Reply to Dr Yong

Sir: We appreciate Dr Yong’s interest in our article [1] and agree that voriconazole is an attractive option in the treatment of refractory cryptococcosis. Our case sought to emphasize the importance of therapeutic drug monitoring (TDM) and pharmacokinetic assessment when voriconazole is co-administered with ritonavir and to describe the use of IFN-γ in the treatment of refractory cryptococcosis.

The case reports listed by Dr Yong are illustrative of the potential efficacy of voriconazole in the treatment of cryptococcosis. However, they may be subject to reporting bias and may not accurately capture the overall efficacy of what remains a salvage regimen. In vitro and murine models of cryptococcal meningitis have, in fact, shown the potential efficacy of voriconazole, yet the efficacy observed in the largest description of the use of voriconazole in the treatment of invasive cryptococcosis was only 38.9% of all patients [2]. This low response rate was likely secondary to the high number of patients with concomitant AIDS and despite the low reported overall efficacy, 89% had stable disease and 94% were alive 90 days after the initiation of treatment.

We believe the treatment of refractory or relapsing cryptococcal meningitis should include: (1) attempts to improve the immune status of the host (reduce immunosuppressants or institute antiretroviral therapy); (2) repeat induction therapy with fluconazole and a lipid formulation of amphotericin B and increase the dose of amphotericin B if lower doses were initially given; (3) optimize the management of increased intracranial pressure; (4) perform antifungal susceptibility testing of cryptococcal isolates; and (5) consider use of adjunctive agents such as interferon-γ.

We agree that a comparative trial of voriconazole versus standard therapy for cryptococcal meningitis would be of interest. However, prior studies comparing other triazoles (fluconazole) to standard induction therapy were disappointing [3]. The results of the latter study are difficult to extrapolate to current practices as lower doses of both fluconazole (200 mg) and amphotericin B deoxycholate (0.4 mg/kg) were given. The lower mean inhibitory concentrations (MICs) of Cryptococcus isolates to voriconazole as compared to fluconazole may allow this agent to become first-line therapy and potentially avoid the hematologic and nephrotoxicity of amphotericin B containing regimens, but these trials seem unlikely to be conducted. Without the availability of further data we concur with the current IDSA guidelines [4] that voriconazole should be reserved for use in the salvage setting.

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References