Editorial

Challenges in the Management of Visceral Leishmaniasis

Visceral leishmaniasis (VL) or kala-azar remains a significant problem in the tropical and subtropical regions of the world. In India most cases are reported from Bihar, West Bengal, Jharkhand and eastern UP(1). Diagnosis of VL depends upon the demonstration of parasites in tissue smears which is often difficult in the endemic regions. Widespread resistance to pentavalent antimony compounds has made situation extremely complex for these antimony refractory patients as it was the only affordable drug. Recent years have seen considerable advance in the diagnosis and treatment of VL. This editorial tries to provide an update on these developments to the readers.

The gold standard for diagnosis remains demonstration of parasites in splenic or marrow smears. While splenic aspiration is highly sensitive, it is associated with the potential risk of fatal hemorrhage whereas the sensitivity of bone marrow aspiration is low, and it is a painful and cumbersome procedure. Often these modalities are not available in disease-endemic areas. Parasite culture is very expensive and is largely confined to research laboratories.

With the consequence, several serological tests have been developed for VL and used in the past. Aldehyde and Chopra antimony tests detect high levels of immunoglobulins, and have poor sensitivity and specificity, and these should be completely abandoned. Specific serological tests including indirect fluorescent antibody (IFA) test, enzyme-linked immunosorbant assay (ELISA) using parasite or recombinant (rK39) antigen have excellent sensitivity and varying specificity depending upon the antigen used(3,4). However, these require expensive equipment, continuous power supply and skilled manpower, and thus are seldom used in endemic regions. Direct agglutination test (DAT), which is based on agglutination of formalin fixed whole parasites by antileishmanial antibodies, is a relatively simple test and has been used in Sudan regularly, but batch to batch variations, requirement of refrigerator, long incubation and multiple pipetting steps are major handicaps and thus DAT has not become popular in India.

A rapid immunochromatic strip test using rK39 antigen has now become available commercially. The test is simple, rapid (10 minutes), inexpensive, requires no other reagents or instruments and can be performed in the field by the paramedics. The test requires only 1 to 2 drops of blood/serum and results can be read visually. It has a sensitivity of 100% and a specificity of 93-98%(5,6). Although it is an excellent test for making a diagnosis of kala-azar, the test cannot be used in predicting response to therapy or relapses, as IgG antibodies persist in blood for long time after successful treatment of infection. Further, significant proportion of healthy endemic controls test positive indicating asymptomatic infection, thus, diagnosis based on a positive rK39 strip test should only be made against a strong clinical backdrop of VL. A new test, based on the detection of antigen in urine of the patients with VL, has been recently described. This latex agglutination test (KATEX) has a specificity of ~100% but a sensitivity of 47.7-100%(7,8). The test becomes negative after

successful therapy. We found the test to be 87% sensitive and the specificity was 99%, and in 97% patients it turned negative after successful treatment(9). Through detection of parasitic DNA by polymerase chain reaction (PCR), it is possible to make a definitive diagnosis using 1-2 ml of peripheral blood, and in 85% patients it turns negative at the end of treatment and in 97% at 3 months(10).

The treatment of kala-azar is extremely unsatisfactory. Drugs are toxic and most are required to be given by parenteral route for prolonged duration to achieve cure. Close monitoring of the patient is required in hospital. Until recently no effective oral drug was available for kala-azar. In HIV coinfected patients the risk of treatment failure and relapse is high. The rising incidence of antimony unresponsive kala-azar, especially in North Bihar, has resulted in the loss of the only affordable antileishmanial drug for patients of this region, whose daily earning remains <1 US$. The prohibitive cost of newer formulations (lipid associated amphotericin B) is beyond the reach of most patients, thus leaving them therapeutic orphans.

