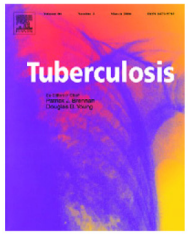
Tuberculosis (2008) **88** Suppl. 1, S93-S100

Available at www.sciencedirect.com

ScienceDirect

journal homepage: http://intl.elsevierhealth.com/journals/tube



Developing new drugs for the treatment of drug-resistant tuberculosis: a regulatory perspective

Leonard V. Sacks*, Rachel E. Behrman

Office of Critical Path Programs, FDA, Room 14B 45, 5600 Fishers Lane, Rockville, MD 20857, USA

KEYWORDS
Drug development;
Multi-drug resistant tuberculosis

Summary
Simplifying and shortening treatment for drug-sensitive tuberculosis and providing new treatment options for drug-resistant tuberculosis constitute two principal goals in the development of novel drugs for tuberculosis. Demonstration of clinical efficacy in drug-sensitive tuberculosis is challenging, given high success rates for existing regimens, concerns about substituting an investigational agent for the most effective agents in a regimen and difficulties in determining the effect size of the components of a combination regimen. Large and prolonged studies would be needed either to show superiority over existing regimens or statistically defensible non-inferiority compared to existing regimens. In contrast, exploring efficacy of novel treatments in the setting of drug-resistant disease may present certain opportunities. In drug-resistant disease, the efficacy of existing regimens is comparatively poor, and companion drugs used to treat drug-resistant disease are weak or ineffective, enabling demonstration of the effect of the new drug. Other advantages of this approach, which has been used successfully in the development of antiretroviral agents, include the possibility of demonstrating drug efficacy using smaller studies, the possibility of accelerated approval based on a surrogate endpoint and the opportunity to address an urgent public health need. Experience with the activity and the safety of new agents in drug-resistant disease may provide a platform from which their indication can be broadened to include drug-sensitive disease.

Introduction

The history of tuberculosis (TB) drug development began in the 1940s with great optimism as streptomycin introduced the promise of a cure for this disease.[1] But within the space of a few years, it became clear that "cures" were short lived as the final outcome for those treated converged with that for untreated patients. A decade later, the discovery of isoniazid (INH) brought renewed hope. This potent agent resulted in rapid sterilization of sputum and, when used in conjunction with streptomycin, reduced the rates of drug-induced resistance. In the 1970s, pyrazinamide and rifampin revolutionized TB treatment, resulting in durable cures with shortened durations of therapy. By the late 1970s, cure rates for TB had exceeded 95%. As TB began to disappear in developing countries, the impetus for TB drug development faltered. For the next 30 years, no novel anti-tuberculous agents would be developed and poor countries, unable to provide the arduous infrastructure and expensive drugs essential for TB control, would continue to suffer its ravages.

Currently available treatment regimens are prolonged, placing unmanageable demands on indigent populations from the perspectives of both supervision

*Corresponding author: Tel.: +1 301 827 1512; fax: +1 301 443 9718
E-mail address: Leonard.sacks@fda.hhs.gov (L.V. Sacks).

1472-9792/$ – see front matter

and adherence. The result is the burgeoning tide of drug resistance. Repeated inadequate courses of therapy in patients with relapsing TB generate incremental increases in the degree of drug-resistance. Highly resistant organisms are virtually untreatable in immunocompetent patients, and when these organisms enter highly immunocompromised HIV-infected populations, mortality rates within weeks of infection approach 100%.[2] Lessons from malaria, HIV, MRSA and innumerable other drug-resistant pathogens have taught us that drug resistance, once established, is almost certain to escalate.[3–5] Unmasked by multi-drug resistance and HIV, TB has re-emerged as a major global health crisis. With soaring incidence and mortality rates world wide and frequent outbreaks of drug-resistant disease, there is a pressing need for new therapies.

