LEISHMANIA AND THE LEISHMANIASES

Anthony Bryceson

Current issues in the treatment of visceral leishmaniasis

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Visceral leishmaniasis (VL) is becoming increasingly common and important in several places. In India the epidemic in Bihar and West Bengal continues and has spread into Pakistan; resistance to antimonials is the rule North of the River Ganges; in addition, the HIV epidemic is spreading from the towns into the country villages.

In Sudan, the epidemic that killed 100,000 people between 1984 and 1996 [1] is spreading along the borders with Ethiopia. In North East Brazil VL has urbanised and is a common cause of admission to hospital [2]. In Southern Europe co-infection with HIV, which has led to difficulties with diagnosis and treatment, is changing the epidemiological pattern of the disease and may be introducing a new, human, reservoir of infection [3].

What are the issues for treatment in these different settings? They may differ between the settings. But they include:

1. What is the best regimen
   a. where money is no object?
   b. in a poor country?
2. How to tackle drug resistance
3. The immuno-suppressed patient
4. The balance between efficacy, cost and speed of treatment.

The best treatment regimen

How should one chose from the 10 or 11 drugs that are available to treat leishmaniasis? How best should one use these drugs? The most effective of the traditional drugs (pentavalent antimonials, pentamidine and amphotericinB deoxycholate) are injectable and toxic to varying degrees. The older oral drugs (allopurinol and the azoles) have only a weak effect when used on their own. The newer drugs are still under trial and not generally available (miltefosine, sitamaquine and aminosidine) or are prohibitively expensive (liposomal amphotericinB).

Liposomal amphotericinB (AmBisome) is the best drug where money is no object and the patient is immunocompetent. Trials carried out through the TDR Programme, in India, Kenya and Brazil determined the least total dose necessary in each of these countries as 6 mg/kg, 14 mg/kg and 21 mg/kg respectively [4]. In Southern Europe 21 mg/kg is also needed. It may not matter whether the drug is given as, for example, 2 mg/kg over 7 days or 3–4 mg/kg over 6–7 days; but treatment should probably be spread over at least 5 days to achieve a cure rate over 95% [5]. AmBisome is so expensive ($US 2,175 for a 15 mg/kg course in a 50 kg patient) that it is important not to waste drug, which should be given in doses of whole 50 mg ampoules. NeXstar, the manufacturer, has contracted with WHO to provide one free ampoule for every three purchased by a developing country; but this will not make the drug any more affordable.

In most poor countries a pentavalent antimonial still provides a cure rate in excess of 95% when properly used in the WHO recommended dosage of 20 mg/kg per day for 21 days, but without a top cut-off dose [6]. Adults tolerate this dose less well than children [7], and I prefer a dose related to body surface area that gradually tails from 20 mg/kg for a 20 kg child to ~12 mg/kg for a 90 kg adult [8]. Albert David in India produces sodium stibogluconate at on tenth the price of Wellcome in UK: SUS 16 cf SUS 150 for an adult course. The exception to this is in Northern Bihar, where only 40% of new patients would be cured by this regimen [9].

Aminosidine (paromomycin) is as effective as the antimonials when used on its own. In vitro, it is synergistic with sodium stibogluconate, and the combined
use in patients with VL enables lower doses of each drug to be used [10, 11]. It is much better tolerated by pa-
tients, but the question of possible oto-toxicity still needs
to be submitted to a controlled phase III trial, scheduled
to take place in India in 2001 under the auspices of
TDR. IDA Pharmamed has repacked the drug for para-
enteral use, and registration is planned for 2003. The
market price has yet to be agreed, but should be not
greater than that of conventional amphotericinB.

Miltefosine may turn out to be the drug of choice for
all patients with VL; oral, highly effective even in North
Bihar, well tolerated and reasonably priced, although
this has yet to be agreed. In India, an adult dose of
100 mg daily for 4 weeks provides a cure rate greater
than 95% [12]. However, it has not yet been studied in
other endemic countries. Unpublished case reports have
shown it to be only temporarily effective in HIV co-
infected patients in Europe, suggesting the possibility
of the development of drug resistance. Unfortunately, its
known teratogenic and abortifacient activities may make
it unsuitable for women of childbearing age. Nor is it
certain that its action on male gonadal function is fully
reversible. The manufacturer AstaMedica plans to regis-
ter the drug in 2003.

