

Treatment of Mediterranean visceral leishmaniasis*

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Up-to-date information is given on the epidemiological situation of zoonotic visceral leishmaniasis (ZVL) in nine Mediterranean countries, and on drug regimens adopted in the management of ZVL patients in each country. Results of experimental and clinical trials on the efficacy and tolerability of liposomal amphotericin B in laboratory animals and in patients with ZVL are presented, as well as conclusions and recommendations on drug regimens to be used in the treatment of ZVL.

Introduction

Zoonotic visceral leishmaniasis (ZVL), caused by *Leishmania infantum*, is endemic in all countries bordering the Mediterranean basin. Although its overall prevalence among the immunocompetent population is low, the focal transmission of the disease may result in case clusters that can be underestimated in the absence of appropriate surveillance, and can present a severe health problem in many rural and peri-urban areas (1). The number of ZVL cases among patients with human immunodeficiency virus (HIV) infection has increased rapidly in recent years, and represents about 50% of all ZVL cases in adults in some areas (2).

The first-line drugs against ZVL for more than 40 years have been pentavalent antimonials. They are available in the form of sodium stibogluconate (Pentostam[®]) and meglumine antimoniate (Glucantime[®]). The dose recommended by WHO is 20 mg Sb(v)/kg daily for 28 days by intramuscular injections (3). However, no information is available on treatment regimens actually employed in different Mediterranean countries, or on drug efficacy and tolerability in different categories of patients (immunocompetent children and adults, HIV-positives, etc.)

Status, by country, and therapeutic approaches

Algeria. The disease affects only children, more than 80% of whom are under 5 years of age. Since 1985, some 150–200 cases were diagnosed each year parasitologically and/or serologically. Most of them originate from Kabylia in north-eastern Algeria, which is a sub-humid bioclimatic zone. No HIV–*Leishmania* co-infections have been reported. The causative agent has been identified isoenzymatically as *L. infantum* MON 1.

Paediatricians treat ZVL with meglumine antimoniate, usually in a dose of 60 mg (18 mg Sb (v)/kg/d for 15 days. After a 15-day rest, a second course is administered for 15 days. Assessment of parasitological cure is made on bone-marrow smears. Unresponsiveness to antimonial treatment occurs in a few cases. These are treated with pentamidine given in a dose of 4 mg/kg on alternate days for 3–5 weeks.

France. *Alpes-Maritimes (Nice area).* Until 1975, ZVL was mainly diagnosed in children. Thereafter, the number of adult cases has steadily increased, and

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from 1985 to 1992 only 18 out of 65 recorded cases (28%) were children. Almost half of the adult cases are now represented by HIV co-infections. About 50 strains have been isolated from ZVL cases and identified isoenzymatically as *L. infantum* MON 1.

Meglumine antimoniate in a daily dose of 60 mg (18 mg Sb(v)/kg, or sodium stibogluconate in a daily dose of 6 ml in adult patients (i.e., about 10 mg Sb(v)/kg) are the first-line drugs used in standard schedules. There is no consensus on the duration of treatment: two courses of 15–21 days with a 15–30-day interval (or a single course for 15–28 days) are commonly employed. No serious side-effects or parasitological or clinical relapses have been recorded. Intravenous amphotericin B (Fungizone®) in a dose of 1 mg/kg/d for 15 to 28 days has been used with success in some immunocompetent patients. In 21 HIV–*Leishmania* co-infection cases, none of the above regimens led to parasitological cure.

Marseilles area. From 1985 to 1992, 150 ZVL cases have been recorded (11 to 24 per year). HIV–*Leishmania* co-infection cases have steadily increased in recent years. From May 1992 to November 1993, ten out of 17 new cases were HIV-positive adults, one was an HIV-negative adult, and six were children. During the same period, 14 relapses were diagnosed in nine immunocompromised patients, of whom seven were HIV-positive. All but one of the immunocompetent patients were successfully treated with two 15-day courses of meglumine antimoniate, using a daily dose of 60 mg (18 mg Sb(v)/kg. Immunocompromised patients relapsed after treatment with meglumine antimoniate, conventional amphotericin B in intralipid 20%, liposomal amphotericin B (AmBisome®), and pentamidine.

