Evaluation of Second-Generation Triazoles in the Treatment of Coccidioidomycosis

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Introduction

- Valley fever, also known as coccidioidomycosis, is a systemic fungal infection endemic to the southwestern United States.
- Since 2000, more than 175,000 people have been infected with this fungus in the United States. In 2016, there were an estimated 2,238 cases of coccidioidomycosis in Kern County alone.
- Although most cases are self-limiting and restricted to the lungs, the disease can disseminate to the bone, soft tissue, and central nervous system in severe cases.
- The management of coccidioidomycosis consists of triazole antifungals (i.e. fluconazole, itraconazole) or amphotericin B.
- In severe infections, these options are not always fully efficacious or well tolerated leading to failure.
- Newer triazole antifungals, such as posaconazole, have demonstrated beneficial results in patients who have failed conventional therapy. However, outcomes data is somewhat sparse.
- Isavuconazonium, a prodrug of isavuconazole, has shown favorable side effect profiles and efficacy in vitro. However, there are no studies regarding its efficacy in vivo.
- Any treatment outcomes data with these agents would contribute significantly to the limited scientific body.

Objectives

- To evaluate the efficacy and safety of isavuconazole, posaconazole, voriconazole in patients with refractory coccidioidomycosis.

Methods

Study Design:
- Retrospective, single center chart review

Study Period:
- January 1, 2010 to April 18, 2018

Inclusion Criteria:
- Age ≥18 years old
- Patients taking posaconazole or isavuconazole for a minimum of 1 month of therapy

Exclusion Criteria:
- <1 month of therapy or no follow up clinic visit after starting medication
- Immunocompromised patient (transplant, chemotherapy, AIDS/HIV)
- Dual therapy with isavuconazole or posaconazole (i.e. intravenous/intrathoracic amphotericin B)

Primary Endpoint:
- Treatment efficacy using severity score for patients on isavuconazole or posaconazole.

Secondary Endpoint:
- Assessment of efficacy of treatment using overall change in MSG score.

Safety endpoint:
- Adverse side effects

Statistical Analysis:
- Wilcoxon Rank Sum Test

Results

Coccidioidomycosis Breakdown

<table>
<thead>
<tr>
<th>Reason for Salvage Tx</th>
<th>N</th>
<th>Median YRS</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone or Joint</td>
<td>11.9%</td>
<td>3.0 (2.5-5.0)</td>
<td>2.25</td>
</tr>
<tr>
<td>Skin or Soft Tissue</td>
<td>11.9%</td>
<td>3.0 (2.5-5.0)</td>
<td>2.25</td>
</tr>
<tr>
<td>Lungs Only</td>
<td>55.5%</td>
<td>6.5 (4.7-8.5)</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Table 1

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isavuconazole</td>
<td>14</td>
<td>4.53</td>
<td>3.53</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>13</td>
<td>4.25</td>
<td>3.54</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>10</td>
<td>3.95</td>
<td>2.55</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Initiation of Refractory T x</th>
<th>Last Visit MSG Score</th>
<th>Δ</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isavuconazole</td>
<td>5</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>6.5</td>
<td>1.5</td>
<td>0.00338</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>5.5</td>
<td>0.5</td>
<td>0.00206</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>First Recorded Refractory T x</th>
<th>Initiation of Refractory T x</th>
<th>Last Visit MSG Score</th>
<th>Change from Initiation to Last Visit</th>
<th>Overall Improvement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isavuconazole</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>0.00328</td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td>6.5</td>
<td>1.5</td>
<td>0.00338</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>5.5</td>
<td>0.5</td>
<td>0.00206</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion

 Favorable outcomes were seen in patients treated with posaconazole, isavuconazole, and voriconazole with statistically significant reductions in overall MSG severity scores seen with each agent.

Conclusions

Isavuconazole, posaconazole, and voriconazole are reasonable options for treatment of severe coccidioidomycosis refractory to standard treatment. All 3 agents provided improvement in MSG score and disease symptom control in patients who previously failed to respond to first generation azoles. Prospective comparative trials are required to further provide further insights into their efficacy and utility.

References