CSHP SEMINAR
2016
TRANSITIONS
IN PHARMACY
DISNEYLAND® RESORT • OCTOBER 27th – 30th
Advances in the Treatment of Invasive Fungal Infections

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10-28-16
Disclosure

I have no conflicts of interest to disclose
Learning Objectives

• Breakdown the current recommendations for the treatment of invasive fungal infections such as aspergillosis and mucormycosis
• Examine the evidence for the advantages/disadvantages of using combination antifungal therapy
• Identify and analyze studies on the PK/PD of antifungal agents such as voriconazole
• Outline isavuconazole’s role in fungal therapy and the current evidence supporting its approval in 2015 and use
• Justify which therapy to initiate in a given patient case
Outline

• Aspergillosis
  • 2016 IDSA updates
  • Combination therapy

• Mucormycosis
  • Review of guidelines

• Pharmacokinetics (PK)/ Pharmacodynamics (PD)
  • Voriconazole + micafungin
Outline

• Isavuconazole
  • PK/PD
  • SECURE trial
    • Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomized-controlled, non-inferiority trial
• VITAL trial
  • Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis
Aspergillosis
Aspergillosis

Update on the 2016 IDSA Guidelines

- Overview of recommendations for treatment
- Salvage + combination treatments
- Adjunctive therapies
Aspergillosis

Predisposing risk factors

• Neutropenia

• Allogenic hematopoietic stem cell transplant (HSCT)

• Solid organ transplant (SOT)

• Inherited/acquired immunodeficiency

• Corticosteroid use

Aspergillosis

Infectious Diseases Society of America Guidelines

- Evidence grading: GRADE methodology

<table>
<thead>
<tr>
<th>Study design</th>
<th>Initial confidence in an estimate of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trials</td>
<td>High confidence</td>
</tr>
<tr>
<td>Observational studies</td>
<td>Low confidence</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reasons for considering lowering or raising confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower if</td>
</tr>
<tr>
<td>Risk of bias</td>
</tr>
<tr>
<td>Inconsistency</td>
</tr>
<tr>
<td>Indirectness</td>
</tr>
<tr>
<td>Imprecision</td>
</tr>
<tr>
<td>Publication bias</td>
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<table>
<thead>
<tr>
<th>Higher if</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Confidence in an estimate of effect across those considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Very low</td>
</tr>
</tbody>
</table>

