

Chemotherapeutics of visceral leishmaniasis: present and future developments

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(Received 28 May 2017; revised 2 October 2017; accepted 3 October 2017; first published online 7 December 2017)

SUMMARY

Treatment of Visceral Leishmaniasis (VL), a neglected tropical disease, is very challenging with few treatment options. Long duration of treatment and drug toxicity further limit the target of achieving VL elimination. Chemotherapy remains the treatment of choice. Single dose of liposomal amphotericin B (LAmB) and multidrug therapy (LAmB + miltefosine, LAmB + paromomycin (PM), or miltefosine + PM) are recommended treatment regimen for treatment of VL in Indian sub-continent. Combination therapy of pentavalent antimonials (Sb^v) and PM in East Africa and LAmB in the Mediterranean region/South America remains the treatment of choice. Various drugs having anti-leishmania properties are in preclinical phase and need further development. An effective treatment and secondary prophylaxis of HIV-VL co-infection should be developed to decrease treatment failure and drug resistance.

Key words: Amphoterecin B, Kala-Azar, Miltefosine, Paromomycin, Visceral leishmaniasis.

INTRODUCTION

Visceral leishmaniasis (VL) is one among the various neglected tropical diseases caused by an obligate intracellular protozoan *Leishmania donovani* and transmitted in Indian subcontinent by the bite of *Phlebotomus argentipes* (Sand fly) (Singh *et al.* 2014). Around 0.2–0.4 million cases are reported globally. Among these, more than 90% of cases are confined to six countries: India, Bangladesh, Sudan, South Sudan, Brazil and Ethiopia (Alvar *et al.* 2012). A joint memorandum was signed in 2005 by governments of India, Nepal and Bangladesh to eliminate VL with the aim to reduce its incidence by 2015 to less than 1 per 10 000 people at sub-district level. However, this target has been recently extended to 2017 (Singh *et al.* 2016). Another collaborative disease eradication programme, the London Declaration on Neglected Tropical Diseases was launched on 30 January 2012 in London. It was inspired by the World Health Organization 2020 roadmap to eradicate or prevent transmission of neglected tropical diseases (London Declaration*). The emergence of co-infection with HIV in VL is one of the major challenges, which makes treatment more complex and increase the chances of drug resistance. Initially, HIV-VL cases were seen from south-western Europe, but now cases are on increase in Ethiopia, South Asia and Brazil. Co-infection has been reported from more than 35 countries (Alvar *et al.* 1997, 2008;

Desjeux and Alvar, 2003). The prevalence of human immunodeficiency virus (HIV) in Bihar, India (which, till recently, accounted for 40% of world's burden of VL) is considered low (0.2–0.3%) (NACO report 2014[#]). Around 2.4% of all VL patients of age ≥ 14 years were unknowingly found to be co-infected with HIV in an Indian study (Burza *et al.* 2014a).

VL clinically manifests as prolonged fever, hepatomegaly, splenomegaly, pancytopenia, progressive anaemia and weight loss and is fatal without treatment. About 50% of patients in Sudan and 1–3% in India after recovery of VL develop a cutaneous manifestation in the form of indurated nodules or depigmented macules known as post kala-azar dermal leishmaniasis (PKDL). These cases are difficult to treat and also serve as a reservoir of *leishmania* (Mukhopadhyay *et al.* 2014).

With no effective vaccine available, the only option for treatment of VL remains chemotherapy. With a limited inventory of drugs and emerging drug resistance, the treatment of VL remains challenging.

Chemotherapy of VL

Pentavalent antimonials (Sb^v). Sodium stibogluconate (SSG) and meglumine antimoniate (MA) are two forms of available Sb^v. It is given in doses of 20 mg kg⁻¹ subcutaneously for 28–30 days. With emerging resistance to this drug in Bihar and adjoining areas of Nepal alternative treatment strategy has been adopted for these areas (Sundar *et al.* 2000; Rijal *et al.* 2003). Its efficacy has been also found to be low in HIV-VL co-infected patients when

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compared with immunocompetent VL patients (Ritmeijer *et al.* 2006). However, in east Africa SSG monotherapy is still effective with 6 month cure rate of 93.9% (Musa *et al.* 2012). It was recommended by WHO as first-line drug for treatment of VL in east Africa along with the combination of SSG-Paromomycin (PM) as the first-line treatment of VL patients in Eastern Africa (WHO, 2010).

