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Utility of itraconazole and terbinafine in mucormycosis: a proof-of-concept analysis

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ABSTRACT

An epidemic of mucormycosis followed the second wave of COVID 19 in the state of Uttar Pradesh, India in May 2021. This epidemic, however, had additional challenges to offer in the form of acute shortage of all forms of amphotericin B, posaconazole and isavuconazole. It was, therefore, planned to assess the trends in minimum inhibitory concentration (MIC) of antifungal agents, viz itraconazole and terbinafine, and provide a template for personalized therapy to see whether the results could be translated clinically. This is an observational, single-center study. Samples comprising nasal swab, nasal and paranasal sinus tissue, brain tissue, brain abscess and orbital content, derived from 322 patients from northern India with mucormycosis, of whom 215 were male and 107 were female, were used for analysis. Cultures were identified both by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) and conventional methods of identification. Antifungal susceptibility was done for amphotericin B, posaconazole, isavuconazole, itraconazole and terbinafine as per Clinical Laboratory Standard Institute M38-A2. The outcome was identification of the species of mucormycosis and susceptibility to itraconazole and terbinafine besides other primary antifungal agents. Patients or the public were not involved in the design, or conduct, or reporting or in the dissemination plans of our research. Of 322 patients, 203 were culture-positive, of whom 173 were positive by both MALDI-TOF and conventional methods of identification. Final antifungal susceptibility testing was available for 150 patients. The most common Mucorales found to cause this epidemic was *Rhizopus oryzae*, followed by *R. microsporus*. Amphotericin B, posaconazole and isavuconazole had low MIC values in 98.8% of all Mucorales identified. The MIC of itraconazole was species-dependent. 97.7% of *R. oryzae* had MIC ≤2 µg/mL. However, only 36.5% of *R. microsporus* had MIC ≤2 µg/mL. For terbinafine, 85.2% of *R. microsporus* had MIC ≤2 µg/mL. We conclude that identification at the species level is required as antifungal susceptibilities seem to be species-dependent. Assessment of the efficacy of itraconazole and terbinafine warrants further studies with clinical assessment and therapeutic drug monitoring as they seem to be potential candidates especially when the primary agents are not available.

Significance of this study

What is already known about this subject?

- The mainstay of treatment for rhino-orbito-cerebral mucormycosis (ROCM) is surgery, along with liposomal amphotericin B.
- Other antifungals such as posaconazole and isavuconazole are also used as step-down therapy or as replacement to liposomal amphotericin B when not available.
- The high cost and the difficulty in procuring posaconazole and isavuconazole make them beyond the reach of many patients.

What are the new findings?

- Majority of cases of ROCM during this epidemic were caused by *Rhizopus oryzae* and *R. microsporus*.
- When tested in vitro, itraconazole and terbinafine showed lower minimum inhibitory concentration to *R. oryzae* and *R. microsporus*, respectively.
- Itraconazole and terbinafine appear to be potential agents for treatment of ROCM caused by *R. oryzae* and *R. microsporus*, respectively.

How might these results change the focus of research or clinical practice?

- Utilization of itraconazole and terbinafine depending on species can bring down the total cost of treatment of patients with mucormycosis.
- Identification of Mucorales at the species level is important as susceptibility to antifungal drugs such as itraconazole and terbinafine varies species-wise.
- These drugs may thus be tried in lieu of posaconazole and isavuconazole.

INTRODUCTION

Mucormycosis is a disease caused by a group of molds called mucoromycetes and has high mortality rate. The second wave of COVID-19 in India lasted from March to June 2021, leaving a huge burden on the healthcare system and intensive care units (ICUs). Severe and critical patients were treated with varied

Table 1 MIC distribution of amphotericin B for 150 Mucorales species determined using the CLSI M38-A2 microdilution method

	Isolates (n)	Isolates (n) with MIC (µg/mL)									
Species	Total (n=150)	≤0.03	0.06	0.125	0.25	0.5	1.0	2.0	4.0	8.0	≥16.0
Rhizopus oryzae complex	98	–	–	1	1	26	38	31	1	–	–
Rhizopus microsporus complex	41	–	–	–	–	10	18	12	1	–	–
Lichtheimia corymbifera	7	–	–	–	–	–	7	–	–	–	–
Rhizopus azygosporus	2	–	–	–	–	–	2	–	–	–	–
Apophysomyces elegans	2	–	–	–	–	–	1	1	–	–	–

