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# Posaconazole or isavuconazole as sole or predominant antifungal therapy for COVID-19-associated mucormycosis. A retrospective observational case series

Rajeev Soman[a], Sourabh Chakraborty[b,*], Geethu Joe[c]

[a] HOD Infectious Disease, Jupiter Hospital, Baner, Pune 411057, India
[b] Infectious Diseases Fellow, Jupiter Hospital, Baner, Pune 411057, India
[c] Consultant Microbiologist, Jupiter Hospital, Baner, Pune 411057, India

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ABSTRACT

The surge of COVID-19 associated Mucormycosis (CAM) in India during the second wave of COVID-19 led to lack of availability of amphotericin B(AmB). We retrospectively evaluated the outcome in 28 consecutive patients with CAM who received posaconazole (PCZ) or isavuconazole (ISVCZ) as sole or predominant therapy, based on factors like availability, affordability, site of infection or lack of treatment response. Therapeutic drug monitoring was used for PCZ in all cases & for ISVCZ in some cases. Higher trough levels were aimed to ensure therapeutic effect. Overall, 16 patients were cured, 5 patients improved, 6 patients died, of which 2 deaths were attributable to mucormycosis and 1 patient was lost to follow-up. The outcomes and survival were comparable to those reported in the literature. Although wider applicability of these results cannot be assumed, it leads to a speculation that treatment of mucormycosis with PCZ or ISVCZ, without AmB, is possible.



During the second wave of COVID-19 in India, there was a surge of COVID-19–associated mucormycosis (CAM). This led to unavailability of amphotericin B (AmB), which has been considered as the drug of choice for mucormycosis. This situation resulted in an opportunity to treat with posaconazole (PCZ) or isavuconazole (ISVCZ) without AmB. Whether either of them can take the place of AmB in primary or salvage treatment has been the subject of clinical investigation in noninferiority trials (Marty et al., 2016; Maertens et al., 2016; Salmanton-García et al., 2019). Whether an incremental benefit of AmB over azoles exists at all (Durand et al., 2021) and whether it is counterbalanced by the greater difficulties in drug administration, toxicity, prolonged hospitalization, and cost needs further consideration.

We retrospectively analyzed 28 consecutive cases of CAM. The extent of involvement was as follows: rhinosinusitis alone in 4 patients; rhinosinusitis and palate involvement in 1 patient; rhinosinusitis, palate, and skull base involvement in 1 patient; rhinosinusitis and skull base involvement in 5 patients; rhinosinusitis and orbit involvement in 4 patients; rhinosinusitis, orbit, and brain involvement in 2 patients; rhinosinusitis, orbit, brain, and skull base involvement in 1 patient; rhinosinusitis, orbit, brain, and ophthalmic involvement in 1 patient; rhinosinusitis, orbit, ophthalmic, and skull base involvement in 2 patients; rhinosinusitis and brain involvement in 1 patient; pulmonary involvement in 5 patients; pulmonary, orbit, and ophthalmic involvement in 1 patient. Underlying comorbidities were diabetes mellitus, hypertension, chronic kidney disease, receipt of steroids, and other immunomodulators. Proven CAM was defined as clinical and radiologic features of rhinosinusitis, orbital, skull base, central nervous system, and pulmonary involvement in various combinations with histopathology showing tissue invasion with hyphae consistent with Mucorales and/or culture. Possible CAM was defined as clinical and radiologic features with smear from relevant specimens obtained from a nonsterile site, showing hyphae consistent with Mucorales and/or culture. Possible CAM was defined as clinical and radiologic features in the absence of histopathology and smear positivity when alternative causes are ruled out. There were 25 cases of proven, 1 case of probable, and 2 cases of possible CAM. Patients were given PCZ or ISVCZ on the basis of factors such as availability, affordability, site of infection, or lack of treatment response. Posaconazole

* Corresponding author.
*E-mail address:* dr.sourabhchakraborty@gmail.com (S. Chakraborty).

