

Posaconazole in the Prevention of COVID-19-associated Mucormycosis: A Concerning Contributor to the Rise in Antifungal Resistance

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INTRODUCTION

The current coronavirus disease-2019 (COVID-19) pandemic has reported a 4–13% incidence for superinfection with invasive fungal infections, with aspergillosis and candidemia being the most commonly implicated.¹ COVID-associated mucormycosis (CAM) is a recently growing concern in individuals infected with and recovering from COVID-19 and has further strained our healthcare services. Unlike COVID-associated pulmonary aspergillosis (CAPA), invasive mucormycosis has been observed even in patients with mild to moderate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. A recent systematic review on 41 CAM patients showed that 94% of them were uncontrolled diabetics with prior corticosteroid usage with an in-hospital mortality rate of 49%.² *Rhizopus*, *Mucor*, and few unspecified Mucorales species had accounted for the majority of the cases.

There are currently three systemic antifungals exhibiting good Mucorales activity, i.e., liposomal amphotericin B, posaconazole, and isavuconazole. Posaconazole is a second-generation triazole antifungal agent. It exerts its action by binding and inhibiting the lanosterol-14a-demethylase, which is present in almost all fungi except *Pneumocystis* and *Pythium*. It has a broader spectrum compared to the other azoles and is less affected by the most common resistance mechanisms, such as efflux pumps and point mutations in the target enzyme.³

POSACONAZOLE—PROPHYLAXIS AND BREAKTHROUGH FUNGAL INFECTIONS

The number needed to treat to prevent one fungal infection was 27 and to prevent one death was 35 when posaconazole was used as prophylaxis in patients with hematologic malignancy who have neutropenia or graft-versus-host disease.⁴ However, there have been case reports of breakthrough invasive fungal infections while patients were on posaconazole prophylaxis. Analysis by the Food and Drug Administration on the pharmacokinetic data from the studies showed a clinical failure of 25%.

The reason attributed was that in actual clinical practice, patients do not take medications as prescribed and require a stringent follow-up for best outcomes. Since oral posaconazole bioavailability is maximized when taken with a high-fat or high-calorie meal, it is important that the prescribing physician recognize this fact and reinforce it with the patient. Therapeutic drug

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monitoring (TDM) has been recommended, and a serum trough level of >1 µg/mL is necessary for optimal drug activity.

POSACONAZOLE IN CAM PREVENTION: IS IT JUSTIFIED?

The fact that the spectrum of posaconazole covers both *Aspergillus* and Mucorales, the fungal pathogens implicated in the current COVID-19 epidemic, one wonders that it would theoretically reduce the risk of mucormycosis cases especially in high-risk patients when administered as prophylaxis. Some authors have even advised the usage of oral posaconazole in immunocompromised individuals who have received more than 3 weeks of mechanical ventilation and systemic steroids in the setting of COVID-19. However, posaconazole is not an elixir.⁵ Compliance issues, suboptimal absorption, and drug–drug interactions have resulted in low posaconazole serum levels and breakthrough mucormycosis infections. In patients treated with posaconazole for prophylaxis, TDM seems to be of particular relevance.

A potential concerning consequence of the COVID-19 pandemic is the propagation of antimicrobial resistance resulting from increased patient exposure to antimicrobials, especially when suboptimally or inappropriately used. Voriconazole has been the primary treatment for invasive aspergillosis since its approval in 2002. However, in less than a decade, the prevalence of voriconazole resistance is as high as 30% seen in some hospitals in Europe. Patients with these resistant isolates had a much higher mortality.⁶ There has been an alarming increase in case reports with triazole-resistant CAPA as well.

CONCLUSION

Posaconazole is one of the few agents in our antifungal armamentarium that is highly potent, less susceptible to resistance mechanisms with a broad spectrum of antifungal activity. Abusing such a drug in the background of an ever-rising antimicrobial resistance pandemic is not justifiable. We need to consider if the incidence of CAM and mortality benefit are significant enough to justify antifungal prophylaxis or are we just abusing another drug.

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