Its use is further limited by associated life-threatening toxicities like cardiac arrhythmias, prolonged QT interval (QTc), ventricular premature beats, ventricular tachycardia, ventricular fibrillation and torsades de pointes. Other adverse effects include arthralgia, myalgia, increased pancreatic and liver enzymes (Sundar and Chakravarty, 2015b).

Amphotericin B and liposomal Amphotericin B

In the Indian subcontinent for the treatment of VL, Amphotericin B deoxycholate is recommended at doses of 0.75–1.0 mg kg⁻¹ given for 15–20 intravenous infusions. For PKDL, AmB is recommended at a dose of 1 mg kg day⁻¹ up to 60–80 intravenous infusions for 4 months (Mishra *et al.* 1992; Thakur, 1997; Thakur *et al.* 1999). Its toxicity profile includes infusion reactions (in most patients), nephrotoxicity, hypokalemia, myocarditis and occasional death, which mandate close monitoring. This along with prolonged hospital stay escalates the cost of therapy. The lipid formulation of AmB has been developed to minimize side effects and for delivery of drug at large daily doses. Liposomal amphotericin B (AmBisome; Gilead Sciences; LAmB), amphotericin B lipid complex (ABLc; Abelcet, Enzon pharmaceuticals) and amphotericin B colloidal dispersion (ABCD; Amphotec, InterMune Corp.) and several generic formulations are available with LAmB being the only drug, which has US FDA approval. Various trials on LAmB has been shown in Table 1.

There is considerable geographical variation in the total LAmB dose (Sundar and Chakravarty, 2015b). In the Mediterranean region and South America, 18–21 mg kg⁻¹, administered in various regimens, has been recommended (Sundar and Chakravarty, 2015b; Davidson *et al.* 1996; Freire *et al.* 1997; Syriopoulou *et al.* 2003; Gradoni *et al.* 2004). Single dose of 10 mg kg⁻¹ has been shown to cure >95% VL cases in India (Sundar *et al.* 2010). Another study showed that when 20 mg kg⁻¹ of LAmB was given over 4–10 days, relapse rate was 2.4% (Burza *et al.* 2014b). In Bangladesh, 10 mg kg⁻¹ single dose of LAmB cured 97% patients (Mondal *et al.* 2014). In another study, LAmB in three doses of 5 mg kg⁻¹ each (total 15 mg kg⁻¹) had a cure rate of >95% (Lucero *et al.* 2015). In Sudan, LAmB is required a much higher dose, when given at 30 mg kg⁻¹ over 10 days in primary VL cases, showed initial cure rate at 6 months of 92% with treatment

failures, deaths and relapses of 1, 5 and 7%, respectively. In relapsed VL cases the initial cure was 94%, treatment failed in 4%, 1% died and 10% relapsed. Six percent were slow responders requiring 50 mg kg⁻¹ of LAmB (Salih *et al.* 2014). In Europe, the total dose of 18–21 mg kg⁻¹ is considered adequate (Sundar and Chakravarty, 2013).

