Sustainable Tuberculosis Drug Development

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Six new antituberculosis compounds in 4 classes are presently in clinical trials. Although these show substantial promise for drug-resistant (DR) tuberculosis, the presently planned studies of these compounds will not inform their optimal use, as each will be tested singly vs placebo with existing drugs, rather than in new regimens. Each successive regulatory approval will increase the size, cost, and complexity of trials for those that follow, causing delays during which suboptimal use will occur and resistance will emerge. This paper proposes the development of a novel regimen with the potential for use in both drug-sensitive (DS) and DR tuberculosis. Adaptive licensing for DR tuberculosis based on 2-month sputum culture would shorten time to initial approval by several years. A global outcomes registry would confirm safety and effectiveness in both DS and DR tuberculosis, making possible the second transformation of tuberculosis treatment. We should do our utmost to see it succeed.

Keywords. tuberculosis; drug development; adaptive licensing; surrogate endpoint; oxazolidinone.

Drug-resistant (DR) tuberculosis has emerged as a distinct threat to world health in the 2 decades since the World Health Organization declared tuberculosis a “global health emergency” [1–3]. Current treatments for DR tuberculosis show inferior efficacy, safety, and tolerability compared to those for drug-sensitive (DS) tuberculosis. Only a small fraction of DR tuberculosis cases globally receive appropriate treatment [4]. Tuberculosis cases in some human immunodeficiency virus (HIV)–infected persons must be treated as DR despite full drug susceptibility, due to the incompatibility of certain antiretroviral drugs with rifampin, a key component of standard tuberculosis treatment. Like DR tuberculosis, HIV tuberculosis cases have more than doubled during the past 2 decades [2].

It is therefore significant that 6 new anti-tuberculosis compounds are being tested in clinical trials. They show substantial promise for DR tuberculosis, as none exhibits cross-resistance with current drugs. Two are presently in late-stage trials, with at least one approval likely to come in 2012. However, planned studies of these compounds will at best show superiority to placebo without informing their optimal use. Each resulting regulatory approval will increase the size, cost, and complexity of subsequent trials. Sponsors of the remaining compounds are unlikely to find this development strategy acceptable, as the costs of phase 3 trials in DR tuberculosis are already disproportionate to the market. More importantly, the suboptimal clinical use of the new drugs will inevitably promote the emergence of resistance, thus reducing their long-term potential to address an important unmet medical need.

This paper explores an innovative proposal for sustainable tuberculosis drug development that enhances value to patients, control programs, and sponsors, yet addresses regulatory concerns regarding the approval of medicines that are safe and effective (Figure 1). It includes these elements:

- Developing an entirely novel DR tuberculosis regimen that may also be tested for use in DS tuberculosis, using findings in one setting to inform the other.
- Adaptive licensing in DR tuberculosis based on 2-month sputum culture status, using a global outcomes registry to confirm safety and effectiveness.
Regimen Selection and Initial Evaluation

Compounds of interest for DR tuberculosis are described in Table 1. In addition to these, the fluoroquinolones and pyrazinamide are often included in empiric or standardized regimens for multidrug-resistant (MDR) tuberculosis. However, recent studies have found fluoroquinolone resistance in up to half of MDR isolates and pyrazinamide resistance in up to 90% [5]. At a minimum, regimens including these drugs would require susceptibility testing prior to starting treatment, and would not be suitable for most MDR patients due to resistance. In practice, performing pyrazinamide testing would be particularly problematic, as no rapid commercial molecular test is presently available, and there is uncertainty as to the interpretation of phenotypic tests.

Distinct mycobacterial subpopulations exist in tuberculosis, differing in their replication, metabolism, and anatomic location, as well as in their susceptibility to the lethal effects of specific drugs. Fully effective new regimens must inhibit the emergence of resistance among replicating mycobacteria, thus preventing treatment failure, and must eradicate dormant or semidormant subpopulations that exhibit phenotypic drug tolerance, thus preventing relapse [6]. Dormant subpopulations are amplified in response to oxygen or nutrient starvation, or pressure from host immune mechanisms.

