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Letter to the Editor

Analysis of bacteriological Index between fixed multidrug therapy and new WHO recommended alternative regimen with ofloxacin, minocycline and clofazimine of rifampicin resistant cases from the hospitals of The Leprosy Mission, India

Sir,

Consequent to the decline in the prevalence of leprosy, in 2005 the vertical programme of the National Leprosy Eradication Programme was gradually merged with the general health system in India. At this juncture of elimination, there have been reports of relapses from many endemic countries, indicating that these relapses might be due to the emergence of mutated resistant strains of *Mycobacterium leprae* under drug pressure or to re-infection. The emergence of drug resistance is a concern and a threat for many infectious disease intervention programmes, especially those that have secondary prevention (chemotherapy) as the main component of their control strategy. According to the World Health Organization (WHO), 3192 relapse cases were reported globally from 51 countries in 2017 [1]. Brazil reported the highest number of relapses (1734), followed by India (457) and Indonesia (267). The Leprosy Mission (TLM) hospitals in India reported 300 relapse cases in the last 5 years. As rifampicin, a bactericidal drug, is the backbone of the multidrug therapy (MDT) regimen for multibacillary (MB) leprosy, it is important to monitor the emergence of rifampicin-resistant cases, followed by immediate administration of an alternative (ALT) drug regimen for controlling the spread of infection in the community. Recent reports and publications have indicated the existence of rifampicin resistance in several endemic areas [2–4]. In the case of resistance to rifampicin, fluoroquinolones become the preferred category of second-line drugs. Unfortunately, quinolone-resistant strains of *M. leprae* have also been reported from several countries [5], probably due to the extensive use of quinolones for treating several types of other common infections in the community. To meet the challenge of containing the disease and to halt the spread of drug-resistant *M. leprae* strains in the population, it is essential to act immediately for the identification and treatment of cases harbouring drug-resistant strains of *M. leprae* in the country and consequently help in the elimination of leprosy from India.

This study was approved by The Leprosy Mission Trust India Ethical Committee. Patients registered at different TLM hospitals in India over a 9-year period (2009–2018) were screened. Data were collected regarding the demographic profile (Table 1) and clinical details, including number of lesions, estimation of bacterial load by determination of bacteriological index (BI) from slit-skin smear examination and PCR for determination of drug resistance. The criteria for the diagnosis of 'resistant' to MDT were as follows: (i) persistent/appearance of new lesions after completing 12 months of the WHO-MB-MDT regimen and (ii) persistent positivity/increase in the BI after 12 months of WHO-MB-MDT-regimen.

Table 1
Basic demographic and bacteriological index (BI) details of patients treated with the WHO-ALT and WHO-MB-MDT regimens.

Treatment group	WHO-ALT[a]	WHO-MB-MDT[b]
Demographic characteristics		
No. of patients	7	8
Male:female ratio	6:1	7:1
Mean age (range) (years)	32 (22–40)	38 (19–68)
Mean enrolment BI	4.377	3.373
Mean BI after completion of treatment	1.476 (P = 0.0009)	2.125 (P = 0.01)
Clinical diagnosis at time of recruitment		
BL	1	1
LL	6	7

WHO, World Health Organization; ALT, alternative; MB, multibacillary leprosy; MDT, multidrug therapy; BL, borderline lepromatous; LL, lepromatous leprosy.
[a] Ofloxacin + minocycline + clofazimine.
[b] Rifampicin + ofloxacin + dapsone.

A total of 564 leprosy cases (389 relapse and 175 new cases) registered between 2009 and 2018 were enrolled in the study. All of these cases were tested for drug resistance to rifampicin using PCR and gene sequencing. Of the 564 cases, 54 (9.6%) were found to be harbouring rifampicin-resistant *M. leprae*, of whom only 15 patients could be followed-up for another 24 months with further drug regimen. Among these 15 patients, 8 patients were administered a repeat WHO-MB-MDT regimen and the remaining 7 patients received a WHO-recommended ALT regimen. The ALT regimen comprised minocycline 100 mg/day, clofazimine 50 mg/day and ofloxacin 400 mg/day for 6 months (intensive phase), followed by ofloxacin 400 mg/day and clofazimine 50 mg/day for the next 18 months (maintenance phase).

