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Prospects for new drugs and regimens in the treatment of tuberculosis

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ABSTRACT Since rifampicin was introduced in 1967, no novel compounds have been approved for first-line chemotherapy of tuberculosis. The inexorable rise in cases of tuberculosis worldwide, fuelled by the HIV epidemic, highlights the need for new drugs, particularly those that can shorten the duration of treatment. The World Health Organization's Stop TB strategy considers that the present high burden of tuberculosis worldwide is related not only to the spread of HIV but also to poverty and the widening gap between rich and poor in various populations, disregard for the disease and lack of appropriate healthcare services. Clinical trials of existing agents such as methoxyfluoroquinolones (e.g. gatifloxacin and moxifloxacin), which are bactericidal and potent against organisms that are not actively multiplying, are proceeding on the basis of efficacy in models of interaction and preliminary clinical data. These may provide a stopgap, but the real breakthrough will come when novel agents with potent sterilising activity are discovered. New agents will provide opportunities to intensify regimens that could be shorter in duration as well as provide more options for the eradication of multi-drug-resistant mycobacteria.

KEYWORDS Gatifloxacin, moxifloxacin, ofloxacin, oxazolidinone, rifapentine, tuberculosis

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Tuberculosis (TB) continues to kill young people[1] and its global incidence is still increasing from 122 per 100,000 population in 1990 to 136 in 2005.[2] Although a six-month regimen was introduced for TB treatment more than 30 years ago, there were still an estimated 8.8 million new TB cases in 2005, 7.4 million in Asia and sub-Saharan Africa.[2] A total of 1.6 million people died of TB, including 195,000 patients infected with HIV.[2] Tuberculosis prevalence and death rates have probably been falling globally for several years.[2] In 2005, the TB incidence rate was stable or in decline in all six World Health Organization (WHO) regions and had reached a peak worldwide.[2] However, the total number of new TB cases is still slowly rising and the caseload continues to grow in Africa, the eastern Mediterranean and southeast Asia.[2]

Today, TB is a worldwide health threat, possibly due to the limitations of current antituberculous drugs. As resistant strains of *Mycobacterium tuberculosis* have slowly emerged, treatment failure occurs too often, particularly in countries lacking the necessary healthcare organisation to provide the long and costly treatment adapted to individual patients. In the past decade, these concerns have led to a renewal of scientific interest. Regimens have been optimised, much has been learnt about the mechanisms of action of antituberculous drugs and many new series of *Mycobacterium tuberculosis* growth inhibitors have been reported.

EVOLUTION OF TREATMENT

Streptomycin, the first truly effective antituberculous chemotherapeutic agent, was introduced into experimental clinical use in 1945.[3] Although there was a striking initial improvement in patients who received streptomycin, they subsequently worsened, and the organisms isolated from these patients were found to be resistant to streptomycin.[4] Tubercle bacilli are liable to mutate and develop resistance to any individual drug. Treatment with drug combinations can ensure that small numbers of initial mutations to a particular drug will be eliminated by companion drugs. This was first validated in a Medical Research Council UK study, in which streptomycin was supplemented by para-aminosalicylic acid (PAS).[5–8]

With the introduction of isoniazid in 1952, it was found that chemotherapy with all three available drugs was highly effective, with very few failures or side effects.[5–8] To prevent single-drug resistance, the combination of isoniazid and PAS with or without streptomycin came to be the standard therapy for tuberculosis.[1] A study conducted in Madras, India, comparing home and sanatorium treatment of pulmonary TB with 12 months' treatment of isoniazid plus PAS, confirmed that it is appropriate to treat the majority of patients at home.[9] In 1967, ethambutol was shown to be an effective substitute for PAS.[10] Ethambutol was readily accepted as a much more tolerable and less toxic companion for isoniazid.[10]