Greece. ZVL is endemic in the mainland and the islands. In the Athens basin area, the majority of cases recorded from 1962 to 1992 (733 out of 792 (91.8%)) occurred on the foothills of the mountains surrounding the area. Several cases are reported from the Ionian islands of Corfu, Cephalonia and Zakynthos. In the north-west of continental Greece, ZVL outbreaks have been recorded, suggesting the presence of unstable foci. The disease affects mainly children; HIV–*Leishmania* co-infections have not been reported. A few *Leishmania* strains have been typed and identified as *L. infantum* MON 1.

The first-line treatment is meglumine antimoniate in a dose of 60–100 mg (18–30 mg Sb(v)/kg/d for 12–15 days. In some cases treatment is repeated after 15–30 days. Toxicity appears to be low (1 death reported among 120 cases treated). In some unresponsive cases or in patients showing hypersensitivity to antimony, pentamidine or amphotericin B is used as second-line treatment.

Italy. ZVL is endemic in continental and insular regions of central-south Italy. The number of cases notified annually has increased from 32 in 1988 to 104 in 1992. This probably reflects both recent active surveillance activities and an increasing number of HIV infections in disease foci, rather than an actual increase of transmission. In the Campania region, active surveillance revealed 10-fold more cases than previously notified, whereas in Sicily they were about 3-fold more. In both regions, paediatric cases represent 50–60% of the total cases recorded. Through a national programme on the surveillance of HIV–*Leishmania* co-infections, a total of 79 cases have been recorded up to November 1993. A steady increase of cases was observed from 1985 to 1991 (from 2 to 24); in the last two years the incidence was 14 and 17 cases. The frequencies of HIV–*Leishmania* co-infections vary by geographical area: in 1992, 6 out of 19 adult cases in Sicily and 0 out of 12 adult cases in Campania were HIV co-infected. About 200 *Leishmania* strains have been characterized isoenzymatically. Almost all the immunocompetent patients were found infected with zymodemes of *L. infantum* MON 1 (in all endemic regions) or MON 72 (in the Campania region), while from 47 HIV-positive patients 10 different zymodemes of *L. infantum* were identified.

Meglumine antimoniate is the first-line drug and used to be administered in a final dose of 100 mg (30 mg Sb (v)/kg/d for 15–20 days, as recommended by the Italian manufacturer, Farmitalia. More recently (in 1988–89), in the main hospitals and university clinics of the endemic regions the WHO-recommended dosage has been adopted. While in children the drug is well tolerated, serious side-effects such as cardiotoxicity or pancreatitis have been reported in a small proportion of immunocompetent adults. A combination of meglumine antimoniate (daily dose of 50 mg (15 mg Sb(v)/kg) and oral allopurinol (15 mg/kg for 20–25 days) has also been used with success. A few patients who did not respond to antimony were usually treated with pentamidine (dose of 4 mg/kg on alternate days for 3–4 weeks) or with conventional amphotericin B (0.5 mg/kg/d for 14 days). HIV-positive patients have also been treated with meglumine antimoniate, but relapses occur in almost all of them; after the first or second relapse, they are treated with pentamidine or with conventional amphotericin B (dose of 0.5–1 mg/kg/d for 14–21 days).

During 1992–93, 75 ZVL cases (both HIV-positive and immunocompetent patients) were enrolled in a clinical trial with liposomal amphotericin B (see below).

Malta. Since 1980, there have been between 2 and 16 ZVL cases a year, mostly in children under the age

of 5 years. No HIV-*Leishmania* co-infection has been reported. A few strains have been typed as *L. infantum* MON 1.

