INTERNATIONAL JOURNAL OF LEPROSY

Volume 57, Number 2
Printed in the U.S.A.

Controlled Clinical Trial for Evaluation of Antimicrobial Drug Activity Against *M. leprae*

It is universally recognized that a controlled clinical trial is required in order to assess the comparative merits of different drug regimens for their antimicrobial activities against human infectious diseases, e.g., urinary tract infection, tuberculosis or infectious diarrhea. The aim of this paper is to emphasize that in leprosy, as in other diseases, the comparative effectiveness of various drug regimens against *Mycobacterium leprae* can only be established by a strictly controlled clinical trial.[1, 2]

To exclude factors which may influence the antimicrobial activity other than the tested drug regimens, the controlled clinical trial in infectious diseases is a scientific investigation in which all efforts should be made to ensure that the only variables whose effects will be measured are the treatment regimens under comparison. Thus, patients with a similar form or type of the disease and past clinical history, harboring the same pathogen with similar drug susceptibility, are randomly allocated to the different drug regimens to be compared; and the drugs should be administered regularly according to the protocol; the antimicrobial activity, together with other beneficial effects and side effects of the regimens under comparison, should be assessed, whenever possible blindly, with relevant predetermined parameters. In order to observe the statistical significance of possible differences in results between the tested regimens, the optimal number of patients in each treatment group should be adequately planned. Finally, to ensure that the trial does not expose patients to unreasonable risks, the protocol of the trial must be reviewed and approved by a competent ethical committee, and the informed consent of the patients involved should be obtained.

Since the spontaneous evolution of an infectious disease can be erratic, and since the response to the drug may be different due to previous treatment, for a controlled clinical trial in which the main purpose is to evaluate the antimicrobial activity in humans, only previously untreated patients with the most evolutive form of the disease should be selected. Under such circumstances, the response to treatment can basically be attributed to the activity of the tested drug regimen. Following the same principle, the activity of different drug regimens against *M. leprae* should be assessed only in previously untreated lepromatous leprosy patients.[3]

From a chemotherapeutic point of view, the following three major factors may explain treatment failure: a) poor antimicrobial activity of the drug(s); b) resistance of the causative organisms to the drug(s); and c) noncompliance of the patient to the treatment. All of these factors should be taken into account when designing a controlled clinical trial.

The prerequisites of the drugs to be tested in a clinical trial should include the following: a) evidence of the antimicrobial activity has been firmly established; and b) absence of major toxic side effects in toxicological studies or from previous clinical trials. For most infectious diseases, the potential benefit of the drug(s), in terms of antimicrobial activity, can be assessed in the test tubes because the responsible pathogens are able to grow *in vitro*. In contrast, since *M. leprae* cannot yet be cultivated *in vitro*, the activity of drugs against *M. leprae* can only be demonstrated in the mouse foot pad system. Of course, the dosage of the drugs to be tested in the mouse should be carefully selected, and the pharmacokinetic differences of the drug(s) between mouse and human must be taken into account in the dosage selection for a human trial. This is of paramount importance because, with careful design, the drug activity in humans can be predicted, at least to date, from the activity obtained in the mouse foot pad system.[4]

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[1] Hirschmann, J. V. and Inui, T. S. Antimicrobial prophylaxis: a critique of recent trials. Rev. Infect. Dis. **2** (1980) 1–23.

[2] Ronald, A. R. Clinical trials of antimicrobial agents following licensure. J. Infect. Dis. **159** (1989) 3–6.

[3] WHO Expert Committee on Leprosy. Sixth Report. Geneva: World Health Organization, 1988. Tech. Rep. Ser. 768.

