Lack of Response to WHO/MDT; a Case Report by Habtemariam and Xabier

TO THE EDITOR:

The standard World Health Organization-recommended multidrug therapy (WHO/MDT) uses a combination of rifampin, clofazimine and dapsone for 24 months for the treatment of a multibacillary leprosy patient. The main rationale for this recommendation is to prevent selection of drug-resistant mutant *Mycobacterium leprae,* which is a certain possibility if any antileprosy drug is used as monotherapy. Any modification of the WHO/MDT is acceptable as long as this principle is strictly adhered to.

In this particular case (IJL:632–634;1993) it seems that this young lady, suffering from lepromatous leprosy, was sequentially treated with brodimoprim, rifampin, dapsone, clofazimine and ofloxacin, often as monotherapy between June 1991 and June 1993. During this period, the patient received the standard WHO/MDT for a period of only 2 months. This regimen was changed since the authors felt that ". . . the response to the antibacterial treatment was poor, i.e., there was no clinical regression of nodules and the reduction in the bacterial index and morphological index was poor."

It is clear that the authors were extremely anxious to cure their patient as quickly as possible but, in their enthusiasm, the patient was treated virtually with sequential monotherapy using different antileprosy drugs. Fortunately, the organisms remained sensitive to rifampin and clofazimine in normal doses. The presence of dapsone resistance was probably expected, given the high prevalence of both primary and secondary dapsone-resistant *M. leprae* in Ethiopia.

Finally, as far as I am aware, so far there are no confirmed reports of any multiple-drug resistance among leprosy patients treated adequately with the WHO-recommended MDT regimens.

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Response to Comments by Dr. Pannikar

TO THE EDITOR:

We are quite aware that the World Health Organization-recommended multidrug therapy (WHO/MDT) is to prevent the selection of drug-resistant *Mycobacterium leprae* mutants and to improve compliance with treatment of patients by shortening the duration of treatment. The introduction of new antileprosy chemotherapy is still a need felt by many for reasons such as further shortening the duration of treatment.

Investigators have shown in mice that brodimoprim has profound synergism with dapsone against *M. lufu* (a species closely related to *M. leprae*) infection in killing even dapsone (DDS)-resistant bacilli.

Our patient was thus enrolled in the brodimoprim trial and received a 3½-month, short-course therapy. Due to her low response to this treatment, however, we had to resort to the treatment as mentioned in the paper, according to ALERT's Hospital policy for the management of highly infectious lepromatous leprosy patients coming from areas where MDT is not as yet implemented.

During the second episode of erythema nodosum leprosy, although the bacterial index reduction was not foreseen, the clinical improvement and the morphological index (MI) was expected to fall to zero, when treated with bacteriostatic drugs, let alone with a rifampin-containing regimen.

Contrary to our assumption, there was no clinical improvement and the MI remained as high as 4% at some sites. In view of 3 weeks of supervised daily rifampin, clofazimine and dapsone + daily dapsone and

clofazimine self-administered for 4 months and followed by 2 months of WHO/MDT and the MI remaining high, at this particular time we could only assume that the patient was harboring multiple-drug resistant *M. leprae*. A mouse foot pad sensitivity study to DDS, rifampin and clofazimine was carried out while the patient was continued on daily rifampin, clofazimine, dapsone and ofloxacin in combination, ofloxacin being given only for 3 months.

To summarize, our patient was on brodimoprim monotherapy for 3½ months for trial and, in retrospect, on clofazimine monotherapy for 4 months because she was found to be fully resistant to dapsone at the end. Our patient has never had either rifampin or ofloxacin as monotherapy.

Indeed, our patient had received intensive WHO/MDT with additional ofloxacin. As we have tried to explain here and in the paper, we hope Dr. Pannikar will realize that we did not do a sequential treatment for our patient.

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Status of HBV DNA and HBsAg in Leprosy Patients

TO THE EDITOR:

Hepatitis due to "B" infection and mycobacterial disease are still major problems of the developing world and a possible association between hepatitis B virus (HBV) infection and leprosy has been proposed ([1, 4]). The data available to date are based on HBsAg status alone and are inconclusive, mainly due to the lack of consistency in the methods used for detection ([6, 7]). In the present study we investigated the correlation of HBV infection with different types of leprosy where, in addition to HBsAg, cloned HBV DNA was used as a marker of ongoing HBV infection.

Forty-one patients belonging to different types of the spectrum of leprosy, classified clinically and histologically according to Ridley-Jopling ([8]), were used in the study. HBV DNA analysis was done by a dot blot assay which had a detection limit of 3×10^4 virus particles (0.1 pg DNA) from 200 μl of patient's serum ([2]). HBsAg was assayed by Abbot EIA using a commercial kit according to manufacturer's instructions. The results are summarized in The Table. It is evident that the incidence of HBV infection is more in LL leprosy, suggesting a correlation between the HBV infection and the cell-mediated immune response to *Mycobacterium leprae*. Almost 50% of the patients in the LL category were found to have either HBV DNA or HBsAg in their serum (The Table, E). However, detailed analyses of individual cases indicated that the presence of HBsAg or HBV DNA alone is not sufficient to draw any conclusions about the status of HBV infection. Out of 41 samples analyzed, only 3 were found to be positive to both HBV DNA and HBsAg. In the LL category, five cases were picked up by the DNA probe although they were negative for HBsAg. This was not surprising, and could be due to a higher sensitivity offered by molecular hybridization assays ([2]).

On the other hand, 4 of 13 BL and 3 of 7 BB leprosy patients did not show any detectable HBV DNA in their sera, although they were HBsAg positive. The presence of HBsAg in serum in the absence of HBV DNA has been reported when HBV DNA becomes integrated into hepatocellular chromosomes ([5]). A similar situation also exists in the case of acute viral hepatitis where HBsAg appears in the serum before HBV DNA. In the high cell-mediated immune response category (BT, TT) only 2 of 10 patients showed HBV DNA; all were negative for surface antigen. The HBsAg carrier rate in India is reported to be 4%–6%. In a control study, out of 150 HbsAg-negative, apparently healthy individuals on the basis of clinico-biochemical criteria, 9 were found to be HBV DNA positive ([2]).