Aspergillosis

Infectious Diseases Society of America Guidelines

- Evidence grading: GRADE methodology

### Table 1. Summary of Recommendations for the Treatment of Aspergillosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Primary</th>
<th>Alternative</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive syndromes of Aspergillosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IPA</strong></td>
<td>Voriconazole (6 mg/kg IV every 12 h for 1 d, followed by 4 mg/kg IV every 12 h; oral therapy can be used at 200-300 mg every 12 h or weight based dosing on a mg/kg basis); see text for pediatric dosing</td>
<td>Primary: Liposomal AmB (35 mg/kg/day IV), isavuconazole 200 mg every 8 h for 6 doses, then 200 mg daily</td>
<td>Primary combination therapy is not routinely recommended; addition of another agent or switch to another drug class for salvage therapy may be considered in individual patients; doses in pediatric patients for voriconazole and for caspofungin is different than that of adults; limited clinical experience is reported with anidulafungin; dosage of posaconazole in pediatric patients has not been defined</td>
</tr>
<tr>
<td><strong>Invasive sinus aspergillosis</strong></td>
<td>Similar to IPA</td>
<td>Similar to IPA</td>
<td>Surgical debridement as an adjunct to medical therapy</td>
</tr>
<tr>
<td><strong>Tracheobronchial aspergillosis</strong></td>
<td>Similar to IPA</td>
<td>Adjunctive inhaled AmB may be useful</td>
<td>Similar to IPA</td>
</tr>
<tr>
<td><strong>Aspergillosis of the CNS</strong></td>
<td>Similar to IPA</td>
<td>Similar to IPA</td>
<td>This infection is associated with the highest mortality among all of the different patterns of IA; drug interactions with anticonvulsant therapy</td>
</tr>
<tr>
<td><strong>Aspergillus infections of the heart (endocarditis, pericarditis, and myocarditis)</strong></td>
<td>Similar to IPA</td>
<td>Surgical resection may be beneficial in selected cases</td>
<td>Endocardial lesions caused by Aspergillus species require surgical resection; Aspergillus pericarditis usually requires pericardectomy</td>
</tr>
<tr>
<td><strong>Aspergillus osteomyelitis and septic arthritis</strong></td>
<td>Similar to IPA</td>
<td>Similar to IPA</td>
<td>Surgical resection of devitalized bone and cartilage is important for curative intent</td>
</tr>
<tr>
<td><strong>Aspergillus infections of the eye (endophthalmitis and keratitis)</strong></td>
<td>Systemic IV or oral voriconazole plus intravitreal AmB or voriconazole indicated with partial vitrectomy</td>
<td>Similar to invasive pulmonary aspergillosis; limited data with echinocandins and poor ocular penetration by this class</td>
<td>Systemic therapy may be beneficial in management of Aspergillus endophthalmitis; ophthalmologic intervention and management is recommended for all forms of ocular infection; topical therapy for keratitis is indicated</td>
</tr>
<tr>
<td><strong>Cutaneous aspergillosis</strong></td>
<td>Similar to IPA</td>
<td>Similar to IPA</td>
<td>Surgical resection is indicated where feasible</td>
</tr>
<tr>
<td><strong>Empiric and preemptive antifungal therapy</strong></td>
<td>For empiric antifungal therapy, Liposomal AmB (3 mg/kg/day IV), caspofungin (70 mg day 1 IV and 50 mg/day IV thereafter), micafungin (100 mg day), voriconazole (6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12 h; oral therapy can be used at 200-300 mg every 12 h or 3-4 mg/kg q 12 h)</td>
<td></td>
<td>Preemptive therapy is a logical extension of empiric antifungal therapy in defining a high-risk population with evidence of invasive fungal infection (eg, pulmonary infiltrate or positive assay result)</td>
</tr>
<tr>
<td><strong>Prophylaxis against IA</strong></td>
<td>Posaconazole: Oral suspension: 200 mg TID Tablet: 300 mg BID on day 1, then 300 mg daily IV: 300 mg BID on day 1, then 300 mg daily</td>
<td>Voriconazole (200 mg PO BID), itraconazole suspension (200 mg PO every 12 h), micafungin (50 mg/day)</td>
<td>Efficacy of posaconazole prophylaxis demonstrated in high-risk patients (patients with GVHD and neutropenic patients with AML or MDS)</td>
</tr>
</tbody>
</table>
# Aspergillosis: Treatment summary updates

<table>
<thead>
<tr>
<th>Indication</th>
<th>2016</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive pulmonary aspergillosis (IPA): primary</td>
<td>Voriconazole po 200-300 q12h or mg/kg</td>
<td>Voriconazole po 200mg q12h</td>
</tr>
<tr>
<td>IPA: alternatives</td>
<td>Created primary and salvage categories; added isavuconazole as an option</td>
<td></td>
</tr>
<tr>
<td>Tracheobronchial</td>
<td>Adjunctive inhaled AmB may be useful</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Posaconazole oral suspension: 200mg TID IV/Tablet: 300mg BID x 1 day then 300mg daily</td>
<td>Posaconazole 200mg q8h</td>
</tr>
<tr>
<td>Prophylaxis alternatives</td>
<td>Added voriconazole and caspofungin</td>
<td></td>
</tr>
</tbody>
</table>


# Aspergillosis: prophylaxis

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged neutropenia (hematologic malignancies, leukemia), graft vs host disease (GvHD), Hx of IA prior to transplant</td>
<td>Primary: posaconazole Alternatives: voriconazole, itraconazole micafungin, caspofungin</td>
<td>Strong, high-quality Strong, moderate-quality Weak, low-quality</td>
</tr>
<tr>
<td>Lung transplant</td>
<td>Voriconazole, itraconazole, or aerosolized amphotericin B</td>
<td>Strong, moderate-quality</td>
</tr>
<tr>
<td>Solid organ transplant (non-lung)</td>
<td>Institution specific</td>
<td>Strong, low-quality</td>
</tr>
</tbody>
</table>

