Visceral Leishmaniasis Treatment, Italy

Luigi Gradoni,* Marina Gramiccia,* and Aldo Scalone*

First-line drug treatment was recorded in 573 immunocompetent patients with visceral leishmaniasis in Italy. In the past 12 years, the proportion of antimonial treatments decreased from 100% to 2.8%, while the proportion of amphotericin B treatments increased from 0% to 97.2%. The countrywide change in therapy is a response to both disease reemergence and increasing antimonial failure.

Zoonotic visceral leishmaniasis is a life-threatening disease caused by the multiplication of the protozoan parasite *Leishmania infantum* in the phagocytes of the reticuloendothelial system. Infections are widespread in the Mediterranean subregion, where the parasite is transmitted in summer by the bites of phlebotomine sand flies, and canids serve as reservoir hosts (1).

In the first half of the 20th century, visceral leishmaniasis was a typical infantile syndrome in Italy with high incidence in southern regions and islands. After World War II, the incidence dropped to 10 to 20 cases per year for 4 decades; the disease reemerged with approximately 200 cases in 2000 and 2001 (Figure 1). This trend can be explained by the following: 1) the appearance of cases in immunocompetent adults that might be attributable to a general decrease in acquired immunity after the reduction of the phlebotomine-vector populations, determined by the massive antimosquito insecticide campaigns for malaria eradication 50 years ago (2); 2) the spreading of the disease from traditional areas of transmission to new stable foci in central and northern regions of Italy, as evidenced by recent colonization of these areas by sand flies and by increased *Leishmania* diffusion and prevalence among the canine reservoir (3); and 3) the occurrence of *Leishmania* infections in immunosuppressed persons, such as those co-infected with HIV (4). Incidence of visceral leishmaniasis in these patients, however, has recently decreased after the introduction of highly active antiretroviral therapy (Figure 1) (5).

Since the 1940s through 1990, meglumine antimoniate has been the only first-line drug for visceral leishmaniasis treatment in Italy (6). From 1991 through 1994, a total of 90 patients of all ages, representing one third of all immunocompetent visceral leishmaniasis case-patients reported in Italy during that period, were enrolled in clinical trials of liposomal amphotericin B (L-AmB), which led to a novel, safe, short course of visceral leishmaniasis treatment as an alternative to meglumine antimoniate (7,8). In the same period, other lipid-associated AmB drugs were registered in Italy for the treatment of fungal infections, i.e., AmB colloidal dispersion (ABCD) and AmB lipid complex (ABLC). Because no official policy exists for visceral leishmaniasis therapy in Italy (physicians can prescribe any registered drug under their own responsibility) and information on drug regimens used is not included in visceral leishmaniasis case reports, we aimed to assess whether changes have occurred, and to what extent, in first-line drug regimens adopted in Italy after lipid-associated AmB was introduced into clinical practice.

The Study

A retrospective analysis was performed on data collected at the Unit of Protozoology of Istituto Superiore di Sanità, Rome, the main reference center for visceral leishmaniasis surveillance in Italy. Diagnosis of visceral leishmaniasis in patients with clinically suspected cases was routinely performed on serum and bone marrow aspirate samples sent by hospitals, mainly from pediatrics, internal medicine, and infectious diseases wards, from throughout the country. If visceral leishmaniasis was confirmed, relevant information on patients was recorded, which included drug regimens used and posttherapy results. Two datasets were analyzed: the first included information from patients in whom leishmaniasis was diagnosed from 1986 to 1990, i.e., before the mass enrollment of patients in the aforementioned study on L-AmB; the second from patients in whom leishmaniasis was diagnosed from 1995 to 2001, i.e., after that study. Immunosuppressed patients (e.g., HIV co-infected persons or transplant recipients), who usually respond poorly to antileishmanial treatments, were not included in our analysis. Fisher exact test was used for comparisons.

*Instituto Superiore di Sanità, Rome, Italy
For the 1986–1990 period, we recorded treatments used for 40 patients in 22 hospitals, representing 29.2% of 137 immunocompetent persons with visceral leishmaniasis. Fourteen (35.0%) were children <14 years of age. As expected, all patients were treated with meglumine antimoniate, given at the standard dose of 20 mg pentavalent antimony (Sb⁵⁺)/kg/day for 3 to 4 weeks (6), either alone (37 patients) or in combination with allopurinol at the daily dose of 15 mg/kg (3 patients). Two patients treated with meglumine antimoniate alone (5.4%) had a visceral leishmaniasis relapse within 6 months from treatment and have been retreated successfully with meglumine antimoniate in combination with allopurinol.

For the 1995–2001 period, we recorded treatment information for 533 patients, representing a large proportion (56.4%; annual range 43.3% to 69.1%) of 945 immunocompetent visceral leishmaniasis patients. About half were children (267; annual range in proportion 42.1% to 64.8%). Every year, patients were referred by 19 to 42 hospitals, with a range of 1 to 30 patients per hospital. Drug regimens recorded are shown in the Table and summarized in Figure 2. Meglumine antimoniate was the first-line drug used in 158 patients (29.6%) at the Sb⁵⁺ dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also received allopurinol (the drug combination used in 158 patients (29.6%) at the Sbv dosages noted previously; 6 also recei...
from southern Europe. This treatment failure could be attributable to the widespread use of meglumine antimoniate in treating infected dogs, which may have caused the spread of \textit{L. infantum} strains less susceptible to antimony (12–14). Efficacy of AmB drugs is very high and, so far, decreased \textit{Leishmania} susceptibility to this compound (AmB is rarely used in veterinary practice) has not been indicated. 3) Although L-AmB and other lipidic formulations of AmB are 30- to 50-fold more expensive than meglumine antimoniate for visceral leishmaniasis therapy at the dosages reported above, in Western countries most of the costs of treating visceral leishmaniasis are inpatient hospitalization expenses rather than drug costs. Therefore, short courses of 6 to 7 days, as required for L-AmB, ABCD, or ABLC (9), are highly cost-effective if compared with 21- to 28-day courses needed for meglumine antimoniate treatment.

Dr. Gradoni is the head of the Protozoology Unit in the Parasitology Department of Istituto Superiore di Sanità in Rome. His main research interests are in the epidemiology and control of leishmaniases.

References


Figure 2. Annual proportion of immunocompetent patients with visceral leishmaniasis treated with meglumine antimoniate (MA) or amphotericin B (AmB) in the period 1995–2001.


14. Carrió J, Portús M. In vitro susceptibility to pentavalent antimony in Leishmania infantum strains is not modified during in vitro or in vivo passages but is modified after host treatment with meglumine antimoniate. BMC Pharmacol 2002;2:11.

Address for correspondence: Luigi Gradoni, Laboratorio di Parassitologia, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy; fax: 39-06-4938-7065; email: gradoni@iss.it