The impact of highly active antiretroviral therapy (HAART) on visceral leishmaniasis in Spanish patients who are co-infected with HIV

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Clinicians in Madrid have been observing and treating HIV-positive patients with visceral leishmaniasis (VL) for over a decade. As their records cover some of the co-infection cases that occurred before and after highly active antiretroviral therapy (HAART) was introduced into Spain, retrospective analysis of the records has allowed some of the effects of HAART on local VL to be determined. Encouragingly, HAART appears to have decreased the annual incidence of VL among local AIDS cases, from 4.81 cases/100 to just 0.8 case/100 (P < 0.0005), a first episode of VL now appearing only when there is obvious HAART failure. Unfortunately, it does not seem to be very good at preventing VL relapses; within 24 months of antileishmanial treatment, 70% of patients who were receiving HAART had such relapses. The mean time between antileishmanial treatment and VL relapse was, however, longer when HAART was used than when it was not (20 v. 13 months). In those receiving HAART, relapses of the VL often occurred despite increasing CD4+ cell counts and undetectable HIV loads, indicating that successful treatment of the viral infection is insufficient to prevent the relapse of the leishmaniasis. These results are in general agreement with other observations made in Spain. VL relapses are possible and even frequent in HIV-positives who have no more than 200 CD4+ cells/μl, but secondary prophylaxis to prevent VL relapses may be safely suspended if a CD4+ count of >200 cells/μl can be maintained using HAART. VL also seems to hamper the immunological recovery of the HIV-positive, although HAART appears to have little effect on the clinical manifestations of VL.

VISCERAL LEISHMANIASIS IN THE HIV-INFECTED: INCIDENCE

Human infection with Leishmania infantum, the cause of visceral leishmaniasis (VL) in Europe, is quite common in the countries that lie in Mediterranean basin, although it is not always symptomatic. In the south of Spain, for example, leishmanial amastigotes can be found in 6% of bone-marrow biopsies collected from asymptomatic HIV-positive patients, although all such patients will probably develop clinical VL (De la Rosa et al., 2001). In southern Europe generally, 2%–9% of AIDS patients will develop VL (WHO, 1999). During the 1990s, most (50%–60%) of the adult VL cases recorded in Spain were co-infected with HIV, and up to 17% of Spanish HIV-positive patients with non-viral fever were found to be suffering from VL (Miralles et al., 1995). The great majority of the new cases of VL detected in Spain now occur in patients with late-stage HIV infection (77%–90%, 7%–22% and only 0%–3% of such cases having <200, 200–500 and >500 CD4+ cells/μl, respectively), and 42%–72% meet the standard criteria for AIDS before or during their first episode of leishmaniasis (WHO, 1995, 1999; Alvar et al., 1997; López-Vélez et al., 1998). A review of HIV-associated VL in Spain has recently been published (Pintado and López-Vélez, 2001).
As VL appears to be an opportunistic infection of the HIV-positive, the incidence of new cases in Europe was expected to drop once the treatment of the HIV-infected with highly active antiretroviral therapy (HAART) became common. In Madrid, the numbers of new cases of VL and of VL/HIV co-infection seen in 1998 — the year after treatment of HIV-infected patients with protease inhibitors (PI) became widespread in Spain — were at least 40% lower than the annual mean numbers recorded over the previous 5 years (Anon., 1999). The annual incidence of new cases of VL among the AIDS cases of Madrid fell from 0.48 case/100 before HAART was introduced to 0.26 case/100 once HAART became routine (López-Vélez et al., 2001). Similar, HAART-attributable drops in the incidence of VL among the HIV-infected have been observed elsewhere in southern Europe. For example, the annual incidence of VL among the HIV-positive (cases/100 HIV-positives) dropped from 0.70 to just 0.13 in Rome (Tumbarello et al., 2000), from 0.80 to 0.12 in Barcelona (C. Tortajada, unpubl. obs.), and from 0.95 to 0.15 in Sevilla (J. A. Pineda, unpubl. obs.).