The problem of drug resistance

Primary resistance to antimonials is found in about 1% of
previously untreated patients with VL in most parts of
the world. Secondary resistance develops in patients
who have relapsed, often after inadequate treatment
[13]. Twice relapsed patients are almost always unre-
sponsive to further courses of antimonials. In endemic
foci where there is a canine reservoir, as in Europe and
Brazil, secondary resistant has not led to an increase in
primary resistance. However, in India, notably in North
Bihar, where man is the reservoir, there has been an
epidemic of primary resistance. In Muzaffarpur, the
epicentre of the outbreak, over 60% of previously un-
treated patients are unresponsive to antimonials [14, 15].
Additional factors that have led to this situation may
include poor compliance and under-dosage, and the use
of a single drug.

Secondary resistance has been reported to pentam-
dine, and amphotericinB [16], including liposomal
amphotericinB, notably in HIV co-infected patients [5].
Resistance to these drugs may pose a problem for the
management of an individual patient, but not for the
community.

A drug that has a short half-life and high therapeutic
eratio like amphotericinB is least likely to induce resis-
tance. Aminosidine has the short half-life, but a low
therapeutic ratio. Miltefosine has a very long half-life
and low therapeutic ratio; and a course of treatment
leaves a sub-therapeutic level in the blood for some
weeks, characteristics that might be expected to en-
courage resistance. Its widespread use as a single agent
in India could well lead to the rapid emergence of
widespread resistance, which would be a disaster.
Careful consideration should be given to using it only in
combination with another drug. This means that trials
of combinations need to be carried out urgently, either
with the weaker oral or a rapidly acting injectable drug.
Long courses of miltefosine, such as may be required for
PKDL, might be especially liable to lead to resistance.

The reservoir of infection of Sudanese VL is not
known. If it proves to be man, then similar problems of
drug resistance could emerge there, and possibly spread
to the neighbouring endemic countries, Ethiopia and
Kenya.

Immuno-suppressed patients

We talk of immuno-competent patients with VL, but in
reality all patients with VL are immuno-suppressed with
respect to Leishmania and to other unrelated antigens,
and are prone to secondary infections [17]. Successful
treatment usually leads to immune recovery. VL shares
with tuberculosis and leprosy some of the problems of
treatment of intracellular organisms in an immuno-
suppressed patient: the need for a long course of treat-
ment and the risk of relapse and of the development of
drug resistance. These problems are seen most sharply in
patients with VL who have an additional cause for im-
munosuppression. The commonest causes are drugs
following renal transplantation, and co-infection with
HIV virus. Co-infected patients respond slowly to
treatment with antimonials [18]. Apparent clinical im-
provement is not matched by parasite clearance from
splenic aspirate smears. Relapse rates are of the order of
60% within 1 year [19]. Conventional amphotericinB
and AmBisome produce similar results. Antimonials are
particularly badly tolerated; clinical pancreatitis has
been reported in up to 20% cases [20], whereas it is
almost unknown in those who are not additionally im-
munosuppressed, despite the frequency of suggestive
biochemical changes.

Experimentally, HIV drives leishmanial infection,
and vice-versa [3]. Response to treatment in patients
varies indirectly with the viral load. Concomitant
treatment with highly active antiviral drugs (HAART)
has improved the efficacy of anti-leishmanial treatment
in Southern Europe, and postponed relapses [19]. In
countries that cannot afford HAART, the spreading
HIV epidemic is likely to aggravate the problems of
management of VL and to encourage the spread of VL
in the community. In foci where man is reservoir, such as
India, it will lead to resistance to whatever single drug is
commonly used.

How, ideally, should one treat the co-infected pa-
tient? One policy is to attempt to eliminate the parasite
by prolonged treatment, monitored by splenic aspirates,
and to follow with maintenance treatment. However,
many centres can carry out such monitoring in a routine
setting, and there have been no studies to determine
which if any treatment is suitable for maintenance.