylaxis for neutropenic patients with myelodysplastic
      syndrome (MDS), acute myeloid leukemia (AML) and patients with significant
      GVHD\textsuperscript{38}
   ii. Evidence for posaconazole prophylaxis is primary hematologic malignancy
       populations\textsuperscript{38}
      1. Majority of evidence with suspension formulation
   iii. Cornely et al. found posaconazole more effective than fluconazole or itraconazole
      for preventing aspergillosis in patients with AML\textsuperscript{39}
      1. Associated with improved survival
   iv. Summary of comparative studies of posaconazole suspension prophylaxis in AML,
       MDS, and HSCT

c. Lung transplant population
   i. Kozuch, et al. 2018 (n=26)\textsuperscript{40}
      1. Two-center retrospective chart review evaluating serum concentrations at
         steady state of posaconazole DR tablet at daily dosages of 100mg to 400mg
         (Table 12)
      2. Doses of 200mg-300mg daily was adequate to achieve target serum
         concentrations

\begin{center}
\textbf{Table 12: Kozuch, et al. 2018}\textsuperscript{40}
\end{center}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
 & 100 mg (n=17) & 200 mg (n=13) & 300 mg (n=13) & 400 mg (n=2) & \textit{p}-value \\
\hline
\textbf{Mean serum concentration* (± SD)} & 0.9 (±0.42) & 1.66 (±0.91) & 2.39 (±1.49) & 1.75 (±0.21) & 0.04 \\
\hline
\textbf{Percent of serum samples ≥ 0.7*} & 63.3\% & 96.9\% & 94.9\% & 100\% & 0.04 \\
\hline
*mcg/mL
\end{tabular}

   ii. Hurtik, et al. 2015\textsuperscript{41}
      1. Retrospective, single center, cohort study
      2. Dual fungal prophylaxis for with nebulized AmB plus 4 months of
         posaconazole DR tablet (POS-DR) or posaconazole suspension (POS-SUS)
      3. Achievement of posaconazole level ≥0.7
         a. 88\% POS-DR tablets vs. 39\% POS-SUS (\textit{p}=0.002)
      4. No patient required dose reduction or discontinuation due to LFT
         elevations and IFIs were “rare”
   d. Thakuria, et al. evaluated the use of posaconazole oral suspension in LuTR\textsuperscript{37}
Table 13. Thakuria, et al. 2015

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Evaluate pharmacokinetic properties of posaconazole oral suspension in LuTRs</th>
</tr>
</thead>
</table>

**METHODS**

**Study Design**
- Prospective, single-center, observational study evaluating 26 CF and non-CF lung transplant recipients at Harefield Hospital in Harefield, UK

**Patient Population**

**Inclusion Criteria**
- Scheduled to undergo lung transplant ≥ 18 years old
- Able to take oral/nasogastric medication

**Exclusion Criteria**
- Treatment with posaconazole within 14 days before transplant
- History of reactions to posaconazole or related compounds

**Intervention**
- All patients received posaconazole 400mg suspension twice daily starting within 12 hours postoperatively
- Calogen 30mL (high fat supplement) twice daily was co-prescribed to increase drug absorption
- Dose was changed to 200mg four times a day (each with Calogen 15 mL) in patients with subtherapeutic serum posaconazole levels (<0.5 mcg/mL)
- Nebulized amphotericin B was given as prophylaxis until hospital discharge

**Primary & Secondary Endpoints**
- Time to prophylactic levels > 0.5 mcg/mL
- Time to peak serum levels
- Initial hospital length of stay (LOS) after surgery and re-admissions within study period
- IFI incidence as defined by EORTC: possible, probable, proven

**RESULTS**

**Baseline characteristics**
- Age (range): CF group: 28 (21-45), Non-CF group: 55 (28-69)
- Indication for lung transplant: COPD 12/26 (46%), CF 8/26 (31%), diffuse interstitial lung disease 3/26 (12%), non-CF bronchiectasis 1/26 (4%), pulmonary hypertension 1/26 (4%), bronchiolitis obliterans 1/26 (4%)
- 10 discontinued POS early due to tolerability issues or various adverse events, which included gastrointestinal upset, liver function test derangement, problematic tacrolimus interactions, renal failure and prophylaxis failure

**Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CF Recipients (n=8)</th>
<th>Non-CF Recipients (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed course of posaconazole, n</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Days receiving prophylaxis</td>
<td>36.5 (12-42)</td>
<td>36 (3-42)</td>
</tr>
<tr>
<td>Proportion of samples with levels ≥ 0.5 mcg/mL (%)</td>
<td>63.4 (40-94)</td>
<td>72 (0-100)</td>
</tr>
<tr>
<td>Time to prophylactic levels of ≥ 0.5 mcg/mL (days)</td>
<td>11.5 (4-28)</td>
<td>8.5 (2-34)</td>
</tr>
<tr>
<td>Time to peak serum levels (days)</td>
<td>20 (3-34)</td>
<td>26.5 (2-41)</td>
</tr>
<tr>
<td>Initial hospital LOS (days)</td>
<td>35 (17-48)</td>
<td>25 (16-153)</td>
</tr>
<tr>
<td>Re-admission within study period, n (%)</td>
<td>3 (38)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Switched to 200mg QID during study, n (%)</td>
<td>3 (38)</td>
<td>3 (17)</td>
</tr>
</tbody>
</table>

**Fungal infection**
- Possible: 1 | 2
- Probable: 0 | 1
- Proven: 0 | 0

**Adverse event related to treatment (n)** | 3 | 5

*Data are median (range) unless otherwise stated*
**Author Conclusions**

Role of posaconazole as primary prophylaxis in perioperative period is uncertain, but if used, TDM may be helpful for determining attainment of therapeutic levels.

**Critique**

**Strengths:**
- Patients received nebulized amphotericin B during hospital stay similar to standard practice

**Limitations:**
- 6/26 patients required transition to four times daily dosing of posaconazole in order to achieve adequate levels
- Suspension and capsule pharmacokinetics differ
- Short duration of follow-up
- Half of CF group did not complete posaconazole course, and 11/18 only completed in Non-CF group

**Reviewer’s Conclusions**

- Overall incidence of IFI was 4/26 (15%); however most were possible IFIs
- Therefore, posaconazole is an option for triazole antifungal prophylaxis
- Given the difference in absorption of suspension and tablet formulation, TDM should be conducted if posaconazole is used for antifungal prophylaxis to ensure appropriate prophylactic levels

---

**V. Isavuconazole**

a. No studies addressing the efficacy of isavuconazole for antifungal prophylaxis

b. Hassouna, et al. (Table 14) evaluated use in hematologic malignancy and solid organ transplant population

c. Unpublished data by Nanayakkara et al. compared voriconazole to isavuconazole

i. Total of 27 patients underwent single or double lung transplantation

ii. Originally, 9/16 patients were newly diagnosed with IA on voriconazole prophylaxis

iii. After system-wide change to isavuconazole prophylaxis, 3/11 patients newly diagnosed with IA

iv. Limitations
   1. Definitions of IA not provided
   2. Duration of follow-up not provided
   3. Weak level of evidence

v. Isavuconazole is a potential option for antifungal prophylaxis in LuTR; however, data is needed to support its use

---

**Table 14. Hassouna, et al. 2018**

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Evaluate treatment response and safety of isavuconazole</th>
</tr>
</thead>
</table>

**METHODS**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Retrospective cohort study of adult inpatients at Cleveland Clinic between June 2015 and October 2017</th>
</tr>
</thead>
</table>

**Patient Population**

- Inpatients administered ≥3 doses of isavuconazole (ISV) 372mg IV or orally for either treatment, primary or secondary prophylaxis

**Definitions**

- Primary prophylaxis: ISV given to patients at risk of IFIs but with no recent infection or evidence of active disease
- Secondary prophylaxis: ISV to patients with no current active IFI but who were recently treated with ISV for IFI within past 4 weeks
- Breakthrough infection: considered to have occurred if patients receiving prophylaxis developed IFI >48 hours after initiating ISV
## Primary & Secondary Endpoints
- 6 week treatment response in patients treated for active IFI with ISV prophylaxis following prophylaxis or treatment with other agents and in patients treated empirically
- Mortality at 6 weeks and breakthrough IFIs in those receiving prophylaxis
- IFI incidence as defined by EORTC: possible, probable, proven

