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Options for Effective Treatment of Visceral Leishmaniasis

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Opinion statement

Visceral Leishmaniasis (VL), also known as kala-azar, is caused by several species of *Leishmania*, a protozoan parasite (*Leishmania donovani)* transmitted to humans by the bite of infected phelobotomine argentipes sandflies. VL is a disease of poverty, affecting the poorest of the poor. It is a major cause of morbidity and mortality in some areas (localized). If the infection is left untreated, the patient dies in about 2 years. Several drugs are now available for the treatment of VL. However, some of them are very costly (miltefosine, lipid amphotericin B). Sodium stibogluconate is an effective drug and the backbone of VL treatment for about six decades. Unfortunately, parasites developed resistance against the drug. In some areas in India, for example in North Bihar, approximately 60% of isolates are resistant to this treatment. In addition, the compound exhibits high cardio-toxity, which is an important limiting factor for its use. Based on the new data, which became available, the WHO/SEARO Regional Technical Advisory Group (RTAG) especially constituted for the kala-azar elimination program undertaken by India, Nepal, and Bangladesh in 2005, recommended that miltefosine should be used as the first line drug. However, the RTAG at its meeting in Dhaka (Bangladesh) in 2009 modified the above recommendation and advised that miltefosine should be phased out and replaced by lipid amphotericin B. The decision to switch over to lipid amphotericin B could have been delayed, because the program had already made substantial progress using miltefosine. In view of drug resistance, low compliance, availability and cost, it is imperative that serious efforts should be made to develop new drugs, preferably oral, for the treatment of VL and PKDL.

Introduction

Visceral leishmaniasis (VL) is also known as kala-azar in the Indian sub-continent. The disease causes prolonged fever, splenomegaly, weight loss, and anemia. Untreated patients usually die in about 2 years due to comorbidities including tuberculosis, severe anemia, and malnutrition. On the other hand, treatment using an effective drug and supportive measures, such as correction of severe anemia by blood transfusion, treatment of concurrent infections using suitable antibiotic, deworming, and nutritional support, cures VL patients. Co-infection with HIV poses a tremendous therapeutic challenge. About 10% of VL patients treated successfully develop dermal manifestations known as post kala-azar dermal leishmaniasis (PKDL) in about 1 to 10 years posttreatment. This article briefly describes the development of effective drugs for the treatment of VL and PKDL.

Development of drugs for the treatment of VL

Urea stibamine

Sir Upendranath Brahmachari, an Indian scientist, synthesized Urea stibamine (carbostibamide) in 1922. He established its effectiveness in the treatment of VL and successfully treated a large number of VL patients [1]. Unfortunately, urea stibamine is no longer available after the death of Brahmachari. A valuable effective drug for treatment VL was lost due to lack of proper documentation of the compound.

Stibogluconate

Stibogluconate was used in Sicily for the treatment of VL in 1915. The drug was first used to treat children and then adults. The discovery of stibogluconate is considered a historic landmark in the treatment of VL. Although the cardiac toxicity of this drug is potentially lethal, VL mortality declined remarkably (~10%) when used. It is estimated that worldwide, the drug saved the lives of millions of VL patients [2••]. Stibogluconate became the cornerstone of effective treatment for VL over many decades. However, after decades of successful use, resistance to stibogluconate developed. Initially, when clinicians became aware of the lack of response of VL patients to the drug, attempts were made to overcome unresponsiveness by escalating the dose. Unfortunately, cardiac toxicity also increased. In the Indian state of North Bihar, about 60% of VL patients could not be cured with even escalating the doses of stibogluconate. The drug may be given by intramuscular or intravenous routes. The intramuscular injections are painful.

