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Mucormycosis, COVID-19 and diabetes: A lethal mix

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Article by Dave Griffin

The number of mucormycosis cases in India hit the headlines recently as infections reached almost epidemic levels in COVID-19 patients with diabetes [1-3]. This usually rare opportunistic fungal infection has taken advantage of the down-regulated immune response in patients being treated with corticosteroids for COVID-19 lung damage, exacerbated by the established organ damage resulting from poorly controlled diabetes [3].

Mucormycosis, often referred to as black fungus, is caused by several moulds belonging to the order Mucorales [4]. The infection tends to progress rapidly, and, despite aggressive surgical intervention and intensive antifungal treatment, the mortality rate is 46% amongst people with sinus infections, 76% with pulmonary infections, and 96% for disseminated mucormycosis [5, 6]. Failure to cure the infection is often a consequence of the fungus' resistance to innate host defences, extensive angioinvasion, and increased virulence [6].

The first-line treatment for mucormycosis is amphotericin B (amB) despite its known renal toxicity [2,6] and the variable susceptibility of Mucorales [6]. Posaconazole and isavuconazole are second-line agents but limited to use in patients where amB is inappropriate [7-9]. Other antifungals such as fluconazole, voriconazole, and echinocandins do not work against Mucorales [7]. There are, however, a few new agents in development that may possess useful activity against Mucorales including the first-in-class agent, fosmanogepix (APX001), the next-generation azoles, termed tetrazoles, VT-1129, VT-1161, and VT-1598, and the novel polyene macrolide antifungal, BSG005 [2, 10].

Demonstrating clinical efficacy is problematic because mucormycosis is generally a rare infection, early diagnosis is difficult due to the non-specific clinical manifestations of this infection, there is a lack of serological methods, and limitations in both culture and molecular methods [6]. Furthermore, no randomised, controlled clinical studies have been published that compare Mucorales-active treatments. Even studies with the "standard care drug", liposomal amB (L-amB) were uncontrolled and performed in a limited number of patients who had a wide range of baseline characteristics and underwent a range of other interventions (e.g., surgery, correction of predisposing conditions) [11].

Clearly, innovative thinking is needed to provide sufficient evidence of clinical efficacy in this rare disease. An example of such thinking is demonstrated with isavuconazole, the most recently developed agent for the treatment of mucormycosis (in patients where amB treatment was inappropriate). This agent was approved based on a single Phase 3, open-label, multicentre clinical study in 38 patients, a review of data from three published amB-based studies considered appropriate for an external comparison of overall response rates, and an analysis based on case-matching each patient who received primary therapy with isavuconazole in the open-label study with patients from the Fungiscope Registry Database [12] who received primary therapy with amB for proven or probable mucormycosis [11].

Summary

In summary, new and more effective treatments are needed to treat patients with mucormycosis, particularly in countries where large numbers of patients are at increased risk due to poorly controlled diabetes, such as India, and especially in light of the exacerbating effects of concomitant COVID-19. Whilst conducting clinical trials in this indication is problematic, they are achievable with the right approach and an innovative development programme.

tranScrip's Infectious Disease team has considerable experience in development and registration of antifungal agents, including isavuconazole and many developmental agents. If you would like assistance with your development programme, please contact us on 0118 963 7846 or email us info@transcrip-partners.com.

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