### Results

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>N=91, mean age (±SD): 59 (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication, n (%):</td>
<td>Treatment then secondary prophylaxis 10 (11), Treatment 75 (82)</td>
</tr>
<tr>
<td>Median duration, days (IQR):</td>
<td>Primary prophylaxis 18 (13-33), Treatment then secondary prophylaxis 203 (81-283), Treatment 23 (8-81)</td>
</tr>
<tr>
<td>Underlying disease/comorbidity, n (%):</td>
<td>acute leukemia 58 (64), neutropenia 57 (63), allogeneic HSCT 13 (14), autologous HSCT 2 (2), lung transplant 5 (5), liver transplant 2 (2), kidney transplant 2 (2), heart transplant 1 (1), intestine transplant 1 (1)</td>
</tr>
<tr>
<td>Combination antifungal therapy, n(%):</td>
<td>amphotericin B lipid complex 8 (9), micafungin 9 (10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISV was used as primary therapy in 40 patients, 25 of whom were evaluable for treatment response, and 68% had complete or partial response</td>
</tr>
<tr>
<td>17 patients administered combination antifungal therapy with ISV plus either amphotericin B lipid complex (N = 8) or micafungin (N = 9); only 4 (24%) exhibited a response</td>
</tr>
<tr>
<td>Reasons for switching treatment included empirically broadening coverage (N = 17), perceived lack of clinical response (N = 12), renal failure (N = 2), toxicity from antifungals (N = 9), avoiding drug-drug interactions (N = 8) and other (N = 1) such as physician preference</td>
</tr>
<tr>
<td>No breakthrough infection was observed in patients receiving primary and secondary prophylaxis</td>
</tr>
<tr>
<td>Most common side effects, n: abdominal pain 1, nausea 5, vomiting 3, diarrhea 4, elevated hepatic function tests 1, dyspepsia 1</td>
</tr>
<tr>
<td>ISV TDM obtained at median of 17 days (IQR = 10-38) in 11 (12%) patients</td>
</tr>
<tr>
<td>5 patients completed TDM at external clinical reference laboratory, mean ISV level was 6.3 (SD = 2.2)</td>
</tr>
<tr>
<td>This was statistically significantly higher and in contrast to the mean level of 2.8 (SD = 1.0) among 6 patients tested internally (P = 0.02)</td>
</tr>
</tbody>
</table>

### Author Discussion & Conclusion

**Author Conclusions**
- Isavuconazole appears to be safe and is associated with treatment response for fungal infections

**Critique**

**Strengths:**
- Allowed evaluation of isavuconazole for both primary and secondary prophylaxis
- Only study evaluating ISV primary and secondary prophylaxis use in LuTR

**Limitations:**
- Sample size and retrospective design
- Majority of patients were on treatment, not prophylaxis
- Majority of infections were due to non-Aspergillus fungal infections
- No details on transplant-specific details provided including type of lung transplant, etiology of lung disease, induction, immunosuppression, etc.

**Reviewer’s Conclusions**
- No breakthrough infections were observed in 5 lung transplant patients on prophylactic ISV
- Limited data exists to support therapeutic drug monitoring in LuTRs
VI. Clinical recommendations
   a. The following factors should be considered in determining agent selection
      i. Risk of skin malignancy, QT prolongation, gastrointestinal adverse effects, subtherapeutic levels, and hepatotoxicity
      ii. Refer to Figure 1 for further recommendations on antifungal prophylaxis
   b. Formulations should be taken into consideration
      i. Avoid use of Sporonox® capsules and posaconazole suspension
      ii. Posaconazole delayed release table is preferred over suspension
      iii. Sporonox® solution has better bioavailability than Sporonox® capsules

IV. Future directions
   a. Tolsura® capsules
      i. Place in therapy has yet to be determined
      ii. Allow for concomitant use of proton pump inhibitors without reduced concentrations
Figure 1: Considerations for antifungal prophylaxis in lung transplant

- **Subtherapeutic Levels**
  - Recommend posaconazole DR tab
  - Caution with isavuconazole
  - Avoid Sporonox® solution

- **Gastrointestinal Upset**
  - Recommend posaconazole DR tab
  - Avoid Sporonox® solution and isavuconazole

- **QT Prolongation**
  - Recommend isavuconazole
  - Avoid Sporonox® solution and posaconazole DR tab

- **Avoid**
  - Sporonox® capsules
  - Posaconazole suspension
  - Voriconazole

- **Future Directions**
  - Tolsura® capsules
    - Improved bioavailability
    - Avoids PPI interaction

- **Poor Bioavailability**
- **Skin Malignancy Risk**
Appendix A.