Pentavalent antimony compounds have been in use for the treatment of VL since 1930s. They are the drugs of choice for reasons of efficacy, cost, availability and familiarity. Two compounds in use are sodium antimony gluconate (sodium stibogluconate; antimony) and meglumine antimonate. The recommended dose is 20 mg/kg/day IV or IM for 30 days. During last 10 to 15 years, widespread resistance to antimony compounds has been reported from Bihar, and now only 35-38% patients respond to antimony compounds (11,12). Thus antimony compounds are no longer the first line drug in Bihar. However, outside Bihar it continues to be effective and is still recommended as first line therapy(11).

Pentamidine isethionate was used as an alternative drug in stibogluconate resistant kala-azar. Although the success rate was high in the beginning, its efficacy declined over the years and its use is also associated with serious toxicity like insulin dependent Diabetes mellitus(13). Thus, its use has been abandoned.

Amphotericin B, a polyene antibiotic, has emerged as a first line drug for antimony unresponsive patients. Its antileishmanial activity is attributed to its ability to inhibit the ergosterol biosynthesis in the parasite membrane, leading to increased membrane permeability and parasite killing. The dose of conventional preparation (amphotericin B deoxycholate) is 0.75-1.0 mg/kg by slow intravenous infusion over 4 to 6 hours on alternate days for 15 doses. Response to treatment is excellent with long term cure rate ~100%. Major problem with its use are infusion related side effects like fever, chills, and thrombophlebitis; occasionally serious toxicity like nephropathy, hypokalemia, myocarditis and rarely death can occur. The desire to develop safer and more effective formulations of amphotericin B to treat systemic fungal infections led to the development of lipid-associated amphotericin B preparations. Currently, three preparations are available: liposomal amphotericin B (AmBisome); amphotericin B cholesterol dispersion (Amphocil, ABCD); and ampho-tericin B lipid complex (ABLC, Abelcet). These drugs have been extensively evaluated for the treatment of VL, and are equally effective with no organ toxicity, and it is possible to deliver the total dose over a short duration(14). Usually, a total dose of 15 mg/kg is likely to produce a cure rate of nearly 100%, but AmBisome even with a total dose of 3.75 mg/kg cured 89% patients(15). Even a single dose of AmBisome (5 mg/kg) cures >90% patients(16).

Till now no effective oral agent was available for the treatment of VL. Several drugs like allopurinol, fluconazole, keto-conazole were tried in the past but with- out much success. Miltefosine, originally developed as an antineoplastic agent, has achieved a cure rate of 94% in VL(17). It has been tested in children from age 2-11 years, and they tolerated the drug exceedingly well without significant hematological or biochemical toxicity. This is a significant advance in the management of VL, eliminating the need for parenteral therapy and prolonged hospitalization. The recommended dose is 2.5 mg/kg/day in divided doses taken after meals for 28 days. Side effects include mild gastrointestinal symptoms like vomiting and diarrhoea, asymptomatic transient elevation of hepatic enzymes, and rarely nephrotoxicity. It is available in India by the trade name of Impavido (Zentaris). It is a teratogenic drug and thus can not be used in pregnant females, and females of child bearing age group must practice contraception for the duration of therapy and for 2 months after therapy.

Paromomycin (aminosidine), an amino-glycoside, has recently been tested in a phase III trial in Bihar and preliminary results of a daily 15 mg/kg intramuscular injection for 21 days indicate excellent safety and efficacy (18). The drug is being made in India with full adult course expected to cost US $ 10.00, and should be approved in India in 2005. Sitamaquine (WR 6026), an oral primaquine analogue, has good antileishmanial activity and has been tested in India in phase II studies, but more trials are needed before it is approved for clinical use.

Considering the burden of disease in poorer sections of society and widespread emergence of drug resistance necessitating costly drug therapy, it is incumbent upon the Government to initiate steps to provide free/subsidized care to these patients. This can be done through primary health care system with directly observed therapy, as is already being done in case of tuberculosis. There is also an urgent need to develop multidrug combination regimens of short duration to improve compliance, and to protect and prolong the life of currently effective drugs.