However, high cost remains the limiting factor for widespread LAmB use in most of the endemic regions. This was addressed by an agreement for preferential pricing with WHO (agreement between Gilead and WHO for donation of LAmB till 2020), which reduced the price of LAmB to \$18 per 50 mg vial for endemic areas of developing countries (Moon *et al.*). Following this, a study was conducted in India in which LAmB was used in a single dose of 10 mg kg⁻¹ and compared with the conventional AmB administered in 15 infusions of 1 mg kg⁻¹, given every other day during 29 days of treatment. At 6 months, cure rates were comparable in the two groups: 95.7% (95% CI 93.4–97.9) in the liposomal-therapy group and 96.3% (95% CI 92.6–99.9) in the conventional-therapy group (Sundar *et al.* 2010). The decreased treatment cost and hospital stay made liposomal preparation as single infusion an excellent option for treatment of VL in the Indian subcontinent. It has been suggested by the WHO Regional Technical Advisory Group (WHO, 2009) and the WHO Advisory Panel for Leishmaniasis Control (WHO, 2010) to use single dose LAmB as the first line drug for the VL elimination program in the Indian subcontinent. The 10 mg kg⁻¹ single dose regimen is being used in by the Control Programmes of India, Nepal and Bangladesh.

However, in East Africa low efficacy of LAmB in a randomized controlled trial lead to its midway termination when given as a single dose of 7.5, 10 mg kg⁻¹ body weight, or multiple doses on days 1–5, 14 and 21. Definitive cure at 6 months was 85, 40 and 58% in patients treated with multiple doses, and single doses of 7.5 or 10 mg kg⁻¹, respectively (Khalil *et al.* 2014).

An indigenous liposomal amphotericin B (Fungisome, developed by an Indian company Lifecare Innovations, Gurgaon, Haryana, India) was tested in a phase 2 study in two cohorts, cohort 1: 10 mg kg⁻¹, cohort 2: 15 mg kg⁻¹. The Initial cure rate of 100% at day 30 and a definitive cure rate of 93.3% at the 6-month follow-up was achieved in both the cohorts (Sundar *et al.* 2015).

For HIV-VL co-infection, LAmB is given at doses of 4 mg kg⁻¹ for 10 doses (days 1–5, 10, 17, 24, 31 and 38) up to a total dose of 40 mg kg⁻¹ (WHO, 2010). Various trails using LAmB for HIV-VL is shown in Table 1.

In a study in Bihar, when intravenous LAmB (20–25 mg kg⁻¹) was administered to 159 VL/HIV co-infected patients (both primary infections and

Table 1. L-AmB trials in VL and HIV-VL co-infection

| Serial no. | Type of study | Author | Dose used | Overall cure rate percentage (%) | Disease |
|------------|---|--------------------------------|--|----------------------------------|---------|
| 1 | Randomized open study | Thakur <i>et al.</i> (1996) | 2 mg kg day ⁻¹ on day 1, 2, 3, 4, 5, 6 and 10 <i>vs</i> days 1, 2, 3, 4 and 10 | 100 | VL |
| 2 | Randomised | Thakur (2001) | 15 mg kg ⁻¹ single dose (i.v) | 100 | VL |
| 3 | Open label, dose finding | Sundar <i>et al.</i> (2001) | 5 mg kg ⁻¹ (single dose) <i>vs</i> 1 mg kg ⁻¹ for 5 days (iv) | 91 <i>vs</i> 93 | VL |
| 4 | Randomized, dose ranging, multicenter | Sundar <i>et al.</i> (2002b) | 0.75 mg kg day ⁻¹ for 5 days (i.v) <i>vs</i> 1.5 mg kg day ⁻¹ for 5 days (i.v) <i>vs</i> 3 mg kg days ⁻¹ for 5 days (i.v) | 89 <i>vs</i> 93 <i>vs</i> 96 | VL |
| 5 | Open label non comparative study | Sundar <i>et al.</i> (2003) | 5.0 mg kg day ⁻¹ for 5 days (i.v) | 90 | VL |
| 6 | Observational cohort | Sinha <i>et al.</i> (2010) | 5.0 mg kg day ⁻¹ (i.v) on 0, 1, 4, and 9 | 98.8 | VL |
| 7 | Retrospective, multicenter | Di Masi <i>et al.</i> (2014) | Variable (40.8 ± 6.7 mg kg ⁻¹ for 12.0 ± 3.4 days) | 72 | HIV-VL |
| 8 | Retrospective, non-comparative, multicentre | Sinha <i>et al.</i> (2011) | 20–25 mg kg ⁻¹ on day 1, 2, 5, 10, 15 (fifth dose for relapsed cases) | 78.2 | HIV-VL |
| 9 | Retrospective, non-comparative, multicentre | Ritmeijer <i>et al.</i> (2011) | 30 mg kg ⁻¹ in six doses of 5 mg kg ⁻¹ alternate day | 66.1 | HIV-VL |
| 10 | Prospective non-comparative, multicentre | Russo <i>et al.</i> (1996) | 4 mg kg ⁻¹ for 10 doses (days 1–5, 10, 17, 24, 31 and 39) | 80 | HIV-VL |
| 11 | Prospective, non-comparative, single centre | Molina <i>et al.</i> (2007) | 4 mg kg day ⁻¹ for 5 days followed by one per week for 5 weeks | 50 | HIV-VL |

