

RESIST-TB:

Research Excellence to Stop TB Resistance

Plan for MDR-TB Clinical Trials: An Overview

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Summary

The current epidemic of Multidrug-Resistant Tuberculosis (MDR-TB) is a major threat to world health. Existing treatment regimens have not been evaluated in clinical trials, and such evaluation could provide data to support more cost-efficient and less toxic patient management. While these regimens fail to cure 40% of patients, new drugs to treat TB may soon become available. These drugs, when used in combination regimens, could revolutionize treatment and prevention of MDR-TB. However, individual sponsors' studies are each focusing on getting licensure for their agent in trials that demonstrate the efficacy of that agent with existing drugs; no studies of combinations of the new drugs are currently planned. Combination trials are critical for developing effective regimens and reducing risk of additional resistance; international cooperation will be essential to this endeavor. New regimens that are simpler and of shorter duration will greatly increase the capacity of programs to scale up MDR-TB treatment. RESIST-TB has developed a plan for designing and implementing a series of MDR-TB clinical trials of combinations of these new drugs, and has the experience and skills to oversee design and to implement such trials.

The ultimate goals of our plan are to identify:

- The best way to use currently available agents in MDR-TB treatment regimens
- A regimen that cures 95% of all MDR-TB patients with less than 5% relapses
- A regimen that lasts 6 months or less
- A regimen that is completely orally administered
- A regimen that is effective in HIV-infected persons with or without antiretroviral therapy
- A regimen that is effective in children, with pediatric formulations available
- A regimen that can be easily and widely disseminated to national TB programs
- A 2-month preventive regimen, oral and easily tolerated, that can reduce secondary cases of MDR-TB by 90%

Background

MDR-TB and Extensively Drug-Resistant Tuberculosis (XDR-TB) are rapidly growing threats to the world's health. A 2008 report from WHO estimated that over 489,000 new cases of MDR-TB occurred worldwide in 2006.¹ WHO has called on governments to commit more resources to MDR-TB treatment, but effective, well tolerated and easily-delivered treatment regimens are not available.² Current treatment regimens for MDR-TB cure roughly 60% of patients treated. As many as 20% of those who fail to respond to treatment die of tuberculosis; those who do not die become chronic carriers and spread MDR-TB to others.³

Current standard treatment regimens for MDR-TB last 18-24 months and are associated with substantial drug intolerance, often leading to failure to complete treatment. Moreover, even in the most experienced hands, failure and death rates are unacceptably high (25-39%).³ In the only reported study to date, 21% of those receiving MDR-TB treatment developed resistance to additional drugs,⁴ and half of those developed XDR-TB. Despite the lack of formal surveillance, XDR-TB has been identified in 50 countries, and nearly 10% of incident cases of MDR-TB have XDR-TB.⁵ Although the lack of effective strategies for treatment of MDR-TB would seem to mandate controlled clinical trials, there have been no large-scale randomized trials of MDR-TB treatment. Although new regimens for drug-susceptible TB using new drugs are currently being explored, these regimens will continue to include a rifamycin for the foreseeable future; such regimens will not be effective in patients with MDR-TB. Therefore, trials that examine new regimens for treatment of MDR-TB are essential.

Now is an opportune time to readdress performing clinical trials to identify optimal MDR-TB treatment for several reasons. First, through the Green Light Committee of the Stop TB Partnership, 87 MDR-TB treatment projects have been approved for treatment around the world. The more experienced programs have demonstrated the feasibility of MDR-TB treatment in resource-limited settings. They can also serve as the infrastructure onto which clinical trials may be introduced. Second, several new drugs for the treatment of TB may become available in the next several years. These drugs are from new classes of antimicrobial agents that do not have cross-resistance with existing anti-TB agents. While these new drugs provide an opportunity to greatly improve MDR-TB treatment outcomes, inappropriate use of them could rapidly lead to drug resistance and a great opportunity would be wasted. Third, recent developments in clinical trial design can permit heterogeneity in background treatment regimens and allow for rapid sequential evaluation of new regimens using adaptive trial design.

