Case Report: Visceral Leishmaniasis Treated with Antimonials/Paromomycin followed by Itraconazole/Miltefosine after Standard Therapy Failures in a Human Immunodeficiency Virus–Infected Patient

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Abstract. Visceral leishmaniasis is an opportunistic infection that affects human immunodeficiency virus–infected persons in leishmaniasis-endemic areas. The standard treatment may not be effective and relapses are common. We report the case of a human immunodeficiency virus-1–infected patient who had several relapses of visceral leishmaniasis after treatment with standard therapies and responded to a combined therapy.

Mediterranean visceral leishmaniasis (VL) is an opportunistic infection caused by the protozoan *Leishmania infantum* that affects human immunodeficiency virus-1 (HIV-1)–infected persons in leishmaniasis-endemic areas. After the introduction of highly active antiretroviral therapy (HAART) in the 1990s, the incidence of VL decreased in southern Europe,¹ but this disease is still observed in some immunosuppressed patients. Co-infection with this parasite is increasingly reported in Africa, Asia, and South America.²

Pentavalent antimonials have been the treatment of choice for VL and continue to be used in countries with limited economic resources. However, widespread use of these agents throughout the world, particularly in disease-endemic areas, has led to resistance of the parasite. Visceral leishmaniasis has become an important health problem in countries with a high rate of resistance to antimonial drugs;³ amphotericin B deoxycholate is the drug of choice in these areas. Liposomal amphotericin B is currently the first-line therapy in Europe because of its better tolerance and similar effectiveness, but the high cost of this drug limits its use in less developed countries. Moreover, this treatment may not be effective and relapses are common in a considerable percentage of HIV-infected patients.

Second-line therapies, such as miltefosine or paromomycin, have shown benefit in HIV-negative persons,⁴ and there is some experience with this treatment in HIV-infected patients.^{5,6} Miltefosine is the only oral agent available for treatment of patients with VL and is well tolerated.⁷ Paromomycin is a parenteral aminoglycoside⁸ that is active against *Leishmania* and has shown noninferiority to amphotericin B⁹ and greater activity than sodium stibogluconate.¹⁰ In addition, the azole itraconazole, which is used mainly to treat the cutaneous form of VL, has been also used as VL maintenance therapy.¹¹ Data from some studies suggest that a combination of these agents would be more effective than a single-agent therapy, but there is little related information in HIV-positive patients.^{12–16}

We describe the case of an HIV-1-infected patient with several relapses of VL after treatment with standard therapies. Based on the experience in HIV-negative patients, we implemented the strategy of combining antimonials with parenteral paromomycin, followed by itraconazole plus miltefosine, as maintenance therapy for this patient.

We report the case of a 45-year-old man in Spain who never traveled abroad, had been an intravenous drug user, and was HIV positive since 1990. The patient had oral candidiasis in 1996 and seborrheic dermatitis in 1997 as opportunistic infections, and he was also infected by hepatitis C virus. He started HAART in 1997 and obtained good control of HIV infection. Nonetheless, in August 2000, he voluntarily stopped HAART. In November 2001, the patient's CD4 cell count was 5 cells/mm³ and viral load had increased to 500,000 copies/mL. He also had pancytopenia (hemoglobin level = 8.5 g/dL, leukocyte count = 1,300 cells/μL, lymphocyte count = 460 cells/μL, platelet count = 51,000 cells/μL), daily fever, and hepatomegaly. HAART was again initiated and the patient underwent bone marrow aspiration. The viral load became undetectable and the CD4 cell count improved, but remained low (23 cells/mm³). Amastigotes were demonstrated on Giemsa-stained smears of a bone marrow aspirate. The treatment for VL consisted of amphotericin B lipid complex, 3 mg/kg/day for 10 days, for the acute episode, but the patient did not complete maintenance therapy. A bone marrow aspirate performed 10 weeks after finishing amphotericin B treatment continued to show *Leishmania* amastigotes.

Subsequently, the patient began treatment with meglumine antimoniate, 20 mg/kg/day for 19 days, followed by a dose every three weeks as maintenance therapy. The bone marrow aspirate was negative at completion of this therapy, but a parasitologic relapse occurred during the maintenance therapy, which required a second antimonial course. Again, a clinical and parasitologic response was observed, but there was a new parasitologic relapse during his maintenance therapy. A course of amphotericin B lipidic formulation (liposomal amphotericin B) failed to achieve a response. We again tried meglumine antimoniate therapy, which had been an effective treatment for an acute episode on two occasions, but there was no favorable response. Miltefosine, 150 mg/day for 28 days, was then given, but was not successful. At that time, combined therapy with liposomal amphotericin B, 4 mg/kg/day, plus miltefosine, 150 mg, was attempted, and a negative bone marrow aspirate was obtained after 30 days of treatment. Although the laboratory findings were satisfactory, the patient started to lose weight and had enlarged peripheral lymph nodes and a lymph node aspirate was positive for *Leishmania*. Thus, this patient, who had persistently undetectable HIV-1 viral load and low CD4 cell count and was receiving HAART, had several episodes of VL over a six-year period, with relapses and lack of response after various treatments, including antimonials, amphotericin B lipid formulations, and miltefosine (Figure 1).