Antimycobacterial drug development

The cornerstone of antimycobacterial drug development is the microbiological proof of efficacy. The potency of candidate agents is investigated by determining the minimal inhibitory concentrations of the drug against cultures of *M. tuberculosis*. Potent agents that promise achievable therapeutic drug levels in humans are pursued. Studies using animal models are undertaken as a bridge between in vitro and human studies, providing important preliminary evidence of tolerability and efficacy. Animal studies have been central in exploring toxicology, pharmacokinetics, combination therapies, dose ranges, and other factors in the design of a therapeutic regimen. With satisfactory animal safety data and preliminary indications of efficacy, initial studies in humans probe the tolerability and pharmacokinetics. Early bactericidal activity (EBA) is often investigated as a preliminary demonstration of antimycobacterial efficacy. EBA studies involve giving patients with TB short courses of monotherapy with the new agent to determine the effect on sputum colony counts, before administering definitive combination therapy. Despite all this important background information, preliminary studies cannot capture the full complexity of projected use. Sterilizing activity in humans (the elimination of active and dormant organisms) constitutes one of the biggest challenges in developing useful regimens for TB and is poorly addressed by these studies. The effect on dormant organisms, the impact on relapses, the penetration into diseased lung tissue, the comparative safety during long-term use and the role of a new agent within the landscape of existing treatments are just some of the issues that need to be tested in clinical trials using a projected treatment regimen.

With public health needs in mind, clinical programs to develop novel drugs for TB have several goals including simplifying and shortening treatment of drug-sensitive TB, identifying new treatments for drug-resistant TB and improving on the safety of existing treatment.[1–3] Both because the need for new therapies is so urgent and because demonstrating efficacy in drug-sensitive disease is challenging, as discussed below, there are reasons to explore the efficacy of candidate drugs in the setting of drug-resistant disease.

Trials in drug-resistant TB

From a public health perspective, the urgency of developing new therapies for drug-resistant TB has already been described. From a scientific perspective, development of new drugs in the setting of drug resistance may circumvent several practical hurdles that complicate the demonstration of clinical efficacy in drug-sensitive TB. Since TB is a life-threatening infection for which current therapy is generally highly efficacious, ethical trials of new therapies for TB are limited to those likely to show superiority or non-inferiority to current standards of care. In the case of drug-sensitive TB, this is a demanding objective since durable cure rates exceed 95% based on 2 years of follow-up.[6] Added to this, the need to use combinations of at least 3 active drugs in the treatment of TB poses a challenge to demonstrating the contribution of a single new drug within a complex regimen. One possible approach is to compare a shortened regimen containing the new drug to the standard six-month regimen. Demonstrating the efficacy of a shorter regimen would serve a major public health need, improving adherence, reducing costs and eliminating other logistic obstacles with a major potential impact on cure rates.

Clearly, large trials are needed to address these statistical constructs and to accommodate attrition during prolonged periods of study.

Traditionally, patients with drug-resistant TB have been excluded from TB trials. Including patients with drug-resistant infections may provide an opportunity to overcome some of the hurdles in clinical efficacy trials for a number of reasons.

First, success rates using the current standard of care for drug-resistant disease are low compared to drug-sensitive disease. In a study of 167 Latvian patients with multi-drug resistant TB (MDR-TB) resistant to a median of 5 drugs, 23% failed to convert to culture negativity, and the median time to culture conversion was 83 days.[7] In a similar study prior to the use of fluoroquinolones, 35% of 171 US patients with MDR-TB resistant to a median of 6 drugs failed to convert to culture negativity, and the median time to culture conversion was 2 months.[8] Similar observational studies have been performed in a number of countries around the world.[9–14] Despite differences in rates of HIV positivity and use of fluoroquinolones and surgery, all studies demonstrate the comparatively poor outcome in MDR-TB. Failure to convert to culture negativity ranges from 15% to 35%, the median interval to culture conversion often exceeds 2 months, and, though variable, all-cause mortality exceeds 25% in several reports (Table 1). In contrast, trials in patients with drug-sensitive TB treated with 6 month courses of therapy (isoniazid, rifampin, pyrazinamide and streptomycin) demonstrate that approximately 98% of patients are culture negative at 2 months.[15,16] Primary failures of therapy are rare, and mortality rates are low.

Table 1 Summary of published outcomes in patients with MDR-TB

Citation	HIV positive subjects	Number of drugs to which TB isolates were resistant†	Time to culture conversion (range)†	% failing to convert culture	Relapse rate	All-cause mortality
(8)*	–	6	2 months (1–8)	35%	10% in 2 years, 14% in 62 months	37% (63/171)
(11)	–	6	–	15% (25/162)	–	25% (51/205)
(7)	–	5	83 days	23%	2% in 2 years	8% (13/167)
(9)	1/65	6	1 month	–	–	26% (17/66)
(12)	0	Mean 3.3	Mean 2.1 months (1–5)	19% (12/63)	2.1% (1/51)	4% (2/53)
(10)	0	6	Mean 2 months (1–10)	17.5% (11/67)	0/52	0
(13)	1.7%	–	–	6.7% (70/723)	2.1% in 2 years	13%
(14)	0	5	Mean 42 days	21% (6/29)	1/44 in 53 months	14%

†Median (or mean where indicated).
– not reported.
* fluoroquinolones not used in this study.

