Editorial

The control of tuberculosis: Progress & prospect

It is appropriate to consider progress in the control of tuberculosis on March 24th, World Tuberculosis Day. While an effective vaccine that would kill dormant tubercle bacilli would be a real solution to eradication of the disease, progress in vaccine development is very slow and unlikely to produce a new vaccine with this desirable property in the near future. Control of the disease therefore rests on treating infectious patients with pulmonary tuberculosis and thus breaking the cycle of infection from patient to contact. The parallel process of preventive treatment is still too uncertain and ineffective for widespread adoption.

What then are the prospects for more effective treatment of infectious pulmonary diseases? We are at the end of an era when for some 30 yr effective multi-drug regimens have been available that could cure almost all cases, however severe the disease. These regimens depend upon rifampicin (R) and pyrazinamide (Z) for their ability to kill persisting bacilli, while isoniazid (H) and ethambutol (E) - the other drugs in the 4-drug intensive phase of treatment contribute little. The problem with the standard regimen of two months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by four months of rifampicin and isoniazid, is the six month duration of treatment. It is during this lengthy period that patients feel well and often stop taking their drugs. As a result, relapse and emergence of drug resistance occurs.

During the next few years, we will see the advent of several new anti-TB drugs that might help to shorten treatment. The two highly active fluoroquinolones, moxifloxacin and gatifloxacin, are in phase II and phase III trials at present. An important comparison of the sterilising activity of moxifloxacin, gatifloxacin and ofloxacin, is currently under study in the European Commission supported Oflotub clinical trial, with preliminary results expects in the spring of this year. In this study, the fluoroquinolones are substituted for ethambutol. An interesting study in experimental mouse tuberculosis suggests that a substitution of moxifloxacin for isoniazid might be more effective. This is also the subject of further studies planned both by the CDC, Atlanta, and in a new study supported by the European Commission. Should these studies provide results as predicted by the mouse studies, we might see treatment shorten to four months or even three months. In the early stages of clinical testing is a diarylquinoline, which seems a particularly exciting drug. It appears to work by blocking production of ATP and should therefore be effective even against dormant bacilli. In mouse studies, it is a more potent sterilizing drug than rifampicin and, in various three-drug combinations seems capable of sterilizing organs after only two months of treatment. Another drug, the nitroimidazopyran, PA 824, is under development by the Global Alliance for TB Drug Development and is at a slightly earlier stage of development. Although not quite as promising as the diarylquinoline, it seems comparable to rifampicin in its sterilizing activity when tested in the mouse. It is of interest that these drugs have been developed in empirical screening of potentially active molecules, and not by identification of targets in the mycobacterial genome. Other drugs are at even earlier stages in development.

With the advent of new drugs, we have to consider optimal strategies for testing them in human disease, with the aim of making accurate assessments and at the same time using ethically sound methods that do not put patients at risk. Phase I assessments will include single dose studies with a range of dose sizes followed by multiple dose studies usually over about 14 days. These give preliminary estimates of toxicity.
and the pharmacokinetics of the new drug. We then enter phase II studies whose form is beginning to take shape. First comes a study of the early bactericidal activity (EBA) of the drug given alone in a range of dose sizes, each measuring the fall in viable bacillary counts during the first 2 daily doses of the drug. The dose range should extend from the highest likely to be used in human disease to a much lower dose size estimated to have no effect. This dose ranging study allows an estimate of the therapeutic margin of each dose size. The therapeutic margin is the ratio between the dose size in question and the dose size that just fails to have an EBA. Therapeutic margin values of 20 have been obtained for the standard 300 mg daily dose of isoniazid, and 4 for the 600 mg daily dose of rifampicin, but only about 2 for 1 g daily dose of streptomycin. We should aim at a dose that has a therapeutic margin of at least 4.

Even if we have much better methods of treatment, we still have a huge problem in case finding which has not improved with the DOTS expansion programme. Most diagnosis in developing countries depends on direct smear examination of sputum. This is a rapid, specific and cheap method but lacks sensitivity. However, the disease in most developing countries is usually smear positive, so that it detects a reasonably high proportion of cases. Diagnosis by chest radiography is also rapid but is much less specific and is more expensive. Diagnosis by culture is still rarely available. Rapid methods for detecting resistance to rifampicin and isoniazid (multi drug resistance, MDR) are urgently required since infections with such strains respond poorly to current therapy. These can either be phenotypic, depending on rapid culture methods, or genotypic, depending on molecular methods. Unfortunately, genotypic methods miss some resistant strains and are very expensive. Investigation of improved diagnostic methods is the priority for FIND diagnostics. What we really need is a dipstick that could be inserted into sputum or urine to indicate the presence of tuberculosis and another that would indicate MDR disease.

However, whatever improvements are made in diagnostic methods, failure to take the first step of investigating patients with symptoms suspicious of tuberculosis is still the most important reason for low rates of diagnosis. Unless steps are taken to increase the “index of suspicion” at primary care levels and within households, improvements in diagnostic methods are unlikely to be fruitful. Essentially, this is an issue of general health education within the community and also increased attention in local clinics to the possibility that patients with coughs lasting over four weeks may suffer from tuberculosis. The problems encountered in Kenya are illustrated in a series of articles, the last in 1987. These studies showed that (i) community leaders were unable to identify potential cases; (ii) cases with chronic coughs could be identified at district hospitals provided that...
they lived near the hospitals; and (iii) that case finding through the Maternity and Child Health service was disappointing. No universally applicable method of identifying potential cases was found.

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References


