Visceral leishmaniasis therapy: statement on the outcome of a meeting

Visceral leishmaniasis is a vector-borne tropical disease that causes 500 000 new cases every year. The disease is strongly linked to poverty and 90% of the cases is in the poorest areas of Bangladesh, Brazil, Ethiopia, India, Nepal and Sudan. If untreated, visceral leishmaniasis is lethal.

The range of drugs available for the treatment of visceral leishmaniasis is limited. It includes pentavalent antimonials (Sb^v), amphotericin B deoxycholate (AB), lipid formulations of amphotericin B, miltefosine (MF) and paromomycin (PM) – all of which have limitations in terms of toxicity, variable efficacy, price and inconvenient treatment schedules. All are parenteral (AB and its lipid formulations by venous infusion, Sb^v and PM by intramuscular injection) except for MF which is administered orally.

Due to the parasite's drug resistance, the most widely used of these drugs – Sb^v – is now of little use in northern Bihar, India, which alone accounts for 50% of the world's burden of visceral leishmaniasis.[1] Resistance to Sb^v has resulted from several concurrent factors, including high drug costs and the absence of functioning health systems, which have led to poor compliance and incomplete treatments. Areas such as Bihar where transmission is anthroponotic (inter-human) are particularly vulnerable to resistance in the absence of an animal reservoir. Thus, resistance could also occur with other drugs.

Sb^v is still useful in the African endemic region but it is potentially toxic and requires 30 days of painful intramuscular injections. In areas of resistance to Sb^v, AB is highly effective but requires hospitalization for clinical and laboratory monitoring during one month of treatment. The formulation of AB in liposomes (L-AB) has been a major advance in the treatment of visceral leishmaniasis since L-AB is very well tolerated and extremely effective, making high-dose short-course treatments possible. However, despite a significant 90% reduction in price, this treatment remains very expensive for endemic countries.

MF is highly effective and has the great advantage of being an oral drug but it has to be administered for 28 days.[2,3] To avoid resistance, adherence must be ensured and administration of MF should take place only under direct observation. Nevertheless, although MF is generally well tolerated, it is potentially teratogenic and should not be used in women who are pregnant or cannot guarantee contraception during the period of treatment and the following two months. PM is effective, safe and very cheap but requires intramuscular injections for 21 days.[4]

Only a small number of new chemical substances will enter clinical trials in the next few years, and it is anticipated that the treatment of visceral leishmaniasis will depend on the

current limited range of drugs for the next 5 10 years. The span of effective use of the current drugs must therefore be prolonged and the further development of drug resistance prevented.

Acknowledging these constraints, the World Health Assembly in 2007 adopted Resolution WHA60.13 on “Control of leishmaniasis”. This resolution encourages “research to find alternative safe, effective and affordable medicines for oral, parenteral or topical administration involving shorter treatment cycles, less toxicity, and new drug combinations”.

A meeting on “Advances in visceral leishmaniasis chemotherapy” was hosted by the Foundation Ramón Areces in Madrid on 18 and 19 June 2009. Those present were: J Alvar and J Jannin (World Health Organization), P Olliaro (WHO/Special Programme for Research and Training in Tropical Diseases), B Pécoul (Drugs for Neglected Diseases initiative), R Chin (Institute of One World Health), R Elcarte (Spanish Agency for International Cooperation), A Lima (Médecins Sans Frontières), S Croft (London School of Hygiene and Tropical Medicine), and S Sundar (Banaras Hindu University, Varanasi, India).

The meeting agreed the following:

1. To urge the manufacturers of Sb^{v}, L-AB, MF and PM to maintain their production in order to avoid shortages, to market these drugs in all endemic countries, and to make them available at the lowest possible price. Manufacturers of diagnostic tools for visceral leishmaniasis, and especially of rapid diagnostic tests, should be urged to do the same.
2. To urge governments to regulate the distribution of antileishmanial drugs in both the private and public sectors in order to avoid inappropriate use that creates a potential risk of emergence of resistance.
3. To encourage investment in long-term support for research in order to discover new drugs and identify the next generation of candidates for drug development, and to develop new rapid diagnostic tests based on parasite components rather than on antibodies.
4. To further the medium-term approach of combination therapy of existing drugs that may:

    reduce the duration and/or total drug doses of treatment, leading to lower toxicity, improved adherence, reduced burden to health systems, and also potentially reduced overall costs of treatment, thereby providing a more cost-effective option;

    prolong the therapeutic lifespan of these drugs and delay the emergence of resistance;[5]

provide an option for severely ill or malnourished patients, and for those coinfected with HIV and *Leishmania*.