Aspergillosis

Primary treatment

• Voriconazole

• Alternatives: amphotericin B (liposomal), isavuconazole
  • SECURE trial: Isavuconazole versus voriconazole
Aspergillosis

Salvage therapy: treatment with antifungals due to prior antifungal intolerance in addition to refractory or progressive disease

• Strategies
  • Changing antifungal class
  • Tapering/reversing underlying immunosuppression
  • Surgical resection
  • Combination therapy

• Amphotericin B*, caspofungin, micafungin, voriconazole*, isavuconazole* posaconazole, itraconazole
  *If not used for primary therapy

Aspergillosis

Combination treatment:
   “Primary combination therapy is not routinely recommended; addition of another agent or switch to another drug class for salvage therapy may be considered in individual patients”

- Synergistic or additive effect with combined therapy
  - triazole + (echinocandin or amphotericin b)
  - Animal/in vitro studies

- Severe disease, particularly hematologic malignancy patients

- Voriconazole + echinocandin (weak, moderate)

Aspergillosis

Combination treatment

• **Objective:** efficacy and safety of combination voriconazole/anidulafungin vs. voriconazole for IA

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**Table 1.** Baseline Demographic Characteristics, Underlying Diseases, and IA Diagnoses in the Modified Intention-to-Treat Treatment Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Monotherapy (n = 142)</th>
<th>Combination Therapy (n = 135)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (range), y</td>
<td>51.6 (18.0–83.0)</td>
<td>52.2 (18.0–79.0)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>98 (69.0)</td>
<td>99 (73.3)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (2.1)</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>35 (24.6)</td>
<td>31 (23.0)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (4.2)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>82 (57.7)</td>
<td>74 (54.8)</td>
</tr>
<tr>
<td>Women</td>
<td>60 (42.3)</td>
<td>61 (45.2)</td>
</tr>
<tr>
<td>Mean BMI (SD), kg/m²</td>
<td>24.0 (4.8)</td>
<td>24.0 (5.1)</td>
</tr>
<tr>
<td>Mean Karnofsky score (SD)</td>
<td>65.0 (15.8)</td>
<td>65.4 (15.3)</td>
</tr>
<tr>
<td>Median baseline serum GM antigen index (IQR)</td>
<td>0.51 (0.22–1.55)</td>
<td>0.52 (0.19–1.23)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Deaths, n/N (%)*</th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
<th>Treatment Difference (95% CI), percentage points†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td>39/142 (27.8)</td>
<td>26/135 (19.5)</td>
<td>-8.3 (-19.0 to 1.5)</td>
</tr>
<tr>
<td><strong>Overall 12-wk mortality</strong></td>
<td></td>
<td>55/142 (39.4)</td>
<td>39/135 (29.3)</td>
<td>-10.1 (-21.4 to 1.1)</td>
</tr>
<tr>
<td><strong>Allogeneic HCT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>12/42 (28.6)</td>
<td>10/44 (22.7)</td>
<td>-5.9 (-24.3 to 12.6)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>27/100 (27.5)</td>
<td>16/91 (17.9)</td>
<td>-9.6 (-21.5 to 2.2)</td>
</tr>
<tr>
<td>Reduced-intensity conditioning</td>
<td></td>
<td>5/15 (33.3)</td>
<td>4/19 (21.1)</td>
<td>-12.2 (-42.4 to 17.8)</td>
</tr>
<tr>
<td>Non-reduced-intensity conditioning</td>
<td></td>
<td>7/27 (25.9)</td>
<td>6/25 (24.0)</td>
<td>-1.9 (-25.5 to 21.6)</td>
</tr>
<tr>
<td>HLA-matched/related donor</td>
<td></td>
<td>7/17 (41.2)</td>
<td>2/14 (14.3)</td>
<td>-26.9 (-56.6 to 2.8)</td>
</tr>
<tr>
<td>HLA-mismatched/unrelated donor</td>
<td></td>
<td>5/25 (20.0)</td>
<td>8/29 (27.6)</td>
<td>7.6 (-15.0 to 30.2)</td>
</tr>
<tr>
<td>High-dose corticosteroids‡</td>
<td></td>
<td>3/6 (50.0)</td>
<td>3/9 (33.3)</td>
<td>-16.7 (-67.2 to 33.8)</td>
</tr>
<tr>
<td><strong>Neutropenia§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>21/86 (24.4)</td>
<td>18/77 (23.5)</td>
<td>-0.9 (-14.0 to 12.2)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>15/47 (33.2)</td>
<td>7/52 (13.7)</td>
<td>-19.5 (-36.1 to -2.8)</td>
</tr>
<tr>
<td><strong>Geographic region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td>21/83 (25.6)</td>
<td>14/75 (18.9)</td>
<td>-6.7 (-19.6 to 6.3)</td>
</tr>
<tr>
<td>Asia/Australia</td>
<td></td>
<td>8/33 (24.5)</td>
<td>6/33 (18.3)</td>
<td>-6.7 (-26.7 to 13.3)</td>
</tr>
<tr>
<td>North America</td>
<td></td>
<td>7/17 (41.2)</td>
<td>5/20 (25.3)</td>
<td>-15.9 (-46.1 to 14.4)</td>
</tr>
<tr>
<td>South America/Latin America</td>
<td></td>
<td>3/9 (33.3)</td>
<td>1/7 (14.3)</td>
<td>-19.0 (-59.3 to 21.1)</td>
</tr>
</tbody>
</table>

