Evaluation of Isavuconazole and Posaconazole for the Treatment of Refractory Coccidioidomycosis

Janet Yoon, Pharm.D., 1 Jeff Jolliff, Pharm.D., 1 Brittany Andrusko, Pharm.D., 1 Arash Heidari, M.D., 2 Royce Johnson, M.D. 2

1 Department of Clinical Pharmacy Services, Kem Medical
2 David Geffen School of Medicine UCLA, Department of Medicine, Kem Medical

Objectives

- 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.
- Isavuconazole, 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.

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 not follow up clinic visit after starting medication
  - Immunosuppressed patient (transplant, chemotherapy, AIDS/HIV)
  - Dual therapy with isavuconazole or posaconazole (i.e., fluconazole and another triazole antifungal)

Primary Endpoint

- Treatment efficacy using severity score for patients on isavuconazole or posaconazole.
- Outcomes were assessed using the Mycoses Study Group (MSG) score (i.e., a composite score for symptoms, serology, radiographic findings and the documented impressments of treating medical practitioners).

Secondary Endpoint

- Assessment of efficacy of treatment using overall change in MSG score

Safety endpoint

- Adverse side effects
- Statistical Analysis: Wilcoxon Rank Sum Test

Introduction

- Valley fever, also known as coccidioidomycosis, is a systemic fungal infection endemic to the southwestern United States.
- Since 2000, more than 150,000 people in the United States have been infected by this fungus.
- In 2016, there were an estimated 2,238 cases of coccidioidomycosis in Kern County alone.
- Many cases are self-limiting, and 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.
- Isavuconazole, 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.

Results

- Overall, favorable outcomes were seen in patients treated with isavuconazole and posaconazole with statistically significant reductions in overall MSG severity scores seen with each agent.
- Posaconazole showed similar efficacy to a previous study by Vo, et al., in which posaconazole had 78% improved outcome.
- Overall skin or soft tissue coccidioidomycosis was associated with the best improvement; 100% improved.
- Pulmonary disease had an 8% improved and 1 stable patient on posaconazole tablets who started with a MSG of 0. CNS was associated with the least improvement. 6 out of 10 CNS coccidioidomycosis patients were stable. Two patients started with MSG score of 0. The remaining two patients had MSG score of 1 and 2 with CFST score <1/2. Bone had three patients who were stable. In all three cases, MSG score was elevated on initiation of posaconazole.

Discussion

- This study had limitations of being a single center study and being retrospective in nature, making the application of points to arrive at MSG score difficult due to variable documentation of symptoms and timing of laboratory studies. Since there was a lack of medical audit, there is a potential for clinical improvement to be a result of the treatment rather than second.

Conclusions

- Posaconazole and isavuconazole are reasonable options for treatment of severe coccidioidomycosis refractory to standard treatment. Both medications were tolerable and provided improvement in MSG score and disease symptom control. Prospective comparative trials are required to provide further insights into their efficacy and utility.

References

1. California Department of Public Health. Coccidioidomycosis yearly summary report. 2012 - 2016. Center for Infectious Diseases, Division of Communicable Disease Control, Infectious Diseases Branch, Surveillance and Statistics Section. 29 September 2017. Available at: https://www.cdph.ca.gov/programs/CDC/EMS/Pages/CDCMS.aspx
5. Noxafil (posaconazole) [prescribing information]. Whitehouse Station, NJ: Merck; 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020073s016s020073lbl.pdf

Safety Results

- There were five adverse drug reactions seen in this retrospective review.
- Isavuconazole: 1 patient complained of epigastric pain
- Posaconazole suspension: 1 patient complained of severe vomiting
- Posaconazole: 1 patient complained of photophobia
- Posaconazole tablets: 1 patient complained of dry lips
- None of the patients that complained of epigastric pain and severe vomiting were switched off the offending medication due to the drug reaction.
- The remaining three patients remained on therapy until treatment failure or death due to Cocci.