CLSI, Clinical Laboratory Standard Institute; MIC, minimum inhibitory concentration.

immunosuppressants, including corticosteroids, the only proven therapy—something that was similarly observed in influenza-associated mucormycosis.[1] Rampant use of these drugs, underlying comorbidities especially uncontrolled sugars, longer ICU stay and many unknown factors culminated in mucormycosis of epidemic proportions, never observed anywhere else in the world.[2]

Initiation of appropriate treatment (within 12 days) is said to improve the outcome of *Mucor* patients.[3] The mainstay of treatment of mucormycosis is debridement of the necrotic areas and liposomal amphotericin B (AMB). Other antifungal agents such as posaconazole (PSC) and isavuconazole (ISC) are also used, either as primary therapy (if liposomal AMB cannot be given), salvage therapy or as step-down therapy.[4] The rapid surge of mucormycosis, with nearly 30,000 patients in a span of 2 months, led to an acute shortage of mainstay drugs. Lack of liposomal AMB, PSC and ISC, coupled with their exorbitant cost, caused a huge gap in the treatment of patients with mucormycosis. A literature search into possible alternative drugs revealed two potential antifungal agents, itraconazole (ITZ) and terbinafine (TRB), which had demonstrated low minimum inhibitory concentration (MIC) against some species of mucormycetes.[5–7] This analysis was, therefore, planned to identify different species of Mucorales affecting patients with COVID-19-associated mucormycosis and identify the MIC trends, with special focus on ITZ and TRB. If adjudged useful, these cheaper alternatives to PSC and ISC may be studied further and may as well be used as step-down or concomitant therapy.

Table 2 Range, mode and % MIC above the ECV of AMB, PSC, ISC, ITZ and TRB for Mucorales species by the CLSI M38-A2 broth microdilution method

		MIC (µg/mL)		% MIC above the ECV (non-wild type)
Species	Antifungal agent	Range	Mode	
Rhizopus oryzae	AMB (98)	0.125–4.0	1.0	0
	PSC (98)	0.125–2.0	1.0	0
	ISC (98)	0.06–8.0	1.0	–
	ITZ (98)	0.06–≥16	1.0	3.06
	TRB (88)	0.5–≥16	≥16	–
Rhizopus microsporus	AMB (41)	0.5–4.0	1.0	2.43
	PSC (41)	0.125–1.0	1.0	0
	ISC (41)	0.25–4.0	1.0	–
	ITZ (41)	0.5–8.0	4.0	–
	TRB (38)	0.125–2.0	1.0	–
Lichtheimia corymbifera	AMB (7)	1.0	1.0	0
	PSC (7)	0.25–1.0	0.5	0
	ISC (7)	1.0–2.0	2.0	–
	ITZ (7)	0.5–2.0	1.0	–
	TRB (2)	0.5–1.0	–	–
Rhizopus azygosporus	AMB (2)	1.0	–	–
	PSC (2)	0.5–1.0	–	–
	ISC (2)	2.0	–	–
	ITZ (2)	1.0–2.0	–	–
	TRB (2)	8.0–≥16	–	–
Apophysomyces elegans	AMB (2)	1.0–2.0	–	–
	PSC (2)	1.0	–	–
	ISC (2)	2.0–4.0	–	–
	ITZ (2)	1.0–2.0	–	–
	TRB (2)	1.0–1.0	–	–

AMB, amphotericin B; CLSI, Clinical Laboratory Standard Institute; ECV, epidemiological cut-off value; ISC, isavuconazole; ITZ, itraconazole; MIC, minimum inhibitory concentration; PSC, posaconazole; TRB, terbinafine.

