Evaluation of Second-Generation Triazoles in the Treatment of Coccidioidomycosis

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

[1] Department of Clinical Pharmacy Services, Kern Medical
[2] David Geffen School of Medicine UCLA, Department of Medicine, Kern Medical

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 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.
- 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. intrathecal/intravenous amphotericin)

Primary Endpoint:

Treatment efficacy using severity score for patients on isavuconazole or posaconazole.

- Outcomes were assessed using the Mycosis Study Group (MSG) score (i.e. a composite score for symptoms, serology, radiographic findings) and the documented impressions of treating medical practitioners.

Secondary endpoint:

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

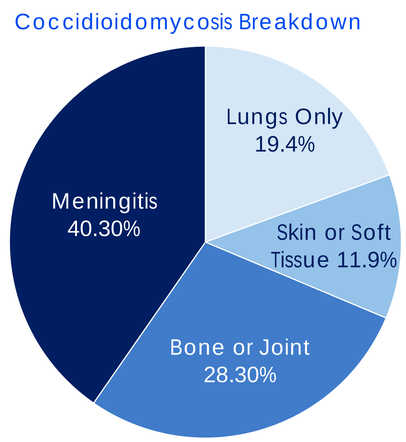
Safety endpoint:

- Adverse side effects

Statistical Analysis:

- Wilcoxon Rank Sum Test

Results



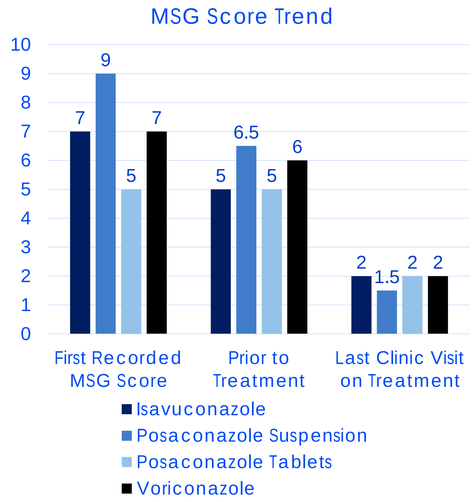


Table 2	Initiation of Refractory Tx MSG Score+	Last Visit MSG Score+	Δ	P-value
Isavuconazole	5 (3.5-7.5)	2 (2-3)	3	0.00328
Posaconazole Suspension	6.5 (3.5-8.5)	1.5 (1-3)	5	0.00338
Posaconazole Tablet	5 (3.5-7.5)	2 (1-2.5)	3	0.0002
Voriconazole	6 (4-7)	2 (0-3)	4	0.00062

Δ=Change from Initiation to Last Visit
+=(Median ,IQR)

Table 1	Isavuconazole (n=15)	Posaconazole Suspension (n=12)	Posaconazole Tablets (n=19)	Posaconazole Total (n=31)	Voriconazole (n=21)	Total (n=67)
Age, Median (Range), Years+	44 (38-51.5)	46.5 (36-64.25)	45 (36.5-55)	45 (36.5-59)	46 (40-55)	45 (36.5-55.5)
Sex *						
Male	10 (66.6)	8 (66.6)	16 (84.2)	24 (77.4)	14 (66.6)	48 (71.6)
Female	5 (33.3)	4 (33.3)	3 (15.7)	7 (22.5)	7 (33.3)	19 (28.4)
Race/Ethnicity *						
Hispanic	12 (80.0)	4 (33.3)	12 (63.2)	16 (51.6)	15 (71.4)	43 (64.1)
Non-Hispanic White	0 (00.0)	1 (8.3)	2 (10.5)	3 (9.6)	3 (14.2)	6 (9.0)
African American	2 (13.3)	5 (41.6)	5 (26.3)	10 (32.2)	1 (4.8)	13 (19.4)
Other	1 (6.6)	2 (16.6)	0 (00.0)	2 (6.4)	2 (9.5)	5 (7.5)
Weight, Average, Kg	80.3	81.4	78	79.3	79.7	79.7
Height, Average, Inches	64	66.7	65.9	66.2	66.5	65.8
Coccidioidomycosis*						
Lung Only	3 (20.0)	2 (16.6)	4 (21.0)	6 (19.3)	4 (19.1)	13 (19.4)
Skin or Soft Tissue	2 (13.3)	2 (16.6)	4 (21.0)	6 (19.3)	0 (00.0)	8 (11.9)
Bone or Joint	4 (26.6)	6 (50.0)	9 (47.3)	15 (48.3)	0 (00.0)	19 (28.3)
Meningitis	6 (40.0)	2 (16.6)	2 (10.5)	4 (12.9)	17 (80.9)	27 (40.3)
Antecedent Treatment*						
Fluconazole	1 (6.6)	6 (50.0)	8 (42.1)	14 (45.1)	18 (85.7)	33 (49.2)
Amphotericin	3 (20.0)	3 (25.0)	7 (36.8)	10 (32.3)	2 (9.5)	15 (22.4)
Voriconazole	6 (40.0)	2 (16.6)	2 (10.5)	4 (12.9)	0 (00.0)	10 (14.9)
Itraconazole	0 (00.0)	0 (00.0)	2 (10.5)	2 (6.4)	1 (4.8)	3 (4.5)
Posaconazole	5 (33.3)	1 (8.3)	0 (00.0)	1 (3.2)	0 (00.0)	5 (9.0)
Reason for Salvage Tx*						
Refractory Infection	5 (33.3)	8 (66.6)	6 (31.6)	14 (45.1)	14 (66.6)	33 (49.3)
Medication Intolerance	5 (33.3)	2 (16.6)	3 (15.7)	5 (16.1)	1 (4.8)	11 (16.4)
Refractory and Intolerant	2 (13.3)	0 (00.0)	3 (15.7)	3 (9.6)	4 (19.0)	9 (13.4)
Not stated in chart	3 (20.0)	2 (16.6)	7 (36.8)	9 (29.1)	2 (9.6)	14 (20.9)
Duration of Antecedent Tx, month+	23 (8.5-20)	11 (3-30.75)	24 (5-48)	15 (3.5-47)	36 (19-62)	66 (63-68)
Duration of Salvage Tx, month+	10 (4.5-14)	31.5 (24.5-45.5)	23 (12-29.5)	25 (15.5-40)	46 (26-63)	25 (12-44.5)
Outcome of Salvage Tx*						
Improved	11 (73.3)	10 (83.3)	15 (78.9)	25 (80.6)	13 (61.9)	49 (73.1)
Stable	4 (26.6)	2 (16.6)	4 (21.1)	6 (20.0)	4 (19.0)	14 (20.9)
Unresponsive	0 (00.0)	0 (00.0)	0 (00.0)	0 (00.0)	4 (19.0)	4 (5.9)
Total Death*	0 (00.0)	0 (00.0)	1 (5.3)	1 (3.3)	1 (4.7)	2 (3.0)
Death due to Cocci	0 (00.0)	0 (00.0)	0 (00.0)	0 (00.0)	1 (4.7)	1 (1.5)