Following completion of the ALT regimen of ofloxacin, minocycline and clofazimine, the mean BI decreased from 4.377 to 1.476; in most cases the reduction in BI was by 2–3 log and in three cases the BI came down to 0. On the other hand, in the WHO-MB-MDT group although a BI of 0 was noted in two patients, in one patient there was a rise in BI by 2 log at the end of 24 months (Table 1). The average reduction in BI in this group was only by 1 log (Fig. 1). Statistical analysis using paired t-test of the reduction in BI was found to be significant (P = 0.0009) in the ALT regimen group. The P-value was 0.01 in the MDT group, showing that difference in mean of BI at Day 0 and Month 24 was significantly different from the P-value of the ALT group of 0.0009.

To prevent the development of multidrug-resistant strains of *M. leprae*, current leprosy control strategies will be of utmost importance and would immediately need the establishment of a built-in mechanism of a surveillance for identification of rifampicin drug resistance early along with its immediate treatment with

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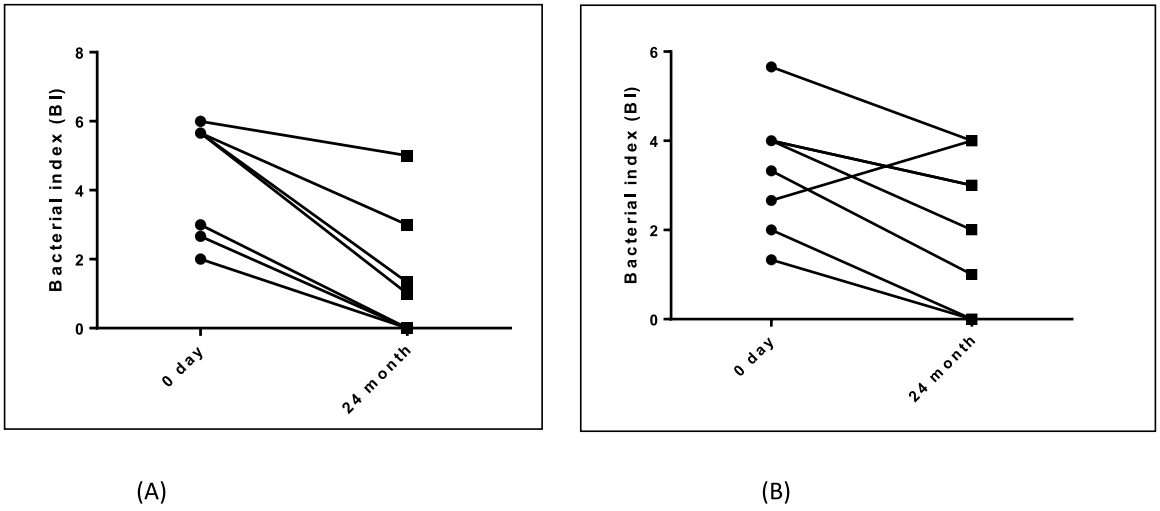

Fig. 1. Comparison of bacteriological index (BI) at Day 0 and Month 24 of treatment in rifampicin-resistant leprosy patients treated with either (A) the ofloxacin, minocycline and clofazimine alternative (ALT) regimen or (B) the multidrug therapy (MDT) regimen.

an ALT regimen as recommended by the WHO [6]. As yet there has been no publication for assessing the effectiveness of ALT regimens in the management of rifampicin-resistant leprosy. In our study, we administered a group of rifampicin-resistant relapse cases with an ALT regimen and compared their BI with another rifampicin-resistant group administered the WHO-MB-MDT regimen. We observed in this study that there was a significant reduction in the BI during the treatment of rifampicin-resistant cases with the ALT regimen (P = 0.0009). Thus, the present study indicated that the ALT regimen should be administered immediately in rifampicin-resistant cases. A limitation of this study is the small sample size, but initially it is worth reporting that ALT treatment is better than MDT in rifampicin-resistant cases.

This is the first report on the ALT regimen for rifampicin-resistant cases of leprosy, as rifampicin is the main drug in MDT. The findings of this study further suggest that there is an urgent need for establishment of a robust surveillance mechanism to identify relapse and rifampicin drug resistance in the National Leprosy Eradication Programme of India.

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Competing interests

None declared.

Ethical approval

Clinical data, including treatments, were retrieved from the patient information database and clinical records kept in The Leprosy Mission Trust India (TLMTI) hospital. The study received ethical approval from the TLMTI Ethical Committee.

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