No single preclinical model can fully assess these diverse activities. The hollow fiber model appears best suited to study emergence of resistance, and presumably its prevention, as clonal outgrowth can occur rapidly under aerobic culture conditions [7, 8]. However, no studies of resistance prevention using novel tuberculosis drug combinations in the hollow fiber model have yet been published. The mouse relapse model has been extensively used to study the treatment-shortening potential of new regimens, with the caveat that it likely has overestimated the sterilizing activity of at least one new drug [9–12]. Last, the whole blood model, which measures bactericidal activity against intracellular, semidormant mycobacteria, may help bridge the preclinical-clinical gap by informing the pharmacokinetic/pharmacodynamic relationship in both in vitro and in phase 1 trials [13]. This model appears to generally reflect sterilizing activity, with the exception of overestimating that of aminoglycosides [14, 15].

Additive or synergistic interactions have been observed in these models for several novel 2-drug combinations, including bedaquiline plus sutezolid (PNU-100480), bedaquiline plus SQ109, and sutezolid plus SQ109 [16–18]. The mouse and
Table 1. Compounds in Development for Drug-Resistant Tuberculosis

<table>
<thead>
<tr>
<th>Class</th>
<th>Target</th>
<th>Compound</th>
<th>Status</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaryquinoline</td>
<td>ATP synthesis [42]</td>
<td>Bedaquiline (TMC207, Janssen)</td>
<td>NDA submitted to FDA for accelerated approval</td>
<td>Increased 2-mo sputum culture conversion from 9% to 53% [43]</td>
</tr>
<tr>
<td>Nitroimidazole</td>
<td>Aerobic: ketomycolate synthesis [44], Anaerobic: NO donor [45]</td>
<td>Delamanid (OPC-67683, Otsuka)</td>
<td>EU NDA submitted</td>
<td>Increased 2-mo sputum culture conversions from 30% to 45% [46]</td>
</tr>
<tr>
<td>Oxazolidinone</td>
<td>23S RNA</td>
<td>Sutezolid (PNU-100 480, Pfizer)</td>
<td>Completed phase 1 [48, 49] and 2-wk phase 2a trial [50]</td>
<td>Both appear superior to linezolid against intracellular Mtb infection [48, 51]</td>
</tr>
<tr>
<td>Ethylene diamine</td>
<td>Cell wall synthesis [52]</td>
<td>SQ109 (Sequella)</td>
<td>Completed 2-wk phase 2a trial</td>
<td>Superior vs ethambutol in mice [53], low concentrations in blood vs lung [54]</td>
</tr>
<tr>
<td>Riminophenazine</td>
<td>Unknown</td>
<td>Clofazimine (Novartis)</td>
<td>Licensed for leprosy [55], appears to improve cure rate in MDR tuberculosis [56]</td>
<td>Highly protein bound [57], low concentrations in blood vs lung [14], causes red-brown skin discoloration</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitor</td>
<td>Host cell (phagolysosomal fusion)</td>
<td>Imatinib (Novartis)</td>
<td>Licensed for CML; shows antituberculosis activity in mice [58]</td>
<td>Unlikely to show early bactericidal activity</td>
</tr>
</tbody>
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Abbreviations: ATP, adenosine triphosphate; CML, chronic myelogenous leukemia; EU, European Union; FDA, Food and Drug Administration; MDR, multidrug resistant; Mtb, Mycobacterium tuberculosis; NDA, New Drug Application; NO, nitric oxide.

Whole blood studies suggest that novel 3-drug combinations that include bedaquiline and sutezolid may be sufficiently active to cure tuberculosis in 6 months or less regardless of resistance status [16, 19]. However, unfavorable interactions (effects that are less than additive or antagonistic) have been reported for combinations that include a nitroimidazole plus bedaquiline and/or sutezolid [16, 20]. This antagonism is most evident when nitroimidazoles are tested under semidormant growth conditions, at early time points, and at low concentrations. Nitroimidazole doses selected by early bactericidal activity trial findings may not be adequate to reach concentrations required for sterilizing activity against dormant mycobacteria, which can exceed minimum inhibitory concentrations by >100-fold [21–23]. This concern is increased for DR tuberculosis strains, which appear to show reduced susceptibility to killing by nitric oxide [24]. These factors, which increase the risks of failure in late-stage trials, may delay or prevent the development of some nitroimidazole-containing regimens.