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was initiated with IV formulation at a dose of 300 mg twice a day, followed by 300 mg gastro-resistant posaconazole tablet once per day. ISVCZ was initiated with IV formulation at a dose of 200 mg 3 times a day for 2 days, followed by 200 mg ISVCZ tablet once per day. Some patients received AmB elsewhere but had disease progression or briefly received additional AmB when it was available. Patients underwent surgical debridement in 1 or more sessions as was necessary and feasible, along with supportive treatment. They were monitored for interactions, adverse drug reactions, and clinical response. Therapeutic drug monitoring (TDM) was used for PCZ in all cases and for ISVCZ in some cases. The commonly recommended therapeutic level is >1.2 mg/L for PCZ, and TDM for ISVCZ is usually not recommended but the trough level is thought to be 3 mg/L with usual doses. PCZ levels between 2.5–3 mg/L and ISVCZ levels between 5–7 mg/L were aimed for assurance of adequate penetration to the sites of infection. Depending on the factors that were mentioned previously, 4 patients were treated with ISVCZ alone (initial IV loading dose followed by tablet ISVCZ), 3 patients were treated with PCZ alone (initial IV loading dose followed by gastro-resistant [GR] PCZ tablet), 2 patients were treated with ISVCZ followed by GR PCZ (as ISVCZ was not available), 2 patients were treated with GR PCZ followed by ISVCZ (in view of bony involvement), 9 patients were treated with IV PCZ and AmB (in perioperative period ranging from 4–13 days) followed by GR PCZ, 4 patients were treated with IV PCZ and AmB (in perioperative period ranging from 8–11 days) followed by ISVCZ (in view of intra cranial extension, orbital, or bony involvement), and 4 patients were treated with AmB and PCZ elsewhere (ranging from 28–52 days) followed by GR PCZ. Treatment duration was based on clinical, radiological, and microbiological stability and improvement. This needed a prolonged period of treatment for some patients, as has been reported in the literature (Cornely et al., 2019). A total of 16 patients were cured with treatment, the duration of which ranged from 65–219 days and remained well during a follow-up, which ranged from 154–290 days. A total of 5 patients improved and are still on treatment as of February 23, 2022, the duration of which has ranged from 238–309 days. A total of 6 patients died, of which 2 deaths were attributable to mucormycosis and had received treatment, the duration of which ranged from 4–24 days. Furthermore, 1 critically ill patient left the hospital because relatives had decided to limit treatment. Hence, he is presumed to have died soon afterwards. These outcomes and survival compare favorably with those reported in the literature. Crude mortality in this series was 25% compared with reported mortality, which ranges from 19%–45.7% in various publications (Marty et al., 2016; Maertens et al., 2016; Patel et al., 2021; Salmanton-García et al., 2019). Although wider applicability of these results cannot be assumed, it leads to a speculation that treatment of mucormycosis with PCZ or ISVCZ, without AmB, is possible.

## CRediT authorship contribution statement

**Rajeev Soman:** Data curation, Writing – original draft, Supervision, Formal analysis. **Sourabh Chakraborty:** Data curation, Formal analysis. **Geethu Joe:** Data curation, Formal analysis.

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The data have been generated as part of routine work.

## Declaration of Competing Interest

RS reports having received honoraria from Pfizer, MSD, Astellas, Gilead, Biomeriux, Mylan, Cipla, Glenmark, Intas, Gufic, and Emcure outside of submitted work. SC and GJ have no conflict of interest to declare.

## Patient consent statement

Patient consent was obtained.

## Ethical statement

The study was approved by Jupiter Hospital Ethics Committee (January 12, 2021).

## Data availability statement

The data that support the findings of this study are available upon request from the corresponding author.

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## References

Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen S, Dannaoui E, Hochhegger B, Hoenigl M, Jensen HE, Lagrou K, Lewis RE, Mellinghoff SC, Mer M, Pana ZD, Seidel D, Sheppard DC, Wahba R, Akova M, Alanio A, Al-Hatmi A, … Arikan-Akdagli SMucormycosis ECMM MSG Global Guideline Writing Group. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. The Lancet. Infectious diseases 2019;19(12):e405–21. doi:10.1016/S1473-3099(19)30312-3.

Durand ML, Kitt TM, Song Y, Marty FM. Isavuconazole treatment of invasive fungal sinusitis: a post hoc analysis of the SECURE and VITAL trials. Clin Infect Dis 2021;73(6):e1380–3. doi:10.1093/cid/ciab386.

Marty FM, Ostrosky-Zeichner L, Cornely OA, Mullane KM, Perfect JR, Thompson GR, et al. VITAL and FungiScope Mucormycosis Investigators. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis 2016;16(7):828–37. doi:10.1016/S1473-3099(16)00071-2.

Maertens JA, Raad II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet 2016;387(10020):760–9. doi:10.1016/S0140-6736(15)01159-9.

Patel A, Agarwal R, Rudramurthy SM, Shevkani M, Xess I, Sharma R, et al. MucoCovi Network3. Multicenter epidemiologic study of coronavirus disease-associated mucormycosis, India. Emerg Infect Dis 2021;27(9):2349–59. doi:10.3201/eid2709.210934.

Salmanton-García J, Seidel D, Koehler P, Mellinghoff SC, Herbrecht R, Klimko N, et al. FungiScope® ECMM/ISHAM Working Group. Matched-paired analysis of patients treated for invasive mucormycosis: standard treatment versus posaconazole new formulations (MoveOn). J Antimicrob Chemother 2019;74:3315–27. doi:10.1093/jac/dkz344.