As HAART is unlikely to affect the transmission of leishmanial parasites, it is assumed that the antiretroviral drugs prevent an asymptomatic infection with L. infantum from becoming symptomatic, or at least slow the development of any clinical manifestations of the leishmanial infection. This assumption is supported by the results of a recent study by De la Rosa et al. (2001), who gave HAART to 11 of 17 HIV-positive patients who had subclinical infections with L. infantum. Although none of the 17 patients had received any antileishmanial drugs, none of those on HAART (but two of those not on HAART) developed VL during follow-up.

There has been speculation that L. infantum may be transmitted to humans not only by sandflies but also, among intravenous-drug users (IVDU), on shared needles (Alvar et al., 1997). As IVDU form the main risk-group for L. infantum/HIV co-infection, some of the drop seen recently in the incidence of new cases of VL among Europeans with HIV infection could be a side-benefit of needle-exchange programmes. As the drop in incidence seen in HIV-positives who are not IVDU is, however, similar to that seen in the IVDU, it seems clear that HAART is largely responsible. Among the patients investigated by Amador et al. (2001), however, the incidence of VL in the year before HAART was the same as that in the year after the patients began antiretroviral treatment (2.2 cases/100).

**PROGNOSIS**

VL usually follows a chronic and relapsing course in HIV-positive patients, the number of relapses and the mean time between them being dependent on immunological state. After a correctly treated initial episode of VL, 60% of HIV-positives will relapse within 6–9 months and 90% within 12 months, the mean period between subsequent relapses becoming ever shorter. Without HAART, 10%–19% of the co-infected patients will die during their first episode of VL and up to 24% will die during the month following the end of antileishmanial treatment. These deaths are attributed to the toxicity of the antileishmanial drugs, to complications arising during the episode, and/or to further opportunistic infections. The mean survival time for a case of L. infantum/HIV co-infection has been estimated at 4–12 months (Alvar et al., 1997; Laguna et al., 1997, 1999; López-Vélez et al., 1998). In terms of prognosis, the benefits of PI treatment are not as clear-cut for leishmaniasis as for other opportunistic infections. Ridolfo et al. (2000), for example, observed extensive disseminated cutaneous leishmaniasis in a patient 8 months after her first episode of VL, even though the patient was receiving treatment with PI and, at the time of her relapse, had 157 CD4+ cells/μl and an undetectable viral load. In the study by Villanueva et al. (2000), five of 20 HIV-positive patients receiving PI (but no
secondary prophylaxis against VL) were found to relapse within about 15 months of their first episode of VL; the relapses could not be attributed to failure of the antiretroviral treatment, since all the patients showed marked immunological improvement (with a mean CD4+ count of 278 cells/μl and a mean viral load of <200 copies/ml). In another, similar study, 10 patients with one or more previous episodes of VL were followed for about 2 years, without secondary prophylaxis but with PI treatment (Casado et al., 2001). Although all 10 responded well to the antiretroviral treatment (with a mean of 230 CD4+ cells/μl and a significant drop in the viral load by the end of the second year), seven (70%) had VL relapses. The mean time taken to relapse (20 months) was, however, significantly longer than that recorded in the patients before they began PI treatment (13 months). In general, it appears that, following antileishmanial treatment, the probability of a VL relapse in a HIV-infected patient is not solely dependent on the immunocompetence of the host (as indicated by CD4+ counts) but is affected by other factors — perhaps the amastigote load and location or the virulence and/or antileishmanial resistance of the infecting strain of L. infantum (Faraut-Gambarelli et al., 1997; Kubar et al., 1998; Di Giorgio et al., 1999). Curiously, the infection of HIV-positives with L. infantum leads, via a switch from a Th1 to a Th2 response, to a drop in CD4+ counts and an increase in viraemia (Medrano et al., 1998). Leishmanial infection therefore tends to limit the immunological recovery expected after the administration of HAART and may increase viral replication and facilitate the progression to AIDS (Clerici et al., 1993; Nigro et al., 1999).

