



Effect of Transitioning Azole Therapies on Outcomes of Coccidioidomycosis

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Disclosure

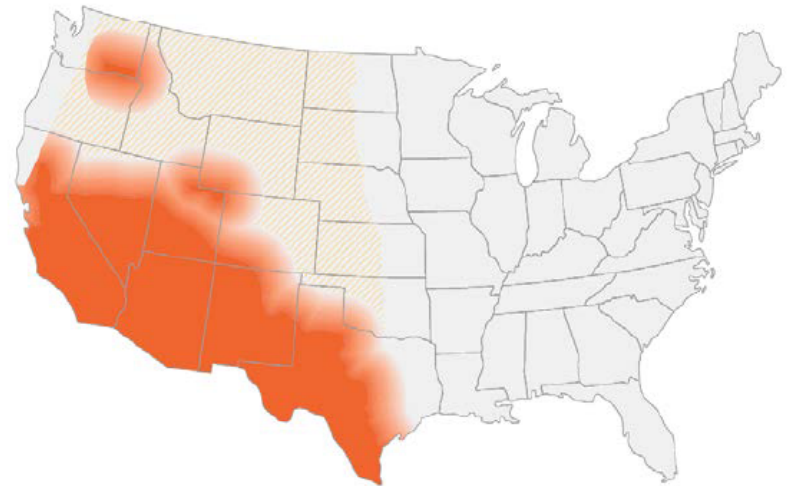
- Rachael Jongsma, PharmD
- Potential conflicts of interest: none
- Sponsorship: none
- Proprietary information or results of ongoing research is subject to different interpretations
- Speaker's presentation is educational in nature and indicates agreement to abide by the non-commercialism guidelines provided

Research Objective

- Assess the change in disease severity when transitioning from isavuconazole to other azole antifungals due to cessation of patient assistance programs or drug exclusion policies in the treatment of coccidioidomycosis

Coccidioidomycosis

- *Coccidioides immitis* and *posadasii*
- 15,611 cases reported to the CDC in 2018
 - Most of which were in Arizona and California
 - Likely underestimates the true number of cases



CDC's current estimated locations of *Coccidioides*

CDC. (2020). Valley Fever (Coccidioidomycosis) Statistics. <https://www.cdc.gov/fungal/diseases/coccidioidomycosis/statistics.html>. Accessed May 9, 2021

CDC. (2020). Estimated areas with blastomycosis, coccidioidomycosis (Valley fever), and histoplasmosis in the United States.

<https://www.cdc.gov/fungal/pdf/more-information-about-fungal-maps-508.pdf>. Accessed May 9, 2021

Nguyen C, et al. *Clin Microbiol Rev.* 2013;26:505–25

Antifungals in the Treatment of Coccidioidomycosis

- Azole antifungals
 - First Line
 - Fluconazole or itraconazole
 - Refractory
 - Voriconazole, posaconazole, or isavuconazole
 - Fungistatic
 - Inhibits lanosterol 14- α -demethylase
 - Lanosterol is not converted to ergosterol (principal sterol composing cell membrane)
 - Increases cell membrane permeability
- Polyene antifungal (Amphotericin)
 - When unresponsive to azoles or severe illness
 - Fungicidal
 - Binds to ergosterol to form pores in cell membrane
 - Leads to leakage of cellular components

Treatment of Refractory Coccidioidomycosis

- Voriconazole, Posaconazole, and Isavuconazole
 - Retrospective chart review of patients with refractory coccidioidomycosis whose therapy was changed to isavuconazole (n=15), posaconazole (n=32), or voriconazole (n=21)
 - Improvement in Mycosis Study Group (MSG) score
 - Isavuconazole: 11/15 (73.3%)
 - Posaconazole: 25/31 (80.6%)
 - Voriconazole: 12/21 (61.9%)
 - Conclusion
 - Reasonable option for the treatment of refractory coccidioidomycosis

Yoon J, et al. *Open Forum Infect Dis.* 2018;5(Suppl 1):S151.

Managed Care Approach to Coccidioidomycosis

- National formularies
 - Insurers and health plans unaware of coccidioidomycosis therapies and the dosages used
- Drug formulary exclusion list
 - A list of drugs that an insurer, health plan, or pharmacy benefit does not cover
- A report published by Doctor-Patient Rights Project
 - Express Scripts and CVS Caremark's drug formulary exclusion lists grew by 160% from 2014 to 2018
- Patients at Kern Medical were recently denied access to isavuconazole due to closure of the manufacturer's patient assistance program or drug exclusion policies by their insurance

The Doctor-Patient Rights Project (2017, December). The de-list: How formulary exclusion lists deny patients access to essential care. Technical report.
https://www.healthstrategies.com/sites/default/files/agendas/2015_PBM_Research_Agenda_RA_110714.pdf.

