New US Food and Drug Administration Approvals Decrease Generic Flucytosine Costs

TO THE EDITOR—Flucytosine is a key component to induction therapy for cryptococcal meningitis. In December 2015, Merry et al reported that the US cost of 14 days of flucytosine was more than \$27 000, in stark contrast to the UK cost of \$300 [1]. In the past year, the US Food and Drug Administration approved 3 new generic flucytosine formulations, and the flucytosine average wholesale price has come down by 78% to \$5900 for a 14-day course for a 70-kg patient. While still significantly more expensive than that in Europe, flucytosine is now more affordable to US payers.

We previously estimated that a 2-week US hospitalization for cryptococcal meningitis costs $\geq$ \$50 000 [2]. The Centers for Disease Control and Prevention estimates that in 2016, 18 160 persons were diagnosed with AIDS in the United States and that in 2014, there were 6712 deaths attributed to human immunodeficiency virus (HIV)/AIDS [3]. If even 5% of those deaths were due to cryptococcal meningitis, the hospitalization costs for this population would be approximately \$16.8 million. Instead, one could screen each of those 18 160 persons with AIDS for cryptococcal antigen (CrAg) and preemptively treat those CrAg+ to prevent fulminant meningitis. Yet the current World Health Organization recommendation for preemptive treatment with fluconazole monotherapy is suboptimal, with a 25% failure rate among asymptomatic CrAg+ persons [4].

Enhancement of preemptive therapy for asymptomatic CrAg+ persons is needed. Short of daily amphotericin infusions, 2 hypothetical possibilities exist for preemptive therapy for asymptomatic CrAg+ persons, extrapolating from

meningitis therapy. An appealing all-oral regimen would be fluconazole and flucytosine [5]; however, the US cost of flucytosine is still quite high. One other unproven regimen that is being investigated for preemptive treatment of asymptomatic CrAg+ persons is single-dose liposomal amphotericin B (10 mg/kg) in addition to high-dose fluconazole (800 mg daily for 2 weeks, followed by 400 mg daily for 8 weeks, followed by 200 mg daily for 6 months). In a phase 2 trial of cryptococcal meningitis, 1 dose of 10 mg/kg appeared as effective as 14 days of therapy [6]. Single-dose 10-mg/kg liposomal amphotericin for preemptive treatment for asymptomatic CrAg+ persons would cost approximately \$2300 for a 70-kg patient. Thus, to screen 18 160 US persons with AIDS could cost as much as \$272 400 (conservatively assuming a CrAg test of \$15 per person). Assuming that only 1% (181/18 160) of asymptomatic CrAg+ are eligible for preemptive treatment, the cost of liposomal amphotericin for this group would be \$416 300. In total, the cost of CrAg screening and treatment would be approximately \$700 000, or 4% of the overall cost of meningitis hospitalization.

More effective regimens to prevent fulminant cryptococcal meningitis are needed. More prospective studies to investigate the benefits of CrAg screening in the US HIV population are needed. While the cost of flucytosine has come down by 78% in the United States, flucytosine remains completely inaccessible in sub-Saharan Africa where the burden and mortality from cryptococcal meningitis is the greatest. Low- and middle-income countries represent a large untapped commercial market for flucytosine manufacturers.

Notes

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Radha Rajasingham and David R. Boulware

Division of Infectious Diseases and International Medicine,
Department of Medicine, University of Minnesota,
Minneapolis

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Correspondence: R. Rajasingham, 689 23rd Avenue SE, Minneapolis, MN 55410 (Radha@umn.edu).

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Reply to Rajasingham and Boulware

TO THE EDITOR—In 2015 there was widespread outrage after the *New York Times* publicized the 5000% increase in the price of pyrimethamine (Daraprim) by Turing Pharmaceuticals, a drug used primarily to treat toxoplasmosis in patients with advanced human immunodeficiency virus (HIV) disease [1].