relapses) in four or five doses of 5 mg kg⁻¹ over 4–10 days, the estimated relapse risk at first year, second year and fourth year was 16.1, 20.4 and 25.9%, respectively (Burza *et al.* 2014c).

In a study in India, excellent initial response was seen with LAmB (a total dose of 20–25 mg kg⁻¹ in 4–15 days) combined with antiretroviral therapy; however, the probabilities of VL relapse after treatment were 0, 8.1, and 26.5% at 6 month, 1 and 2 years, respectively (Mahajan *et al.* 2015). In a retrospective study in Bihar, India, a combination of LAmB and miltefosine was tested in 102 HIV-VL co-infected patients. LAmB was given at doses of 30 mg kg⁻¹ divided into six infusions on alternate days, along with oral miltefosine for 14 days. At 6, 12 and 18 months follow-up, the cumulative incidence of all-cause mortality was 11.7, 14.5 and 16.6%, respectively. Relapse rates were 2.5, 6.0, 13.9%, at 6, 12 and 18 months, respectively (Mahajan *et al.* 2015). Secondary prophylaxis is also important and found to be effective in HIV-VL co-infected patients as with other opportunistic infections. It has been shown that Amphotericin B lipid complex (3–5 mg kg⁻¹ per dose once) every 3 weeks for 12 months has 22% relapse rate as comparison with 50% in patients devoid of secondary prophylaxis at 1 year (Lopez-Velez *et al.* 2004). LAmB at dose of 5 mg kg⁻¹ administered every third week has been also studied for use as secondary prophylaxis with relapse-free probability of 89.7, 79.1, 55.9 and 55.9% at 6, 12 months, 24 and 36

months, respectively (Molina *et al.* 2007). In a retrospective study from eastern India (2005–2015), the protective efficacy of monthly amphotericin B (AmB) for secondary prophylaxis in patients with HIV–VL coinfection was done. Secondary prophylaxis was provided in 27 HIV-VL with monthly 1 mg kg⁻¹ AmB (15 liposomal, 12 deoxycholate). At 6 month, none in secondary prophylaxis group relapsed or died. Secondary prophylaxis remained the sole significant predictor against death in multivariate Cox regression. HIV–VL patients had higher 6-month relapse rate, less relapse-free 12-month survival and higher mortality than VL mono-infection. (Goswami *et al.* 2017).

Miltefosine. Miltefosine, an alkylphospholipid compound, was the first effective oral anti-leishmanial drug in VL. Following a phase III trial, miltefosine was registered in India as a first oral antileishmanial drug in 2002. The cure rate of 94% was seen with 50–100 mg day⁻¹ of miltefosine given for 28 days (Sundar *et al.* 2002a). Another phase 4 study showed a cure rate of 95% (Bhattacharya *et al.* 2007). Because of its high efficacy and ease of administration, it was adopted by VL elimination programme in India, Nepal and Bangladesh (Sundar *et al.* 2008a). Unfortunately, after a decade of its use, the efficacy decreased and there was doubling of relapse rate (Sundar *et al.* 2012; Burza *et al.* 2013). In Nepal, relapse rates of 10.8 and 20% were seen at 6 and 12 months,

