

## REPLY: B JI and J-H GROSSET

Sir,

The following is in response to the above letter from Dr Almeida regarding our editorial entitled 'Recent advances in the chemotherapy of leprosy'.<sup>1</sup>

The backbone of the current multidrug therapy (MDT) regimens is rifampicin (RMP) because of its great potency; the major objective to combine it with other drugs is to prevent the selection of RMP-resistant mutants during RMP-monotherapy, due to the huge bacterial population in untreated multibacillary (MB) leprosy patients.<sup>1</sup> Both pefloxacin and ofloxacin displayed very powerful bactericidal activities in lepromatous patients: 99.99%, or 4 'logs', of organisms viable on D0 were killed by 22 doses of either pefloxacin 800 mg or ofloxacin 400 mg<sup>2</sup>; and the average size of RMP-resistant *Mycobacterium leprae* in an untreated lepromatous patient is no more than 10<sup>4</sup>, or 4 'logs'. By definition, RMP-resistant mutants should be killed by fluoroquinolones at the same speed as RMP-susceptible organisms, thus, all the RMP-resistant mutants may be eliminated after 22 doses of either pefloxacin or ofloxacin. It is, therefore, possible that the combination of RMP and ofloxacin may considerably shorten the duration of MDT.

However, we have never claimed that 1 month of ofloxacin will be able to eliminate  $5 \times 10^{11}$  viable (non-persister) *M. leprae* as described by Dr Almeida. Because of the limitations of the tools, we know that at best, we are only able to measure the initial 5 or 6 logs of the killing even using nude mice for monitoring the bactericidal activity.<sup>2</sup>

Dr Almeida has calculated the declining rates of viable organisms during treatments with various drugs. It is difficult to verify the validity of these calculations simply because of the lack of a sensitive tool. Nevertheless, it is unlikely that the declining rate of viable organisms remains the

same as the initial killing, at least during the course of treatment with RMP.<sup>3</sup> In addition, unless one can demonstrate that 3 months of clofazimine can kill about 4 logs of organisms in a previously untreated lepromatous patient, it seems over-optimistic to assume that 3 months of daily RMP and clofazimine could be sufficient for the treatment as suggested by Dr Almeida.

Plenty of information has already demonstrated the seriousness of dapsone-resistant leprosy, and that its prevalence increases with time if dapsone monotherapy is continued.<sup>4</sup> The later results<sup>5</sup> from other areas were entirely consistent with the earlier assessments. The dapsone susceptibility of the *M. leprae* strains isolated from previously untreated patients had changed significantly: the primary dapsone-resistant *M. leprae* was virtually nonexistent before 1977;<sup>6</sup> whereas the organisms from one-third<sup>4</sup> to one-half<sup>5</sup> of the MB patients diagnosed in the 1980s were resistant to dapsone. In addition, regular administration of dapsone in an adequate dosage could not effectively prevent the relapse, because after 20 years of supervised sulphone therapy, in which a majority of the patients had received the dapsone equivalent of at least 100 mg daily, the annual relapse rate still remained 1%.<sup>7</sup> Therefore, it was clear that the attempts to control leprosy by dapsone monotherapy were failing, and the justification to further evaluate the 3-year dapsone monotherapy, as proposed by Dr Almeida, is weak.

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## References

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- <sup>2</sup> Grosset JH, Ji B, Guelpa-Lauras CC, Perani EG, N'Deli L. Clinical trial of pefloxacin and ofloxacin in the treatment of lepromatous leprosy. *Int J Lepr*, 1990; **58**: 281–95.
- <sup>3</sup> Subcommittee on Clinical Trials of the Chemotherapy of Leprosy (THELEP) Scientific Working Group of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. Persisting *Mycobacterium leprae* among THELEP trial patients in Bamako and Chingleput. *Lepr Rev*, 1987; **58**: 325–37.
- <sup>4</sup> Ji B. Drug resistance in leprosy—a review. *Lepr Rev*, 1985; **56**: 265–78.
- <sup>5</sup> Guelpa-Lauras CC, Cartel J-L, Constant-Desportes M, Millan J, Bobin P, Guidi C, Brucker G, Flageul B, Guillaume J-C, Pichet C, Remy J-C, Grosset JH. Primary and secondary dapsone resistance of *M. leprae* in Martinique, Guadeloupe, New Caledonia, Tahiti, Senegal, and Paris between 1980 and 1985. *Int J Lepr*, 1987; **55**: 672–9.
- <sup>6</sup> Shepard CC, Rees RJW, Levy L, Pattyn Sr, Ji B, Dela Cruz EC. Susceptibility of strains of *Mycobacterium leprae* isolated prior to 1977 from patients with previously untreated lepromatous leprosy. *Int J Lepr*, 1986; **54**: 11–15.
- <sup>7</sup> Waters MFR, Rees RJW, Laing ABG, Fah KK, Meade Tw, Parikshak N, North WRS. The rate of relapse in lepromatous leprosy following completion of twenty years of supervised sulphone therapy. *Lepr Rev*, 1986; **57**: 101–9.