The new challenges for chemotherapy research

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Summary Scientific knowledge is constantly expanding, and needs are changing; therefore, efforts must be made to adapt the treatment of leprosy and the manner in which it is implemented to the newly identified needs. Because an effective vaccine against leprosy remains to be identified, multidrug therapy (MDT) is the only tool available for leprosy control. At present, therefore, the priority is to make MDT available in all endemic countries for all patients, even those living in difficult-to-access areas. The remaining important issues in chemotherapy research are to improve the quality of leprosy case-finding, improve the quality of MDT, identify the areas in which leprosy patients are not receiving proper MDT, and find the means necessary to ensure delivery to all of appropriate MDT. The MDT regimens recommended by the World Health Organization are of too long duration, require correct classification of the patients as PB or MB, and rely upon the daily self-administration of dapsone and clofazimine to prevent selection of rifampicin resistant mutants among MB patients. Thus, research leading to the development of new drug regimens should be directed toward overcoming the shortcomings of the presently recommended regimens. The drugs required to permit use of regimens of shorter duration, that may be employed among both PB and MB patients, and that enable fully supervised drug administration may be already in hand, and the necessary clinical trials to confirm efficacy and acceptability should be carried out.

Introduction

Because of the great efficacy of the multidrug regimens recommended by the World Health Organization (WHO) for chemotherapy of leprosy,[1,2] it is tempting to think that there is no need for further research into the chemotherapy of leprosy. One might consider that implementation of the WHO-recommended regimens alone, the efficacy of which is now well demonstrated, would be sufficient to achieve the goal of elimination of leprosy as a public health problem by the year 2005. However, such a consideration is a bit too simple and optimistic for the following reasons. First, scientific knowledge is constantly expanding, and needs are changing; therefore, efforts should be made to adapt the treatment of leprosy and the way it is implemented to the newly identified needs. Second, even if elimination can be achieved by regular administration of the WHO-recommended regimens, it can hardly be expected that elimination of the disease as public health problem (to less than 1 case per 10,000 inhabitants, i.e. fewer than 600,000 patients world-wide) could be sustained by employing current methods of diagnosis and treatment, without adaptation to the new epidemiological situation.

In fact, for leprosy, as for other diseases, stopping research would mean that leprosy has

disappeared and no longer requires the interest of the public and the scientific community. However, because there is no clear indication that leprosy is a disappearing disease, efforts to control leprosy must be sustained, and the treatment of leprosy must be adapted to the present situation, and especially to the post-elimination era. Therefore, research should be promoted.

The following list of possible, perhaps necessary improvements of the chemotherapy of leprosy is given as an illustration of the new challenges for chemotherapy research in leprosy.

Better use of existing tools

Without doubt, multidrug therapy (MDT) is the most important tool for leprosy control. Since their introduction in 1981, the WHO-recommended MDT regimens have cured more than 10 million leprosy patients, with an extremely low rate of complications and relapses.[3,4] Because an effective vaccine against leprosy remains to be identified,[5] MDT is the only tool available for leprosy control. At present, therefore, the priority is to make MDT available in all endemic countries for all patients, even those living in difficult-to-access areas. The remaining important issues in chemotherapy research are: (i) to improve the quality of leprosy case-finding in order to identify all existing leprosy patients, and only leprosy patients; (ii) to improve the quality of MDT, i.e. not only the delivery of drugs, but also their intake by the patients for the duration recommended; (iii) to recognize the areas in which leprosy patients are not receiving proper MDT; and (iv) to identify the causes for this, and to find suitable solutions.

Because elimination of leprosy requires that all existing patients be treated, and that the numerous operational obstacles be overcome, the research activities to be conducted for better use of existing tools are mainly operational, and require much more imagination and effort than laboratory-based research.

New drug regimens

Although the WHO-recommended MDT regimens are highly effective and well tolerated, they require, in addition to monthly supervised doses of rifampicin or rifampicin + clofazimine, the daily self-administration of dapsone for 6 months by PB patients, and of dapsone + clofazimine for 12–24 months by MB patients. Consequently, the WHO-recommended regimens have three shortcomings: (i) they are of long duration, even though the 6-month and 12- to 24-month treatments are much shorter than the treatments that had been required before the era of MDT; (ii) they require correct classification of the patients as PB or MB, because PB and MB patients are prescribed different drug regimens; and (iii) among MB patients, they rely upon the daily self-administration of dapsone + clofazimine to prevent selection of rifampicin resistant mutants. Research leading to the development of new drug regimens should be directed toward finding means of overcoming the shortcomings of the presently recommended regimens.

Drug regimens of shorter duration

Among the three components of the regimen recommended for MB patients, rifampicin is a

strongly bactericidal drug, whereas dapsone and clofazimine are mainly bacteriostatic. The only role of dapsone and clofazimine is to kill all naturally occurring rifampicin resistant mutant *Mycobacterium leprae*; for this purpose, both drugs must be administered daily for 1 or 2 years. If new drugs with greater bactericidal activity against *M. leprae* than dapsone and clofazimine were available and could be given in combination with rifampicin, killing of the rifampicin resistant mutants would be much more rapid, and the duration of MDT could be shortened. In fact, these drugs, members of the tetracycline and fluoroquinolone families,[6–9] exist. Experimentally in the mouse, and clinically in man, the activities of minocycline and ofloxacin against *M. leprae*, although inferior to that of rifampicin, are far superior to those of dapsone and clofazimine. Given in combination, minocycline and ofloxacin were almost as bactericidal as rifampicin and the three-drug combination minocycline + ofloxacin + rifampicin, and did not induce antagonism.