Thus, demonstration of superiority of a new drug regimen compared to the standard of care is more feasible in the setting of MDR-TB. In situations of extensive drug-resistance or XDR-TB infections, where the standard second line drugs may have little or no efficacy at all, the efficacy of a new drug may be very clear even when small numbers of patients are studied.

Second, drug-resistant infections may help differentiate the effects of the new drug from those of the rest of the drugs in the regimen. In drug-sensitive disease, the effect of experimental drugs, when tested in combination with existing anti-tuberculous drugs, may be completely overshadowed by the effect of potent companion drugs. Thus, when comparing efficacy of drug combinations in non-inferiority studies, it may not be possible to distinguish the contribution of the investigational component of a regimen from the contribution of the companion drugs in the regimen. For example, the effect size of rifampin within combination regimens is large and dominates the treatment response. Indeed, in patients treated with "first line therapy", INH resistance may not have a detectable influence on outcome provided the infecting strain is susceptible to rifampin.[17] When rifampin is rendered ineffective as a result of drug-resistance, success rates plummet. Mitchison and Nunn reported primary failure of therapy or relapse in 8 of 11 patients with initial rifampin resistance who were treated with traditional first line drugs.[17] This is consistent with experience from early trials confirming the large effect size for rifampin. In these trials, patients who were treated with rifampin-containing regimens showed approximately a 30% more rapid conversion rate for sputum culture compared to those treated with isoniazid, streptomycin and ethambutol alone.[18] Thus, in the presence of rifampin resistance, it may be comparatively easy to demonstrate the effect of new agents.

Another strategic pitfall in the initial development of new drugs for drug-sensitive TB relates to new drugs that are weaker than our current first line therapies. While new drugs with activity levels comparable to those of ethambutol may still offer considerable benefit in MDR-TB, they may well be rejected from initial consideration based on apparent disappointing performance in combination regimens for drug-sensitive disease. This was illustrated in a trial of ciprofloxacin used with isoniazid and rifampin compared to standard therapy for drug-sensitive TB. Culture conversion was slower in the ciprofloxacin arm than the comparator arm (mean 2.3 months and 1.8 months, respectively), with higher relapse rates in an HIV-infected subgroup.[19] These results, however, should not lead one to abandon development of ciprofloxacin, which might be potentially useful in MDR-TB. Drug-resistant disease provides an appropriate setting in which to evaluate what might usually be considered "second-line" therapy because the efficacy of potent companion drugs is ablated by resistant mutations in the target organism.

In drug-resistant infection, we may be forced to accept more modest goals for treatment than for drug-sensitive disease where anything less than a durable cure is unsatisfactory. For example, early sterilization of infectious sputum would be a laudable step to reducing transmission and, therefore, from a public health point of view, would be a medically meaningful endpoint. In dire situations, even a temporary effect of the drug may translate into a significant prolongation of life. Conceivably, short of a true cure, suppression of infection would be acceptable when no treatment options exist, as is true in many chronic diseases.

Lessons from HIV trials

Many of the problems in designing clinical trials for new TB drugs are similar to those in designing trails for new HIV drugs. Consequently, experience in HIV drug development should inform our approaches to TB. In common with TB, HIV disease is treated with a combina-

Table 2 Summary of primary efficacy outcomes for antiretroviral agents approved for treatment of drug-resistant HIV

Treatment arms	% of patients with <50 copies/mL at 24 weeks	% of patients with >1 log reduction in viral load at 24 weeks
darunavir/ritonavir +OBR versus comparator protease inhibitor+OBR[20]	45% versus 12.1%	69.5% versus 21%
tipranavir/ritonavir +OBR versus comparator protease inhibitor+OBR[21]	23% versus 9%	40% versus 18%
Maraviroc + OBR versus OBR + placebo[23]	45.3% versus 23%	69.2% versus 35.9%
Raltegravir+OBR versus OBR + placebo[24]	62.6% versus 33.3%	
	% of patients with <50 copies/mL at 48 weeks	% of patients with >1 log reduction in viral load at 48 weeks
Enfuvirtide +OBR versus OBR[22]	23% versus 8%	46% versus 18%