METHODS

The study was conducted at King George's Medical University (KGMU), Lucknow, a tertiary care dedicated to COVID-19 and a mucormycosis facility in the northern part of India. Samples comprising nasal swab, nasal and paranasal sinus tissue, brain tissue, brain abscess and orbital content comprising exenterated fat tissue or vitreous tap or globe from 322 patients with rhino-orbito-cerebral mucormycosis (ROCM) admitted to the dedicated *Mucor* referral facility at KGMU from May 1, 2021 and July 31, 2021 were analyzed. Samples were taken from patients as per the defined protocol for suspected *Mucor* patients.[8]

Samples were received and processed in the referral mycology laboratory of the university for potassium hydroxide microscopy and fungal culture. Mucorales grown on Sabouraud dextrose agar were identified by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS; Vitek MS, bioMérieux, France), as well as by slide cultures and Lactophenol cotton blue (LCB) preparations. Cultures identified as the same both by MALDI-TOF and slide culture/LCB were included in the study for antifungal susceptibility testing (AFST). Antifungal susceptibility was done for AMB, PSC, ISC, ITZ and TRB as per the Clinical Laboratory Standard Institute (CLSI M38-A2) guidelines.[9] MIC value interpretation for wild type (WT) and non-wild type (non-WT) was based on the epidemiological cut-off values (ECV) suggested by

Table 3 MIC distribution of posaconazole for 150 Mucorales species determined using the CLSI M38-A2 microdilution method

	Isolates (n)	Isolates (n) with MIC (µg/mL)									
Species	Total (n=150)	≤0.03	0.06	0.125	0.25	0.5	1.0	2.0	4.0	8.0	≥16.0
Rhizopus oryzae complex	98	–	–	3	11	38	45	1	–	–	–
Rhizopus microsporus complex	41	–	–	3	3	15	20	–	–	–	–
Lichtheimia corymbifera	7	–	–	–	1	3	3	–	–	–	–
Rhizopus azygosporus	2	–	–	–	–	1	1	–	–	–	–
Apophysomyces elegans	2	–	–	–	–	–	2	–	–	–	–

CLSI, Clinical Laboratory Standard Institute; MIC, minimum inhibitory concentration.

Espinel-Ingroff *et al*.[10] Thus, derived from available data, the reference cut-off for AMB for *Rhizopus oryzae* was taken at 4 µg/mL, and for *R. microsporus*, *Lichtheimia corymbifera* and *Mucor circinelloides* this was taken at 2 µg/mL. Similarly, the cut-off for PSC for *R. oryzae*, *R. microsporus* and *L. corymbifera* was taken at 2 µg/mL and for *M. circinelloides* at 4 µg/mL. Finally, the cut-off for ITZ for *R. oryzae* was taken at 2 µg/mL.

RESULTS

Out of 322 patients, 203 were culture-positive for mucormycetes. Of these, 173 samples could be identified by both MALDI-TOF MS and slide cultures/LCB. Among these, 110 were identified as *R. oryzae*, 51 as *R. microsporus,* 7 as *L. corymbifera*, 2 as *R. azygosporus*, 2 as *Apophysomyces elegans* and 1 as *M. racemosus*. AFST was done on 150 out of a total of 173 cultures, which were all tested for AMB, PSC, ISC and ITZ, while 132 were tested for TRB (owing to delayed availability of the antifungal agent). The remaining 23 isolates, including *M. racemosus*, were not tested as their singular growth (purity) could not be ascertained.

All isolates of *R. oryzae* had AMB MIC of ≤4 µg/mL and were labeled WT, whereas 97.5% of *R. microsporus* and all strains *of L. corymbifera*, *R. azygosporus* and *A. elegans* had AMB MIC ≤2 µg/mL. Also in the case of AMB, 2.43% of *R. microsporus* had MIC above the ECV (tables 1 and 2). For PSC, 98.9% of *R. oryzae* and 100% of *R. microsporus*, *L. corymbifera*, *R. azygosporus* and *A. elegans* had MIC ≤1 µg/mL (WT) (table 3). For ISC, 98.9% of the isolates of *R. oryzae* and 100% of *R. microsporus*, *L. corymbifera*, *R. azygosporus* and *A. elegans* had MIC ≤4 µg/mL (table 4). For ITZ, 97.9% of *R. oryzae* had MIC ≤2 µg/mL, that is, were WT strains (3.06% of *R. oryzae* had MIC above ECV for ITZ). In contrast, only 26.8% of *R. microsporus* had MIC ≤2 µg/mL (tables 2 and 5). All isolates of *L. corymbifera*, *R. azygosporus* and *A. elegans* had MIC ≤2 µg/mL for ITZ (table 5). All strains of *R. microsporus* had MIC ≤2 µg/mL for TRB. In contrast, 90.9% of *R. oryzae* had MIC ≥16 µg/mL for TRB (table 6).