The standard drug used for treatment is sodium stibogluconate. Between 1980 and 1988 the regimen was very variable, but since 1989 it has been standardized to 20 mg Sb(v)/kg/d for 30 days combined with oral allopurinol 10 mg/kg/d. Since 1980, no deaths or serious side-effects have been recorded. In the period 1980-88, 8 patients relapsed; since 1989, there has only been one relapse out of 35 patients treated. All relapsing patients received a further 21-day treatment with sodium stibogluconate, while three received an additional course of pentamidine.

Morocco. Foci of ZVL are found in many provinces of the country. They are concentrated mainly in the north, in villages on the slope of the Rif chain, and in mountainous areas of the Middle Atlas, Anti-Atlas and, to a lesser extent, in the central plains and highlands. About 50 disease cases are estimated to occur annually, affecting mainly children; 70% are under 6 years of age. Adults are also affected, and one case of HIV-*Leishmania* co-infection has recently been recorded. Several *Leishmania* isolates have been identified as *L. infantum* MON 1.

Meglumine antimoniate in a daily dose of 60-100 mg (18-30 mg Sb(v)/kg for 10-21 days, and pentamidine in a dose of 2-4 mg/kg/d for 10-20 days are used alternately. If persistence of parasites and/or symptoms are observed, two or more courses are administered. An analysis of more than 100 hospitalized cases of ZVL has shown that about 50% of patients received one course of treatment, 40% needed a second course, and 2% a third course. Lethality rate among cases under treatment was 3%.

Portugal. ZVL, which occurs sporadically in the whole country, has three major foci: the Alto-Douro region in the north, where more than 80% of all cases occur; the Algarve region, in the south; and the Lisbon Metropolitan region. From 1987 to 1992, 169 cases were diagnosed (mean, 28 per year). From 1971 to 1983, 88.9% of the patients were children under 4 years of age, which decreased to 81.7% in the period 1987-92. A few cases of HIV-*Leishmania* co-infections have been diagnosed. *L. infantum* MON 1 was identified as the causative agent.

Meglumine antimoniate is used in a dose of 60-100 mg (18-30 mg Sb(v)/kg/d for 10-20 days. Two courses are usually administered with a 15-30-day interval. While this regimen is effective in immunocompetent patients, relapses are observed in HIV-infected patients. Relapses were also found to occur in immunocompromised patients treated with liposomal amphotericin B.

Spain. About 100 ZVL cases were reported annually up to 1987. Since then, the incidence in adults has dramatically increased due to the occurrence of a large number of HIV-*Leishmania* co-infections. An average of 10 new cases are diagnosed yearly in the Infectious Diseases Department of Hospital Ramón y Cajal in Madrid. Of 57 ZVL cases examined, 47 (82%) were in immunodepressed individuals, of whom 45 were HIV-positive. A prevalence study has shown that 47 out of 620 AIDS cases examined (7.6%) developed leishmaniasis as an opportunistic infection. *Leishmania* isolates have been identified as belonging to three zymodemes of *L. infantum* (MON 1, MON 29 and MON 33).

Meglumine antimoniate, used as a first-line drug, gives very good results in the treatment of immunocompetent patients, with no relapses. On the other hand, multiple relapses are diagnosed in immunosuppressed patients treated either with antimony, or with pentamidine, amphotericin B, allopurinol, ketoconazole and itraconazole. Of these drugs, amphotericin B seems to be the most effective. Common side-effects caused by these drugs appear to be much more severe in immunosuppressed patients. Prophylaxis against relapse with pentamidine, administered intravenously every 3-4 weeks, has been attempted in 7 HIV patients. Five had no relapses during 19 months of follow-up.