OBR=optimized background regimen.

tion of effective drugs. In drug-sensitive disease, potent antiretroviral agents used in combination with investigational drugs would potentially obscure the contribution of the new drug. Moreover, the effect size of each component in a complex regimen may be difficult to discern. Therefore, trials that replace one component of the combination with an experimental drug may be difficult to interpret. Targeting initial development at resistant disease is an approach that has been quite successful in the HIV setting. Typically, patients with resistant virus who are failing current therapy are selected for study, both because the need is greatest and because there exists a potential for demonstrating efficacy. In these patients the experimental drug added to "optimized background therapy" is compared to optimized background therapy plus placebo. In some trials, the best available drug has been used as an active comparator drug instead of placebo, though many of the patients will have already developed resistance to this drug.

Such study designs have enabled a statistically significant demonstration of superior efficacy using new agents. Tipranavir, darunavir, enfuvirtide, maraviroc and raltegravir have been approved for resistant HIV infection based on superior suppression of viral load after 24 or 48 weeks compared to background therapy with or without a placebo or protease inhibitor (Table 2).[20–24]

Of course, HIV therapy differs from TB therapy in several respects. The endpoint in these HIV trials is not cure but suppression of the circulating plasma viremia. This biomarker is recognized as a robust and specific indicator of antiretroviral activity and has been demonstrated to correlate with clinical prognosis. A corresponding biomarker for TB does not exist. Sputum culture conversion rate 2 months after initiation of therapy has been proposed as a biomarker, correlating with late relapses, but lacks sensitivity since relapses in patients with negative 2 month cultures are well recognized.[25,26] Other potential biomarkers, all of which have yet to be validated, include time to sputum culture conversion, presence of mycobacterial DNA , and differential gene expression in the blood of patients with active, latent or cured TB.[27,28]

Development of such biomarkers, urgently needed to better the public health, is a major focus of the FDA's Critical Path Initiative.

Lessons from fluoroquinolones

Although fluoroquinolones have not yet been approved for the treatment of TB, there exists a body of clinical evidence that suggests that these drugs may be effective in the setting of MDR-TB. In a retrospective analysis, 30% (9/30) of patients with MDR-TB who did not receive a fluoroquinolone experienced microbiological failure compared with 12% (16/132) who did receive a fluoroquinolone (odds ratio for success 3.11 (95% CI 1.21–7.95). A significant effect on all-cause mortality was also seen (40% (17/42) versus 21% (34/163), respectively).[11] In a study of 63 patients with MDR-TB treated with fluoroquinolones, those failing therapy were significantly more likely to have had quinolone resistance in vitro compared to those treated successfully (odds ratio 13.5, 95% CI 2.2–83.1), effectively pointing to the activity of fluoroquinolones in MDR-TB.[12] This retrospective experience suggests that MDR-TB is a useful platform for demonstrating the efficacy of new anti-TB agents. Despite a paucity of rigorous trials, the microbiological and clinical data were sufficient to motivate widespread use of these agents in MDR-TB. They have been adopted as the standard of care, and it is unlikely that prospective, placebo-controlled randomized trials of fluoroquinolones will ever be performed in this setting.[29]

Study design

Because existing therapies are unsatisfactory, trials of new agents in the setting of drug-resistant disease are

designed to show superiority of a new agent compared to available regimens. Borrowing from the design of HIV trials, one option would be to compare best available background therapy plus either the new investigational drug or matching placebo. As is the case in any trial involving a serious disease, FDA encourages the use of a Data Monitoring Committee to evaluate the progress of the trials and the provision of a crossover option in the event that the control regimen fails. An alternative strategy might employ the immediate use of the new agent in one arm and delayed use in a second arm. The drug effect would be demonstrated by more rapid sputum culture conversion among the patients treated immediately with the new agent compared to those on delayed treatment.

The duration of experimental therapy would be dictated largely by toxicological constraints and microbiological strategy, but could be envisaged to continue as long as MDR-TB therapy is administered. In the design of such studies, the 95% confidence interval around the difference in success rates (experimental regimen minus comparator) must exceed zero. Some additional important considerations in trial design include the selection of appropriate study populations, laboratory diagnostics to detect drug resistance, the choice of study endpoints and safety considerations.

