Effectiveness of Posaconazole in the Treatment of Rare Invasive Fungal Infections: A Systematic Literature Review

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Introduction

- Chromoblastomycosis, fungal mycetoma, hyalohyphomycosis/ phaeohyphomycosis, and mucormycosis are rare, potentially life-threatening invasive fungal infections (IFI)[1-6]
- Several antifungal agents, including posaconazole, have been used alone or in combination to treat these 4 IFIs[1-3,5,7]
- The length of therapy can range from several weeks to even years,[1,5-10] and disability and/or mortality rates are high[1,3,6,11-15]
- As the numbers of immunocompromised patients, including pediatric patients, continue to rise, IFIs play a significant role in the morbidity and mortality seen in this population[16]
- Given the few effective treatment options, this systematic literature review (SLR) was conducted to take an in-depth view of the clinical use of posaconazole for these rare IFIs

Objective

- To understand the efficacy/effectiveness of posaconazole monotherapy or combination therapy in treating invasive chromoblastomycosis, fungal mycetoma, hyalohyphomycosis/phaeohyphomycosis, and mucormycosis infections

Methods

Search Strategy and Data Sources

- A search of MEDLINE and Embase databases was conducted via ProQuest to identify literature on the treatment of IFIs with posaconazole published from Jan. 1, 2005 (year of posaconazole approval) through Oct. 30, 2019
- Studies were selected using predefined selection criteria. Efficacy/ effectiveness outcomes of posaconazole monotherapy or combination therapy were analyzed by first-line or second-line treatment of the following IFIs:
  - Chromoblastomycosis (ie, *Fonsecaea, Phialophora, Cladosporium, Exophiala,* and fungi not specified)
  - Fungal mycetoma (ie, Eumycetoma, Mycotic Mycetoma, and fungal mycetoma not specified)
  - Hyalohyphomycosis/phaeohyphomycosis (ie, *Fusarium, Scedosporium, Pseudallescheria, Talaromyces,* and *Penicillium spp*)
  - Mucormycosis (ie, *Rhizopus, Mucor, Cunninghamella, Apophysomyces, Lichtheimia (Absidia), Saksenaea, Rhizomucor, Mucormycetes* not specified, and *Zygomycosis* not specified)
- Studies evaluating prophylactic use of posaconazole or infections caused by fungal species other than the included fungal species were excluded

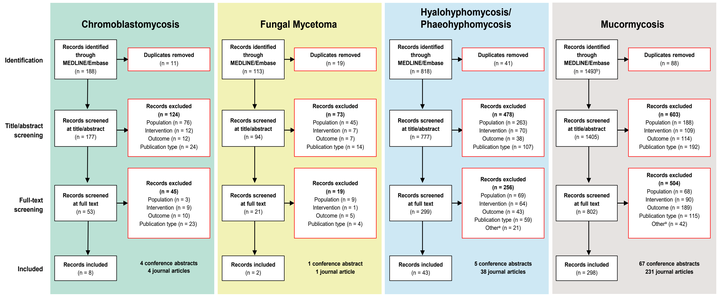
Study Selection and Data Extraction

- Data were screened for eligibility and extracted based on predefined PICOS criteria
- Efficacy/effectiveness outcomes included cure, response, relapse, radiologic improvement, mortality, and any other effectiveness measures reported
- Study quality was assessed using National Institute for Health and Care Excellence-recommended checklists[17]
- A narrative descriptive summary was used to summarize study findings

Study Demographics

- Of 2612 articles identified, 351 articles were included (**Figure 1**)
  - 8 publications for chromoblastomycosis, 2 publications for fungal mycetoma, 43 publications for hyalohyphomycosis/phaeohyphomycosis, and 298 publications for mucormycosis

Figure 1. PRISMA Diagram



[a]Other defines articles excluded for other reasons, including duplicate copies.
[b]Includes one additional publication in press from Merck (Schauwvliegne, 2020[9]).

Results

Overall Positive Efficacy

- Positive response was defined as any reported positive efficacy measure (ie, no relapse, response, cure, radiological improvement, clinical/symptom improvement, or survived therapy)
- Positive clinical outcomes with posaconazole therapy were observed in 53.3%-100% of patients across the IFIs examined (**Figure 2**)
- Overall survival[a] was ~70% or greater across the IFIs examined

Figure 2. Overall Positive Efficacy Outcomes

Chromoblastomycosis	Fungal Mycetoma	Hyalohyphomycosis/ Phaeohyphomycosis	Mucormycosis
• 23 patients	• 2 patients	• 92 patients	• 845 patients
• 73.9% positive efficacy outcome	• 100% positive efficacy outcome	• 53.3% positive efficacy outcome	• 66.7% positive efficacy outcome
• 100% overall survival[a]	• 100% overall survival[a]	• 70% overall survival[a]	• 71.8% overall survival[a]

[a]Overall survival is defined as alive at last measurement while on posaconazole therapy.

Efficacy by Line of Therapy and Combination Therapy vs Monotherapy (**Table 1**)

- Posaconazole efficacy and mortality differed by line of therapy as well as for monotherapy vs combination therapy
- Positive response was higher in second-line monotherapy than first-line monotherapy in chromoblastomycosis and mucormycosis
- Higher mortality was observed with combination therapy than monotherapy in hyalohyphomycosis/ phaeohyphomycosis and mucormycosis infections (except for first-line use in mucormycosis)

Disclosures

This study was sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.
Hetty Waskin, Nicole Cossrow, and Havilland Campbell are employees of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.
Mark Bernauer, Dipen Patel, and Allysen Kaminski are employees of Pharmerit, an OPEN Health Company, and were paid consultants to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, in connection with this study.