HCT = hematopoietic cell transplantation.
* Deaths shown are at 6 wk unless otherwise indicated. Percentage of deaths is based on the Kaplan-Meier product limit estimator for each variable.
† Combination therapy - monotherapy.
‡ Prednisone equivalents, ≥1 mg/kg/d, for >3 wk.
§ Absolute neutrophil count <0.500 × 10⁹ cells/L.
Outcomes in the positive galactomannan subgroup

Cumulative incidence of death in the modified intention-to-treat population with probable invasive aspergillosis based on radiographic abnormalities and positive galactomannan antigen. Log-rank, \( P = 0.049 \).

6-week mortality rate by range of maximum serum galactomannan index values at baseline. The middle boxes indicate the point estimate of the mean and the outer circles are the 95% CIs for that point estimate.
Aspergillosis

Combination treatment

• Conclusion: combination therapy was associated with nonsignificant, but meaningful survival benefits

  • Patients switched to oral voriconazole were dosed at 300mg q12h (Package insert = 200mg q12h)
  • Higher rate of hepatobiliary adverse effects with combination (12.7% vs. 8.4%)
  • Higher rate of mortality than predicted → decreased power

Aspergillosis

Thoughts: Combination therapy

• Strongest evidence for combination therapy in:
  • Hematologic malignancy
  • Hematopoietic cell transplantation population
  • (+) galactomannan
• Are all echinocandins created equal?
• Concerns: safety + cost

“Probability of achieving another appropriately powered and comparative, double-blinded, multicenter trial for primary or, for that matter, refractory IA therapy is infinitesimally small, given practice and logistical concerns.”

Aspergillosis

Supportive treatment

• Reduce/eliminate immunosuppressants

• Colony-stimulating factors may be considered

• Granulocyte transfusions may be considered

• Surgery when feasible

Mucormycosis
Mucormycosis

- Prophylaxis
- Treatment
- Salvage
- Adjunctive Therapies
Mucormycosis

Predisposing risk factors

- Granulocytopenia
- Immunosuppression
- Diabetes
- Penetrating trauma
- Less common than aspergillosis in haematological malignancies

Mucormycosis

European Society for Clinical Microbiology and Infectious Diseases and European Confederation of Medical Mycology joint guidelines

• Evidence grading
  • A: strongly support a recommendation for use
  • B: moderately support a recommendation for use
  • C: marginally support a recommendation for use
  • D: support a recommendation against use

**Mucormycosis Prophylaxis**

Percentage of invasive fungal disease
- Posaconazole: 18.9%
- Itraconazole: 38.7%
  \[P<0.001\]

Overall mortality
- Posaconazole: 3.5%
- Itraconazole: 9.7%
  \[P=0.02\]

**Figure Details**
- Survival proportion over analysis time (days)
- Log-rank test: \[P=0.002\]

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Mucormycosis

• Prophylaxis (C)
  • Primary antifungal prophylaxis during high risk periods of immunosuppressed patients
  • Acute myeloid leukemia (AML), GvHD
  • Posaconazole 200mg TID