In general, the nature of the study population would be dictated by practical and scientific considerations driven by the acute public health need. The baseline covariates with a potential impact on outcome that must be balanced between the study arms or treated by stratification include: the number of drugs to which the isolate is resistant, the presence of cavitation on chest radiograph, prior treatment for MDR-TB and initial sputum colony count.[7] Others include HIV status and other underlying diseases.

The profile of MDR-TB varies depending on the resistance pattern of the organism and the nature of the host. These considerations are important in developing enrollment criteria.

MDR-TB in immunocompromised HIV-infected patients

Outbreaks of MDR-TB have been frequently reported among highly immunocompromised HIV-infected populations.[2,30–32] In these populations, the disease spreads rapidly, the progression of disease is often fulminant and death rates are very high. In this critical setting, a potent new agent might demonstrate a striking clinical benefit. However, from a practical standpoint, highly immunocompromised patients may be less suitable for study in a controlled trial given the rapid evolution of the disease and the sporadic and unpredictable nature of these outbreaks.

MDR-TB in non-immunocompromised patients

On the other hand, patients who acquire MDR infection after repeated treatment for TB often languish in institutions for months with persistently positive sputum. Such cases are not rare. Global surveys indicate among patients with active TB who have been treated previously, an average of 18.5% will have MDR-TB (range 6.3–39.9%).[33] These patients are usually well known to local health care providers and TB control programs. Hence, they may be easily identified and rapidly recruited. The indolent nature of these infections may also permit a strategy for rescue therapy if cultures fail to convert. However, many such infections are accompanied by extensive structural lung disease. Poorly vascularized cavitary lesions pose a challenge to the best of antimicrobials, demanding not only potent antimycobacterial activity, but excellent drug penetration. When physiologically feasible, surgery is frequently a component in the treatment of these patients. New agents with excellent tissue penetration may be expected to perform well in this setting. However, agents with limited biodistribution may fail despite good antimicrobial activity. In addition, these patients typically exhibit varying degrees of drug resistance and adequate numbers of trial subjects would be needed to ensure a balanced prognosis in all study arms.

Primary MDR-TB in non-immunocompromised hosts

Newly diagnosed, primary MDR-TB provides a relatively unconfounded setting in which to study a new drug. Recruitment can be restricted to patients infected with organisms showing limited drug resistance (e.g. to isoniazid and rifampin), a population with a relatively homogeneous prognosis. The confounding effects of prior treatment are eliminated, and extensive structural lung disease is less likely in such primary infections, facilitating the demonstration of drug efficacy. But practical challenges include identification of adequate numbers of patients. In a survey of incident MDR-TB in 184 countries, primary MDR was estimated to occur in an average 2.7% of cases (range 1–9.9%).[29]

Taking the difficulties with each strategy into account, it may be prudent to take a multi-pronged approach, nesting different population groups within a study.

Laboratory testing in MDR-TB trials

Screening of study subjects for drug resistance is time consuming. Traditional culture on Löwenstein-Jensen medium takes approximately 3 weeks. Microscopic observation drug susceptibility testing (MODS) reportedly reduces the turnaround time on samples obtained before treatment to about 8 days.[34] Nevertheless, the delay between screening and diagnosis of drug resistance is sufficient to enable initial empiric therapy to interfere with the evaluation of new drugs. Thus, newer diagnostic tests for the immediate identification of drug resistance are a research priority, expediting recruitment and limiting the confounding effects of suboptimal therapy during the time it takes to identify drug resistance.

Endpoints

Ideally, durable clinical and microbiological cure, 18 or more months after initiation of therapy, is the recommended endpoint in clinical TB trials.[35] While many relapses occur soon after cessation of therapy, relapse rates for different regimens have been shown to continue to diverge up to 120 weeks after the start of treatment, emphasizing the importance of prolonged follow-up.[26]

Interestingly, in those published studies of MDR-TB where fluoroquinolones were used and treatment regimens were prolonged, relapse rates were low (2.1% or less) (Table 1). This suggests that unlike the experience in drug-sensitive disease where initial clinical response rates are excellent but relapses threaten the control of the disease, the main challenge in MDR-TB is achieving an initial clinical response, and early endpoints are likely to be predictive of ultimate clinical benefit. However, where fluoroquinolones are not used and treatment regimens are short (7 months or less), relapse rates as high as 40% are reported. Extended follow-up is integral to understanding the failings of these treatment regimens.[36]

