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Availability of miltefosine for the treatment of kala-azar in India

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Miltefosine, an alkylphospholipid, was registered in India for the treatment of visceral leishmaniasis (kala-azar) in 2002. The identification of miltefosine was an important therapeutic advance because it is the first effective oral agent for treating kala-azar, including infection that is resistant to conventional therapy with pentavalent antimony (1, 2), and it has opened the door to outpatient management. However, these clinical advances are being undermined and action is required.

India carries approximately 50% of the world’s burden of kala-azar. Ninety per cent of cases of kala-azar in India occur in people living in poverty in rural Bihar State where daily family income is approximately US\$ 1; infection there remains epidemic and transmission (anthroponotic) is high (1–4). Bihar is also the only endemic region where large-scale resistance, probably the result of years of suboptimal treatment (4), has ended the usefulness of antimony treatment (4). Thus, approximately 45% of the world’s kala-azar patients are in a precarious position.

In Bihar, most patients with kala-azar are expected to purchase the treatment drug themselves. The cost of miltefosine, initially US\$ 200 per 28-day course of treatment and now US\$ 145, has predictably either prevented access for many impoverished patients, or encouraged purchase of small sup-

plies of the drug — often just enough treatment to allow the patient to begin to feel better and return to work or school. That individuals can buy as much of the drug as they can afford reflects the Indian system of drug dispensing — miltefosine is now widely available over the counter without prescription or restriction on the quantity dispensed.

Regulatory authorities must act now to end the above-mentioned practices and firmly regulate this critically important antileishmanial drug. Miltefosine should be prescribed only by qualified physicians, experienced in kala-azar management, after a proper diagnosis has been established, and it should be provided in a controlled manner at government-designated outlets. A form of directly observed therapy, similar to that already well-established in India for tuberculosis, could be instituted rapidly, ideally with government-purchased miltefosine. The need for this type of logical mechanism is underscored by the experience at one centre in Bihar which enrolled 367 of 1167 participants in India’s first outpatient miltefosine trial. Despite monitoring adherence and distributing 1 week’s supply of medication at a time for 4 weeks, 10 patients discontinued their treatment early or were lost to follow-up and 23 (6%) apparent responders subsequently relapsed — yielding a 92% cure rate at this centre

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(S. Sundar, unpublished data). If this 8% overall failure rate is confirmed in the final study analysis, it would represent a disturbing doubling of the 3% failure rate observed in the strictly-monitored, phase 3 study in inpatients (1). This situation also underscores the need to develop strategies for using miltefosine in combination with other drugs to reduce the likelihood of developing resistance.

Consideration of the already voiced concerns about the potential development of resistance to miltefosine (5) and the experience with, and loss of usefulness of, pentavalent anti-

mony in Bihar (4), shows that unrestricted use of miltefosine needs to end. Although not a simple undertaking, we believe that now is the time to pull back and provide miltefosine through a strictly supervised public distribution system, free of charge in accordance with the prevailing national policy on the treatment of visceral leishmaniasis, lest the only oral (and therefore precious) antileishmanial drug becomes another therapeutic relic in India. ■

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