Tunisia. ZVL is reported mainly in children (97.2%), of whom 77% are under 5 years of age. Classical foci are found in the north, but during recent years the disease has spread to central regions, which has been linked with the development of irrigation schemes in that area. The mean annual incidence of cases has thus increased from 72 in the period 1982-89 to about 130 during 1992-93. Owing to the increase of HIV infections (354 cases, from 1986 to 1992), active serological detection of *Leishmania* in HIV-positive patients was started in 1992; of 104 patients examined, 23% had specific antileishmanial antibodies. Two cases were confirmed parasitologically. Parasite strains isolated from both children and HIV patients have been identified as *L. infantum* MON 1.

Meglumine antimoniate is the first-line drug. Before 1992, it was used in a daily dose of 60 mg (18 mg Sb(v)/kg for 14 days, which was usually repeated after 15 days. In unresponsive cases, pentamidine was used in a dose of 5 mg/kg/d 3 times weekly for 3 weeks. An analysis of 413 children treated with meglumine antimoniate showed that 70% were cured after 1-3 courses; 5% died at the beginning of treatment, and 4% during treatment; 1% were unresponsive; and 20%, who received 1 or 2 courses, had no follow-up. Antimony toxicity and

intolerance were reported in 2% and 6% of cases, respectively. A new meglumine antimoniate regimen was adopted in 1992: 90 mg (27 mg SB(v)/kg/d, administered in three divided doses daily, for 20 days. Preliminary results on 22 cases have been encouraging, in terms of both efficacy and tolerability.

Liposomal amphotericin B (AmBisome)

In experimental visceral leishmaniasis

The activity of multiple doses of a liposomal formulation of amphotericin B (AmBisome) on *L. infantum* in BALB/c mice was investigated, and the amphotericin B concentration in liver and spleen was determined. Groups of infected mice were treated intravenously with 3, 5 or 7 doses of AmBisome (3 mg/kg) over 3, 10 and 25 days, respectively. The antileishmanial activity of the drug was compared with that of meglumine antimoniate (28 mg Sb(v)/kg/d for 21 days). Three consecutive daily doses of AmBisome were sufficient to clear all parasites from the liver of mice, while antimony did so only after 21 doses. At 24–48 h after their last dose all AmBisome-treated mice showed very high amphotericin B concentrations in their livers (61.2–76.2 µg/g) and spleens (39.8–72.1 µg/g), with no overt signs of toxicity. Mice which received 2 or 4 doses at intervals of 5 to 8 days maintained drug levels over 11 and 26 days, respectively, as high as those detected after 3 consecutive doses. Treatment of visceral leishmaniasis could therefore be on an intermittent or outpatient basis, thereby greatly reducing the costs.

In Mediterranean visceral leishmaniasis

Summary of trials in progress. Conventional amphotericin B (deoxycholate formulation, Fungizone) is a powerful antileishmanial agent but remains a second-line drug because of toxicity. Liposomal amphotericin B (AmBisome) is far less toxic for treating visceral leishmaniasis, the drug's particulate nature being targeted on the macrophages. AmBisome has been shown to be highly effective against *L. infantum* in a mouse model (see above) and in published case reports (4–6). To establish the efficacy and tolerability of AmBisome in children and adults with ZVL acquired in the Mediterranean region, a total dose of 21–35 mg/kg was first administered over 21 days and then 10 days later, with the aim of further reducing the duration of treatment if this was successful. A group of immunocompromised patients, in whom chemotherapy of ZVL is notoriously difficult, was also included.

The studies began in June 1991 and are continuing. Originally this was an Europe-wide multicentre study, but now almost all the patients are enrolled from Italy (Naples, Genoa, Palermo and Catania), with parasitological confirmation of *L. infantum* in bone marrow or splenic aspirates. Aspirates were taken again on day 21 for all but one of the groups (see below), and on day 45 for group 7, 7 days after the last dose of AmBisome. Treatment regimens were as follows.