A clinical trial will be required to evaluate these candidate regimens with regard to efficacy and safety (Figure 1). Early bactericidal activity trials of ≤2 weeks’ duration do not appear adequate to assess the efficacy of new regimens. For example, 2 studies with 64 subjects in total were unable to differentiate potentially curative from noncurative treatments (isoniazid plus rifampin vs isoniazid alone), or a modern regimen capable of curing tuberculosis in 6 months (isoniazid, rifampin, streptomycin plus pyrazinamide) from one requiring 18 months (isoniazid, streptomycin plus thiacetazone) by measuring sputum colony counts during the first 2 weeks of treatment (Supplementary Figure 1) [25–27]. Although these studies were small, their lack of prognostic capability does not appear to arise from variability, as independent, similarly sized studies of 7–14 days’ duration of single drugs and regimens have shown very similar results [22, 25, 27, 28]. This instead appears to be an intrinsic limitation of short duration trials. The earliest documented surrogate endpoint for efficacy at present is sputum culture status after 2 months of treatment. An analysis of the relationship of 2-month culture status to relapse conducted by Wallis and colleagues in 2010 [15] included 30 pairs of regimens in trials conducted in 5561 patients in 4 global regions by the British Medical Research Council from 1946 to 1986. Studies were selected if rates of sputum culture conversion at 2 months and relapse 18–24 months after completion of therapy were reported, and if the tested regimens differed either only in the first 2 months or consistently throughout all of treatment. Twenty-four and 27 of the regimen pairs contained rifampin and pyrazinamide, respectively, in at least one arm. Meta-regression analysis showed a highly significant relationship between 2-month status and relapse rate (P < .00001). Consistent results were observed when different studies tested the same intervention in different global regions (Supplementary Figure 2).

These findings increase confidence regarding the predictive power of 2-month culture status to evaluate the efficacy of
new candidate regimens. However, they do not directly inform the required duration of treatment of the new regimen. A second analysis was therefore performed to examine the relationship between required treatment duration and 2-month culture conversion rate (Figure 2). This analysis included all treatment arms in British Medical Research Council and US Public Health Service trials that reported 2-month culture status, total duration of therapy, and relapse rate 18–24 months after treatment.

Figure 2. Relationship between required duration of treatment and 2-mo culture conversion rate. The regimens of eligible study arms in British Medical Research Council and US Public Health Service tuberculosis trials were classified according to inclusion of rifampin (R) and pyrazinamide (Z); those classified as R± included rifampin only for the first 1–2 months and/or at reduced doses. The first step of this analysis (left) examined the relationship between treatment duration and relapse rate for each class of regimens. Each circle represents a single study arm; its diameter reflects the number of subjects evaluable for relapse. The solid lines in each figure indicate the regression of treatment duration vs relapse rate, weighted according to number of subjects. The intersections of solid and dotted lines indicate the duration of treatment of each class of regimen with a predicted 5% relapse rate (summary panel, upper right). The meta-analysis panel (lower right) indicates, among regimen classes, the relationship between the required duration of treatment to achieve a 5% relapse rate and the corresponding 2-month sputum culture conversion rate. In this panel, circles indicate a single regimen class, color coded to correspond to the small panels. Circle diameters reflect the number of subjects, using a scale 10-fold less than in the figures to the left. Meta-regression analysis, weighted according to total number of subjects, was performed to determine the relationship of required treatment duration to 2-month culture conversion. A new regimen with a conversion rate of 95% is predicted to result in a 5% relapse rate if administered for 4 months.
completion of therapy (Supplementary Table 1). Ninety treatment arms, including >11 000 patients, were identified. Regimens were classified according to inclusion of rifampin and pyrazinamide, the 2 drugs that permitted DS tuberculosis treatment to be shortened from 18 months to 6 months. Those that included rifampin for less than the full course of treatment or at less than standard doses were classified as R#. Within each regimen class, the relationship between treatment duration and relapse rate was determined, as shown in the 6 panels in the left of Figure 2. Regression analysis weighted according to numbers of subjects was performed to determine the duration of treatment for each class expected to yield a 5% relapse rate. The resulting set of 6 roughly parallel regression lines are summarized in the upper right panel of Figure 2. A meta-analysis was then conducted to determine the relationship among the regimen classes between the reported 2-month sputum culture conversion rate and required duration of treatment for 5% relapse (Figure 2). The analysis revealed that a conversion rate of 95% likely will support a confirmatory trial with a treatment duration of 4 months.