respectively (Rijal *et al.* 2013). The cure rate of only 85 and 75.8% was found in studies in Bangladesh and Ethiopia, respectively (Ritmeijer *et al.* 2006; Rahman *et al.* 2011). Similarly, for PKDL, miltefosine at doses of 50 mg thrice daily for 60 days or twice daily for 90 days was found to be effective (Ramesh *et al.* 2011). Another study showed that, miltefosine given as 100 mg day⁻¹ for 12 weeks in PKDL produced high cure rates (Sundar *et al.* 2013). It is recommended for the treatment of PKDL in the Indian subcontinent at the dose of 50–100 mg for 12 weeks (WHO, 2010).

Miltefosine is associated with gastrointestinal adverse events chiefly vomiting and diarrhoea. Occasionally hepatotoxicity and nephrotoxicity might occur. It has a long half-life (~1 week), which renders it vulnerable for the development of its resistance in the parasites. It also has teratogenic potential, so women of child-bearing age are advised contraception for the duration of treatment and for three additional months after the end of therapy (Sundar and Chakravarty, 2015b).

Paromomycin (aminosidine). Paromomycin (PM) is an aminoglycoside antibiotic, which act by interference with protein synthesis in the ribosome of the target organism and inhibit the respiration (Chawla *et al.* 2011). In a phase II study of VL patients, PM at a dose of 16 mg kg day⁻¹ for 21 days led to cure in 93% (Jha *et al.* 1998). A Phase III trial of PM at a dose of 15 mg kg⁻¹ (11 mg base) for 21 days showed 95% cure rate (Sundar *et al.* 2007). PM was approved by the Indian government for VL treatment in the Indian subcontinent in August 2006. However, PM was found to be ineffective in curing PKDL with the efficacy of only 37.5% (Sundar *et al.* 2014).

In Bangladesh, in an open-label Phase IIIb multicentre study where PM showed a cure rate of 94.2% at 6 months when administered at 11 mg kg⁻¹ (base) intramuscularly once daily for 21 consecutive days (Jamil *et al.* 2015). In a phase II study in Sudan, Ethiopia and Kenya, its efficacy was low compared with SSG alone and the combination of SSG and PM (Hailu *et al.* 2010). In East Africa, PM efficacy was significantly lower than SSG (84.3% *vs* 94.1%) in a multi-centre randomized-controlled trial (Musa *et al.* 2012). In Sudan, in a dose-finding phase II study, PM showed efficacy of 80% (95% CI 56.3–94.3%) and 81% (95% CI 58.1–94.6%) when used for a longer duration (15 mg kg day⁻¹ for 28 days) or at a higher dose of 20 mg kg day⁻¹ for 21 days, respectively (Musa *et al.* 2010). Pain at the injection site, reversible ototoxicity and hepatic transaminitis are common adverse effects. Although low cost of PM is an advantage, its parenteral route of administration limits its use in a control program. Monotherapy also poses a danger for the development of resistance.

Pentamidine. Pentamidine was used as an alternative treatment for refractory VL in India. However, side effects such as insulin-dependent diabetes mellitus and declining efficacy preclude its further usage (Jha *et al.* 1991). Injection site pain, indurations and abscess, nausea, vomiting, myalgia, headache, dizziness, hypotension, syncope, transient hyperglycemia and hypoglycaemia are other adverse effects of this drug (Sundar and Chakravarty, 2015b). It is currently recommended for secondary prophylaxis in HIV-VL co-infection as in a study from Ethiopia revealed relapse-free survival probability of 79 and 71% at 6 months and at 12 months, respectively (Diro *et al.* 2015).

Multidrug therapy. Multidrug therapy advocated for other diseases like malaria, tuberculosis, leprosy, etc. has also been explored for VL treatment. The rationale behind it is to use drugs with synergistic or additive activity making the duration of therapy short with a decrease in drug doses, which lowers the occurrence of adverse effect and treatment cost (Sundar and Chakravarty, 2015b). Further with monotherapy, there is always a higher chance of development of drug resistance.