• Secondary Prophylaxis (A)
  • Previous diagnosis
  • Surgical resection + secondary antifungal prophylaxis
  • Same agent + dose as previous treatment

Mucormycosis

Treatment (A)

- Surgical + medical
- Immediate initiation of treatment
  - If ≥ 6 days, 12 week mortality doubled
- Liposomal amphotericin b dosed at ≥ 5mg/kg
- CNS infection: Liposomal amphotericin b dosed at 10 mg/kg
  - Renal toxicity: 40%
- Posaconazole 200mg QID preferred to 400mg BID (B)
- Amphotericin B deoxycholate is not recommended (D)
Mucormycosis

Salvage Treatment

• Posaconazole 200mg QID or 400mg BID (A)
• Amphotericin B (B)
• Amphotericin B + posaconazole (B)

Mucormycosis

Salvage Treatment: Amphotericin B + posaconazole

- Population: N=32, haematologic malignancies, most with AML
- Majority of cases received amphotericin B as 1st line treatment with the addition of posaconazole when they were unresponsive
- No difference in toxicity between 3 and 5 mg/kg of amphotericin B
- 56% had clinical improvement
- 16% had stable disease
- 28% did not respond

Thought: Combination amphotericin B + posaconazole may be considered for very aggressive or as salvage therapy for invasive mucormycosis

Pharmacokinetics & Pharmacodynamics
Voriconazole + Micafungin
PK/PD: Voriconazole

• Dosing in Renal Function

• Bioavailability/PO dosing

• Dosing in Obesity

• Pharmacogenomics
PK/PD: Voriconazole

Renal Dosing

- Package Insert: CrCl < 50 mL/min

“There are no specific dosage adjustments provided in the manufacturer’s labeling. Due to accumulation of the intravenous vehicle (cyclodextrin), the manufacturer recommends the use of oral voriconazole in these patients unless an assessment of the benefit:risk justifies the use of IV voriconazole; if IV therapy is used, closely monitor serum creatinine and change to oral voriconazole when possible. IV therapy has been used in select patients with CrCl <50 mL/minute using varying doses (median duration of treatment 7 to 10 days).”
PK/PD: Voriconazole

Renal Dosing

• Retrospective study, 26 patients with CrCl < 50 on IV voriconazole, almost 800 SCr values included
  • Conclusion: no effect on renal function in patients with baseline dysfunction

• Randomized study, 41 patients with CrCl of 30-50 mL/min patients received voriconazole
  • Conclusion: IV voriconazole group had no changes in SCr

Thought: the cyclodextrin in IV voriconazole, in patients with baseline renal dysfunction, is not a factor for worsening renal function
PK/PD: Voriconazole

Bioavailability/PO Dosing

- Package Insert
  - Bioavailability: reported at 96%
  - Recommended dose: 200mg q12h PO; 6mg/kg x 2 then 4mg/kg IV

- Bioavailability (Pascual, 2012)
  - Actual range: 25-96%; estimated 60%

<table>
<thead>
<tr>
<th>Dose</th>
<th>% above 1.5 mg/L</th>
<th>% above 4.5 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>200mg q12h PO</td>
<td>49</td>
<td>8</td>
</tr>
<tr>
<td>400mg q12h PO</td>
<td>78</td>
<td>29</td>
</tr>
<tr>
<td>300mg q12h IV</td>
<td>87</td>
<td>37</td>
</tr>
</tbody>
</table>

PK/PD: Voriconazole

Bioavailability/PO Dosing

• Authors recommended 400mg po q12h or 300mg IV q12h

Thought: evidence to support larger dose conversions than 1:1 when moving from IV to PO voriconazole
PK/PD: Voriconazole

Dosing in obesity

• Weight based dosing + potentially harmful drug + obese patients = higher chance for toxicity

• Which weight should be used
  • Actual
  • Ideal
  • Adjusted

• What weight/BMI is concerning
Figure 2.
Voriconazole serum concentrations for normal-weight and obese patients. Voriconazole mean, range and IQR are shown for normal-weight patients and obese patients receiving 4mg/kg based on actual weight, ideal body weight and adjusted body weight.
PK/PD: Voriconazole

