Chemoprophylaxis against leprosy: expectations and methodology of a trial

P. VIJAYAKUMARAN*, P. KRISHNAMURTHY*, P. RAO* & E. DECLERQ**
**The Damien Foundation India Trust, Chetput, Chennai, India and **The Damien Foundation, Brussels, Belgium*

Summary Because of the great efficacy of multidrug therapy (MDT), it had been hoped that the widespread use of MDT would bring about a rapid decrease of the incidence of leprosy. To the present, a decrease of incidence has not been observed, possibly because of the long incubation period of the disease, and because general implementation of MDT is still recent. Other reasons, such as environmental sources of infection or the role of healthy carriers in transmitting *Mycobacterium leprae*, cannot be excluded. Therefore, one must seek alternative or supplementary strategies, such as chemoprophylaxis. Household contacts of leprosy patients are at greater risk of developing leprosy than is the general population. Therefore, a randomized, controlled trial of chemoprophylaxis, using a single 10 mg/kg dose of rifampicin, or a placebo, is planned in nine projects in India, among the household contacts of newly detected leprosy patients. Based upon assumptions of a protective efficacy of the chemoprophylaxis of 50%, an annual incidence of 2 per 1000 contacts, a desired power of the study of 90%, and a level of significance of 95%, 15,000 household contacts will be allocated randomly by household to each arm of the study, and followed for 5 years. Considered as household contacts will be all persons living in the same household as an index case and sharing the same kitchen. Pregnant women and infants will be excluded. To be certain that transmission of the organisms from the index case cannot occur once the prophylaxis is administered, rifampicin will be administered 2 months after diagnosis of the index case. Diagnosis of leprosy will be clinical, and confirmed independently. Although household contacts usually constitute only a small proportion of the new patients detected in a control programme, their high-risk status makes them particularly appropriate for a study of the potential effect of chemoprophylaxis. Following the trial, one could evaluate the usefulness and feasibility of using the same strategy in other population-groups, based on the number of persons necessary to treat to prevent one case.

Introduction

The introduction of multidrug therapy (MDT) has led to remarkable results, in terms of the reduction of the prevalence of leprosy. According to statistics published by the World Health Organization (WHO),[1] the registered prevalence has decreased by 85% in the course of the last 15 years. Although it had been hoped that a decrease of prevalence, and thus a reduction of the reservoir of infection, would bring about a reduction of incidence, this has not yet been demonstrated. There could be several reasons for this. The reason most often invoked deals

with the incubation period; it is often argued that leprosy has such a long incubation period that insufficient time has passed since the introduction of MDT, but that the decrease of incidence will eventually occur. Other possible reasons could be environmental sources of *Mycobacterium leprae*, including non-human hosts, the existence of healthy carriers capable of transmitting the infection, and the usually long delay before diagnosis, which permits infectious patients to disseminate their organisms to many non-infected contacts before they are finally diagnosed and treated. In any case, there appears a need for alternative or additional strategies to MDT.

Chemoprophylaxis of well-defined populations could be such a strategy. In earlier trials, both dapsone and acedapsone were shown to be effective in reducing the incidence of leprosy in the population-groups to which it was administered, although the effect waned with time.[2–7] Then, at the end of the 1980s, a trial of a single dose of rifampicin administered to the entire population was carried out in the Southern Marquesas Islands, using the same population as historical control.[8,9] More recently, in an attempt to accelerate the elimination of leprosy, a combination of rifampicin, ofloxacin and minocycline (ROM) was administered to the entire population of some Pacific Islands.[10] We intend to launch a trial, the objective of which is to examine whether a single 10 mg/kg dose of rifampicin is capable of producing a significant reduction of incidence among the household contacts of newly diagnosed leprosy patients.

Materials and methods

The trial will be launched in nine projects in India that are supported or directly operated by the Damien Foundation India Trust. Altogether, the projects include a population of about 2,250,000. About 3500–3800 new patients are detected every year in these projects, with an annual new-case detection-rate ranging from 4·0 to 42·5 per 10,000. Among household contacts, the rate ranged from 12·4 to 64·5 per 10,000 in 1999.

The trial will be randomized, double-blind, and placebo-controlled. It was decided that the chemoprophylaxis regimen to be tested should be safe, cheap and easy to administer, if it was to be applied later on a large scale; thus, a single-dose regimen was mandatory. The choice of regimen was restricted to rifampicin alone, or rifampicin combined with ofloxacin and minocycline (ROM), which was recognized by the WHO Expert Committee on Leprosy as an acceptable alternative for the treatment of single-lesion paucibacillary leprosy.[11] Although at first sight possibly more attractive, the ROM regimen has several drawbacks: it could have more side-effects or contraindications; it is much more expensive, and, even if proven effective, the cost of chemoprophylaxis will be an important factor in determining its future applicability; finally, after consultation with several experts in the chemotherapy of leprosy, it appeared that the addition of minocycline and ofloxacin in a single dose does not significantly enhance the bactericidal activity of rifampicin. It could prevent selection of the rifampicin-resistant mutants in individuals harbouring large bacterial populations. However, because such individuals are unlikely to be encountered in the setting of the trial, it was decided that the trial would be based on a single 10 mg/kg dose of rifampicin.

A rapid population survey will be undertaken in the projects, in an attempt to detect the largest possible number of patients. The new patients who are detected routinely in the course of the following 18 months will also be enrolled. All of the newly diagnosed patients will be

immediately placed on MDT. After a delay of 2–3 months, their contacts will be examined, and those not showing any sign of leprosy will receive either rifampicin or the placebo. The delay of several months between the start of treatment of the index case and administration of the chemoprophylaxis to the contacts was planned, in order to be certain that the contacts could not become infected by the index case after they themselves have received chemoprophylaxis.