5. To ensure that monitoring of side-effects is implemented since patients with potential complications are generally not included in phase III trials.
6. To establish delivery strategies that are effective in the basic circumstances in which the majority of patients live (i.e. with poor access to prevention, diagnosis, treatment and mitigation therapy) and that should, where possible, be integrated into a comprehensive national health plan.

It was further agreed that clinical trials should be conducted to test and optimize drug combinations that will provide various treatment options in the coming years, according to geographical regions and the host status. The success of combination therapy will depend on regional demands and will require region-specific studies. However, governments of the endemic countries are encouraged to facilitate the registration of the different drugs that are already available and to incorporate combination strategies into national policies as quickly as possible, balancing the need for local studies with the urgency of avoiding the emergence of resistance.

Until the drug combinations are available, the more vulnerable drugs – MF and PM – should be safeguarded. Available evidence indicates that L-AB is less prone to parasite resistance and is amenable to short or single-dose treatment regimens in India, which give it undisputable practical advantages despite its relatively higher cost. L-AB's safety and efficacy are especially important in large-scale control or elimination programmes in which the monitoring of patients is difficult.

Participants in the meeting agreed on the priority provision of L-AB monotherapy to patients on the Indian subcontinent until combinations are available. Although PM requires 21 days of injections, it may qualify as an alternative monotherapy since it is currently the cheapest drug on the market. MF monotherapy should not be encouraged at large scale programmes because pilot deployment has showed a low compliance when direct observation treatment (DOT) cannot be ensured. However, it is a very promising candidate for a future combination regimen.[6]

Further studies are needed to establish the most cost-effective use of L-AB in different foci of visceral leishmaniasis, particularly in Africa and Latin America. Considering the devastating effects of visceral leishmaniasis in East Africa, the meeting recognized the urgent need for proof-of-concept clinical studies in that region. Participants further called for immediate use

worldwide of L-AB as compassionate treatment in patients who are pregnant, severely ill, malnourished or elderly (i.e. over 45 years), as well as HIV-coinfected patients who also require other drugs – namely MF and PM – for compassionate treatment of relapses.[7 11]

The availability of drugs for visceral leishmaniasis will depend on timely forecasts of needs to manufacturers. Lack of access to visceral leishmaniasis drugs due to delays in production and temporary quality problems is a recurring problem in treatment programmes. With the roll-out of mass treatment programmes, WHO leadership is essential in order to prime manufacturers for a significant increase in demand, to establish buffer stocks to prevent gaps in supply, to ensure acceptable standards of quality and long-term guarantees of cost, to coordinate purchases so that lower prices may be obtained, and to continue negotiations about price and/or sustainable donation schemes. There is also a need to involve generic manufacturers in order to alleviate the problem of single-source production – as is the case for PM, MF and discounted L-AB. A central supply facility may be required where needs (e.g. in case of outbreaks) can be met immediately and where demands are pooled.

The meeting also recognized that the availability of drugs and the identification of efficacious drug combinations will not be sufficient to reduce the burden of visceral leishmaniasis. A clear plan is needed to reach patients in areas where there is no access to health care. The spread of HIV/*Leishmania* coinfection in East Africa and the remoteness of the endemic areas make development of a plan for this region an urgent priority in view of the epidemic nature of the disease. Any such plan should be designed to be integrated into a more comprehensive national health plan in order to ensure access to health services and to guarantee the sustainability of specific interventions.

The meeting recognized the role of WHO in the development of a comprehensive global strategy for the control of leishmaniasis and in coordinated action to achieve the common goal of controlling visceral leishmaniasis, especially in the most severely affected regions (the Indian subcontinent and East Africa) as requested by World Health Assembly Resolution WHA60.13.

In view of the current situation and the limited options available, the participants in the meeting expressed their support for WHO initiatives to make all efforts to improve treatment of visceral leishmaniasis in line with the above statement.

Madrid, 19 June 2009

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