Prior Studies for Refractory Coccidioidomycosis



Current Study



Methods

- Retrospective, single-center, observational study
- Subject identification via pharmacy management system
- Disease severity
 - Modified Mycosis Study Group (MSG) Score
 - MSG Score for Central Nervous System (CNS) Infections
- Disease severity assessment
 - Prior to isavuconazole
 - During isavuconazole
 - On newer agent

Modified MSG Score Components

Clinical Scoring System	
Symptom	Score
Fever	1
Pain	1
Productive Cough	1
Hemoptysis	1
Swelling	1
Pleural rub	1

Serology Scoring System	
Complement Fixation Serology	Point
1:4	0
1:8	1
1:16	2
1:32	3
1:64	4
1:128	5
1:256	6
> 256	7

Chest Radiograph Scoring System	Score
Size	
< 5 cm	1
Less than right upper lobe zone	2
More than above	3
Spread	
Unilateral	1
Bilateral	2
Miliary	3
Cavitation	1
Hilar adenopathy	1
Mediastinal adenopathy	2
Small effusion	1
Large Effusion	2

Course of Serial Changes on Chest Films, Bone Scans, or Gallium Scans	Change
Marked deterioration	+2
Worsening slightly	+1
No change	0
Partial or slight improvement	-1
Substantial but incomplete improvement	-2
Clearing all but scarlike residual	-3
No residual lesions detected	-4

Catanzaro A, et al. *Am J Med.* 1983;74(1B):64-69.

CNS Infection MSG Score Components

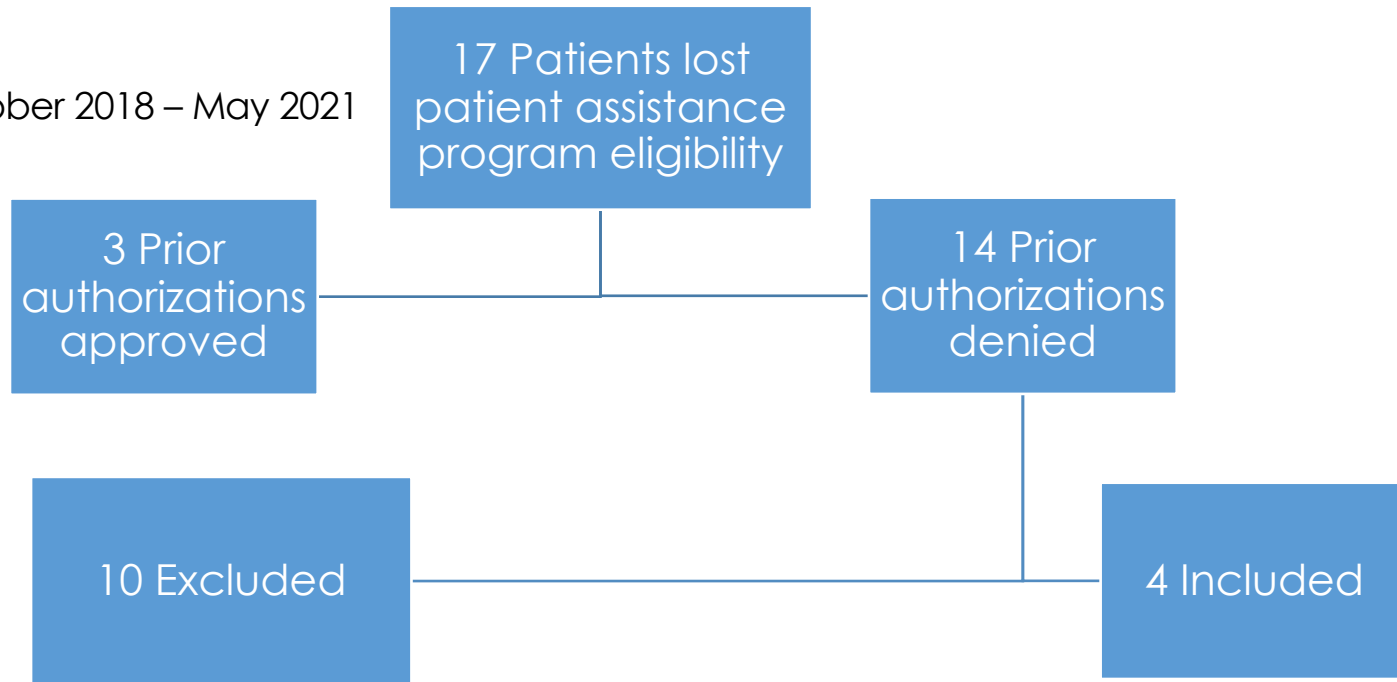
Criteria	Score	
	Before Therapy	During or After Therapy
Direct laboratory evidence of causative fungus		
Positive culture of CSF, brain tissue, &/or meningeal tissue	3	3
Positive India ink demonstration of yeast forms compatible with <i>Cryptococcus neoformans</i>	1	1
Histopathology of brain &/or meningeal tissue showing organisms	2	2
Maximum for Category	3	3
Serologic evidence of infection		
Presence of unconcentrated CSF of antibodies of <i>Coccidioides immitis</i> (measured by CF or immunodiffusion test)	3	3
Presence in CSF of <i>C. neoformans</i> antigens (Measured by latex agglutination method. Titer of $\geq 1:8$)	3	3
Persistently measurable titer in CSF of <i>C. neoformans</i> antigen	n/a	1
Maximum for Category	3	3
Abnormalities of CSF		
Glucose level <50% of simultaneous glucose level in blood	1	1
Protein level >50 mg/dl	1	1
WBC >50/mm ³	1	1
Maximum for Category	1	1
Presence of clinical features compatible with fungal meningitis		
Symptoms: Fever (>38 C), vomiting, headache, confusion, personality change, &/or seizures	3	3
Signs: fever (>38 C), papilledema, meningeal irritation, lethargy, obtundation, stupor, coma, cranial nerve palsy, ataxia, &/or pathologic reflexes	3	3
Maximum for category	3	3

