Sertraline for HIV-associated cryptococcal meningitis

Joshua Rhein and colleagues[1] used measurements of sertraline plasma concentrations and the minimum inhibitory concentrations (MICs) for sertraline to determine the probability of achieving therapeutic sertraline concentrations in the brains of patients with cryptococcal meningitis. As mentioned by Joseph Jarvis and colleagues in the accompanying Comment,[2] no clear dose-response relation between the sertraline dose and early fungicidal activity was found. In the study, fluconazole concentrations and MICs of fluconazole were not measured. A currently accepted breakpoint for fluconazole against *Cryptococcus neoformans* is 2 mg/L or lower,[3] with an area under the concentration-time curve over 24 h divided by the MIC of at least 389 associated with a favourable outcome.[3] However, it is predicted that monotherapy with 1200 mg of fluconazole per day results in sufficient drug exposure in only two-thirds of patients; this proportion will be considerably lower when 800 mg fluconazole per day is used.[3] Therefore, we would encourage the authors to determine fluconazole concentrations and the in-vitro fluconazole susceptibility of the *Cryptococcus* spp isolates and verify whether fluconazole exposure was sufficient and could help to explain their results.

We agree with the authors that further investigation of adjunctive sertraline for cryptococcal meningitis in randomised clinical trials is justified. In addition to trials in combination with amphotericin, sertraline could have a role in the development of more effective oral therapy and randomised controlled trials in combination with high-dose fluconazole should be considered. Oral therapies are desirable for resource-poor settings and to treat asymptomatic antigenaemia, where they might have cost and tolerability advantages.[4] Thus, better understanding and optimisation of exposure to fluconazole and adjunctive sertraline could lead to a promising treatment of cryptococcal meningitis.

To achieve this, dried blood spot sampling could be used to determine individual patient drug exposure and thus tailor the dose of oral drugs in relation to the MIC of their isolate. We have shown that dried blood spot sampling (based on simple fingerprick blood collection) has high sample stability allowing accurate determination of fluconazole drug concentrations.[5] Additionally there is little biohazard risk during transportation of the samples. With a full oral regimen, a new treatment regimen might be ready for evaluation in a randomised controlled trial for cryptococcal meningitis in resource-limited settings.

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Authors' reply

We agree with Anette Veringa and colleagues regarding the importance of pharmacological analyses in the assessment of antifungal efficacy for cryptococcal meningitis treatment. Yet, we caution the translation of single-drug pharmacological analyses to combination therapy. Fluconazole 800 mg/day monotherapy as induction therapy for cryptococcal meningitis has poor outcomes: fluconazole's area under the curve (AUC) exposure is suboptimal with respect to the cryptococcus minimum inhibitory concentration (MIC).[1] This concern is certainly justified in the setting of our research, in which we have observed a decrease in fluconazole susceptibility over time. In our analysis[2] of the first 95 of the 128 cryptococcus isolates reported in our trial,[3] only 24 (25%) had MICs equal to or less than the 2 μg/mL breakpoint, 47% were 4 μg/mL or less, and 78% were 8 μg/mL or less.[2]

However, our sertraline trial,[3] examined the use of combination induction therapy with ampho tericin B, fluconazole, and sertra line. We did measure plasma samples (n=99) between day 7 and 28 from participants who were receiving fluconazole 800 mg/day (appendix). The median plasma concentration of fluconazole at steady state was 37 μg/mL (IQR 24–51; 95th percentile 72), equating to a median AUC of 990 μg × hr/mL (720–1260). Day 14 fluconazole cerebrospinal fluid (CSF) concentrations (n=39) were similar to those measured in plasma (median 39 μg/mL [IQR 28–53], 95th percentile 69); the concentrations in CSF were a median 90% (IQR 68–115) of steady state plasma concentrations (n=24). The median fluconazole AUC-to-MIC

See Online for appendix