In Sudan a study showed initial cure rate of 97% with combination therapy of PM at a dose of 15 mg kg⁻¹ (equivalent to 11 mg kg⁻¹ of PM base) plus Sb^v at a dose of 20 mg kg⁻¹ for 17 days compared with cure rate of 92.4% with Sb^v monotherapy given for 30 days (Melaku *et al.* 2007). It became the preferred regime in the region following another large multicentre, trial which showed the comparable efficacy of combination therapy for 17 days with SSG monotherapy (Musa *et al.* 2012). A prospective pharmacovigilance study sponsored by the Ministries of Health, Médecins Sans Frontières (MSF) and Drugs for Neglected Diseases initiative (DNDi) was recently conducted at 12 centres in a cohort from Sudan, Kenya, Uganda and Ethiopia for PM plus Sb^v combination therapy in VL. The initial cure rate was 95.1% with no geographical variation. Thirty-four percent (34%) and 1.96% of patients had at least one adverse event (AE) and serious adverse event (SAE) during treatment, respectively. Mortality occurred in 1.0% of patients. HIV/VL co-infected patients had initial cure rates of 56%, which was significantly lower than that in VL patients without HIV (Kimutai *et al.* 2017).

Combination of miltefosine and LAmB was recently evaluated in Sudan and Kenya where a phase II open-label, the non-comparative randomized trial was conducted. Three regimens [10 mg kg⁻¹ single dose LAmB plus 10 days of SSG (20 mg kg day⁻¹), 10 mg kg⁻¹ single dose LAmB plus 10 days of miltefosine (2.5 mg kg day⁻¹) and miltefosine alone (2.5 mg kg day⁻¹ for 28 days)] were evaluated for efficacy and safety. Although safe, the definitive cure was <90% in all treatment arms so

none regimen was evaluated for phase 3 trials (Wasunna *et al.* 2016).

In a multidrug randomized, non-comparative, group-sequential, triangular design study 181 patients were randomly assigned to 5 mg kg⁻¹ of LAmB alone, 5 mg kg⁻¹ of LAmB followed by MIL for 10 days or 14 days or 3.75 mg kg⁻¹ of LAmB followed by miltefosine for 14 days. When efficacy of all regimens was apparent, 5 mg kg⁻¹ of LAmB followed by miltefosine for 7 days were given 45 additional patients. All groups had similar cure rates (>95%) (Sundar *et al.* 2008b).

In a Phase III study in India, three multidrug regimens were tested (Single injection of 5 mg kg⁻¹ LAmB and 7-day oral miltefosine or 10-day 11 mg kg⁻¹ intramuscular PM; or 10 days each of miltefosine and PM). The cure rate of >97% was found in all the three-drug regimens used (Sundar *et al.* 2011a). The cure rate of 91.9% with a single dose of LAmB 5 mg kg⁻¹ with miltefosine 2.5 mg kg day⁻¹ for 14 days was shown in another study (Sundar *et al.* 2011b).

Combination therapy is also an attractive option for the treatment of PKDL (Ramesh *et al.* 2014). Combination therapy is excellent and effective alternative strategy to decrease the cost of therapy by decreasing duration of treatment, side effect associated with drugs and hospital stay. Moreover, combination therapy delays drug resistance, thus prolongs use of the drugs.

Newer drugs, Immunotherapy and Vaccine development:

The various new compounds at various stages of development have been included in Drugs for Neglected Disease Initiative (DNDi) portfolio as shown in Table 2. Each of them is in preclinical stages.