A more recently developed fluoroquinolone, moxifloxacin, is more potent than ofloxacin:[10] in the mouse, a single 150 mg/kg dose of moxifloxacin, equivalent to a dose of 200 mg in man, was much more active than the same dosage of ofloxacin and as active as a single 10 mg/kg dose of rifampicin. Also in the mouse, a single 10 mg/kg dose of rifapentine, a long-acting rifamycin derivative, demonstrated greater bactericidal activity against *M. leprae* than did a single 10 mg/kg dose of rifampicin, and the combination rifapentine + moxifloxacin + minocycline was significantly more bactericidal than the combination rifampicin + ofloxacin + minocycline. The clinical confirmation of these experimental data is in progress. It should be possible, therefore, to design drug regimens that are potentially much more active than the 12- to 24-month WHO-recommended regimen, and, therefore, could be administered for a shorter duration of time with equal efficacy.[11]

Because the WHO-recommended regimens have displayed excellent results in the field, the effectiveness and possible side-effects of any newly proposed drug regimen must be carefully tested in controlled clinical trials and in field trials before being applied in the field, in order not to deprive patients of a treatment of already demonstrated efficacy. What should be done was exemplified a few years ago by the decision to compare the efficacy and side-effects of the standard WHO-recommended regimens with those of a daily regimen consisting of rifampicin + ofloxacin administered for 4 weeks. WHO has launched a double-blind, controlled clinical trial involving more than 3000 patients, in which the long-term efficacy of the treatment is to be measured in terms of relapse rate. Because the results of the trial are not yet available, the tested regimens cannot be recommended for use in the field. Moreover, the selection of an ofloxacin resistant mutant after 1 month of treatment with ofloxacin + rifampicin in a previously treated patient harbouring a strain of *M. leprae* resistant to rifampicin dictates the need for extreme care.[12] Perhaps, as is the case with the WHO-recommended regimen for MB leprosy, only three drug regimens, e.g. rifampicin + ofloxacin + minocycline, or, better, rifapentine + moxifloxacin + minocycline, will be acceptable to minimize the risk of resistance to one of the prescribed drugs.

Same regimen for PB and MB patients

At present, the drug regimens recommended for PB and MB patients differ in duration and components, requiring accurate classification of PB and MB patients, and different management of the drugs for PB and MB patients. A first simplification would be to treat every patient with the three-drug combination rifampicin + dapsone + clofazimine, the only

difference between the regimens intended for PB and MB patients being the duration of treatment. Were this done, the tasks of the programme manager and the health worker responsible for drug delivery would be simplified.

A second, more radical simplification would be to treat PB and MB patients with the same drug regimen for the same duration. As every field worker knows, a practical difficulty in the field is to classify PB and MB leprosy with acceptable accuracy by skin smears. Because preparing and reading smears require a degree of expertise not always available in the field, WHO has recently recommended classifying leprosy patients on the basis of the numbers of their skin lesions;[5] by definition, MB patients are those exhibiting more than five skin lesions, whereas PB patients have five or fewer lesions. Such a classification is certainly less demanding than the smear-based classification, but it is certainly not totally accurate. For routine chemotherapy of leprosy, especially in the post-elimination era, it would be more convenient for the patient and the public health manager to prescribe not only the same drug regimen for PB and MB patients, but also to prescribe it for the same duration, as is done in the chemotherapy of tuberculosis. Of course, because of the tremendous difference of bacterial load between PB and MB patients, the duration of the common regimen should be a compromise between too long for PB and too short for MB, tentatively 3–6 months. Because of their great bactericidal activity, rifapentine and moxifloxacin might well be the key drugs of that regimen.

Fully supervised drug regimens

The cure of all diseases, infectious or not, that requires long-term self-administration of drugs is often compromised by irregularities of drug administration, if not by the complete cessation of treatment by the patients as soon as the symptoms disappear. To overcome this difficulty, the treatment must be fully or partly supervised. Because daily supervision is operationally not feasible when treatment is ambulatory, the daily components, dapsone + clofazimine, of standard MDT are self-administered, whereas administration of the monthly components, 600 mg rifampicin + 300 mg clofazimine, is supervised.

Experimental studies in the mouse[7–9] and a clinical trial[11] have demonstrated that the activity against *M. leprae* of a single dose of the combination clarithromycin + minocycline, with or without ofloxacin, did not differ significantly from that of the combination dapsone + clofazimine administered daily for 1 month. Because the combination rifapentine + moxifloxacin + minocycline appears more active against *M. leprae* than the combination rifampicin + ofloxacin + minocycline,[10] it may be possible to replace the daily dapsone + clofazimine component of the current MDT regimen with a monthly dose of a fluoroquinolone and minocycline, in order to provide a fully supervised monthly regimen, WHO is currently assessing the activity, acceptability and tolerance in patients of the combination rifampicin + ofloxacin + minocycline (ROM). In the near future, a similar trial involving rifapentine, moxifloxacin and minocycline should be conducted.

Conclusion

In leprosy endemic countries, it will be even more difficult after the year 2005 than at present to maintain diagnostic facilities and a network for drug delivery of sufficient quality to ensure

detection and cure of a majority of leprosy patients. Therefore, developing a drug regimen of short duration that may be used among both MB and PB patients will be of great operational importance.

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