I. Pharmacokinetics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Available formulations</th>
<th>DOSING</th>
<th>PO bioavailability (%)</th>
<th>Protein binding</th>
<th>Vd</th>
<th>Cmax</th>
<th>AUC</th>
<th>CSF penetration (%)</th>
<th>Metabolism</th>
<th>Elimination</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>PO – older capsules, solution, Tolsura (new capsules)</td>
<td>Sporonox solution/capsules: 200 mg PO once or twice daily - Tolsura capsules: 130 mg PO once or twice daily</td>
<td>IV or DR tablets: 300 mg twice daily x 2 doses, then 300 mg daily Suspension: 200 mg PO thrice daily</td>
<td>Older caps (55%), higher on empty stomach Tolsura (80-90%), more consistent absorption using SUBA technology</td>
<td>PO bioavailability (%): Older caps (55%) Solution (70-78%), higher on empty stomach Tolsura (80-90%), more consistent absorption using SUBA technology</td>
<td>Protein binding: 11 L/kg</td>
<td>Cmax: Steady state, IV = 3280 ng/mL (3.28 mcg/mL) Steady state, PO DR = 2764 ng/mL (2.76 mcg/mL)</td>
<td>CSF penetration (%): &lt; 10%</td>
<td>Metabolism: Hepatic Active metabolite (\rightarrow) hydroxyitraconazole</td>
<td>Elimination: Hepatic/Biliary (\rightarrow) 1-10% excreted unchanged in urine</td>
<td>40 hours (solution) Active metab = 20 hrs</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>PO/IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>PO/IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>PO/IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No data</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Available formulations: PO – older capsules, solution, Tolsura (new capsules)

Dosing: Sporonox solution/capsules: 200 mg PO once or twice daily - Tolsura capsules: 130 mg PO once or twice daily

PO bioavailability (%): Older caps (55%) Solution (70-78%), higher on empty stomach Tolsura (80-90%), more consistent absorption using SUBA technology

Protein binding: > 99%

Vd: Oral, multiple-dose: 0.6 mcg/mL (Tolsura(TM) caps 130 mg once daily); 1.6 to 1.7 mcg/mL (Tolsura(TM) caps 130 mg twice daily) 1.5 to 2 mcg/mL (itra caps 200 mg twice daily)

Cmax: Oral, multiple-dose: 0.6 mcg/mL (Tolsura(TM) caps 130 mg once daily); 1.6 to 1.7 mcg/mL (Tolsura(TM) caps 130 mg twice daily) 1.5 to 2 mcg/mL (itra caps 200 mg twice daily)

AUC: Increased AUC with oral solution and Tolsura caps

CSF penetration (%): < 10% No data 60% No data

Metabolism: Hepatic Active metabolite \(\rightarrow\) hydroxyitraconazole Hepatic (glucoronidation) Hepatic = **extensive** Substrate for 2C19*, 2C9, and 3A4 Blood Active metabolite is substrate of CYP 3A4

Elimination: Hepatic/Biliary \(\rightarrow\) 1-10% excreted unchanged in urine Fecal \(\rightarrow\) < 2% excreted unchanged in urine Renal \(\rightarrow\) <2% excreted unchanged in urine Fecal/Renal \(\rightarrow\) < 1% excreted unchanged in urine

Half-life: 40 hours (solution) Active metab = 20 hrs 25 hours 6 hours 130 hours (IV)

II. Adverse effects

<table>
<thead>
<tr>
<th>Agent</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>N/V/D, abdominal issues, HA, rash, Inc LFTs (hep tox), rhinitis/sinusitis/URIs, SJS/TEN, pancreatitis, triadof HTN, hypokalemia, peripheral and pulmonary edema QTc prolongation, black box warning for cardiotoxicity (monitor signs/symptoms of heart failures)</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Visual disturbance (blurred vision – reversible), hallucinations, confusion, renal dysfunction Cutaneous (alopecia, nail changes, severe photosensitivity), N/V/D, transient transaminitis, hepatotox), , increased risk of skin cancer, QTc interval prolongation</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>N/V/D, hypokalemia, HA, fever, rare hepatitis/hepatotoxicity, QTc interval prolongation</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>N/V/D, HA, increase LFTs, hypokalemia, peripheral edema, hepatotoxicity Shortening of QT interval</td>
</tr>
</tbody>
</table>
References