Everyone living with an index case diagnosed during the enrolment period and sharing the same kitchen will be considered a contact. It is expected that about 3000 patients will be newly diagnosed, and that 30,000 contacts will be included in the trial.

All diagnoses of leprosy, both of the original cases and among their contacts, will be confirmed independently by the medical officer and the non-medical supervisor of each project. When there is disagreement, the suspect will be examined by a third assessor who will be both independent and experienced. Slit-skin smears will be taken from all new patients.

Systematic examination of all of the contacts will be done annually for 5 years. All of the contacts from the same household will be administered the same regimen, either rifampicin or the placebo. Allocation of each household to one of the groups will be done centrally. Patients, contacts and staff at the project level will not be aware of who receives rifampicin and who receives the placebo.

People with respiratory symptoms will be investigated for tuberculosis, and referred for treatment if the diagnosis is confirmed. Pregnant women and children under 6 months of age will be excluded from the study.

Assuming an annual incidence rate of 2 per 1000 among the contacts, a 50% reduction of incidence induced by rifampicin, a power of 90%, and a significance level of 95%, it has been calculated that each arm of the study should include 5140 contacts, to be followed for 5 years. To take into account the cluster effect and the risk of losing a number of contacts during follow-up, it has been decided that 15,000 household contacts will be enrolled in each arm of the study.

Expectations

The choice of the population for the trial is, of course, important. We have selected a population of household contacts of leprosy patients, because it is well known that they are at greater risk of developing leprosy than the general population.[12,13] Thus, household contacts appear particularly appropriate for a trial of chemoprophylaxis, which, for obvious reasons, would not be feasible in a population at small risk. Another advantage of selecting a contact population is the fact that they are usually easily identifiable. One could argue that, although their individual risk is great, the new cases detected among the contacts usually represent a small proportion of the new cases in an endemic community, thus limiting the impact of such a strategy on the total incidence. However, the proportion of contacts among the new cases is not everywhere negligible, and this proportion is likely to be larger in areas of lower endemicity. The degree of efficacy of a chemoprophylactic regimen is also not likely to be influenced by the absolute risk of developing the disease. Thus, if a chemoprophylactic regimen proved effective among contacts, its feasibility and usefulness in other subpopulations could then be evaluated, on the basis of the number of people needed to be treated in order to prevent one case, and the costs involved. We would imagine, for instance, that in the

future, in some areas of high endemicity, chemoprophylaxis could be administered to all of the people shown to be infected with *M. leprae*, the so-called healthy carriers. Or the definition of contact could be broadened, to include neighbours, or, because patients with leprosy are found in clusters, to the entire population of some villages. It is also possible that chemoprophylaxis could be combined with other strategies, such as vaccination. However, before contemplating such combined trials, it is necessary to gather information on the efficacy of each of the components.

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DISCUSSION

Professor Smith: Is there any evidence that chemoprophylaxis could precipitate clinical disease in someone already infected by killing the organisms, resulting in an immune response that precipitates clinical manifestations? If there were such evidence, it would be necessary to take this possibility into account in interpreting the results of this trial.

Dr Noordeen: This possibility was examined in the dapsone-prophylaxis study. During the first few months of treatment, no difference was observed between the dapsone and placebo groups. However, one must also consider the possibility of missed cases, should new cases be detected among those who had received chemoprophylaxis.

I'd like to ask another question. Is a placebo-control justified?

Dr DeClercq: The efficacy of chemoprophylaxis with ROM or rifampicin has not yet been measured with precision. Therefore, a well-controlled trial, employing concurrent controls, is still justifiable. We should not be required to rely upon historical controls, particularly in the face of a changing (decreasing) new-case detection rate.

Professor Grosset: In tuberculosis, it is very well established that, on an individual basis, but not on a public-health basis, chemoprophylaxis of household contacts is very efficacious, provided that the correct regimen is employed. Perhaps, in your programme, the 'control-regimen' should not be placebo, but rather rifampicin or ROM administered for longer durations, for example, 1 week and 1 month.

Dr DeClercq: I think that there is need for more than one trial. However, to test additional regimens in this trial would be to complicate it greatly.

Dr Cartel: Professor Grosset, did I understand you to say that you were considering a trial of various dosages of chemoprophylaxis?

Professor Grosset: No. I did not intend to suggest a trial of rifampicin or ROM administered for different durations, but rather than the single dose be compared with several doses rather than with placebo.

Dr Colston: I understand that our interest in chemoprophylaxis stems from the fact that the new-case detection rate has not diminished following implementation of MDT. Perhaps more important, do we understand why the new-case detection rate has not fallen following implementation of MDT? And can we expect the addition of chemoprophylaxis to MDT to cause this rate to fall more rapidly?

Dr Noordeen: Because we don't have a regimen for chemoprophylaxis that is 100% effective, and because household contacts account for only about 30% of the new cases in endemic areas, we cannot expect the addition of chemoprophylaxis to MDT to cause a more rapid decrease of the new-case detection rate, although it will undoubtedly prevent clinically evident leprosy in individuals.

Professor Ji: I don't think it a good idea to compare several doses of ROM or rifampicin with a single dose. A patient with PB leprosy is treated by a single dose of ROM. How can one ask an apparently healthy member of the patient's household to accept treatment by more than a single dose? In addition, I think that our purpose should be to determine whether or not a single-dose chemoprophylaxis regimen is active. If it is not, we should either forget about chemoprophylaxis, or search for a more effective single-dose regimen.