Immunocompetent patients:

- Group 1: 10 patients (6 children) received 1–1.38 mg/kg/d for 21 days, a total dose of 21–29 mg/kg.
- Group 2: 10 patients (9 children) received 3 mg/kg/d for 10 days, a total dose of 30 mg/kg.
- Group 3: 10 patients (6 children) received 4 mg/kg/d on days 1, 2, 3, 4, 5 and 10, a total dose of 24 mg/kg.
- Group 4: 17 patients (12 children) received 3 mg/kg/d on days 1, 2, 3, 4, 5 and 10, a total dose of 18 mg/kg.
- Group 5: 31 patients (15 children) received 3 mg/kg/d on days 1, 2, 3, 4, and 10, a total dose of 15 mg/kg.

Immunocompromised patients:

- Group 6: 11 patients (7 co-infected with HIV, of whom 4 with AIDS) received 1.38–1.85 mg/kg/d for 21 days.
- Group 7: 13 patients (10 co-infected with HIV) received 4 mg/kg/d on days 1, 2, 3, 4, 5, 10, 17, 24, 31 and 38, a total dose of 40 mg/kg.

All patients in groups 1 to 4 were cured without significant adverse events and without relapse during follow-up (this was more than 12 months for groups 1 and 2). In group 5, one child had a clinical and parasitological relapse 4 months after treatment. Eight patients in group 6, after initial cure, relapsed at 3–22 months. In group 7, six HIV patients relapsed within 6 months. Those with more than two relapses after AmBisome were unresponsive to any further AmBisome.

Though strictly not comparable, these results imply a clear superiority of liposomal amphotericin B over pentavalent antimonials in terms of toxicity, ease of administration, and time spent in hospital. Immunocompetent patients, including infants and those with previous relapses, need only short courses, and the inpatient stay can be as short as 5 days. The reduced hospitalization costs may offset the high

cost of AmBisome, which at present precludes its wide use in India and East Africa, the areas endemic for *L. donovani*. Patients with underlying immunosuppression, including those with HIV co-infection, will almost certainly require interval or maintenance therapy to prevent relapses. The only advantage of AmBisome in such patients may be its low toxicity.

In epidemic visceral leishmaniasis

As a consequence of migration due to civil war, famine and flood, and probable ecological changes in favour of the vector *Phlebotomus orientalis*, a devastating epidemic of anthroponotic visceral leishmaniasis (AVL) began in southern Sudan around 1988–89. Untreated, the mortality in this epidemic is at least 69%. A conservative estimate of deaths due to AVL is 40 000 in a population of perhaps less than 1 million. Over 15 000 patients have been treated by Médecins sans Frontières.

As the epidemic progressed, increasing unresponsiveness (incomplete response or relapse following treatment) to sodium stibogluconate (Sb(v)) 20 mg/kg/d for 30 days, with or without aminosidine 12–15 mg/kg/d for 17 days, has become apparent. An open field trial of liposomal amphotericin B was therefore instituted to determine:

- whether the drug would be effective in severe and complicated drug-resistant cases;
- whether 'short course' treatment would be practicable in both severe and less severe cases.

Forty-three patients, from 6 months to 70 years old, were recruited between February and October 1993 in three treatment centres. Diagnosis was established by splenic or lymph node puncture in 41 cases (95%). Assessment of treatment efficacy was made, as above, in 37 out of 38 surviving patients. Three AmBisome regimens were adopted:

- (1) 20 patients received 3–5 mg/kg/d on days 0, 3 and 10, a total dose of 9–15 mg/kg.
- (2) 11 patients received 3–5 mg/kg/d on days 0, 3, 5, 7, 9 and 11, a total dose of 18–30 mg/kg.
- (3) 12 patients received 4–5 mg/kg/d on days 0, 2, 5 and 7, a total dose of 16–20 mg/kg.

Patients for the first two regimens were selected according to one or both of the following criteria: primary or secondary unresponsiveness to Sb(v) and aminosidine (29/31); severe illness, including bleeding and moribund condition (15/31).

