J Parasit Dis (July-Sept 2016) 40(3):1094–1095
DOI 10.1007/s12639-014-0607-3

TECHNICAL NOTE

Treatment of visceral leishmaniasis: anomalous pricing and distribution of AmBisome and emergence of an indigenous liposomal amphotericin B, FUNGISOME

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Received: 5 September 2014 / Accepted: 18 October 2014 / Published online: 1 November 2014

Abstract Visceral leishmaniasis (VL) is one of the severest forms of parasite borne diseases worldwide with a mortality rate second only to malaria. Treatment of VL patients with currently available chemotherapeutic agents poses problems of large scale failure, toxicity, prolonged hospitalization time, high treatment cost and drug resistance. However, most of these problems can be overcome by the use of liposomal formulations of Amphotericin B (L-AmB). Of the two L-AmBs currently available in Indian market, AmBisome is imported and FUNGISOME is indigenous. Initially AmBisome remained exorbitantly costly and therefore inaccessible to most of the VL patients. However, with the launch of FUNGISOME in India, Gilead in agreement with WHO started a donation program of AmBisome in developing countries through a slashed price of US $18 per vial. The price reduction is, however, restricted to clinical trials thus eluding majority of the VL patients. In fact, India was not included in this program and AmBisome was sold in Indian market at prices higher than the WHO proposed price of US $18 per vial. FUNGISOME, on the other hand, produced consistently good results against VL both clinically and experimentally. In the context of unavailability and price anomaly of AmBisome, successful emergence of FUNGISOME could mark it as the major L-AmB against VL.

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Keywords Visceral leishmaniasis · Treatment · Liposomal amphotericin B · Fungisome · AmBisome · Pricing

Visceral leishmaniasis (VL) or kala-azar, a deadly and disseminated infection of the lymphoreticular system, is caused by the protozoan parasites of *Leishmania donovani* complex. An estimate of 0.2–0.4 million global VL cases are reported each year with more than 90 % of them occurring in India, Bangladesh, Sudan, South Sudan, Brazil and Ethiopia (Alvar et al. 2012). In India, the state of Bihar, parts of Eastern Uttar Pradesh and West Bengal are endemic foci of VL (Verma et al. 2010) with an estimated annual incidence (cases from 2004 to 2008) ranging from 146,700 to 282,000 and mortality rate of 2.4 % (853/34,918) (Alvar et al. 2012).

Conventional therapy for VL consists of pentavalent antimony but since 1990 there was a large scale failure of antimony treatment in the state of Bihar. This led to the introduction of Amphotericin B (AmB) as an active antileishmanial agent with long term cure rate of ~98 %. However, the major disadvantage of this drug is its toxic side effects which could be significantly reduced by the introduction of liposomal formulation of Amphotericin B (L-AmB). Among the different L-AmB formulations studied, AmBisome can produce a cure rate of 89–100 % in Indian subcontinent depending on the doses administered (Mondal et al. 2010). Of the two L-AmBs that have established safety and efficacy through clinical trials, AmBisome is imported and FUNGISOME is indigenous and would be economical for control programs. Following the launch of FUNGISOME in 2003, Gilead Sciences of UK announced WHO negotiated prices of AmBisome (US $20 per vial in 2006, then US $18 per vial in 2008) to

increase access to L-AmB in developing countries notably in MSF (Médicines Sans Frontiérs) and DNDi (Drugs for Neglected Disease initiative) projects (Gilead sciences 2013). However, AmBisome available at slashed prices is only through the WHO/Gilead donation program (Monge-Maillo and López-Vélez 2013) intended for clinical trials remaining otherwise inaccessible to majority of VL patients. In December 2011 Gilead Sciences signed an agreement with WHO to commit donation of 445,000 vials of AmBisome over a period of 5 years (approximately 4240–8,900 patients per year depending on total dose/patients) starting 2012 in eligible countries in East Africa (Sudan, South Sudan, Ethiopia and Kenya) and South Asia (Bangladesh and Nepal). Although India has the highest VL burden representing 25 % of global VL cases, it is an irony that they are not included in this donation program according to published reports (WHO 2013). However, this charity to less than 1 % of the total patients for a limited period of 5 years (MSF statement 2011) impacted undermining and pre-empt India's own superior alternative FUNGISOME whose development was supported through R&D funding from DBT and PATSER (*Program Aimed at Technological Self-Reliance*) of DSIR.

In fact, in India AmBisome kept on selling at prices much higher than the WHO proposed price of US $18 (roughly equivalent to Rs. 1,100/-) per vial. This price anomaly in addition to the limited supply of AmBisome for MSF, DNDi or other WHO mentioned VL programs encouraged the development and application of FUNGISOME and as the efforts continued the outcome of various clinical trials (Bodhe et al. 1999) and studies (Mondal et al. 2010) of VL treatment with FUNGISOME in the last 20 years has always been most promising. Considering all these facts FUNGISOME could be looked upon as a potential alternative to AmBisome not only in India but also from a global point of view.

Acknowledgment Financial supported by Indian Council of Medical Research (ICMR), India and Council of Scientific and Industrial Research (CSIR), India.

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