Acta Derm Venereol 2014; 94: 242–243

SHORT COMMUNICATION

Combination Therapy with Amphotericin-B and Miltefosine for Post-kala-azar Dermal Leishmaniasis: A Preliminary Report

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Accepted Dec 17, 2012; Epub ahead of print Aug 27, 2013

Post-kala-azar dermal leishmaniasis (PKDL) is a recalcitrant dermatosis following apparent cure from visceral leishmaniasis (VL). Patients with PKDL are considered the sole reservoir for the parasite during inter-epidemic periods of VL in India (1). Mono-drug therapy has been recommended to date in PKDL, with the newer drug for PKDL are Miltefosine and Amphotericin-B while older drug is Sodium Stibogluconate. Combination treatments advocated for VL have yet to be formulated in PKDL. We describe here the treatment of 3 cases of PKDL that demonstrate the greater effectivness of treatment with a combination of amphotericin-B (AmB) and miltefosine (MIL) over AmB alone.

CASE REPORTS

Case 1

A 20-year-old man with no history of VL, presented with 1 year's duration of facial eruptions (Fig. 1 A–B). He had been diagnosed elsewhere with PKDL and treated with 850 mg sodium stibogluconate (SSG) intravenous (i.v.) daily for 4 months without relief. On cutaneous examination multiple circumscribed nodules were found on his face, lips and ears, and hypopigmented macules on his limbs and trunk. Histopathology revealed a dense diffuse dermal infiltrate of lymphocytes, histiocytes and plasma cells abutting and effacing the epidermis. Although Leishman-Donovan bodies (LDB) were absent on slit-skin smear, positive rK39 strip test and PCR established *Leishmania donovani* infection. Absence of LDB in smear may be due to low sensitivity of slit-skin smear, which is reported to be approximately 58% (2). Quantitative real-time PCR (Q-PCR) revealed a moderately high parasite load in tissue biopsy (6,614 parasites per µg DNA) (3). The patient was given daily i.v. infusion of 50 mg AmB, with strict monitoring of renal functions. For complete subsidence the infusions were continued to a total dosage of 4.5 g AmB, given over 100 days (Fig. 1A, B). Liver and renal functions were found to be within normal limits during the treatment. Biopsy performed at 2 months' post-treatment revealed insignificant dermal infiltrate and no detectable parasite in Q-PCR.

Cases 2 and 3

Subsequently, 2 men aged 24 years (case 2) and 26 years (case 3), treated with SSG for VL at the age of 8 and 10 years, respectively, presented to our hospital. Case 2 had extensive nodulation over his face, limbs, genitalia, tongue and buccal mucosa, while case 3 exhibited papulonodules over his face, limbs and genital skin, with hypopigmented macules on his trunk (Fig. 1 C–D). Both patients had had the eruptions for the previous 5 years. They underwent Venereal Disease Research Laboratory test (VDRL), HIV, rK39 strip test and examination of slit-skin smear. The results confirmed PKDL, as rK39 strip test and LDB slit-skin smear were positive in both cases. Blood VDRL and HIV tests were negative. Histopathology revealed a grenz zone in the dermis and a pandermal infiltrate of lymphocytes, plasma cells and histiocytes, with LDB. PCR-RFLP confirmed *L. donovani* as the causative species. The parasite burden determined by Q-PCR was very high (590,000 parasites/µg tissue DNA) in case 2, while it was moderate in case 3 (1,627 parasites/µg tissue DNA) (3). The relatively low parasite burden in case 3 was probably due to the fact that he had earlier taken a few

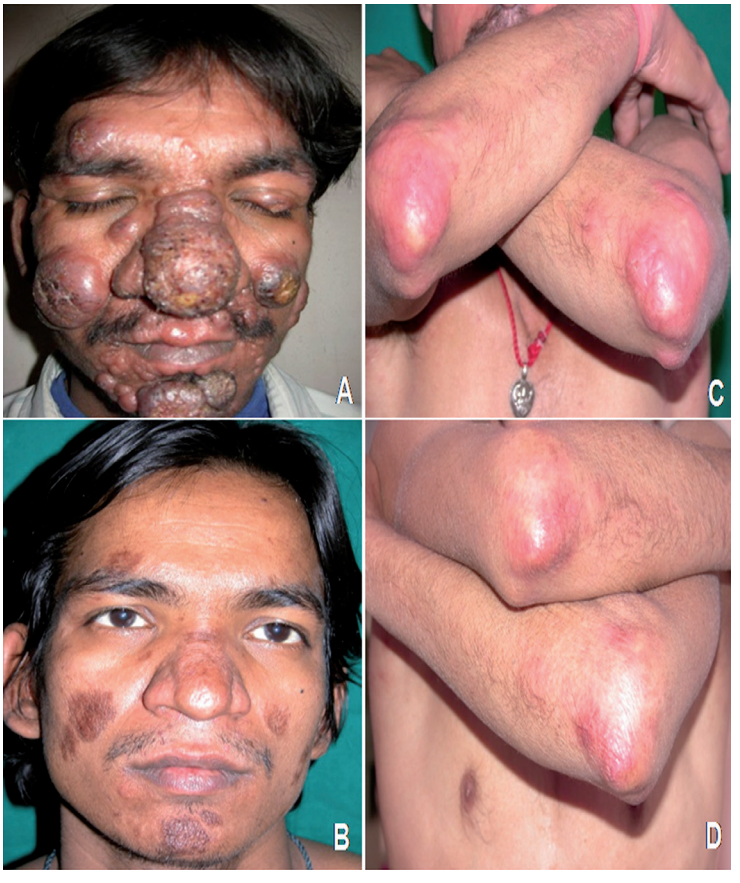

Fig. 1. Patients with post-kala-azar dermal leishmaniasis (PKDL) treated successfully with amphotericin-B (AmB) alone, and with AmB in combination with miltefosine (MIL). Case 1. (A) Tumour-like nodules on the face before, and (B) regression after treatment with AmB alone. Case 2. Large indurated plaques (C) before, and (D) cured after treatment with combination of AmB and MIL.

