Breakthrough in The Management of Visceral Leishmaniasis

BB Thakur

A breakthrough has come about in the management of a dreaded disease that has aptly been called an orphan disease. While the medicines required for these ailments cannot be defined as orphan drugs in a strict sense, the diseases can well be categorised as ‘orphan diseases’ owing to the practical neglect in their treatment and eradication by all concerned. For Kala-azar or leishmaniasis, there has been a dearth of effective drug treatments.

Leishmaniasis constitutes one of the six entities on the WHO TDR list of most important diseases. The increasing interest in leishmaniasis in industrialized countries is attributable to the increase in travel and the migration of population in the present global economy. The association of visceral leishmaniasis with AIDS has further compounded the problem and drawn the attention of international community since both the diseases have immunosuppressive effect on the host system that allows the parasites to survive within the phago-lysosomes.

Leishmaniasis currently threatens 350 million men, women and children in 88 countries around the world. In India it is known to have existed since 1850 in Bengal extending to Assam along the plains of the Brahmaputra river and extending along the Ganges river to the plains of Bihar and eastern UP. Since then several epidemics have swept the Ganga-Brahmaputra plains of northern India, taking a huge toll of human lives and inflicting unimaginable misery. In recent years it has also extended to Nepal. The recent epidemic of the disease started in India in the early seventies, and since then the disease continues to affect predominantly North Bihar and sporadically West Bengal, eastern Uttar Pradesh and Nepal. It affects approximately two million people of 26 districts of Bihar (all districts of North Bihar and some districts of central Bihar along the river Ganges) and adjoining Nepal. Over 20% of the world’s estimated 0.5 million annual cases occurred in the Indian states of Bihar, West Bengal and Uttar Pradesh. India along with Brazil, Sudan and Bangladesh contributes to 90% of the global burden of VL. Even the ancient Indian scriptures mention ‘kala-azar’ - or ‘black fever’ - which discolours the skin black (referring to post-kala-azar dermal leishmanoid - PKADL). Leishmaniasis as a medical problem was encountered during the Persian Gulf war also.

It is a rural disease and man is the main reservoir of infection. Untreated and progressive Kala-azar leads to fatal complications and patients die due to severe hemorrhage, septicemia and intercurrent infection. Mortality rates of 12% to 30% have been reported during this epidemic.

Sand fly (Phlebotomus argentipes), the vector of kala-azar, breeds in mud shelters located in peri-domestic and animal shelters. Poverty is a major determinant of the disease affecting the poor population who have little access to health facilities and cannot afford treatment.

The leishmaniases are parasitic diseases with a wide range of clinical symptoms: cutaneous, mucocutaneous and visceral leishmaniasis (VL) - also known as Kala-azar: characterized by irregular bouts of fever, substantial weight loss, swelling of the spleen and liver, and anaemia (occasionally serious). In mucocutaneous forms of leishmaniasis, lesions can lead to partial or total destruction of the mucous membranes of the patient causing permanent scar, a stigma that can cause serious social prejudice.

Since early 1980’s, research has been done on the biological, immunological and therapeutic aspects of this disease that has helped make a break-through in the early diagnosis and treatment of Kala-azar. Unfortunately some of the recent techniques are not yet available in this underdeveloped part of the world for field study.

The parasite in India has developed varying degrees of drug resistance. Conventional therapy for VL consists of parenteral pentavalent antimony (sodium stibogluconate and meglumine antimoniate), given for 28 days (20 mg/kg/day). Severe adverse reactions such as pancreatitis and cardiac toxicity have limited its use. Relapse is common and resistance to antimony is alarming (about 50%). Alternative drugs too are not free from disturbing side-effects. Pentamidine isethionate, a toxic drug has been shown to cause diabetes mellitus in over 10 per cent of cases and its efficacy is also declining. Thus, in these areas Amphotericin B remains the only drug that can be used. Although it cures > 97% patients, infusion-related adverse events are common and occasionally serious toxicity like myocarditis or death can occur. In recent years, India has been the center for clinical development of new antileishmanial drugs like lipid formulations of amphotericin B, parenterally administered aminosidine and oral miltefosine. It has become possible to treat kala-azar successfully with a single dose of liposomal amphotericin B.
but its cost prohibits its use in poor patients. Aminoglycoside aminosidine has also been found to be effective, but is not being manufactured at present.

These drugs are administered parenterally, often under strict medical supervision. The treatment costs are high and therapeutic efficacy is limited.

Preliminary results have been promising for other drugs but clinical experience is not adequate to justify their general use. The types of drugs include cytokines such as interferon-gamma and granulocyte-macrophage colony-stimulating factor (GM-CSF) (both used in combination with pentavalent antimony); aminoglycosides such as paromomycin (used as monotherapy or with pentavalent antimony); oral antifungal agents such as ketoconazole (monotherapy); and allopurinol (used with pentavalent antimony). Local treatments of CL, such as intralesional antimony, and topical paromomycin (15%) plus methylbenzethonium chloride (12%) in combination with antimony injections, have also been studied.

**Miltefosine - The Long-Awaited Therapy For Visceral Leishmaniasis?**

The first oral treatment for an often fatal tropical disease has been found. The treatment is easy to administer and is convincingly effective. It may revolutionize treatment of visceral leishmaniasis. It cures about 98% patients. It satisfies all the criteria of an ideal drug as it is indigenous, has negligible side effects, does not require refrigeration for storage, and has been used successfully to treat cases resistant to conventional antimony therapy. Since the drug can be administered orally, it has the potential to be used as a simple and affordable public health tool to treat patients effectively at the community level and even during epidemics.