Elimination of dormant infection and prevention of relapse remains one of the most challenging aspects of TB therapy. It is easy to detect the ability of a drug to eliminate viable organisms from the sputum, but demonstration that relapse has been prevented requires years of clinical follow-up. The identification of new biomarkers for sterilizing activity would revolutionize the development of new TB agents. For example, failure of sterilization at 2 months has been shown to correlate with failure to convert to smear negativity during longer periods of observation.[37] However, correlation with relapse rates is less clear. More specific markers of residual organisms, such as antigenic, DNA/RNA, immunological, or imaging tools, are urgently needed to predict long-term treatment outcome.

Drug safety

The requisite data supporting the safety of new drugs for TB should not differ appreciably for drug-sensitive and drug-resistant disease. However, given the possible life-saving benefit in the face of untreatable drug resistance, greater tolerance of potential risks may be defensible and appropriate.

Accelerated approval

In the case of a serious disease such as MDR-TB in which there are no satisfactory alternative therapies, drugs may qualify for "accelerated approval". Under the provisions of these regulations, approval may be based on a surrogate endpoint (a biomarker that is reasonably likely to predict clinical benefit), with confirmatory studies of clinical benefit being completed after the drug is approved. Surrogate endpoints for MDR-TB drug development may eventually be validated, as was the case with antiretroviral drugs where measurement of HIV-RNA was initially considered a surrogate endpoint and later was qualified as a basis for traditional approval. In the case of MDR-TB trials, a convincing demonstration of superior efficacy may be possible, looking at time to culture conversion in a comparative trial, in the context of a battery of supportive data, such as in vitro minimal inhibitory concentrations, animal models, early bactericidal activity and 2 month culture conversion rates. Given that culture positivity in patients with MDR-TB is prolonged and often exceeds 2 months, new drugs with potent bactericidal activity may have a substantial impact on this interval, providing a benefit not just to the patient but to the public as well. Finally, when high mortality rates from MDR-TB prevail, it may be possible to demonstrate a mortality benefit using a new agent, and survival curves may diverge relatively early during follow-up.

Moving beyond

In general, drugs that are effective against drug-resistant organisms should be effective against drug-sensitive organisms if the target of the drug is present in both. Thus, data on the performance of a drug in drug-resistant infection may support its use in drug-sensitive infections. Use of a drug in a drug-resistant setting would bolster confidence in efficacy, paving the way for more probing use in drug-sensitive disease — e.g. replacement of rifampin or significant shortening of therapy — paradigms that would enable approval for drug-sensitive disease. Safety information might support replacement of the more toxic drugs used in current regimens for drug-sensitive disease.

Given this approach, trials in MDR-TB should not be viewed as competing with trials in drug-sensitive disease. The MDR-TB platform should be viewed as one component in a strategy to develop drugs for all forms of TB, potentially addressing some of the obstacles to trials in drug-sensitive disease. The appropriate drug development plan should take into account the logistics required by a variety of approaches. Small programs may find themselves well served by smaller trials limited to MDR-TB; large programs might consider embracing the full spectrum of TB. Since neither the populations suffering from TB nor the institutions diagnosing and treating TB separate themselves on the basis of drug sensitivity tests, it seems prudent to consider maximizing existing infrastructures to study MDR-TB and drug-sensitive TB concurrently whenever possible.

How might MDR-TB trials fail?

There are several issues to take into account when considering how a trial might fail to show an effect despite drug activity. As in any clinical study, the statistical power of the study to demonstrate a difference between the arms will depend on the number of subjects and the inherent activity of the drug. The amount of structural lung disease, fibrosis and cavitation in patients who suffer MDR disease over many years may present a

challenge to even the best of drugs. The effect of concurrent medications may obscure the efficacy of the experimental drug. The selection of impractical endpoints may complicate drug evaluation. MDR-TB studies may also face practical difficulties, e.g. the ability to recruit adequate numbers of patients.

Summary and conclusions

Despite a resurgence of TB, development of new drugs to treat the disease has stagnated in the face of numerous scientific and economic obstacles. The demonstration of clinical efficacy in drug-sensitive TB is challenging since replacement of the most effective agents may not be ethical, and determining the effect size of the components of a combination regimen may not be possible. Demonstration of the superiority of new agents constitutes the most convincing clinical evidence of drug efficacy, but in the case of drug-sensitive disease this may be infeasible given the high efficacy rates of existing regimens, the need for extended follow-up, and the large number of participants required to support statistical conclusions.

