Clinical development of anti-tuberculosis drugs

D. A. Mitchison*

St George’s, University of London, Division of Cellular & Molecular Medicine,
Cranmer Terrace, London SW17 0RE, UK

In the clinical development of new anti-tuberculosis drugs, the most important step is efficient Phase II studies to show whether the drug is likely to be able to shorten treatment and with what other drugs it has the greatest sterilizing activity. The use of non-linear mixed effects modelling applied to serial sputum cfu counts appears to be the most effective technique, but we know little about the optimal design of such novel studies. A paper in the current journal reports on the relative efficiencies of various timing patterns in sampling sputum.

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There is general agreement amongst those working for better control of tuberculosis that the biggest advance would be to shorten the current 6 month duration of treatment.1 Shortening might be obtained by the better use of current drugs, for instance using a higher dose of rifampicin or rifapentine, a long-acting rifamycin.2 However, in the longer term, the biggest advances are going to be gained by the use of new anti-tuberculosis drugs. Currently, those that are reaching the stage of clinical assessment are the fluoroquinolones moxifloxacin and gatifloxacin, the diarylquinoline being developed by Johnson & Johnson as R207910 and by Tibotec as TM207, the nitroimidazopyran PA824 developed by the Global Alliance for Tuberculosis Drug Development, the nitrodihydroimidazo-oxazole OPC 67683 developed by Otsuka and a pyrrole LL3858 developed by Lupin. At earlier stages of development are several other drugs under development by several of the larger pharmaceutical companies. Once these new drugs have got through Phase I studies, where they are first tested for toxicity and pharmacokinetics in human subjects, they enter Phase II development in which it is necessary to prove that they are active in human disease and capable of shortening the duration of treatment. Studies in Phase II are performed before the drug is tested in large Phase III licensing studies.

The most important current aim in improving clinical trial methodology is the delineation of efficient ways of carrying out Phase II studies. It is usually agreed that the first step is a study of early bactericidal activity in pulmonary tuberculosis.3,4 Such a study proves that the drug is bactericidal against tubercle bacilli in cavities by measuring the fall in the bacillary content in sputum during the first days of treatment. If the dose of the drug is titrated downwards in such a study, accurate dose-ranging assessments can also be made allowing a rational choice of the dose to be used in further development.

The next step is an 8 week study to show whether the speed of killing of the bacilli can be accelerated in regimens containing the new drug. This type of study has the dual aim of proving that a new drug can accelerate killing and also investigating in what combinations with other drugs it is most effective. Several different drug combinations usually require testing, guided by studies in experimental murine tuberculosis.5 Hence, efficiency in design and analysis is of the greatest importance. The gold standard in assessing a regimen is the proportion of patients who relapse after the end of treatment. Historically, the proportion of patients whose sputum become negative on culture at 8 weeks was correlated with the proportions of patients who relapse after the end of treatment in a series of clinical trials.6 However, this procedure, while convenient, is very inefficient since it depends on a single categorical attribute (culture positive or negative) for each patient rather than a measurement of a continuous variable. Attention has been drawn recently to the use of frequent counts of viable tubercle bacilli in sputum during the 8 week period.7 Such a procedure is given the acronym SSCC standing for serial sputum cfu counts. In the analysis of the regressions characterizing the results, care must be taken to distinguish between the errors involved in multiple counts on any one patient and the variation between the patients themselves. One then needs a ‘mixed effects’ or a hierarchical analysis in which these two sources of error are kept separate. This was done by calculating a regression coefficient, measuring the fall in counts in unit time for each patient and then analysing the regression coefficients themselves. However, a more efficient method of doing this type of analysis arises from studies in pharmacokinetics using non-linear mixed effects modelling programs such as WinNonLin (Pharsight, Mountain View, CA, USA) and NONMEM.8 Such models have been employed for the first time for measuring the sterilizing action of anti-tuberculosis drugs by Davies et al.9

*Corresponding author. Tel: +44-208-8725-5704; Fax +44-208-8672-0234; E-mail: dmitchis@sgul.ac.uk

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They seem to be the most efficient way of proceeding. Modelling techniques are highly dependent on algebraic procedures and require considerable mathematical expertise for efficient use. However, they do seem to be the way forward for the critically important Phase II development of new drugs. This methodology is currently being explored by the Oflotub consortium, supported by the European Commission and WHO/TDR, in the analysis of a Phase II clinical study comparing the sterilizing activities of the fluoroquinolones ofloxacin, gatifloxacin and moxifloxacin when substituted for ethambutol in a conventional 4-drug initial 8 week phase of treatment.

In the current issue of the journal there is a paper considering the efficiency of a number of different designs for SSCC studies. It will be appreciated that it is far cheaper to do more bacteriology than to have more patients in a study. For this reason, the SSCC approach is likely to be much more efficient than measuring the proportions of patients with positive sputum at 2 months. It also has an advantage in showing that the best model describing the killing curves is bi-exponential rather than mono-exponential, and it can estimate the rate of kill in each of the two phases. In doing this, we can distinguish between the earlier effects of drugs, probably on rapidly dividing organisms, and the later sterilizing action on persisters, which is probably the most appropriate measure of their ability to shorten treatment. These approaches are essential for the efficient clinical development of both old and new anti-tuberculosis drugs.

Transparency declarations

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References