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REFERENCES

1. Bora D. Epidemiology of visceral leishmaniasis in India. Nat Med J Ind 1999; 12: 62-68.
2. Piarroux R, Gambarelli F, Dumon H, Fontes M, Dunan S, Mary C, *et al.* Comparison of PCR with direct examination of bone marrow aspiration, myeloculture and serology for diagnosis of visceral leishmaniasis in immunocompromised patients. J Clin Microbiol 1994; 32: 746-747.
3. Sundar S, Rai M. Laboratory diagnosis of visceral leishmaniasis. Clin Diag Lab Immunol 2002; 9: 951-958.
4. Singh S, Sachs AG, Chang KP, Reed SG. Diagnostic and prognostic value of K39 recombinant antigen in Indian leishmaniasis. J Parasitol 1995; 81: 1000-1003.
5. Sundar S, Reed SD, Singh VP, Kumar PCK, Murray HW. Rapid accurate field diagnosis of visceral leishmaniasis. Lancet 1998; 351: 563-565.
6. Sundar S, Pai K, Sahu M, Kumar V, Murray HW. Immunochromatographic strip-test detection of

anti-K39 antibody in Indian visceral leishmaniasis. Ann Trop Med Parasitol 2002; 96: 19-23.

7. Attar ZL, Chance ML, Safi S El, Carneg J, Azazy A, Hadi M. El. et. al. Latex agglutination test for detection of urinary antigens in visceral leishmaniasis. Acta Trop 2001; 78: 11-16.

8 Rijal S, Boelaert M, Regmi S, Karki BM, Jacquet D, Singh R, *et al*. Evaluation of a urinary antigen-based latex agglutination test in the diagnosis of kala-azar in eastern Nepal. Trop Med Int Health 2004; 9: 724-729.

9. Sundar S, Agrawal S, Pai K, Chance M, Hommel M. Detection of leishmanial antigen in the urine of patients with visceral leishmaniasis by latex agglutination test (KATEX). Amer J Trop Med Hyg (in press) 2005.

10. Maurya R, Singh RK, Kumar B, Salotra P, Rai M, Sundar S. Evaluation of PCR in the diagnosis and assessment of cure in Indian kala-azar. J Clin Micro (in press) 2005.

11. Sundar S, More DK, Singh MK, Singh VP, Sharma S, Makharia A, et al. Failure of pentavalent antimony in visceral leishmaniasis in India: report from the center of the Indian epidemic. Clin Infect Dis 2000; 31: 1104-1107.

12. Thakur CP, Narayan S. A comparative evaluation of amphotericin B and sodium antimony gluconate, as first-line drugs in the treatment of Indian visceral leishmaniasis. Ann Trop Med Parasitol 2004; 98: 129-138.

13. Thakur CP, Kumar M, Pandey AK. Comparison of regimens of treatment of antimony-resistant kala-azar patients: A randomized study. Am J Trop Med Hyg 1991; 45 : 435-441.

14. Sundar S, Mehta H, Suresh AV, Singh SP, Rai M, Murray HW. Amphotericin B treatment for Indian visceral leishmaniasis: Conventional versus lipid formulations. Clin Infect Dis 2004; 38: 377-383.

15. Sundar S, Jha TK, Thakur CP, Mishra M, Singh VR, Buffels R. Low-dose liposomal amphotericin B in refractory Indian visceral leishmaniasis: a multicenter study. Am J Trop Med Hyg. 2002; 66: 143-146.

16. Sundar S, Agrawal G, Rai M, Makharia MK, Murray HW. Treatment of Indian visceral leishmaniasis with single or daily infusions of low dose liposomal amphotericin B: randomised trial. Brit Med J 2001; 323: 419-422.

17. Sundar S, Jha TK, Thakur CP, Juergen E, Herbert S, Christina F, *et al*. Oral miltefosine for Indian visceral leishmaniasis. N Eng J Med 2002; 347: 1739-1746.

18. Jha TK, Olliaro P, Thakur CP, Kanyok TP, Singhania BL, Singh IJ, et al. Randomised controlled trial of aminosidine (paromomycin) v sodium stibogluconate for treating visceral leishmaniasis in North Bihar, India. Brit Med J 1998; 316 : 1200-1205.