In regimen 1, there were 11 cures, 5 incomplete responses, 1 late relapse and 3 deaths; 5 out of 6 patients who did not respond to treatment were cured by further treatment with AmBisome 3 mg/kg/d for 10 days. In regimen 2, there were 10 cures and one

death. Combining the patients in regimens 1 and 2, there was a significant decrease in spleen size and increase in haemoglobin, but no change in weight. In regimen 3, there were 8 cures, 3 incomplete responses and 1 death.

The overall cure rate in survivors was 33/38 (87%). Liposomal amphotericin B therefore was proven to be effective in severe, complicated drug-resistant AVL, even in the tragic circumstances of the southern Sudanese epidemic.

Conclusions and recommendations

Epidemiological data show the following general situation of zoonotic visceral leishmaniasis in the Mediterranean region.

- During the last few years, the number of cases recorded has globally increased. This phenomenon may be attributed to an actual increase of *Leishmania* transmission, and/or to improvement of case surveillance/recording systems, and/or to diffusion of immunosuppressive agents.
- In southern countries of the region, the endemicity appears higher and the disease affects almost exclusively children, usually below 4–6 years of age. In northern Mediterranean countries the endemicity seems to be lower, but larger proportions of adults (40–70%) are affected.
- Differences in epidemiological patterns are not parasite-related, since the same parasite strain (*L. infantum* zymodeme MON 1) has been identified as the main agent of ZVL cases in all the countries of the region.
- HIV–*Leishmania* co-infections are widespread in three countries (France, Italy and Spain). A lower number of cases has been identified in Portugal. Co-infections are being identified in Tunisia and Morocco, concomitant with the spread of HIV infections in these countries.

Investigations show that there is a lack of consistent treatment regimens of ZVL throughout the Mediterranean countries. Most experience is with pentavalent antimonials, but dosages and regimens vary greatly in different countries or even among hospitals of the same region. There is an indication that these drugs may be associated with toxicity (cardiotoxicity and pancreatitis) both in adults and, to a lesser extent, in children. Sb(v) intolerance, as well as primary and secondary unresponsiveness, have been shown in a small number of immunocompetent patients.

The meeting agreed that four first-line treatment regimens were acceptable for the management of ZVL in immunocompetent patients.

(1) Organic pentavalent antimonials in the form of sodium stibogluconate solution or meglumine antimoniate solution. The recommended dose of antimony is 20 mg/kg/d for 20–28 days.

(2) Antimonials (20 mg/kg/d) in combination with allopurinol (15 mg/kg/d) for 20–28 days.

(3) Liposomal amphotericin B (AmBisome) at 3 mg/kg/d on days 0, 1, 2, 3, 4 and 10, giving a total dose of 18 mg/kg.

(4) Aminosidine was also considered as an acceptable first-line drug, but doses and treatment duration were not defined. It was used either alone, or in combination with pentavalent antimonials, in a dose of 12–16 mg/kg for 14–63 days (7).

It was recommended that physicians in Mediterranean countries should use one of these regimens and record their results on an agreed proforma, which would be centrally collated in order to obtain comparative information on drug efficacy and tolerability.

Currently there is no consensus on the treatment of ZVL in immunodeficient patients. It was recommended that ZVL be categorized as an AIDS-defining diagnosis in the Mediterranean region, and that WHO should collect, centralize and periodically rediffuse all epidemiological data concerning HIV–*Leishmania* co-infections in these countries.

Résumé

Traitement de la leishmaniose viscérale méditerranéenne

Cet article fait le point de la situation épidémiologique de la leishmaniose viscérale zoonotique (ZVL) dans neuf pays méditerranéens, et indique les schémas thérapeutiques actuellement en usage dans chacun de ces pays pour la prise en charge des malades atteints de ZVL. On y trouvera les résultats des essais en laboratoire et des essais cliniques sur l'efficacité et la tolérance de l'amphotéricine B couplée à des liposomes, chez l'animal et chez l'homme, ainsi que des recommandations sur les schémas thérapeutiques à adopter pour le traitement de la ZVL.