An alternative approach is to use immunotherapy and/or immunochemotherapy against VL. IFN- γ , a cytokine capable has been found to kill intracellular *Leishmania* by activating macrophages (Murray and Cartelli, 1983). Accelerated clearance of parasite is seen on addition of IFN- γ . Treatment of VL with IFN- γ plus Sb^V showed a cure rate of >80% cure rate (Badaro, 1988; Badaro *et al.* 1990; Sundar *et al.* 1994) and enhanced the clinical efficacy of conventional Sb^V therapy (Sundar and Murray, 1995). Similarly, results were seen in a study in Kenya where Sb^V or Sb^V plus IFN- γ for 30 days was

given in two groups for VL treatment with combination therapy showing quick parasite clearance (Squires *et al.* 1993). In India in a large study, however, low cure rates of 36, 49 and 42% were obtained at 6 months of treatment with 30 days of Sb^V alone, or 30 days of Sb^V plus IFN- γ at dose of 10⁷ U mg day⁻¹, or 15 days of Sb^V plus IFN- γ respectively, with maximum efficacy in immunotherapy group (Sundar *et al.* 1997). Low cure rates in this study led to the stoppage of the development of IFN- γ as an adjunct to anti-leishmania drugs.

No vaccine is recommended for treatment of VL till now. To be an effective vaccine apart from eliciting prolong immunity it should be protective broadly against VL and CL. Infectious Disease Research Institute has developed vaccines such as Leish-F1, F2 and F3 based on selected *Leishmania* antigen epitopes, and has found to be immunogenic and safe in clinical trials with Leish-F2 completed phase 2 study. The Sabin Vaccine Institute is investigating on the immunogenicity by combination of sand fly salivary gland antigen with the recombinant *Leishmania* antigens (Chakravarty *et al.* 2011). Recently, a first-in-human dose escalation Phase I trial to assess the safety, tolerability and immunogenicity of a prime-only adenoviral vaccine (ChAd63-KH) was conducted in 20 healthy volunteers for human VL and PKDL. ChAd63-KH was found to be safe and immunogenic and need further development to emerge as a novel third-generation vaccine for VL and PKDL (Osman *et al.* 2017). Various recombinant antigens have been studied to have a protective role against *Leishmania* infection however limited to experimental level with minimal experience in preclinical human studies.(Connell *et al.* 1993; Gurunathan *et al.* 1997; Stober *et al.* 2005; Rafati *et al.* 2006; Carrillo *et al.* 2008; Noazin *et al.* 2009; Kumar *et al.* 2010; Chakravarty *et al.* 2011; Singh *et al.* 2012; Sundar and Chakravarty, 2015a).

Concluding remarks

With meagre treatment options in chemotherapy and emerging risk of resistance to available drugs, the discovery of new drugs with anti-leishmania activity is the need of the hour. Combination therapy of Sb^V with PM and LAmB are recommended in Africa and Mediterranean region,

Table 2. Newer compounds in pipeline for Visceral leishmaniasis in various stages of development

| Serial no. | Drugs/compound | Stage of development | Reference |
|------------|--------------------------------------|----------------------|-------------------------------------|
| 1 | Nitroimidazooxazine (DNDi-0690) | Translation phase | DNDi (2017) leishmaniasis portfolio |
| 2 | Oxaboroles (DNDi-5421 and DNDi-5610) | Lead optimization | |
| 3 | Oxaboroles (DNDi-6148) | Translation phase | |
| 4 | CGH VL Series 1 | Lead optimization | |
| 5 | Aminopyrazoles | Lead optimization | |

respectively. Newer approaches with other drug combination need to be investigated in these different geographical areas. PKDL patients serve as a reservoir of infection. Shorter and effective treatment is warranted for the success of VL Elimination programme. Drugs for Neglected Diseases Initiative (DNDi) have taken the initiative of finding new novel agents with anti-leishmania agents. Also, the feasibility of use of LAmB at district and public health centre in South Asia has also been explored by DNDi. The burden of HIV VL co-infection in increasing and LAmB found effective in Mediterranean region has limited efficacy in Ethiopia having high HIV-VL co-infection burden. Thus newer treatment regimes for this region need to be explored.

ACKNOWLEDGEMENT

This work was supported by National Institute of Allergy and Infectious Diseases, NIH grant number U19AI074321.

FINANCIAL SUPPORT

This work was supported by the Extramural Program of the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) Tropical Medicine Research Centres [TMRC Grant No P50AI074321].

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