+=Median ,IQR; *= Percentage

Table 3	First Recorded MSG Score+	Initiation of Refractory Tx MSG Score+	Last Visit MSG Score+	Change from Initiation to Last Visit+	Overall Improve (%)
Lungs					
Isavuconazole	5 (4.5-6)	4 (4,7)	2 (1-2)	2	100%
Posaconazole Suspension	9 (8-10)	6 (4.5-7.5)	2 (2,2)	4	100%
Posaconazole Tablet	8 (5.75-9.75)	5.5 (2.25-8.75)	1 (0.75-1.5)	4.5	75%
Voriconazole	3 (3-6.5)	3 (2.5-4.75)	1.5 (0.75-3.75)	1.5	50%
Skin or Soft Tissue					
Isavuconazole	7.5 (5.75-9.25)	5 (4-6)	2 (2,2)	3	100%
Posaconazole Suspension	6 (6-6)	8 (7-9)	4 (3-5)	4	100%
Posaconazole Tablet	4 (4,4)	4.5 (4-6)	2.5 (2-3)	2	100%
Bone					
Isavuconazole	8.5 (7.75-0.25)	6.5 (5.5-7.25)	2 (2-2)	4.5	100%
Posaconazole Suspension	9 (9-10)	7.5 (6.25-8)	1 (1-3.25)	6.5	83.3%
Posaconazole Tablet	7 (5-8)	5 (4-5)	1 (1-2)	4	77.7%
CNS					
Isavuconazole	6 (3.75-7.5)	4.5(2.5-5)	3 (1.25-4.75)	1.5	33.3%
Posaconazole Suspension	1 (1-1)	2 .5 (1.75-3.25)	0.5 (0.25-.75)	2	50%
Posaconazole Tablet	3 (2.5-3.5)	4 (2-6)	1 (0.5,1.5)	3	50%
Voriconazole	7 (6-8.25)	6 (4-7)	2 (0-3)	4	64.7%

+=Median ,IQR; *= Percentage

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. Posaconazole showed similar efficacy to a previous study, in which 75% of previously refractory patients had improved outcomes[7]. Overall skin and soft tissue coccidioidomycosis was associated with the best improvement; 100% improved. Pulmonary disease had 9 out of 11 (82%) improved. Bone had three patients who were stable. CNS was associated with the least improvement, especially in the isavuconazole group. Voriconazole had 4 stable patients and 2 unresponsive patients. 3 out of 4 patients were started with MSG score of 0-1. The remaining patients had MSG score of 5 with down-trending CSF titers.

Limitations

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 medication washout, there is a potential for clinical improvement to be a result of the prior treatment rather than second.

Conclusions

Posaconazole, isavuconazole, 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 provide further insights into their efficacy and utility.

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