Shortcomings of this analysis must be acknowledged. The small numbers of study arms in the R+Z and R-Z classes prevent formal estimation of the confidence limits of the prediction. Although the R-Z data have relatively little influence on the outcome of the analysis, the R-Z data do provide an important anchor point for the meta-regression. In that case, however, confidence that long courses of treatment are indeed required for regimens lacking these 2 key drugs is increased by experience in MDR tuberculosis, which requires similarly long treatment. Readers may also ask how the failure of the Tuberculosis Research Unit’s treatment-shortening trial [29], which used 2-month sputum culture conversion as the main entry criterion to a study of a 4 month regimen, might affect the validity of these conclusions. However, that study used a single 2-month sputum culture for individualized treatment decisions, a circumstance recognized to have low sensitivity and low predictive value. These issues notwithstanding, it appears unlikely that any more rigorously defined predictive tools will emerge in the near future to guide the design of trials to test these new regimens.

Safety will be the second main endpoint of the regimen selection trial. Risks are increased when multiple new compounds are tested simultaneously in phase 2 trials, particularly as safety in small phase 1 trials may not be adequately predictive. Sponsors may be reluctant to place their compounds at risk in a new regimen unless each has a distinct, nonoverlapping toxicity profile. Minor safety signals may become significant if shared by multiple compounds in the regimen. Possible examples include QTc prolongation and liver injury. Recent studies indicate depletion of intracellular glutathione predisposes to oxidative tuberculosis drug-induced liver injury, and that this may be prevented by dietary N-acetylcysteine supplementation [30–32]. New toxicities may become evident when drugs are combined, and unexpected pharmacokinetic drug–drug interactions may occur [33]. Regulatory precedents exist for the simultaneous clinical testing of multiple new chemical entities in HIV, hepatitis C virus, and oncology; however, discussions with regulators regarding required preclinical toxicology and pharmacology for specific new tuberculosis drug combinations will be essential. Equipose mandates that the potential risks and benefits be balanced when clinical trials of new therapies are considered. Regimens containing clofazimine may be most appropriately studied in DR tuberculosis patients, owing to the recognized risks of clofazimine of QT prolongation and skin discoloration. Conversely, entirely novel regimens for which the main concern is uncertain efficacy may be most appropriately studied in DS tuberculosis patients, as even in the worst outcome—treatment failure with emergence of resistance—the likelihood of subsequent cure by standard therapy would be unaffected. Ethical and regulatory review will be required to determine the most appropriate patient population (DS or DR tuberculosis) for this trial.

CONFIRMATORY TRIAL CONSIDERATIONS

The unique value of an entirely novel regimen appropriate for both DR and DS tuberculosis becomes apparent as one considers the practical issues of conducting large confirmatory trials in DR tuberculosis. Cases are most prevalent in regions with poorly functioning tuberculosis control programs. It is estimated that in 2009 <5% of all MDR tuberculosis cases received World Health Organization–approved care [4]. Sites lacking the capacity to diagnose and treat MDR tuberculosis are unlikely to be able to conduct registration-quality trials. Drug susceptibility testing, if required, may delay enrollment. Direct patient care costs of 30 times those for DS tuberculosis have been reported [34]. Lung resection surgery may compromise subject evaluability. Most DR tuberculosis patients receive some period of ineffective therapy, reducing trust and confidence in study personnel. The potential impact of these factors is illustrated by the experience of the CDC’s Tuberculosis Trials Consortium Study 30, a placebo-controlled trial of linezolid in DR tuberculosis conducted in Durban, South Africa [35]. More than 380 patients were screened over 1 year to enroll 36, of whom 11 subsequently withdrew consent, most within the first 2 weeks after enrollment. The team concluded that it had greatly underestimated the magnitude of the challenge and the number of study personnel required to recruit, retain, and follow DR tuberculosis patients.

The conduct of the confirmatory trial primarily in DS tuberculosis would be ethically acceptable with a finding in phase 2 of a novel regimen with satisfactory safety and tolerability.
capable of curing tuberculosis in ≤6 months. There are no a priory expectations of differential efficacy in DR tuberculosis, since the distinct mutations that exist for each current tuberculosis drug class do not affect the activity of these new drugs. Indeed, an online search failed to identify any studies in which new tuberculosis drugs were tested in animals using MDR strains. One study, which used a DS tuberculosis strain to examine the impact of bedaquiline on current MDR tuberculosis strains, was particularly telling [36]. While the authors commented that results could not be extrapolated to strains with resistance to pyrazinamide or second-line agents, they saw no reason to expect contrary results in MDR tuberculosis otherwise. The use of DS tuberculosis data to inform adaptive licensing in DR tuberculosis can substantially accelerate the introduction of a new regimen to patients in greatest medical need.