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FIGURE 1. Clinical course, including bone marrow aspirate, lymph node aspirate, CD4 cell count, treatment for visceral leishmaniasis, and highly active antiretroviral therapy, for the patient. ABLC = amphotericin B lipid complex; BMA = bone marrow aspirate; Itra = itraconazole; LipAB = liposomal amphotericin B; MA = meglumine antimoniate; Milt = miltefosine; PM = paromomycin.

In this context, we decided to use combined therapy with meglumine antimoniate, 20 mg/kg intramuscularly per day, plus parenteral paromomycin, 16 mg/kg intramuscularly per day, for 30 days. Five weeks later, the patient showed an increase in hemoglobin, lymphocytes, CD4 cell count, and platelets (10.5 g/dL, 960 cells/ μ L, 106 cells/ mm^3 , and 119,000 cells/ μ L, respectively), and a clear clinical improvement, with weight gain and disappearance of the enlarged lymph nodes. A bone marrow aspirate after treatment demonstrated an absence of *Leishmania*. Reversible ototoxicity was the only adverse effect related to the treatment. At completion of the acute-episode therapy, the patient received maintenance therapy consisting of itraconazole, 400 mg/day (200 mg twice a day) plus miltefosine, 150 mg/day, with a one-month on, two-months off schedule. After 19 months of treatment with the combined therapy, he is completely asymptomatic, his CD4 cell count is 204 cells/ mm^3 , and his hematologic parameters are normal. We plan to continue with the secondary prophylaxis until the patient achieves a CD4 cell count of 350 cells/ mm^3 for 3–6 months.

Visceral leishmaniasis in HIV-infected patients is associated with a lower treatment response rate and a higher incidence of mortality and relapses than in the general population.¹⁷ The experience obtained in the non-HIV-infected population with resistance to first-line therapy may be useful to treat difficult HIV cases. The efficacy of antimonial stibogluconate has been widely evaluated in non-HIV-infected patients as a single agent¹⁰ and in association with different doses of paromomycin,^{12–16} which is known to act synergistically with antimonials.¹⁸ Reported data have shown that at doses of 20 mg/kg and 16–20 mg/kg of antimonial stibogluconate and paromomycin, respectively, the combined therapy is more effective and associated with a lower rate of therapeutic failures (relapses and partial cures) than stibogluconate alone, even in situations where there is a high rate of resistance to antimonials. In addition, paromomycin is well tolerated and a low incidence of transient, reversible ototoxicity has been reported with its use

(2%).⁹ As a single agent, paromomycin at doses of 16–20 mg/kg is more effective than antimonials,¹⁰ but there is a greater possibility of developing resistance. Paromomycin showed noninferiority to amphotericin B in an open-label study.⁹ Thus, the available data suggest that paromomycin may have a role in the treatment of VL, at least in patients failing standard regimens and particularly in combination with another agent. To our knowledge, there is little published experience with paromomycin in HIV-infected patients.⁶

Maintenance therapy or secondary prophylaxis is a crucial strategy to avoid relapses of opportunistic infections in immunosuppressed HIV-infected patients. Compared with *Pneumocystis jiroveci* pneumonia and toxoplasmic encephalitis, the experience in leishmaniasis is more limited and less successful. Antimonials and liposomal amphotericin B have shown some effectiveness, but a considerable percentage of patients relapse despite secondary prophylaxis with these agents. Miltefosine can be used as treatment and maintenance therapy of VL. There is little information on the use of this drug in HIV-positive patients, but one study has reported that it is not effective as a single agent in patients with several relapses.⁵ Thus, combined therapy may be a better option for maintenance treatment or secondary prophylaxis of this infection. Itraconazole is mainly used for the cutaneous form of leishmaniasis, and there is some reported data on successful treatment of gastrointestinal VL with this drug.¹⁹ Itraconazole has also been used successfully as secondary prophylaxis for VL in HIV-infected patients.²⁰ There are no clinical trials confirming the efficacy of the combination of itraconazole plus miltefosine, but because both drugs are active against *Leishmania* and our patient had no other options, we chose this regimen in the schedule described above.

The results in this case suggest that a combination of parenteral paromomycin plus antimonials in the acute episode, followed by secondary prophylaxis with oral itraconazole plus miltefosine, may be a successful alternative for HIV patients with visceral leishmaniasis and repeated previous failures with standard therapy. Moreover, given the high failure rates of standard therapies in HIV-infected patients, the role of this approach as first-line therapy should be examined.

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