Development of new TB drugs to treat drug-resistant infections may provide opportunities for addressing some of these challenges. Experience in developing treatments for drug-resistant HIV infection, where several new agents show superiority, support such an approach. In the setting of drug-resistant disease, smaller studies may suffice if large differences in efficacy between experimental and comparator regimens are likely. Use of preliminary endpoints may be possible, resulting in accelerated drug approval. In a situation of dire medical need, large potential benefits may outweigh minor risks. But most important, given the pressing need for new drugs to treat resistant TB, this approach will bring the promise of new drugs to an area of major public health concern.

Acknowledgements

The authors thank Nancy Derr for critical revision of the manuscript.

Funding: None.

Competing Interests: None declared.

References

1. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units 1946–1986 with relevant subsequent publications. *Int J Tuberc Lung Dis* 1999;**3**: s231–s279.
2. Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, Zeller K, Andrews GF. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 2006;**368**:1575–1580.
3. Moran JS, Bernard KW. The spread of chloroquine-resistant malaria in Africa. Implications for travelers *JAMA* 1989;**262**:245–258.
4. Grant RM, Hecht FM, Warmerdam M et al. Time trends in primary HIV-1 drug resistance among recently infected persons. *JAMA* 2002;**288**:181–188.
5. Chambers H. The changing epidemiology of *Staphylococcus aureus*. *Emerg Infect Dis* 2001;**7**:178–182
6. Combs DL, O'Brien RJ, Geiter LJ. USPHS tuberculosis short-course chemotherapy trial 21: effectiveness, toxicity and acceptability. *Ann Intern Med* 1990;**112**:397–406.
7. Holtz TH, Sternberg M, Kammerer S, Laserson K, Riedstina, V, Zarovska E, Skripconoka V, Wells CD, Leimane V. Time to sputum culture conversion in multidrug-resistant tuberculosis: Predictors and relationship to treatment outcome. *Ann Intern Med* 2006;**144**:650–659.
8. Goble M, Iseman MD, Madsen LA, Waite D. Ackerson L, Horsburgh R. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med* 1993;**328**: 527–532.
9. Mitnick C, Bayona J, Palacios E, Shin S, Furin J, Alcantara F, Sanchez E, Sarria M, Ecerra M, Smith Fawzi MC, Kapiga S, Neuberg D, Maguire JH, Kim JY, Farmer P. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. *N Engl J Med* 2003;**348**:119–128.
10. Park SK, Kim CT, Song SD. Outcome of chemotherapy in 107 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *Int J Tuberc Lung Dis* 1998;**2**: 877–884.
11. Chan ED, Laurel V, Strand MJ, Chan JF, Huynh MN, Goble M, Iseman MD. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. *Am J Crit Care Med* 2004;**169**:1103–1109.
12. Yew WW, Chan CK, Chau CH, Tam CM, Wong P C, Lee J. Outcomes of patients with multidrug resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. *Chest* 2000;**117**:744–751.
13. Nathanson E, Lambregts-van Weezenbeek, Rich ML, Gupta R, Bayona J, Blondal K, Caminero JA, Cegielski JP, Danilovits M, Espinal MA, Hollo V, Jaramillo E, Leimane V, Mitnick CD, Mukherjee JS, Nunn P, Pasechnikov A, Tupasi T, Wells C, Raviglione MC. Multidrug-resistant tuberculosis, management in resource-limited settings. *Emerg Infect Dis* 2006;**12**:1389–1397.
14. Geerligs WA, van Altena R, de Lange WCM, van Soolingen D, van der Werf TS. Multidrug-resistant tuberculosis: long-term treatment outcome in the Netherlands. *Int J Tuberc Lung Dis* 2000;**4**:758–764.
15. Singapore Tuberculosis service/British Medical Research Council. Clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. *Am Rev Respir Dis* 1979;**119**:579–585.
16. Singapore Tuberculosis service/British Medical Research Council. Assessment of a daily combined preparation of isoniazid, rifampin and pyrazinamide in a controlled trial of three 6-month regimens for smear-positive pulmonary tuberculosis. *Am Rev Respir Dis* 1991;**143**:707–712.
17. Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. *Am Rev Respir Dis* 1986;**133**: 423–430.
18. Nitti V. Antituberculosis activity of rifampin. Report of studies performed and in progress (1966–1971). *Chest* 1972;**61**:589–598.
19. Kennedy N, Berger L, Curram J. Fox R, Gutmann J, Kisyombe GM, Ngowi FI, Ramsay ARC, Saruni AOS, Sam N, Tillotson G, Uiso LO, Yates M, Gillespie SH. Randomized