ADAPTIVE LICENSING

The licensing of new drugs has historically been viewed as a binary event, at which time an experimental therapy is deemed safe and effective for general use. In contrast, an evolving model known as adaptive or progressive licensing is one in which the approval process is iterative, containing multiple phases of data collection and regulatory review (Figure 1) [37]. Adaptive licensing is a focus of discussion of the Massachusetts Institute of Technology (MIT) New Drug Development Paradigms (NEWDIGS) initiative, a program led by the MIT Center for Biomedical Innovation that includes regulators, pharmaceutical companies, healthcare providers, payers, and other stakeholders. Proposals for adaptive licensing have been advanced in several jurisdictions, including the United States, Canada, Singapore, the United Kingdom, and elsewhere in the European Union. In some instances it appears that the legal frameworks necessary for their implementation are already in place; in others, new legislation may be required. Although the proposals differ in some respects, they share common features that make them particularly attractive for the development of new tuberculosis regimens. One such feature is the initial specification for licensing in an enriched population with greatest medical need, for whom greater uncertainty regarding efficacy and safety would be acceptable. This concept is readily applicable to DR tuberculosis, with an initial license for patients with extensively DR disease. Subsequent licensing would broaden the eligible patient population to MDR and to HIV tuberculosis patients requiring protease inhibitors as the safety and effectiveness of the new treatment became better understood. A specific requirement of this approach is that a mechanism be in place to ensure that access to the new therapy is limited to the specified patient population. Such a restriction could be readily implemented by national or regional tuberculosis control programs, as recent data indicate very few DR tuberculosis cases are treated by private physicians, even in countries where they provide a substantial fraction of routine tuberculosis care [38].

A second common feature of many adaptive licensing proposals is initial licensing based on a less-than-fully-validated surrogate marker, with subsequent licensing based on a traditional clinical endpoint. This represents an evolutionary change from the accelerated approval mechanism (subpart H of 21 CFR 314), which in the United States permits accelerated approval of new drugs for serious or life-threatening illnesses based on a surrogate endpoint that is “reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit.” In 2009, an Advisory Committee convened by the US Food and Drug Administration recommended nearly unanimously in favor of accelerated approval of new drugs for DR tuberculosis based on sputum culture conversion. Experience indicates that once licensing based on a surrogate endpoint is granted, subsequent confirmatory randomized controlled trials become difficult or impossible to design and conduct owing to the perceived superiority of the new treatment. For new DR tuberculosis regimens, this may be viewed as an opportunity to balance the efficacy data generated in clinical trials with effectiveness data derived from ordinary clinical use [39]. Patient registries can facilitate the collection of uniform observational data from a broad range of patients. In this case, the critical outcome measures will be rates of relapse-free cure without serious adverse events. Findings will be compared to those in concurrent DS tuberculosis patients treated with standard therapy. The main challenge faced by registries is that of bias due to lack of randomization. The use of prespecified propensity scores, stratification, or matching according to recognized, measurable risk factors for poor outcomes can help minimize the effects of bias [40]. Tuberculosis control programs have historically collected and reported data for public health purposes using a relatively short list of international standards describing diagnosis, treatment, and outcome. There is increasing use of electronic medical records, even in remote regions [41]; these can facilitate timely reporting of safety and effectiveness data to a global registry. These represent expanded roles for registries, which until now have primarily been used to monitor safety rather than effectiveness, and for tuberculosis control programs, which historically have been distinct from research centers. It will also require intensified efforts by control programs to identify relapses.

A CALL FOR REGULATORY AND CLINICAL INNOVATION

The possibility now exists to undertake the second transformation of tuberculosis treatment, coming nearly 50 years after the first. The elements outlined in this white paper can help
its realization. This represents a new paradigm for drug development, based on cooperation and transparency among industry, payers, regulatory and public health agencies, and philanthropic organizations. The opportunity before us is unique. We should do our utmost to see it succeed.

**Supplementary Data**

Supplementary materials are available at Clinical Infectious Diseases online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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**References**