The next major advance in chemotherapy for tuberculosis resulted from the discovery of rifampicin.[11] In a six-month United States Public Health Service (USPHS) trial of an isoniazid and rifampicin regimen, positive cultures were found in only 6.1% of the patients between three and six months after treatment began. Strikingly, during the six months of treatment, 16.8% of the patients were withdrawn from the study due to delinquency from clinic visits,[12] highlighting the need for regimens of shorter duration. Studies of chemotherapy then began to focus on the possible benefits of pyrazinamide.[13–17] Mitchison and Dickinson demonstrated that rifampicin is an effective killer of intracellular organisms and that pyrazinamide is especially effective. This led to the suggestion that the addition of pyrazinamide would strengthen the isoniazid-rifampicin combinbation.[14,15,18] Thus, a six-month regimen of isoniazid and rifampicin supplemented by pyrazinamide and ethambutol or streptomycin for the initial two months is now recommended as standard treatment for most patients with pulmonary tuberculosis.[16,17]

In Thailand, a six-month regimen with once-a-day dosage has been introduced by the National Tuberculosis Control Program as recommended by the WHO since 1985 (initial two months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by four months of isoniazid and rifampicin for previously untreated cases).[1,19]

Drugs in present use

The first-line drugs used for previously untreated cases are isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin. The second-line drugs preserved for first-line drug-resistant cases are cycloserine, ethionamide, streptomycin, amikacin, kanamycin, capreomycin and PAS.[1]

DEVELOPING NEW DRUGS AND REGIMENS

Because of public health considerations related to TB, successful therapy should be viewed as the primary objective of those supervising the care of patients in what is termed directly observed treatment, short course (DOTS).[1,20,21] Because of the increased global notification rate and the increasing burden of drug resistance,[2] we urgently need new drugs to prevent relapse following shorter treatment regimens and to cope with the mounting resistance problem. The following points are of particular importance when developing new drugs:

1. Lasting antimycobacterial activity in vivo and reduced treatment duration is desirable, thereby avoiding drug toxicity. In addition, these compounds could be administered intermittently with longer drug-free intervals, consequently facilitating enhanced patient compliance.
2. Compounds to combat both sensitive and multi-drug-resistant tuberculosis are urgently needed.
3. Compounds that eradicate slowly metabolising and, if possible, dormant populations of *Mycobacterium tuberculosis* organisms responsible for relapse could markedly reduce the incidence of active tuberculosis in persons who are latently infected.[22,23]

Unfortunately, with the exception of rifabutin and rifapentine, no new drugs have been marketed for TB in the 40 years since the release of rifampicin. Consequently there has been no change in the standard regimens for tuberculosis treatment for more than 30 years, and a minimum treatment period of six months is still required.[24] Although a number of constraints have deterred companies from investing in the discovery of new antituberculous drugs, greatly increased funding from the international Stop TB Partnership is boosting global research and should speed up the general availability of drugs that prove effective.[2]

A Japanese clinical trial of twice-weekly intermittent maintenance of 2HRZE/4HR (H: isoniazid, R: rifampicin, Z: pyrazinamide, E: ethambutol) under directly observed treatment resulted in treatment success rates of 97.6%, compared with 95.6% in patients on self-administered daily treatment. The relapse rates were not significantly different.[25] Using currently available services, a two-month regimen has already proven to be effective in recent trials and, if generally introduced by 2012, could prevent nearly 20% of new cases and 25% of tuberculosis deaths in southeast Asia between 2012 and 2030.[26] If effective treatment with existing drugs expands rapidly, overall incremental benefits of shorter regimens would be lower but would remain considerable (13% and 19% reductions in incidence and mortality, respectively, between 2012 and 2030).[26] A ten-year delay in the introduction of new drugs would erase nearly three-quarters of total expected benefit.[1]