Dosing in obesity

*Thought:* Adjusted body weight should be used for voriconazole dosing in patients with BMIs ≥ 35 to achieve therapeutic levels

- Ideal body weight would be the second choice

PK/PD: Voriconazole

CYP2C19 Polymorphisms

- Primary enzyme for metabolism
- Account for the largest variability in voriconazole exposure
  - Other factors: age, sex, weight, liver disease
- Polymorphic
  - Poor, intermediate, extensive, ultrarapid

Thoughts:

- Poor metabolizers $\rightarrow$ higher risk for toxicity
- Ultrarapid metabolizers $\rightarrow$ higher risk for subtherapeutic levels

PK/PD: Micafungin

Dosing in obesity

- Clearance is directly related to weight
  - Obese patients have higher clearance
  - Heavier patients → likely decreased efficacy rates
- Monte Carlo simulation compared to PK/PD study of ~ 500 patients for external validation, 68kg patients
- Based on AUC/MIC > 3,000

<table>
<thead>
<tr>
<th>Patients or micafungin exposure</th>
<th>Simulation of 5,000 patients</th>
<th>Observed in 493 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum AUC\textsubscript{0–24} (mg*h/L)</td>
<td>46.6</td>
<td>76.1</td>
</tr>
<tr>
<td>Median AUC\textsubscript{0–24} (mg*h/L)</td>
<td>95.5</td>
<td>94.1</td>
</tr>
<tr>
<td>Maximum AUC\textsubscript{0–24} (mg*h/L)</td>
<td>224.1</td>
<td>118</td>
</tr>
<tr>
<td>Minimum AUC\textsubscript{0–24}/MIC</td>
<td>11.9</td>
<td>41.3</td>
</tr>
<tr>
<td>Maximum AUC\textsubscript{0–24}/MIC</td>
<td>31,452</td>
<td>98,716</td>
</tr>
<tr>
<td>Patients with AUC\textsubscript{0–24}/MIC &gt;3,000</td>
<td>3,690 (70%)</td>
<td>277 (76.69%)</td>
</tr>
</tbody>
</table>

PK/PD: Micafungin

Dosing in obesity

- Formula (> 66kg, ≤ 200kg)
  
  \[
  Dose \ (mg) = \text{patient weight} + 42
  \]
PK/PD: Micafungin

- Case report of a single 220kg patient treated with 100mg daily of micafungin

Figure 1.
Micafungin serum concentrations in a morbidly obese patient compared with published data. *Serum micafungin concentrations were measured by the Fungus Testing Laboratory in San Antonio, TX, USA using HPLC methods. SCT = SCT recipients; concentrations are estimates from graphical representation of data.
PK/PD: Micafungin

Dosing in obesity

Thoughts:

- Obese patients likely need higher doses of micafungin
- Difficult to make changes with simulations and not actual clinical trials
- Safety data seen in patients who received 8 mg/kg/day (mean of 600mg) were well tolerated; maximum tolerated dose inferred to be ≥ 8mg/kg/day


Isavuconazole
Isavuconazole

Approved

• Treatment of invasive aspergillosis and mucormycosis on March 8, 2015

Mechanism of Action

• Inhibition of fungal cell membrane
  • Specifically ergosterol synthesis through cytochrome P450-dependent 14α-lanosterol demethylation

• Side arm provides broader activity than other azoles
  • Comparative to amphotericin B spectrum

• Prodrug Isavuconazonium
  • Rapidly hydrolyzed to isavuconazole


Isavuconazole

PK/PD

• Oral and IV formulations
  • Highly water soluble → no cyclodextrin vehicle for IV (vs. voriconazole + posaconazole)

• Bioavailability: 98%

• Linear kinetics

• Volume of distribution: 450L, > 99% protein bound

• Half-life: 100-130 hours

• Metabolism: liver, CYP3A4 + CYP3A5


Isavuconazole

SECURE trial

• Primary Outcome:
  “Compare efficacy and safety of IV and PO isavuconazole to voriconazole in the primary treatment of invasive mold disease caused by Aspergillus or other filamentous fungi”

