

# Chemotherapeutic Trials in Patients with Non-Lepromatous Leprosy

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The only way to determine whether a leprosy patient is cured is to discontinue anti-leprosy treatment and continue follow up to see if his disease recurs. Trials of this type are required in non-lepromatous leprosy: their aim should be to determine, in different types of leprosy, the minimum period of treatment required to give an acceptable relapse rate. Such trials may also serve to identify promising new drugs or drug combinations for the treatment of lepromatous leprosy, for a regime which shortens the time required to cure lepromatous leprosy may be expected to reduce the relapse rate in non-lepromatous cases.

For the past 15 years or so it has been largely assumed that drug trials should be carried out only on patients suffering from lepromatous leprosy (Waters *et al.*, 1967). The purpose of this paper is to re-examine this axiom, and suggest that for certain purposes it is essential to undertake drug trials in non-lepromatous leprosy.

At the most basic level, the following information is required about any drug for use against leprosy:

(1) Does it kill *Mycobacterium leprae*?

This information should be obtained primarily from experimental infections in the mouse footpad. Short term (about 6 months) pilot trials, assessing chiefly the bacillary kill, will confirm the footpad findings (Rees, 1971). For such trials patients with lepromatous leprosy are required.

(2) What are the complications during treatment?

In the case of leprosy, this means primarily the reactions: how frequent, how severe, what relationship to drug dosage, and what is the comparison with a "Standard" regime. The reactions in leprosy vary very greatly in type and severity according to the classification of the disease (Ridley, 1969); therefore such trials must include patients suffering from all types of leprosy. These studies should continue for as long as patients are liable to develop reactions—probably about five years on average, though less in tuberculoid cases, and longer in lepromatous. Such trials will also serve to evaluate drug toxicity.

(3) Does the drug cure leprosy, and if so how long does it take?

The only way to see if a patient is cured is to stop treatment and see if the patient relapses. Such trials clearly require patients with all types of leprosy, and their duration will depend on the classification. The aim will be to determine, in each type of leprosy, the shortest period of treatment which will bring about an acceptable relapse rate.

When these three requirements are set against our knowledge of drug therapy in non-lepromatous leprosy, it is clear that much work remains to be done. There is little information on the relationship of particular drugs or dosages on the incidence, severity or duration of reactions; and no systematic study has been made of the relapse rates following various periods of treatment in different types of leprosy. It appears, then, that in non-lepromatous leprosy (i.e. for at least three-quarters of leprosy patients) we do not know what drug to use, in what dosage, or for how long. After a quarter of a century of experience with dapsone, this is unsatisfactory.

Drug trials in non-lepromatous leprosy are therefore urgently required, to give accurate information on optimal practical drug regimes. There is, however, a further application for such trials, namely, to use non-lepromatous leprosy as a model to study the therapy of lepromatous leprosy. This application can be clearly seen when applied to the problem of "persisting" bacilli.

Probably the most serious problem of therapy in lepromatous leprosy is the time that is required to cure a patient. Even after many years of treatment with adequate doses of dapsone or other drugs, patients are liable to relapse when treatment is stopped. In such cases, bacilli must have survived anti-leprosy treatment; these bacilli are usually drug sensitive, for relapse cases normally respond *satisfactorily* to treatment with the original drug. It is the prolonged survival of these persisting bacilli which makes it necessary to continue dapsone treatment in lepromatous leprosy for decades rather than years. Any drug or drug combination which shortens the time required to cure leprosy must do so by virtue of an action on these persisters.

Persisting bacilli can be demonstrated in peripheral nerve, and smooth and striated muscle, in patients with lepromatous leprosy, as well as in skin (Waters and Rees, in preparation). These sites are probably not the only ones. However, the numbers are on the edge of detectability even with the most sensitive techniques available, and it is most unlikely that it will be possible to isolate "persisters" from patients under treatment for non-lepromatous leprosy: there will be too few bacilli. Nevertheless, the fact that there is a significant relapse rate in borderline and tuberculoid leprosy even after 2 years of effective chemotherapy (long enough to cure most cases of pulmonary tuberculosis) indicates that persisters are to be found even in these types of leprosy.

Direct study of persisters in lepromatous leprosy is difficult and in non-lepromatous leprosy probably impossible; but in all types of leprosy they can be studied indirectly, for if a patient relapses after a course of treatment, viable bacilli must have persisted. A few such cases will, no doubt, be due to reinfection; but the majority will be recurrences of the original infection. However, studies of this type in lepromatous leprosy would require a time scale of 2 decades (10 years at least of treatment, 10 years of follow up) and it is clearly desirable that the benefits of a new drug or drug combination should be demonstrated more rapidly than this.

It is likely that this could be achieved if non-lepromatous leprosy were used as a model for lepromatous. Persisting bacilli, with consequent relapse, are to be found in all types of disease, and it seems unlikely that the greater degree of cell mediated immunity to be found at the tuberculoid end of the spectrum will affect the results of a comparative trial of standard versus new therapy. Subpolar tuberculoid patients would probably prove most suitable for such a trial. The relapse rate after about 2 years of standard treatment might well be in the order of 10%, and the majority of these relapses would occur in the first 2 years after stopping treatment. Any drug which acted on persisters (and so had a chance of reducing the time required to cure lepromatous leprosy) would significantly reduce the relapse rate in these non-lepromatous cases.

There is, of course, no certainty that a drug or drug combination which reduced the relapse rate in tuberculoid cases would do so in lepromatous leprosy. But it is hard to conceive that a regime which failed to alter the relapse rate in tuberculoid cases would have any effect in lepromatous leprosy, in which cell mediated immunity is virtually absent. The attraction of this type of study is that it suggests a rational means of determining, in a reasonable period, whether any new therapy is likely to shorten the time required to cure lepromatous leprosy. The method deserves trial.

### References

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