DISCUSSION OF ONGOING STUDIES

Ongoing randomised controlled trials and treatment strategies for TB are shown in Table 1. Gatifloxacin and moxifloxacin have been shown in a number of in vitro studies to have a much lower minimum inhibitory concentration (MIC) than those for other quinolones. For instance, in one study[27] the MICs for gatifloxacin and moxifloxacin were 0.5 and 0.25 mg/ml, respectively, compared with 1.0–2.0 for ofloxacin, and if we accept the requirement for a lower concentration as a definition of the ability to overcome resistance, both compounds may be useful for treating patients with low levels of quinolone resistance.[28–31] This might explain why some authors advised against the future use of moxifloxacin and gatifloxacin as first-line antituberculous drugs and their reservation for drug-resistant TB. However, the confidence limits on relapse rate in the Chennai study in Table 1 are wide, and there was no four-month control comparator regimen of standard treatment without ofloxacin.

TABLE 1 Ongoing randomised controlled trials and treatment strategies for tuberculosis

Objective of study: substitution to shorten the standard four-drug regimen	**Regimen**	**Phase**	**Outcome**
Moxifloxacin for ethambutol or isoniazid[36]	2MRZE/4HR	II/III	Ongoing
Moxifloxacin for isoniazid in the initial phase, and moxifloxacin and rifapentine for isoniazid and rifampicin in the continuation phase[32]	2MRZE/2PM (2 months of daily M, R, Z, E, followed by 2 months of twice weekly P, M); 2MRZE/4PM (2 months of daily M, R, Z, E followed by once weekly P, M)	III	Ongoing
Moxifloxacin or gatifloxacin or ofloxacin for ethambutol[33]	2MHRZ/4HR 2GHRZ/4HR 2OHRZ/4HR	II/III II/III II/III	• Compared with the control, moxifloxacin and gatifloxacin killed bacilli significantly faster initially and at equal rates later. • Ofloxacin substitution had no significant effect. • The observed increased killing rate during phase II supports possible reduction in the duration of at least one month. • Serial sputum colony counting could be the basis of future phase II studies. • Overall rate of dysglycaemia associated with gatifloxacin was 1.10%. • Gatifloxacin-related hypoglycaemia occurred mainly in diabetic patients.
Ofloxacin for ethambutol[34]	3OHRZ 3OHRZ/1 HRZ 3OHRZ/2HRZ 2OHRZ/2HRZ	III III III III	Ofloxacin-containing regimens of 4–5 months achieved more than 95% efficacy with no increased incidence of adverse drug reactions, minimal relapses of 8%, 4%, 2% and 13% respectively, permitting shortening of treatment.
Mouse study: nitroimidazopyran (PA-824) for isoniazid or rifampicin or pyrazinamide[35]	2HRZ-PA-824/4HR-PA-824 2HZ-PA-824/4H-PA-824 2RZ-PA-824/4R-PA-824	Mice	• Mean spleen weight for mice receiving the control regimen 2HRZ/4HR and 6 (HR-PA-824) for 2 months were 142+/-8 mg and 177+/-9 mg, respectively; higher than those for all other treatment groups. • Substitution of PA-824 for isoniazid (2RZ-PA-824/4R-PA-824) resulted in lower lung and spleen CFU counts (2.38+/-0.62 log10 CFU, $p<0.01$). • Substitution of PA-824 for rifampicin and pyrazinamide was detrimental [2HZ-PA-824/4H-PA-824 and 6(HR-PA-824)]; relapse rates after 3 months of treatment completion were 5%, 11%, 79%, and 0% in regimens 2HRZ-PA-824/4HR-PA-824, 2RZ-PA-824/4R-PA-824, 6(HR-PA-824), and 2HRZ/4HR (control), respectively.
Oxazolidinone-PA-824 as a single-dose, 7 days multi-dose, renal effect study and ADME study[36]	Single-dose: 50, 250, 500, 750, 1,000, 1,250, 1,500 mg; Days multi-dose: 200, 600, 1,000, 1,400 mg; Renal effect study: 800, 1,000 mg, 8 days; ADME study: [14C]-PA-824 OS	I	• Single-dose study: well tolerated, no dose-limiting adverse effects or abnormal laboratory results. No effects on electrocardiogram, vital signs or physical examination. T max 4–5 hours, T½ about 18 hours. 7 days. • Multi-dose study: 1,000 mg/days, 5 days moderate creatinine elevation: reversed during 7-day washout period. No consistent effect on BUN, 1,400-mg cohort not enrolled. T max 4–5 hours, T½ about 17 hours. • Renal effect study: ongoing. • ADME study: 91% of dose recovered in urine and faeces (about 65% in urine and about 26% in faeces). No significant radioactivity captured as [14C]-CO_2. Metabolite analysis in process. T max 4.5 hours, T½ about 17 hours.