• Phase 3, double blind, global multicenter, comparative-group study

• Treatment
  • Isavuconazole: 200mg TID x 2 days, then 200mg qday
  • Voriconazole: 6 mg/kg IV x 2 doses; 4 mg/kg IV x 2 doses; then either 4 mg/kg BID or 200mg PO BID

Isavuconazole

SECURE trial

• No difference between either:
  • All-cause mortality at Days 42 + 84 for:
    • ITT (N=516)
    • Modified ITT (N=272)
    • Mycological ITT (N=231)
  • End of treatment (ITT)
    • Success
    • Failure
    • Clinical response
    • Mycological response

Figure 2.
Survival from first dose of study drug to day 84.
Patients were censored on the day of their last known survival status, represented by the circles.
Figure shows data for ITT population. ITT=intention to treat; all randomized patients who received study drug.
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Isavuconazole (n=257)</th>
<th>Voriconazole (n=259)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>247 (96%)</td>
<td>255 (98%)</td>
<td>0.122</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>174 (68%)</td>
<td>180 (69%)</td>
<td>0.705</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>152 (59%)</td>
<td>158 (61%)</td>
<td>0.719</td>
</tr>
<tr>
<td>General disorders and administrative site conditions</td>
<td>148 (58%)</td>
<td>144 (56%)</td>
<td>0.658</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>143 (56%)</td>
<td>147 (57%)</td>
<td>0.859</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>108 (42%)</td>
<td>121 (47%)</td>
<td>0.289</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>95 (37%)</td>
<td>89 (34%)</td>
<td>0.582</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>86 (33%)</td>
<td>110 (42%)</td>
<td>0.037¶</td>
</tr>
<tr>
<td>Investigations (abnormal laboratory tests)</td>
<td>85 (33%)</td>
<td>96 (37%)</td>
<td>0.357</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>77 (30%)</td>
<td>82 (32%)</td>
<td>0.703</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>70 (27%)</td>
<td>86 (33%)</td>
<td>0.151</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>69 (27%)</td>
<td>77 (30%)</td>
<td>0.495</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>67 (26%)</td>
<td>77 (30%)</td>
<td>0.378</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>55 (21%)</td>
<td>58 (22%)</td>
<td>0.832</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>43 (17%)</td>
<td>57 (22%)</td>
<td>0.148</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>39 (15%)</td>
<td>69 (27%)</td>
<td>0.002¶</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td>33 (13%)</td>
<td>39 (15%)</td>
<td>0.526</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>23 (9%)</td>
<td>42 (16%)</td>
<td>0.016¶</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>20 (8%)</td>
<td>25 (10%)</td>
<td>0.533</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified</td>
<td>19 (7%)</td>
<td>31 (12%)</td>
<td>0.101</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>14 (5%)</td>
<td>13 (5%)</td>
<td>0.846</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>8 (3%)</td>
<td>13 (5%)</td>
<td>0.373</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>5 (2%)</td>
<td>3 (1%)</td>
<td>0.503</td>
</tr>
<tr>
<td>Congenital, familial, and genetic disorders</td>
<td>3 (1%)</td>
<td>2 (1%)</td>
<td>0.685</td>
</tr>
</tbody>
</table>
| Social circumstances                           | 0                     | 1 (<1%)              | >0.999  

Isavuconazole

SECURE trial

• Conclusion: isavuconazole is non-inferior to voriconazole for the primary treatment of suspected invasive mold disease, with substantially fewer drug-related adverse events

Thoughts:

• Set, package insert dosing of voriconazole administered with no therapeutic drug monitoring or adjustments
• Both outcomes are directly affected by voriconazole being in therapeutic range

Isavuconazole

VITAL trial

• Primary Outcome:

  *Assess the efficacy and safety of isavuconazole for the treatment of mucormycosis and compare its efficacy with amphotericin B*

• Single-arm, global multicenter, open-label; case-control analysis

• Treatment
  • Isavuconazole: 200mg TID x 2 days, then 200mg qday

Isavuconazole

VITAL trial

- Amphotericin comparative arm
- Matched case-control analysis (Fungiscope)
- FDA approved for study of rare diseases

Criteria

- Severity of disease
- Haematological malignancy
- Surgical treatment within 7 days of antifungal initiation
- If unable to match based on all 3 criteria; second match based on the 1st two