Miltefosine

The grim situation described above was circumvented when miltefosine, the first ever oral drug, was developed for the treatment of VL. Initially, the drug was developed for the treatment of skin metastasis from breast cancer. The pivotal phase 4 study of miltefosine done in North Bihar, India, showed that miltefosine can be dispensed in field conditions, and patient compliance was reasonably acceptable for the elimination program. Similar was the experience in Nepal and Bangladesh. It was also documented in controlled phase 3 study that the drug-related side-effects were seen mostly in the first week of treatment and included nausea, vomiting, diarrhea, mild fever, and abdominal cramps. To mitigate gastrointestinal side-effects, it was recommended that miltefosine should be given orally after taking food and that the patient should be hydrated with oral rehydration salt solution (ORS). Those VL patients, who are severely anemic, should receive blood

transfusions that will correct anemia and facilitate better tolerance to miltefosine (called "building up" the patient). To prevent the occurrence of untoward side-effects, miltefosine should be given after these measures were completed. The field trial reported that in ~2% of cases treated with miltefosine manifested serious side-effects. Miltefosine was licensed in India, Germany, Bangladesh, and Nepal soon after the drug was available for administration in human.

Paromomycin

The next drug developed in quick succession to miltefosine was paromomycin [3•]. This is an effective injectable aminoglycoside antibiotic given for 21 days. Its efficacy is similar to that of miltefosine, but it has to be administered by intramuscular injections. Paromomycin is an alternative drug to miltefosine for the treatment of VL, especially in women who are unlikely to use or adhere to scheduled doses of the contraceptive. Both miltefosine and paromomycin were developed in India by Indian scientists in collaboration with Zentaris, Germany and OneWorld Health, USA respectively.

Pentamidine

Pentamidine, an effective anti-leishmanial drug, is no longer recommended for the treatment of VL because it may cause irreversible diabetes mellitus [4•] in about 6% of patients treated with the drug. Ketoconazole *(*anti-fungal drug) and anti-tubercular drugs were found ineffective.

Amphotericin B

Amphotericin B is a highly effective anti-leishmanial drug and is available for intravenous infusions only. This drug causes dose-related nephrotoxicity. Amphotericin B has been in use as a second line drug for visceral and mucosal leishmaniasis [5•] patients, especially for those who are refractory to antimonial treatment in the Indian sub-continent and in Latin America. Amphotericin B deoxycholate has been used in India for treatment of VL for several decades as it is highly effective for the treatment of *Leishmania donovani* infection. The drug was promoted as an alternative treatment upon the appearance of significant resistance to conventional pentavalent antimony therapy in North Bihar, India. The drug was administered to treat VL patients by giving one infusion of 1 mg/kg of body weight on alternate days for 15 infusions. It is also used by giving daily infusions 1 mg/kg body weight for 20 days. Amphotericin B is recognized as an alternative effective treatment for kala-azar in India, but it has to be given by intravenous infusions after admitting the patient in a hospital and the duration of the treatment is long. Adverse effects are mild fever, chills, rigor, and diarrhea. These side-effects can be easily controlled by using paracetamol, anti- histamines, and oral rehydration therapy. Nephrotoxicity and ototoxicity are serious toxic effects of the drug and may lead to acute renal shutdown and deafness, respectively.

Liposomal amphotericin B

Lipid formulation of **a**mphotericin B is associated with significantly lower renal toxicity than **a**mphotericin B, which is dose-limiting. It is an effective and well tolerated drug licensed for treatment of VL in India. It is the safest and most efficacious of all anti-leishmanial drugs currently available. In

India and East Africa, it is used mainly to treat resistant cases of VL and VL/HIV/TB co-infections. Adverse effects to **l**ipid amphotericin B may occur, including chills, rigors**,** and fever. The side-effects are controlled with simple anti-histamines and **p**aracetamol**,** respectively. Liposomal amphotericin B is now recommended as first line treatment for VL patients in the kala-azar elimination program undertaken by India, Bangladesh**,** and Nepal in 2005. RTAG held in Bangladesh (2009) recommended to phase-out **m**iltefosine and use single dose of this drug [6••]. Recent studies demonstrate that the efficacy and safety of **l**ipid amphotericin B exceeds 95% for single doses of 5–15 mg/kg. It is argued that, since this drug has an excellent safety profile and is highly effective, it should replace **m**iltefosine. Since this is a single dose treatment, full compliance is ensured. Single-dose indigenous **l**iposomal amphotericin B in the treatment of Indian visceral leishmaniasis was found to be effective and safe [7•].