Study Quality Assessment

- As the IFIs examined are rare, it was not surprising that no randomized clinical studies were found in the body of literature. The included publications consisted of observational research (cohort, case-controlled, case series, or case reports) of small sample size. Further, many studies failed to adequately describe the dose and/or duration of posaconazole therapy. Caution should be exercised in interpreting the results and conclusions from this SLR
  - One cohort study in chromoblastomycosis was assessed; the quality was adequate, although the validity of the outcomes measured was not clear
  - The 2 included fungal mycetoma articles were both case reports and thereby not eligible for study quality assessment
  - The study quality seemed adequate in only 3 (21.4%) of the 14 appraisable hyalohyphomycosis/ phaeohyphomycosis publications
  - The study quality seemed adequate in only 7 (14.0%) of the 50 appraisable mucormycosis publications

Table 1. Overall Summary of Posaconazole Efficacy

Study Type	Total Cases Reported, % (n/N)	Positive Response to Treatment[a]	Negative or No Response to Treatment[b]	Overall All-Cause Mortality
Chromoblastomycosis[c]				
First-Line Use				
Monotherapy	56.5% (13/23)	61.5% (8/13)	38.5% (5/13)	0% (0/13)
Combination therapy	4.3% (1/23)	100% (1/1)	0% (0/1)	0% (0/1)
Second-Line Use				
Monotherapy	34.8% (8/23)	87.5% (7/8)	12.5% (1/8)	0% (0/8)
Combination therapy	0% (0/23)	NA	NA	NA
Fungal Mycetoma				
First-Line Use				
Monotherapy	0% (0/2)	NA	NA	NA
Combination therapy	50% (1/2)	100% (1/1)	0% (0/1)	0% (0/1)
Second-Line Use				
Monotherapy	0% (0/2)	NA	NA	NA
Combination therapy	50% (1/2)	100% (1/1)	0% (0/1)	0% (0/1)
Hyalohyphomycosis/Phaeohyphomycosis[d]				
First-Line Use				
Monotherapy	22.8% (21/92)	61.9% (13/21)	38.1% (8/21)	4.8% (1/21)
Combination therapy	25.0% (23/92)	56.5% (13/23)	43.5% (10/23)	39.1% (9/23)
Second-Line Use				
Monotherapy	40.2% (37/92)	56.8% (21/37)	43.2% (16/37)	43.2% (16/37)
Combination therapy	7.6% (7/92)	28.6% (2/7)	71.4% (5/7)	71.4% (5/7)
Mucormycosis[e]				
First-Line Use				
Monotherapy	20.9% (177/845)	64.4% (114/177)	35.6% (63/177)	30.5% (54/177)
Combination therapy	30.2% (255/845)	67.5% (172/255)	32.5% (83/255)	29.4% (75/255)
Second-Line Use				
Monotherapy	22.5% (190/845)	74.2% (141/190)	25.8% (49/190)	8.4% (16/190)
Combination therapy	6.4% (54/845)	64.8% (35/54)	35.2% (19/54)	38.9% (21/54)

NA, not applicable.
[a]Positive response is defined as reporting of a positive efficacy measure (ie, no relapse, response, cure, radiological improvement, clinical/symptom improvement, or survived therapy).
[b]Negative or no response is defined as reporting of a negative efficacy measure (ie, no relapse, response, cure, radiological improvement, clinical/symptom improvement, or survived therapy), or no change in efficacy status with treatment.
[c]The total number of chromoblastomycosis cases reported includes 1 case where the line of therapy could not be determined.
[d]The total number of hyalohyphomycosis/phaeohyphomycosis cases reported includes 4 cases where the line of therapy could not be determined.
[e]The total number of mucormycosis cases reported includes 169 cases where the line of therapy could not be determined.

Limitations

- The IFIs examined are rare and likely to not have been studied in a well-controlled clinical trial
- Included publications consisted of observational research
- Sample sizes in individual included studies were likely insufficient to draw statistically robust comparisons
- Potential inconsistency or heterogeneity among patients in the included studies may exist, especially with individual case reports
- Selection bias may exist due to selective reporting of cases
- Outcome definitions varied among the included studies, and many studies failed to adequately describe the dose and/or duration of posaconazole therapy
- Overall quality of evidence for much of the data was not able to be assessed because much of the evidence was from individual cases and quality assessment tools were not available to assess conference abstracts or case reports

Discussion

- Despite the rarity of these IFIs, 351 publications (mostly case reports) have been published describing the effectiveness of posaconazole in the treatment of chromoblastomycosis, fungal mycetoma, hyalohyphomycosis/ phaeohyphomycosis, and mucormycosis
- Several agents are recommended for the treatment of these rare IFIs, including amphotericin B, voriconazole, itraconazole, and posaconazole[18]
- However, amphotericin B has dose-limiting toxicities,[19] itraconazole is not an optimal choice for central nervous system (CNS) infections due to its high protein binding and poor CNS penetration,[18] and voriconazole is contraindicated in patients receiving co-administration of P450–CYP3A4 substrates and may not be the best drug of choice in patients with mild-to-moderate renal impairment.[18] Thus, posaconazole may be an alternate option
- The real-world evidence demonstrates that posaconazole is an effective therapeutic option alone or in combination for the treatment of these rare IFIs

Conclusion

- The evidence from this comprehensive SLR can be an important resource to understand real-world experiences and effectiveness of posaconazole in treating these rare IFIs

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