Dismukes WE, et al. *Rev Infect Dis.* 1980;2(4):535-545.

Determining Optimal Sample Size

- Utilizing results from a previous study conducted at Kern Medical
 - 80% power, $\alpha = 0.05$
 - Clinically meaningful change in MSG score
 - 50% change
 - 31 patients required
 - Treatment failure
 - Doubling of MSG score
 - 8 patients required

Timeline: October 2018 – May 2021



Number of Patients	Reason for Exclusion
1	Seroreactivation while off therapy for 6 months Recently transitioned to posaconazole
1	Lack of data while on isavuconazole
1	Monitored off of therapy
1	Moved and is seeing a new provider
2	Lost to follow-up
1	Nonadherent
3	Transitioned, but pending follow-up data

Inclusion Criteria
18 years and older
Within Kern Medical system outpatient setting
Treated with isavuconazole for coccidioidomycosis
Transitioned from isavuconazole due to drug exclusion policies or loss of patient assistance program eligibility
On latest agent for at least 6 months

Results

Patient Number	Age	Sex	Cocci Location	Agent prior to Isavuconazole	Reason for Switch to Isavuconazole	New Agent
1	29	M	Meningitis	Liposomal amphotericin B IV	Patient convenience	Itraconazole 300mg q12h
2	48	F	Meningitis	Fluconazole 1000mg daily	Intolerance	Itraconazole 200mg q12h
3	40	M	Pulmonary	Fluconazole 400mg daily	Failure	Itraconazole 200mg q12h
4	41	F	Pulmonary	Fluconazole 800mg daily	Failure	Voriconazole 200mg q12h

Results

Patient Number	Cocci Location	MSG Scores			New Agent
		Prior Agent	Isavuconazole	New Agent	
1	Meningitis	4	1	4	Itraconazole
2	Meningitis	1	0	0	Itraconazole
3	Pulmonary	4	2	0	Itraconazole
4	Pulmonary	4	0	0	Voriconazole

Results

Patient Number	Cocci Location	MSG Scores			New Agent
		Prior Agent	Isavuconazole	New Agent	
1	Meningitis	4	1	4	Itraconazole
2	Meningitis	1	0	0	Itraconazole
3	Pulmonary	4	2	0	Itraconazole
4	Pulmonary	4	0	0	Voriconazole

Friedman test
P = 0.048

Results

Patient Number	Cocci Location	MSG Scores			New Agent
		Prior Agent	Isavuconazole	New Agent	
1	Meningitis	4	1	4	Itraconazole
2	Meningitis	1	0	0	Itraconazole
3	Pulmonary	4	2	0	Itraconazole
4	Pulmonary	4	0	0	Voriconazole

Sign test
P = 0.02

Results

Patient Number	Cocci Location	MSG Scores			New Agent
		Prior Agent	Isavuconazole	New Agent	
1	Meningitis	4	1	4	Itraconazole
2	Meningitis	1	0	0	Itraconazole
3	Pulmonary	4	2	0	Itraconazole
4	Pulmonary	4	0	0	Voriconazole

Sign test
P = 1.0

Discussion

- Overall mixed results
- Unable to make meaningful judgement on the effect of the drug exclusion policies
- Literature review from 2016
 - 26 studies pertaining to drug exclusion policies
 - Mixed impact on patients

Chambers JD et al. *Am J Manag Care*. 2016;22(8):524-531.

Limitations

- Underpowered
- Small number of study patients included
 - Difficult to draw conclusions when directly comparing agents
- Unable to assess patient long-term tolerance of latest agent
- MSG scores
 - Limited applicability in clinical practice
 - Not widely available for all patients given retrospective nature of study
 - MSG 2.0

Conclusion

- Cohort of four patients transitioned from isavuconazole
 - One experienced worsening coccidioidomycosis meningitis
 - One experienced improved pulmonary coccidioidomycosis
 - Two patients experienced no change in their disease control
- Overall results are inconclusive to date

Future Direction

- Further study warranted to determine long-term disease control in patients
 - Will also expand study population to include those with pending follow-ups
 - Evaluate the long-term effects of switching azole therapy

Questions?