DISCUSSION

Of 173 culture-positive samples in our study, the most common isolate detected was *R. oryzae* (63.6%), followed by *R. microsporus* (29.5%). AFST revealed that, besides AMB, ISC and PSC, some species showed low MIC to ITZ and TRB. With such species-wise variation in antifungal susceptibility, it is imperative that species identification becomes an integral part of formulating a treatment regimen for patients with mucormycosis. While this helps in personalizing the treatment plan, it may also help in reducing the total cost of therapy in those with susceptible isolates.

Our results indicate that the current epidemic of COVID-19-associated ROCM, first ever of such a magnitude, was primarily caused by *R. oryzae* and *R. microsporus*, accounting for just over 93% of all Mucorales identified. Although *R. oryzae* (also known as *R. arrhizus*) is a previously known most common species of *Rhizopus*, *R. microsporus* has not so commonly been reported.[6] One of the reasons for this difference could be the use of MALDI-TOF MS for identification, which has revolutionized the diagnostic mycology workflow and is augmenting conventional identification methods.[11] Other species listed in the tables also marked their presence but are too low in numbers in terms of their overall share. A study done in Iran in 2017–2018 isolated the maximum number of *R. arrhizus* from 196 soil samples and also found seasonal variation in isolation of Mucorales. In their study a seasonal variation in the frequency of Mucorales in soil was detected, with a maximum of culture-positive soil samples detected in wet autumn (43.2%), followed by winter (23.4%), summer (19.7%) and spring (13.6%).[12]

Majority of these species have low MIC to AMB and PSC. Espinel-Ingroff *et al*[10] have also demonstrated similar findings in a multicentric study done in 13 centers worldwide.

Table 4 MIC distribution of isavuconazole for 141 Mucorales species determined using the CLSI M38-A2 microdilution method

	Isolates (n)	Isolates (n) with MIC (µg/mL)									
Species	Total (n=150)	≤0.03	0.06	0.125	0.25	0.5	1.0	2.0	4.0	8.0	≥16.0
Rhizopus oryzae complex	98	–	1	2	8	19	47	14	6	1	–
Rhizopus microsporus complex	41	–	–	–	3	10	13	11	4	–	–
Lichtheimia corymbifera	7	–	–	–	–	–	2	5	–	–	–
Rhizopus azygosporus	2	–	–	–	–	–	–	2	–	–	–
Apophysomyces elegans	2	–	–	–	–	–	–	1	1	–	–

CLSI, Clinical Laboratory Standard Institute; MIC, minimum inhibitory concentration.

Table 5 MIC distribution of itraconazole for 150 Mucorales species determined using the CLSI M38-A2 microdilution method

	Isolates (n)	Isolates (n) with MIC (µg/mL)									
Species	Total (n=150)	≤0.03	0.06	0.125	0.25	0.5	1.0	2.0	4.0	8.0	≥16.0
Rhizopus oryzae complex	98	–	1	–	7	30	30	27	1	–	2
Rhizopus microsporus complex	41	–	–	–	–	1	2	8	25	5	–
Lichtheimia corymbifera	7	–	–	–	–	2	3	2	–	–	–
Rhizopus azygosporus	2	–	–	–	–	–	1	1	–	–	–
Apophysomyces elegans	2	–	–	–	–	–	1	1	–	–	–

CLSI, Clinical Laboratory Standard Institute; MIC, minimum inhibitory concentration.

Almyroudis *et al*[5] also demonstrated that, for Mucorales as a whole, AMB was the most active antifungal agent, with the majority of strains displaying an MIC near the suggested breakpoint of ≤1 µg/mL. A study done by Badali *et al*[13] from the USA also demonstrated that AMB had the most potent in vitro activity, with geometric mean (GM) MIC of ≤0.25 µg/mL against all genera, with the exception of *Cunninghamella* species (GM MIC of 1.30 µg/mL).[13] We also noted that the most common MIC for AMB was 1 µg/mL, followed by 2 µg/mL. Only one strain of *R. microsporus* displayed an MIC of 4 µg/mL for AMB (tables 1 and 6); this strain falls outside the ECV suggested by Espinel-Ingroff *et al*.[10] However, strains with higher MICs may still respond to liposomal AMB as these formulations of AMB are known to achieve concentrations far exceeding the MIC.[5] Thus, the response to treatment in such patients needs to be further studied.

