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Letters to the Editor

Regimens To Treat Lepromatous Leprosy

It was previously found for lepromatous leprosy patients that following discontinuation of treatment after 18 or more years of dapsone monotherapy, relapses began almost immediately and at a steady rate of 1% per year for up to 9 years (23). However, when rifampin was part of the treatment regimen, relapses occurred much later and on average 8 years after treatment had been discontinued (11). Thus, demonstration of the cure of lepromatous leprosy with finite regimens including World Health Organization (WHO) multidrug therapy (MDT) (24), when rifampin is part of the treatment, requires prolonged follow-up. As noted by Ji et al. (14), there are several articles attesting to the effectiveness of WHO MDT; however, except in one case (12), a significant number of truly lepromatous patients were not monitored for such prolonged durations. In that single study (12), 20% of patients were found to relapse and fully 40% with initial bacteriological indices greater than 4 relapsed. Thus, current claims for cure remain premature.

In previous studies with lepromatous patients carried out by ourselves and other investigators, single doses of minocycline (2, 8) or clarithromycin (1, 5) and even several doses of each did not result in a significant decrease in numbers of viable *Mycobacterium leprae* organisms in patients undergoing initial therapy for lepromatous leprosy. All these studies—contrary to what is reported by Ji et al.—including a thorough statistical analysis of our own work (8), are indeed at odds with the current one of Ji et al. (14), wherein a single dose of 200 mg of minocycline and 2 g of clarithromycin resulted in the killing of *M. leprae*. Ji et al. (14) ascribe their discrepant results to the fact that only in their work were *M. leprae* "titrated" and mice inoculated with less than 5×10^3 *M. leprae* cells (namely, 5×10^2 and 5×10^1), allowing for greater sensitivity in detecting killing of *M. leprae*. However, there are other explanations, perhaps equally credible, to explain these discrepancies. The mouse footpad technique is at best only semiquantitative, and systematic variations between results found in different laboratories are encountered. Variability might arise because of different patient populations and delays between obtaining patient biopsy specimens and performing mouse inoculation that ultimately affect *M. leprae* viability. For example, in the studies of Ji et al. (13, 14) biopsy specimens were obtained in Africa and inoculated into mice in Paris, while in our studies (5, 6, 8) biopsies were performed in California and mice were inoculated there. Variability also might be imposed by technical differences in processing specimens wherein mincing, osmotic and gentle mechanical dislodging of intracellular *M. leprae* organisms (which are known to clump) from cells, removal of footpads, processing of tissue, and microscopic counting (including variations in technique and number of fields assessed) all may affect the actual determination of the number of observed *M. leprae* organisms.

Shortly after the pioneering study by Shepard demonstrating growth of *M. leprae* in the mouse footpad, his laboratory and that of Levy exchanged technicians, shared specimens, and obtained reasonably uniform results (17). However, this has not been done since. In fact, the results of the killing of *M. leprae* by rifampin in patients obtained by Shepard et al. (20, 21) were found consistently superior to those of Rees et al. (18) and Waters et al. (22), who headed the other prominent footpad laboratory of this early era. While Shepard, Levy, and Fasal found that in lepromatous patients, a few days after the initiation of rifampin therapy viable *M. leprae* organisms were uniformly lost from the dermis, Rees, Waters, and coworkers found that in a significant fraction of patients, this required more than 2 to 3 weeks. It is further noteworthy that the killing of *M. leprae* by daily doses of minocycline was found to be more rapid in Paris (13) than in San Francisco (6). While Ji et al. (13) found that 9 of 10 patients treated with 100 mg of minocycline daily had no viable *M. leprae* at 1 month and 10 of 10 patients had none by 2 months, by the same techniques we (6) found that of patients given the same therapy, at 1 month 5 of 8 had viable *M. leprae* and by 2 months 2 of 8 had viable *M. leprae*. Because the actual proportion of viable *M. leprae* prior to therapy was much higher in the study of Ji et al. (13) than in our own (6), these findings are even more discordant than the preceeding figures alone imply.

Also, Ji et al. (14) uniquely compare the viability of organisms from one of two pretreatment biopsy specimens selected for higher bacteriological and morphological indices and presumably higher viability with viability of organisms in only one specimen obtained after therapy. Since the authors found a very wide range in viability of *M. leprae* from pretreatment skin biopsy specimens obtained from different patients (0.006 to 30%), surely also viability must similarly vary among different biopsy specimens from the same patient. Their approach prejudices results toward finding increased killing. This might explain not only their aberrant results with single-dose minocycline-clarithromycin therapy but the unanticipated killing they observed following daily treatment with dapsone and clofazimine. In short, the current results of Ji et al. (14) are indeed different from those found by others, and the previous ones cannot be dismissed simply as being a consequence of insensitive techniques.