[4] Proceedings of the Workshop on Experimental

In the treatment of an infectious disease, normally the active drug is an antimicrobial agent. To compare the activity of different drug regimens, it is necessary to ascertain that the causative organisms are susceptible to the tested drug(s) and therefore the patients harboring organisms resistant to these (as a consequence of primary or secondary resistance) must be excluded, otherwise assessment of the drug activity will be distorted. Hence, bacterial susceptibility to the tested drugs should be measured before starting any controlled clinical trial aiming to compare the activity against *M. leprae* between various drug regimens, especially when dapsone and rifampin are contained in the regimens. In this connection, it should be emphasized that, as in the case of the paucibacillary form of tuberculosis, paucibacillary leprosy patients must not be selected for the trial to compare antimicrobial activity of drug regimens, since neither the initial drug susceptibility of the organisms nor the response of the organisms to the prescribed drugs can be directly measured.

In order to measure the drug activity in a clinical trial, it is essential that patients should be administered the drug(s), and only the prescribed ones, regularly. To ensure regular treatment, all drugs should be given under supervision, and all efforts should be made to prevent patients surreptitiously taking drug(s) other than the prescribed ones, especially during the course of surveillance after stopping chemotherapy. The most effective way to prevent noncompliance during chemotherapy is to hospitalize the patients. Hospitalization will also facilitate the carrying out of various examinations and monitoring the side effects of the treatment. The most difficult issue is to prevent patients surreptitiously taking drugs during the surveillance period when they will undoubtedly be followed up as outpatients. Dapsone is easily accessible to most patients and although rifampin is not so easily obtained, a few doses of the drug may dramatically influence the outcome of surveillance, especially when the tested regimens do not contain rifampin. Therefore, special efforts should be made during the surveillance period, such as prescribing placebos, urine dapsone analysis and health education. In order to detect whether rifampin is being surreptitiously administered, a simple urine test should be developed.

Two other major issues remain: a) the choice of reliable parameters for the assessment of drug activity against *M. leprae* and b) the number of patients to be selected for the trial. In most infectious diseases, reliable parameters are the speed of microbial killing, the percentage of patients in whom the microbes have been killed, and the percentage of patients remaining without signs of viable organisms at a given time of surveillance after stopping treatment. All of these parameters directly measure antimicrobial activity. The clinical and histopathological parameters are only indirect markers of antimicrobial activity, and most immunological parameters are irrelevant to the antimicrobial activity of the drug. This is also true in leprosy. Reliable parameters are the length of treatment needed to render the organisms unable to infect mice, the percentage of patients whose organisms became noninfective to mice after a given period of treatment, and the rate of bacteriological relapse (confirmed by mouse foot pad inoculation) after stopping treatment. Although these parameters are laborious and time consuming to apply, they are the only ones directly related to the antimicrobial activity of the drug.

Last, but not least, an important issue is the sample size of the trial, i.e., the number of patients per regimen. In general, there is a better chance to observe the statistical significance of possible differences between the results if the sample size is larger. However, one should not admit the largest possible number of patients into the trial and then calculate whether or not the differences are statistically significant at the end of the trial. The standard approach is to collect all available information related to the expected differences and then to determine the sample size required in each treatment group for the expected differences to reach a significance level of 5% and a power of 90%. In other words, consultation with experienced statisticians is extremely important when designing a controlled clinical trial, especially in leprosy, since both the number of

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Chemotherapy of Leprosy. Int. J. Lepr. **55** Suppl. (1987) 803–900.

the tools and their sensitivities in measuring the difference of antimicrobial activity against *M. leprae* are extremely limited, and to handle an excessively large number of patients under trial conditions for a long period of time will be difficult and very expensive.

Based on the above-mentioned principles, obviously it is not an easy task to plan and conduct a controlled clinical trial which compares the antimicrobial activity against *M. leprae* between different drug regimens. However, in order to obtain meaningful and clear-cut results, one should not give up the intention to conduct a strictly controlled clinical trial if promising new drugs, or concepts of new combined regimens, are available. The best way to avoid equivocal results on the antimicrobial activity against *M. leprae* by various drug regimens is for investigators never to be satisfied with carrying out a trial in a compromising way.

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