Conclusions et recommandations

Les données épidémiologiques font ressortir la situation générale suivante en ce qui concerne la leishmaniose viscérale zoonotique dans la région méditerranéenne.

- Ces dernières années, le nombre de cas enregistrés a globalement augmenté. Ce phénomène

peut être attribué à une augmentation réelle de la transmission de *Leishmania*, à une amélioration de la surveillance des cas et du système d'enregistrement, et/ou à la diffusion d'agents immunosuppresseurs.

- Dans les pays du sud de la région, l'endémicité paraît plus forte et la maladie frappe presque exclusivement les enfants, en général au-dessous de 4 à 6 ans. Dans les pays du nord de la région, l'endémicité semble plus faible, mais la maladie touche une plus forte proportion d'adultes (40–70%).

- Les différences au niveau du tableau épidémiologique ne sont pas dues au parasite lui-même, puisque la même souche parasitaire (*L. infantum* zymodème MON 1) a été identifiée en tant qu'agent principal des cas de ZVL dans tous les pays de la région.

- Les co-infections à VIH et *Leishmania* sont répandues dans trois pays, l'Espagne, la France et l'Italie. Un nombre plus faible de cas a été identifié au Portugal. On trouve maintenant ces co-infections en Tunisie et au Maroc, parallèlement à la progression de l'infection à VIH dans ces pays.

Les investigations montrent que le traitement de la ZVL dans les différents pays de la région méditerranéenne n'est pas uniforme. Les médicaments les plus employés sont les antimoniés pentavalents, mais les posologies varient largement d'un pays à l'autre et même entre les hôpitaux d'une même région. Il semble que ces médicaments aient des effets toxiques (cardiotoxicité et pancréatite) chez l'adulte et, dans une moindre mesure, chez l'enfant. Une intolérance aux Sb(v), de même qu'une absence primaire ou secondaire de réponse au traitement, ont été observées chez un petit nombre de sujets immunocompétents.

Les participants à la réunion sont convenus que quatre schémas posologiques de première intention pouvaient être recommandés pour la prise en charge de la ZVL chez les sujets immunocompétents.

- 1) Antimoniés pentavalents organiques, sous forme de solution de stibogluconate de sodium ou de solution d'antimoniate de méglumine. La dose d'antimoine recommandée est de 20 mg/kg par jour pendant 20 à 28 jours.

- 2) Antimoniés (20 mg/kg par jour) en association avec l'allopurinol (15 mg/kg par jour) pendant 20 à 28 jours.

- 3) Amphotéricine B couplée à des liposomes (AmBisome) à raison de 3 mg/kg par jour les jours 0, 1, 2, 3, 4 et 10, soit une dose totale de 18 mg/kg.

4) L'aminosidine a également été considérée comme acceptable pour le traitement de première intention, mais la posologie et la durée du traitement n'ont pas été définies. Elle a été utilisée soit seule, soit en association avec les antimoniés pentavalents, à la dose de 12–16 mg/kg pendant 14 à 63 jours.

Les participants ont recommandé que les médecins des pays méditerranéens utilisent l'un de ces schémas et enregistrent les résultats sur un formulaire agréé; les formulaires seront ensuite centralisés afin d'obtenir des données comparatives sur l'efficacité et la tolérance des divers médicaments.

Actuellement, il n'existe pas de consensus sur le traitement de la ZVL chez les sujets immunodéprimés. Il a été recommandé de classer la ZVL parmi les diagnostics définissant le cas de SIDA dans la région méditerranéenne, et également que l'OMS recueille, centralise et diffuse périodiquement toutes les données épidémiologiques concernant les co-infections à VIH et à *Leishmania* dans ces pays.

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