In the various clinical trials, the toxic effects associated with miltefosine have usually been tolerable and reversible, although the therapeutic window appears to be narrow. Gastrointestinal symptoms, such as vomiting and diarrhea, although common, have typically been brief and of only mild-to-moderate severity. Some patients have had reversible hepatotoxicity or nephrotoxicity. Although the toxicity associated with miltefosine sounds milder than that with some parenteral therapies, gastrointestinal symptoms could be of more consequence in severely ill patients, such as those who are malnourished or dehydrated. The treatment of women is complicated by the fact that pregnancy is a contraindication to the use of miltefosine because it is a teratogenic in animals.

To summarise, Miltefosine is the first effective oral remedy against visceral leishmaniasis, a disease that often results in death. The healing process is practically complete in four weeks with a success rate of 98%. Success of the treatment does not depend on whether the patients are resistant to the conventional pentostam therapy. The healing process is noticeable after three days: the fever drops and the patient regains strength.

The side-effects are negligible. Epidemics would be controllable with this oral treatment. The active substance has a simple chemical structure and is producible in tonnes. It is cheap (taking into account the cost of current drugs, hospital stay, loss of working days and the loss of life) and can be stored indefinitely between 0 and 40 deg Celsius. 5.6 tonnes of miltefosine would be needed annually on the basis of about two million new infections per year and a necessary amount of about 2.3 g miltefosine per patient.

Dose depends on age and body weight: Children from 2 to 12 years (8-20 kg body weight) receive 2.5 mg/kg; Children 12 years and older with a body weight above 25 kg and adults receive 100 mg miltefosine (2 capsules 50 mg). The capsules should be taken with meals.

The drug was licensed for manufacture in India in 2002, has been marketed and will be available for patients now. From the country where Leishman and Donovan independently isolated the parasite for the first time, another first is emerging. The availability of an oral anti-leishmaniasis drug may revolutionize the treatment and control of kala-azar and alleviate the sufferings of the millions of adults and children in affected countries.

Will miltefosine continue to be highly effective and acceptably tolerated when more patients are treated? How broadly applicable will miltefosine therapy be for the diversity encompassed by human leishmaniasis, which includes several clinical syndromes, caused by about 21 leishmanial species in 88 countries? Will miltefosine become one more option for treating a particular type of patient, or will it become the drug of choice for most patients who require systemic antileishmanial therapy? Studies of other leishmanial syndromes, including American cutaneous leishmaniasis, are in progress of being planned. Studies of visceral leishmaniasis outside India are still needed, as are clinical trials that include severely debilitated patients and patients infected with HIV.3

Miltefosine, the fruit of careful basic-science and clinical research, be the long-awaited orally administered drug for treating visceral leishmaniasis? It could be. Optimism tempered by caution is warranted. Miltefosine could join the list of agents that appeared promising but fell by the wayside. However, the best-case scenario is the fact that miltefosine is affordably priced so that it can benefit the patients who need it the most, proves effective and safe in actual use and fundamentally changes our approach in treating visceral leishmaniasis and perhaps other leishmanial syndromes, such that parenteral therapy is rarely needed.

Currently there are no drugs or vaccines for the prevention of Leishmaniasis. Leishmaniasis is an intracellular infection. Ideally a vaccine would elicit a strong Th1 response as a Th2 response has been implicated in chronic, non-healing disease. Live-attenuated candidates have been proven to create this kind of response, but the dangers associated with them have hindered their use. With the help of adjuvants and cytokines whole-killed vaccines seem to show great promise.
NEW CANDIDATES READY TO ENTER INTO DEVELOPMENT

Maesa balansae, the source of PX6518 has good anti-leishmanial activity. The standard current treatments for visceral leishmaniasis, and also treatment with miltefosine, require multiple administrations of the drug and correspondingly long treatment courses. A natural product with good anti-leishmanial activity after a single injection in animal models, PX6518, is being progressed through pharmacokinetic and toxicological studies, and would significantly shorten treatment times if successful. Other projects include studies of pyrophosphate metabolism as a possible drug target in Leishmania, and mechanisms of parasite resistance to arsenical anti-leishmanial drugs are also underway.

In addition to the monotherapy, efforts for the development of combination chemotherapy are needed if the menace of drug resistance is to be contained.

Poor control strategies compounded by non-implementation of control programmes, lack of diagnostic facilities, abuse of pentavalent antimonials leading to alarming rise in drug resistance, have lead to the continued transmission of the disease during the last three decades. Both diagnosis and treatment of kala-azar are far from ideal, and considering the fact that this ailment affects poor people living in difficult field conditions, containment of this disease remains a Herculean task.

Dare we also hope for a future in which effective prevention and control measures markedly reduce the need for antileishmanial therapy?

With the introduction of this wonderful oral drug, the likelihood is high that it may be possible to conquer and eradicate black fever by a two-pronged approach: treatment of cases of kala-azar and PKDL and spray of DDT or malathion or pyrethroids to kill the sandfly. If this is continued for five years, the disease can be eradicated.

REFERENCES
