

Is shorter treatment of visceral leishmaniasis promising?

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Treatment of leishmaniasis remains difficult, due to the multiplicity of the existing *Leishmania* species, and their often variable susceptibility to available drugs, which are old, toxic and expensive products. Resistance to the existing products is developing in some foci, such as India.

There have been no significant changes in the treatment of leishmaniasis for many years. Since the 1920s, treatment has been based on pentavalent antimonial compounds. Following the increasing incidence of visceral leishmaniasis (VL) cases in immunocompromised patients and the rise of acquired resistance to antimonials, amphotericin B, mainly in its liposomal form, the present trend has been focused on antimonials as a first-line drug for leishmaniasis. Miltefosine, a new oral compound, has shown promising results and appears to be an efficient alternative for the treatment of Indian kala-azar. Other products, such as aminosidine or imidazoles, could find new applications, but there is no really new product in development at present time. Alternative drugs are investigated for many years without passing the step of clinical trials (1).

Visceral leishmaniasis may be treated as soon as diagnosis is completed. The efficiency of treatment is dependent on the evolution duration, advanced stages responding less to antileishmanial drugs.

Treatment requires confirmed first-line products, principally antimonials and amphotericin B.

The conventional treatment is based on a 28-day course of pentavalent antimonial at a dose of 20 mg sb^v/kg per day. A single course is not always sufficient to obtain a complete cure, and should be repeated after a pause. Due to its excellent results, liposomal amphotericin B tends to be used in first intention, with five daily injections (3 mg/kg per injection), and a final injection on the 10th day (total dose 18 mg/kg). Its use is limited by cost in poor countries.

Management of visceral leishmaniasis (VL) cases includes correcting nutritional deficiencies in patients severely wasted, blood transfusion in case of dramatic anemia, and treating with appropriate antibiotics any secondary bacterial infection (2).

Clinical response is slow, the patient becoming afebrile in 4-5 days, other clinical symptoms and biological parameters slowly regressing and evolving to normal. Circulating antibodies progressively decrease and disappear in the end, 6-8 months after patient cure. Relapses are uncommon in immunocompetent patients.

Antimony resistance has reached impressive levels in some Indian foci, where antimony has become inadequate. Alternative treatments include liposomal amphotericin B, miltefosine and aminosidine. Antileishmanial drug combinations could have multiple benefits preventing drug resistance development, reducing the overall dose and duration of treatment. Paromomycin plus

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antimony trial has proven the efficacy and safety of the association. Other combinations are presently being tested, including miltefosine, paromomycin and single dose liposomal amphotericin B (3).

The standard treatment for visceral leishmaniasis (VL), or kala azar, has been a painful 30-day course of intramuscular injections with sodium stibogluconate. In addition to the prolonged regimen, the treatment is associated with serious side effects including pancreatitis, myalgia (muscle pain) and cardiac failure.

Over the past decade, Tropical Disease Research (TDR) and partners in India successfully brought to registration a 28-day oral drug, miltefosine, for visceral leishmaniasis. The only existing oral treatment, miltefosine has proven highly effective in both children and adults. However, at roughly US\$ 72 per treatment, miltefosine is costly.

Now it appears that a shorter, easier and lower-cost treatment for visceral leishmaniasis (VL) may be on the horizon. Preliminary results of a TDR-sponsored clinical trial of AmBisome followed by 14 days of oral miltefosine treatment are very promising.

The trial led by Indian Authorities, one in Varanasi and the other in Patna. The latter is the capital of Bihar, where close to 50% of the Indian subcontinent's visceral leishmaniasis (VL) cases occur.

According to Tropical Disease Research (TDR) scientist, combining one injection of AmBisome with the 14-day miltefosine course appears highly effective as a treatment. This regime also improves patient adherence to the therapy, which helps stave off parasite resistance to the new visceral leishmaniasis (VL) drugs. "Patients tend to feel much better after a short time of taking miltefosine – and then they often stop taking the pills, Which could emerge the resistant organism.

A shorter miltefosine course would be less costly and would reduce gastrointestinal side effects often experienced with the 28-day oral

miltefosine regime. Still, as visceral leishmaniasis (VL) researchers know too well, no single drug regime is a cure-all for this neglected disease of poverty. Active case detection efforts as well as improved access to care, disease surveillance, integrated vector management and social mobilization all are critical (4).

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