controlled trial of a drug regimen that includes ciprofloxacin for the treatment of pulmonary tuberculosis. *Clin Infect Dis* 1996;**22**:827–833.
20. Aptivus package insert, Boehringer Ingelheim Pharmaceuticals Inc, 2007.
21. Prezista package insert, Tibotec Inc 2006.
22. Fuzeon package insert, Roche Laboratories Inc and Trimeris Inc 2007.
23. Sezentry package insert, Pfizer Inc 2007.
24. Isentress package insert, Merck &Co Inc 2007.
25. Mitchison DA. Assessment of new sterilizing drugs for treatment of pulmonary tuberculosis by culture at 2 months. *Am Rev Respir Dis* 1993;**147**:1062–1063.
26. The tuberculosis trials consortium. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. *Lancet* 2002; **360**:528–534.
27. R Hernández-Pando, M Jeyanathan, G Mengistu, D Aguilar, H Orozco, M Harboe, GAW Rook, G Bjune. Persistence of DNA from *Mycobacterium tuberculosis* in superficially normal lung tissue during latent infection. *Lancet* 2000; **356**:2133–2138.
28. Mistry R, Cliff JM, Clayton CL, Beyers N, Mohamed YS, Wilson PA, Dockrell HM, Wallace DW, van Helden PD, Duncan K, Lukey PT. Gene-expression patterns in whole blood identify subjects at risk for recurrent tuberculosis. *J Infect Dis* 2007;**195**:357–365.
29. Centers for disease control and prevention. Treatment of Tuberculosis. *MMWR* 2003 **52** (RR11):1–77.
30. Sacks LV, Pendle S, Orlovic D, Blumberg L, Constantinou C. A comparison of outbreak- and non-outbreak-related multidrug-resistant tuberculosis among human immunodeficiency virus-infected patients in a South African hospital. *Clin Infect Dis* 1999;**21**:96–101.
31. Ritacco V, Di Leonardo M, Reniero A et al. Nosocomial spread of human immunodeficiency virus-related multidrug resistant tuberculosis in Buenos Aires. *J Infect Dis* 1997;**176**:637–642.
32. Agerton TB, Valway SE, Blinkhorn RJ, Shilkret KL, Reves R, Schluter WW, Gore B, Pozsik CJ, Plikayatis BB, Woodley C, Onorato IM. Spread of strain W, a highly drug-resistant strain of *Mycobacterium tuberculosis*, across the United States. *Clin Infect Dis* 1999;**29**:85–92.
33. Zignol M, Hosseini MS, Wright A, Lambregts-vanWeezenbeek, Nunn P, Watt CJ, Williams G, Dye C. Global incidence of multidrug-resistant tuberculosis. *J Infect Dis* 2006;**194**:479–485.
34. Moore DA, Mendoza D, Gilman RH, Evans C, Delgado M, Guerra J, Caviedes L, Vargas D, Ticona E, Ortiz J, Soto G, Serpa J. Microscopic observation drug susceptibility assay a rapid reliable diagnostic test for multidrug resistant tuberculosis suitable for use in resource– poor settings. *J Clin Microbiol* 2004;**42**:4432–4437.
35. Hopewell P, Cynamon M, Starke J, Iseman M, O'Brien R. Evaluation of new anti-infective drugs for the treatment and prevention of tuberculosis. *Clin Infect Dis* 1992;**15** (Suppl 1):s282–295.
36. Migliori GB, Espinal M., Danilova ID, Punga VV, Grzemska M, Raviglione MC. Frequency of recurrence among MDR-TB cases "successfully" treated with standardized short-course chemotherapy. *Int J Tuberc Lung Dis* 2002;**6**: 858–864.
37. Rieder HK. Sputum smear conversion during directly observed treatment for tuberculosis. *Tubercle and Lung Disease* 1996;**77**:124–129.
38. 21 Code of Federal Regulations, Sec 314.500 and 314.510.