<table>
<thead>
<tr>
<th>Underlying disorder</th>
<th>Isavuconazole</th>
<th>Amphotericin B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppressant use</td>
<td>9 (43%)</td>
<td>9 (27%)</td>
</tr>
<tr>
<td>Baseline neutropenia</td>
<td>4 (19%)</td>
<td>8 (24%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (19%)</td>
<td>6 (18%)</td>
</tr>
<tr>
<td>HSCT</td>
<td>4 (19%)</td>
<td>5 (15%)</td>
</tr>
<tr>
<td>GVHD treatment</td>
<td>4 (19%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>1 (5%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Disseminated disease</td>
<td>8 (38%)</td>
<td>8 (24%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Isavuconazole</th>
<th>Amphotericin B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude all-cause mortality</td>
<td>7/21 (33%; 14.6–57.0)</td>
<td>13/33 (39%; 22.9–57.9)</td>
<td>p=0.775</td>
</tr>
<tr>
<td>Weighted all-cause mortality</td>
<td>33%; 13.2–53.5</td>
<td>41%; 20.2–62.3</td>
<td>p=0.595</td>
</tr>
<tr>
<td>Crude mortality by matching covariates (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematological malignancy</td>
<td>5/11 (45%)</td>
<td>7/18 (39%)</td>
<td>NA</td>
</tr>
<tr>
<td>Severe disease</td>
<td>6/12 (50%)</td>
<td>8/13 (62%)</td>
<td>NA</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>4/9 (44%)</td>
<td>3/13 (23%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 5.
Primary treatment with isavuconazole-treated cases (VITAL) versus amphotericin B-treated controls (FungiScope).
95% CI are based on an exact binomial distribution (crude) or normal approximation (weighted).
Calculated from Fisher's exact test.
Weights were applied according to the ratio of the number of controls matched to each case.
Figure 2.
Kaplan-Meier analysis of patients who received isavuconazole as primary treatment (VITAL) compared with amphotericin B-treated matched controls (FungiScope). Hazard ratio (HR) and 95% CI are calculated from a Cox model without covariates. Patients were censored on the day of their last known survival status, represented by the circles.
Isavuconazole

VITAL trial

• Conclusion: isavuconazole use is supported as a primary treatment option for mucormycosis, its use in refractory cases, and in amphotericin B intolerant patients

Thoughts:

• Case-control analysis of mucormycosis patients from another time period and studies
• Median duration of treatment (days): Isavuconazole 102; amphotericin B 18

References


References


References


Test question #1

Which combination therapy has the most supportive evidence for the treatment of aspergillosis?

a) Triazole + echinocandin
b) Triazole + amphotericin B
c) Amphotericin B + echinocandin
d) Combination therapy is never supported
Test question #1

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a) Triazole + echinocandin
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c) Amphotericin B + echinocandin
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Test question #2

TB currently is being treated for pulmonary Aspergillus with voriconazole. He develops kidney dysfunction (CrCl 35mL/min) several days into treatment. Based on the presented evidence, the use of voriconazole in patient’s with CrCl < 50 mL/min supports?

a) Switching to an oral formulation
b) Switching to a different class of antifungal
c) Continued use of the IV formulation at the same dose
d) Continued use of the IV formulation at a lower dose
Test question #2

TB currently is being treated for pulmonary Aspergillus with voriconazole. He develops kidney dysfunction (CrCl 35mL/min) several days into treatment. Based on the presented evidence, the use of voriconazole in patient’s with CrCl < 50 mL/min supports?

a) Switching to an oral formulation
b) Switching to a different class of antifungal
c) **Continued use of the IV formulation at the same dose**
d) Continued use of the IV formulation at a lower dose
Test question #3

The new triazole, isavuconazole, is currently FDA approved for the treatment of which of the following fungal infections (select all that apply)?

a) Candidiasis
b) Coccidioidomycosis
c) Aspergillosis
d) Mucormycosis
Test question #3

The new triazole, isavuconazole, is currently FDA approved for the treatment of which of the following fungal infections (select all that apply)?

a) Candidiasis
b) Coccidioidomycosis
c) Aspergillosis
d) Mucormycosis
Session Code:

1. Write down the course code. Space has been provided in the daily program-at-a-glance sections of your program book.

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