Combinations

Combination treatments have several advantages over the single-drug regimes. Amphotericin B infusions (1 mg/kg) on alternate days for 30 days was compared with three drug combinations comprising a single injection of 5 mg/kg liposomal amphotericin B plus 7 days of oral miltefosine (50 mg daily) or 10 days of intramuscular injections of paromomycin (11 mg/kg); or 10 days of miltefosine plus paromomycin in an open-label, parallel-groups, non-inferiority, randomized, controlled, clinical trial in two hospital sites in Bihar, India [8••] Patients aged 5–60 years with parasitologically confirmed VL were included in the study. The numbers in the intention-to-treat groups with definitive cure at 6 months were 146 (cure rate 93.0%; CI 87.5–96.3) for amphotericin B alone, 156 (cure rate 97.5%; CI 93.3–99.2) for amphotericin B plus miltefosine, 154 (cure rate 97.5%; CI 93.24–99.2) for liposomal amphotericin B plus paromomycin, and 157 (cure rate 98.7%; CI 95.1–99.8) for miltefosine plus paromomycin. All combinations were non-inferior to the standard treatment in both the intention-to-treat and per-protocol treatments groups. Combination treatments for VL are safe and efficacious and curtails duration of therapy, encouraging adherence, and possibly preventing or delaying emergence of drug-resistant parasites.

Sitamaquine

A phase II study of sitamaquine for the treatment of VL in India has been carried out [9•]. Adverse events that occurred during treatment were nausea, vomiting, and dyspepsia; oral sitamaquine was found to be effective for VL treatment and was well tolerated.

PKDL

Post **k**ala-azar **d**ermal **l**eishmaniasis (PKDL) is an important complication of VL, which is seen in about 10% of treated VL cases in the Indian sub-continent and about 50% in Sudan. While PKDL is self-cured in Sudan, but in the Indian sub-continent it remains for many years, often for life. PKDL, though infrequently, has also been reported in untreated active VL cases. PKDL occurs as macular, papular**,** or nodular lesions in the face, back**,** and other parts of the

body. The macular lesions are often confused with leprosy and is stigmatized. PKDL patients having macular lesions frequently do not seek treatment because of long duration of therapy (administration of several courses of stibogluconate) requiring hospitalization, and this injection is painful when given intramuscularly. Several courses of amphotericin B are also effective. In the context of drug used for treatment of VL, it has been observed that post VL treatment using stibogluconate has higher frequency of development of PKDL. This phenomenon has been observed in Bangladesh. PKDL treatment is usually of long duration, which reduces patients' compliance. Of late, miltefosine has been tried for the treatment of PKDL and was found to be effective, when a 12-week treatment was given [10••] Keeping in view the rapid development of drug resistance, it is imperative to initiate intensive research for development of new, safe, and effective drug for treatment of VL and PKDL.

VL/HIV co-infection

VL patients sometimes get infected with HIV. Since both VL and HIV cause immunosuppression, the condition of the patient deteriorates more rapidly than in those patients with VL alone [11•]. Treatment is less effective in co-infected patients, unless concomitant anti-retroviral treatment is also given; however, relapses are common. Uncommonly, overlapping of VL, HIV, and TB has been reported and poses not only a therapeutic challenge but also may cause drug-drug interactions. Often HIV infections carry the potential to activate a previously undiagnosed case of TB and VL [12••]. These cases may add to the pool of new cases after the elimination goal is achieved.

In conclusion, although several effective drugs are currently available, developing new, safe and effective, cheap, oral drugs to treat kala-azar and PKDL is an urgent necessity In this context, national, and international collaboration and mobilization of resources are expected to hasten new drug development for treatment of VL patients. In view of cost, rapid emergence of drug resistance, this aspect should get priority. The kala-azar elimination program is almost nearing completion, and certainly will reach the elimination target in all the three countries; it will certainly alleviate the tremendous suffering of the people from VL and eliminate a long standing public health problem in the region. We should not shut our eyes after the elimination of VL from the three countries, but it is crucial to remain vigilant for its sustenance.

Compliance with Ethical Standards

Conflict of Interest

Dr. Sujit Bhattacharya and Prabhat Sinha worked for development of miltefosine (zentris) and paromomycin (OneWorld Health Organization), and the funds were received by Rajendra Memorial Research Institute of Medical Sciences, Patna, India. Md Jamal Khan, and Sabahat Azim declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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