antimonial injections for PKDL treatment. As both patients had widespread lesions, an attempt was made to institute combination therapy. Our aim was to use an effective regimen with reduced dosage and duration compared with monotherapy. Hence, a combination of daily i.v. infusions of 50 mg AmB for 20 days plus 50 mg oral MIL three times a day for 40 days was prescribed for both cases; however, in case 3 the dose of MIL had to be reduced to twice daily for 60 days to avoid vomiting (4). Signs of subsidence appeared after 10 days of therapy, with complete regression by the end of treatment (Fig. 1C, D). Biopsy at 2 months post-treatment revealed mild superficial perivascular infiltrate in the dermis, while no parasites were detected in Q-PCR. The liver and renal functions monitored at pre-, mid- and post-therapy remained normal in the 2 cases, with no other side-effects.

Follow-up

All 3 cases were followed-up post-treatment for 2 years; all remained healthy with no signs of relapse.

DISCUSSION

Relapse and refractoriness following antimonial therapy (5) has made AmB the currently recommended treatment for PKDL (6). AmB, when used alone to treat PKDL, has shown a trend of rising dosage from 717.5 mg to 3 g (6) and up to 4.5 g, as in Case 1 above, similar to the trend observed for antimonials in the past (7). However, the high dose of AmB may not be tolerated by all patients with PKDL because of its nephrotoxicity. The advent of oral MIL (50 mg given three times daily for 60 days or twice daily for 90 days) heralded a breakthrough, but in patients with extensive disease the duration of therapy had to be prolonged (4). Moreover, there are already reports of relapses following MIL treatment in VL as well as PKDL (8, 9). On the basis of efficacy and safety of AmB-MIL combination in animals (10), liposomal AmB with MIL was evaluated and found to be effective for treating VL (11). Here, we show that the dose and duration of MIL and AmB when used alone could be substantially reduced when the 2 drugs are used in combination. When given alone, irreversible renal damage due to AmB (5) and the gastrointestinal side-effects of MIL can be serious limiting factors (7). Combination therapy has the advantage of reduced dose and duration, and hence better tolerance and compliance compared with mono-drug therapy. It would also reduce the chance of the emergence of microorganisms resistant to a single drug. Thus, we conclude that AmB-MIL combination is the preferred regimen over AmB or MIL alone in PKDL, particularly in those with extensive disease.

ACKNOWLEDGEMENTS

Financial support. Miltefosine capsules were supplied by the National Vector Borne Diseases Control Program of the Department of Health, Government of India. Partial financial support, provided by the Indian Council of Medical Research, New Delhi, India, is gratefully acknowledged. KA and VS are grateful to the Council for Scientific and Industrial Research and the University Grant Commissions, India, respectively, for fellowships.

Ethics. The study was approved by the ethics committee of Safdarjung Hospital, India. All patients or responsible adults provided written informed consent for the sample collection and subsequent analysis.

Financial interests. No organization with any financial interest was involved in this study.

The authors declare no conflicts of interest.

REFERENCES

1. Thakur CP, Kumar K. Post kala-azar dermal leishmaniasis: a neglected aspect of kala-azar control programmes. Ann Trop Med Parasitol 1992; 86: 355–359.
2. Salotra P, Singh R. Challenges in the diagnosis of post kala-azar dermal Leishmaniasis. Ind J Med Res 2006; 123: 295–310.
3. Verma S, Kumar R, Katara GK, Singh LC, Negi NS, Ramesh V, Salotra P. Quantification of parasite load in clinical samples of leishmaniasis patients: IL-10 level correlates with parasite load in visceral leishmaniasis. PLoS One 2010; 5: e10107.
4. Ramesh V, Katara GK, Verma S, Salotra P. Miltefosine as an effective choice in the treatment of post-kala-azar dermal leishmaniasis. Br J Dermatol 2011; 165: 411–414.
5. Thakur CP, Narain S, Kumar N, Hassan SM, Jha DK, Kumar A. Amphotericin B is superior to sodium antimony gluconate in the treatment of Indian post-kala-azar dermal leishmaniasis. Ann Trop Med Parasitol 1997; 91: 611–616.
6. World Health Organization (WHO). Control of the leishmaniasis. Technical Report Series 2010; 949: 49–90.
7. Thakur CP, Kumar K. Efficacy of prolonged therapy with stibogluconate in post-kala-azar dermal leishmaniasis. Ind J Med Res 1990; 91: 144–148.
8. Sundar S, Singh A, Rai M, Prajapati VK, Singh AK, Ostyn B, Boelaert M, Dujardin JC, Chakravarty J. Efficacy of miltifosine in the treatment of visceral Leishmaniasis in India after a decade of use. Clin Infect Dis 2012; 55: 543–550.
9. Bhandari V, Kulshrestha A, Deep DK, Stark O, Prajapati VK, Ramesh V, Sundar S, Schonian G, Dujardin JC, Salotra P. Drug susceptibility in Leishmania isolates following miltefosine treatment in cases of visceral leishmaniasis and post kala-azar dermal leishmaniasis. PLoS Negl Trop Dis 2012; 6: e1657.
10. Seifert K, Croft SL. In vitro and in vivo interactions between miltefosine and other antileishmanial drugs. Antimicrob Agents Chemotherap 2006; 50: 73–79.
11. Sundar S, Sinha PK, Rai M, Verma DK, Nawin K, Alam S, Chakravarty J, et al. Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomized controlled trial. Lancet 2011; 377: 477–486.