In the past decade, minocycline (2, 4, 6, 8, 13, 15) and clarithromycin (1, 3, 5, 10, 13, 15) have been found bactericidal for *M. leprae* in mice and, upon daily administration as single agents or combined together, highly effective in short-term clinical trials with lepromatous leprosy patients. Not only do patients clearly improve, but viable *M. leprae* organisms in the dermis are cleared faster than with established agents, dapsone and clofazimine, but not as fast as with rifampin (19), the three components of WHO-recommended MDT (24). The issue is then how to incorporate minocycline and clarithromycin into a regimen to actually treat leprosy patients. I would advocate consideration of their daily administration. There are ample studies with animal models demonstrating that daily administration of these agents is a profoundly more potent regimen than monthly dosing regimens (7, 9, 16). The full promise of daily therapy with these agents in combination with rifampin should be realized first before lesser regimens are considered.

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Authors' Reply

We sincerely appreciate the interest of Dr. Gelber in our article (8). His letter has raised several interesting points regarding the issues surrounding clinical and experimental chemotherapy in treatment for leprosy. Some of them, such as relapse in multibacillary leprosy patients after treatment by the WHO MDT regimen, are extremely important topics but are beyond the scope of our article.

Although it has been claimed that no detectable bactericidal effect has been observed in leprosy patients after treatment with a single dose of clarithromycin (CLARI) (1, 5) or minocycline (MINO) (2, 4) in clinical trials conducted by other investigators, we have observed certain bactericidal activity by a single dose of CLARI-MINO, with or without ofloxacin (OFLO) (8). We have mainly attributed the discrepancy to the more sensitive "titrating" technique we used for measuring the bactericidal effect (8); of course, the difference between a single dose of drug used in monotherapy by others and combined therapy by us in the trials may also be an explanation for the discrepancy. We are pleased that Dr. Gelber accepts in his letter that the titrating technique has greater sensitivity, as he pointed out previously (4). It might be possible that the delays between obtaining biopsy specimens and mouse inoculation and the procedures followed in processing the specimens may affect the viability of *M. leprae*; however, the delays and the procedures are always the same in our laboratory and their potential effects, if any, on the viability of *M. leprae* should be similar to their effects on the bacilli derived from pre- and posttreatment biopsies. Consequently, these factors can hardly be applied as credible explanations for the discrepancy in bactericidal effect of a single dose of drug between different trials.

Based on published data, Dr. Gelber concludes that the killing of *M. leprae* by daily MINO in our trial (6) was more rapid than in his (3). In fact, by Fisher's exact probability calculation, his conclusion was valid only for the results at 1 month ($P < 0.05$) and not for those at 2 months ($P > 0.05$). In our view, such a difference in therapeutic effect is not uncommon, especially when the sample sizes in the trials are small (3, 6). The most important observation is that both trials clearly demonstrated the promising bactericidal effect displayed by daily treatment with MINO.

We compared the viability of *M. leprae* from one of the two pretreatment biopsy specimens, selected based on a higher bacterial index and morphological index, with that of *M. leprae* from one posttreatment biopsy specimen (6, 8). Dr. Gelber thinks that this approach prejudices results toward finding increased killing. It is important to point out that, because we were fully aware of the possibility of variation in viability of *M. leprae* organisms from different biopsy sites, the posttreatment biopsy specimen was taken from one of the two pretreatment sites that provided *M. leprae* for mouse inoculation. This is probably one of the best approaches to minimize the variation.

Regarding the future application of CLARI and MINO for the treatment of leprosy, Dr. Gelber proposes that the drugs should be administered daily. As we pointed out earlier, in combination with rifampin, CLARI-MINO, with or without OFLO, could be administered once monthly; otherwise, these drugs should be given daily (7). Unfortunately, the health infrastructures in rural areas of developing countries, where the great majority of leprosy patients are located, are still very primitive; from an operational point of view, monthly treatment is far less demanding than daily administration.

Finally, we would like to emphasize that it is completely normal for different results to be obtained by different investigators; this is one of the important factors in stimulating the progress of science. We have never deliberately dismissed the earlier results obtained by other investigators, because we know this is not our job and there is no need to do so.

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