SECONDARY PROPHYLAXIS AGAINST LEISHMANIASIS

Antileishmanial treatment is usually associated with clinical recovery from the VL but rarely prevents numerous relapses in those co-infected with HIV. Encouragingly, the results of several studies now indicate that secondary prophylaxis can help to prevent the relapses, although most of these investigations were non-randomized and carried out without any comparative control groups (Pérez-Molina et al., 1996; Ribera et al., 1996; Pintado et al., 2001; F. Pasquau, unpubl. obs.). Laguna et al. (1997) found such prophylaxis to have little value but most of their patients were already seriously ill and/or had already relapsed several times. The only prospective and randomized trial to compare the effectiveness of secondary prophylaxis (3 mg amphotericin B lipidic complex/kg, given every 21 days) with non-prophylaxis, using a 12-month follow-up, demonstrated that the prophylaxis was beneficial, increasing the probability of being free of illness at 12 months from 22%, seen in the control group, to 50% (unpubl. obs.). There has been a recent report on the beneficial effect of the combination of HAART and monthly secondary prophylaxis, with liposomal amphotericin B, in two co-infected patients who showed no sign of relapsing after 10–12 months (Mastroianni et al., 2000). It therefore seems sensible to use maintenance therapy systematically, beginning soon after the first episode of VL, the aim being to prevent an early relapse and the associated switch from a Th1- to a Th2-type response. Once the patients have fully recovered their immune function, thanks to the PI treatment, suspension of the prophylaxis could be considered. Berenguer et al. (2000) investigated 15 co-infected patients who had previously been treated for at least one episode of VL. When, after these patients had received monthly prophylaxis with antimonials or liposomal amphotericin B as well as HAART for over a year (64–70 weeks), the secondary prophylaxis was suspended, only three relapsed within the next year (the three relapsing cases had 128–182 CD4+ cells/μl). In another study, neither of the two VL cases under HAART and monthly
prophylaxis with pentamidine relapsed in 18 months of follow-up after the prophylaxis was stopped (Soriano et al., 2000).

**CLINICAL MANIFESTATIONS**

The clinical manifestations of leishmaniasis in the HIV-infected cover a particularly wide spectrum. Clinical forms that would be atypical in the immunocompetent are quite common in the immunocompromised and appear unaffected by PI treatment. Recently, first episodes of VL were observed in three very immunodepressed patients to whom HAART had just begun to be administered. Although all three had low CD4+ counts (30–94 cells/μl) when their leishmanial infections became symptomatic, they also had undetectable viral loads, raising the possibility that their symptoms were a consequence of PI-attributable immune restoration (Jiménez-Exposición et al., 1999). This phenomenon has not, however, been detected in any other studies, even those of patients with proven, subclinical, *L. infantum* infection when they commenced HAART (De la Rosa et al., 2001).

**CONCLUSIONS**

Currently, there are simply too few data available to be able to draw many definitive conclusions on the impact of HAART on VL in Spain and elsewhere, especially when related investigations have given discordant results. Nevertheless, the data that have been collected indicate that HAART: (1) decreases the number of new cases of VL (such cases generally appearing only when the antiretroviral treatment has failed); (2) delays but, unless the CD4+ count rises above 200 cells/μl, fails to prevent VL relapses; and (3) may allow secondary prophylaxis (maintenance therapy) to be safely suspended once the CD4+ count can be maintained at >200 cells/μl. They also indicate that VL negatively influences the immunological recovery of patients, although HAART seems to have little impact on the clinical manifestations of *L. infantum* infection in the HIV-positive. Further, prospective and multi-centre studies are clearly needed to elucidate the full impact of HAART on VL.

**REFERENCES**