Similarly, majority of isolates showed MIC of ≤4 µg/mL to the newer azole, ISC. The ECV for ISC has not been decided yet, but if we analyze their MIC values it is observed that the majority of them fall within ≤4 µg/mL. Of note, CLSI decides the ECV when the MIC of a particular antifungal comes within range for ≥95% of the isolates.[10] The final response to treatment of patients with ISC needs to be further studied; this will also help us in deciding the clinical breakpoint.

In our study, MIC for ITZ seems to be species-dependent. It is low in the case of most of the *R. oryzae*, but high for most of the isolates of *R. microsporus* (tables 4 and 6). Similar findings have been observed by Almyroudis *et al*[5] and Espinel-Ingroff *et al*.[10] Since the majority of infections have been caused by *R. oryzae*, ITZ may therefore be tried as an alternative, especially when AMB, PSC or ISC is not available. Moreover, it is a cheaper drug and is easily available as it is commonly used for treatment of dermatophytic infections and aspergillosis. However, its in vivo effect needs to be studied further by correlating its clinical response with serial serum trough levels. It may also be tried in few cases of *R. microsporus* infections, wherever susceptibilities are available. The ECV for *R. microsporus* is yet to be decided; from our MIC data, an ECV of 8 µg/mL can be proposed. However, studies on more isolates of *R. microsporus* need to be done to affirm our findings.

In contrast to ITZ, TRB was found to be more active against *R. microsporus* than against *R. oryzae* in our study. This contrasting pattern potentially opens up a whole new set of permutations and combinations when different isolates are detected. Similar findings were found by Dannaoui *et al*[6] in the past. Primarily designed for superficial mycoses, TRB has also been found to be effective in the treatment of systemic fungal infections, such as aspergillosis or pseudallescheriasis.[6] TRB was tested for its efficacy in non-neutropenic mice by Dannaoui *et al*,[14] but found no beneficial effects against *R. microsporus* and *L. corymbifera* despite documented absorption of the drug. Overall, only limited correlations have been observed between MICs determined in vitro vis a vis in vivo efficacy of this drug. However, a combination of oral TRB with AMB has been successfully used to treat a case of invasive zygomycosis.[15] Thus, its role in combination with other antifungal agents may also be studied. The ECV of Mucorales for TRB has never been established. We propose a level of ≤2 µg/mL for TRB based on our results. A study on a greater number of *R. microsporus* isolates needs to be done to propose an ECV.

To conclude, ITZ and TRB appear to be potential agents for treatment of infections caused by *R. oryzae* and *R. microsporus*, respectively, especially when the primary agents are sparingly available. It may be recommended that AFST be done, wherever facilities exist, in all patients with mucormycosis to aid in the logical selection of antifungal agent. Besides being scientific following the principles of evidence-based medicine, these therapies are more cost-effective and decrease the burden on pharmacy services in a given setting. However, further studies on their clinical efficacy are required as all in vitro results may not translate to comparable in vivo (animal/human) efficacy and may

Table 6 MIC distribution of terbinafine for 132 Mucorales species determined using the CLSI M38-A2 microdilution method

	Isolates (n)	Isolates (n) with MIC (µg/mL)									
Species	Total (n=132)	≤0.03	0.06	0.125	0.25	0.5	1.0	2.0	4.0	8.0	≥16.0
Rhizopus oryzae complex	88	–	–	–	–	7	–	–	1	–	80
Rhizopus microsporus complex	38	–	–	1	1	13	20	3	–	–	–
Lichtheimia corymbifera	2	–	–	–	–	1	1	–	–	–	–
Rhizopus azygosporus	2	–	–	–	–	–	–	–	–	1	1
Apophysomyces elegans	2	–	–	–	–	–	2	–	–	–	–

CLSI, Clinical Laboratory Standard Institute; MIC, minimum inhibitory concentration.

depend on factors ranging from absorption to attainment of therapeutic concentration in the tissue of interest.

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