Abbreviations: ADME: absorption, distribution, metabolism, elimination; BUN: blood urea nitrogen; CFU: colony-forming unit; E: ethambutol; G: gatifloxacin; H: isoniazid; M: moxifloxacin; O: ofloxacin; OS: overall survival; P: rifapentine; PA: nitroimidazopyran; R: rifampicin; T max: time to peak plasma concentration of drug; T½: time taken for plasma concentration of drug to reduce by 50% or elimination half life; Z: pyrazinamide.

Gatifloxacin and moxifloxacin have similar antituberculous activity both in vitro and in vivo, but gatifloxacin is cheaper to manufacture than moxifloxacin and a low-cost generic is in production.[33] The use of moxifloxacin- or gatifloxacin-containing regimens may shorten the standard four-drug regimen by at least one month.[31] However, concomitant rifampin administration can result in a 27% decrease in mean moxifloxacin concentration-time curve-24 hours (AUCO-24),[37] and additional studies are required to understand the clinical significance of this moxifloxacin-rifampicin interaction.[37] Six months of a rifabutin-containing standard regimen proved useful for HIV-infected tuberculosis patients as a rifapentine-containing standard regimen is contraindicated in these patients.[23]

Because of its significant antituberculous activity, unique mechanism of action and lack of cross-resistance with existing antituberculous drugs, PA-824 (PA: nitroimidazoPyrAn) may also have the potential to contribute to entirely novel regimens when combined with other new investigational drugs.[37] Although PA-824 is currently in phase I, it is not known if the dose used in mice (Table 1) will be the dose required in humans, and whether the dose used in the current phase I study underestimates or overestimates the value of PA-824 in combination chemotherapy.[35] Following completion of phase I, the next major milestone for PA-824 development will be a phase II proof-of-concept study, conducted in adults with active pulmonary TB using tests of bacterial activity to confirm its efficacy.[36]

Some immunotherapy trials with *mycobacterium vaccae* (SRL 172) (SRL: Stanford Rook Pharma, London – part of the Stanford Rook group of companies) demonstrated no benefit with regard to survival, bacteriological outcome or roentgenographic chest responses in both HIV-infected and HIV-negative patients,[38–40] but others showed a benefit.[41–48]

It is important to note that clinical trials of antituberculous drugs require a minimum of six months of therapy, with a follow-up period of at least one year. In addition, it is hard to demonstrate an obvious benefit of a new antituberculous agent over pre-existing drugs, since clinical trials involve comparator tests against multi-drug combination therapy using highly effective current antituberculous drugs. Although there is a perceived lack of commercial return to companies engaged in the development of new antituberculous drugs, since more than 95% of cases worldwide are in developing countries,[22] the use of genomics to discover new drug targets and the use of molecular diversity together with combinatorial chemistry and proteomics should make it easier and speedier to produce new lead compounds for turning into drugs to treat active, latent and multi-drug-resistant TB more effectively.

In conclusion, new drugs, adjunctive immunotherapy and potential treatment-shortening regimens (including gatifloxacin-containing regimens) require careful assessment in clinical trials, but existing markers of treatment outcome, clinical cure and relapse require prolonged follow-up of patients.

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