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.