Existing Drugs: Room for Improvement

Current MDR-TB treatment guidelines are based on clinical experience and recommend that treatment for MDR-TB be continued for 18-24 months after sputum culture conversion is achieved. However, these recommendations have never been prospectively evaluated; many clinicians believe that equivalent results could be achieved with shorter duration of the post-culture-conversion phase of treatment, especially with regimens containing later-generation fluoroquinolones. Demonstration that shorter regimens could be successfully used would greatly expand the ability of programs to treat MDR-TB patients with existing resources.

In addition, most MDR-TB treatment regimens currently include at least one injectable agent. Delivery of these agents is painful, requires clinical encounters, and is associated with substantial toxicity. Variable duration of injectable use - from 6 to 15 months - without evidence of association with improved outcomes, suggests that shorter durations of administration of these agents may be adequate. Thus, a clinical trial to determine the optimal duration of therapy with injectable agents could substantially simplify treatment and minimize toxicity.

Lastly, most programs monitor patients with monthly sputum smears and cultures, at least until culture conversion is achieved. For the duration of the consolidation phase, various degrees of intensity are applied, from monthly cultures for the duration, to every three months. It is not clear whether the more intensive monitoring regimens contribute to improved patient outcomes, or are only associated with increased cost. These costs are substantial, both for laboratory tests and clinical staff time. Thus, investigation of the costs and benefits of less versus more intensive patient monitoring protocols could lead to more efficient use of program resources.

New Drugs: Opportunities and Challenges

The first new drug for the treatment of TB in almost 40 years, TMC-207, is expected to receive approval in 2010. Within 4 years, several other new drugs may also become available, including OPC-67683, PA-824, PNU-100480 and SQ-109. All of these agents are from new drug classes and are not expected to have cross-resistance with existing agents (although OPC-67683 and PA-824 may have cross-resistance with each other). This means that they will be excellent candidates for the treatment of MDR-TB. However, if used alone or introduced sequentially, resistance to each may develop, as occurred in the 1990s with the sequential introduction of new antiretrovirals for HIV treatment and with the introduction of quinolones for TB treatment. It is therefore essential that these new drugs be promptly studied in combination.

Each of these agents is being developed by a different company or organization. Four are being studied for their safety and efficacy in MDR-TB treatment when combined with a

background regimen of second-line drugs, but none of the developers has plans to study its drug in combination with any of the other new agents for MDR-TB. Therefore, it is essential that the scientific community prepare for combination trials that could begin as soon as the agents become available for study.

Designing a plan to evaluate these new agents in combination clinical trials will require flexibility and contingency planning. Several outcomes must be anticipated. First, drug development plans may be delayed, resulting in the drug becoming available for study later than anticipated, or unanticipated toxicities may lead to its withdrawal. Existing companion agents (e.g., quinolones) may become limited due to further emergence of resistance. Lastly, interactions with antiretroviral agents may require dose adjustment or separate trials for persons co-infected with HIV and MDR-TB.

Clinical Trial Site Development

Clinical trials to define the optimal regimen for treatment of MDR-TB will require a number of sites that can contribute patients, perform laboratory studies, collect and manage data, and follow patients after treatment, so that registration-quality results are obtained. Trials will need to be large (~500 patients per arm) and be enrolled promptly, and results should be generalizable to important subpopulations (such as HIV-infected patients, chronic cases, and children). Therefore, it will be important to maximize the number of potential clinical trial sites. Trials by Tibotec and Otsuka are currently in progress at sites in many countries, including South Africa, Russia, India, Thailand, Brazil, Peru, Latvia, Estonia, China, Korea, the Philippines, Japan and the U.S.

Coordination between the drug developers will be essential to prevent wasted energy and resources while ensuring rapid advancement of new agents. RESIST-TB has positioned itself as an independent and honest broker in this area, and will continue to ensure that collaboration is maximized. We will also prepare a roster of potential new MDR-TB treatment sites that could, with modest investment, be brought up to required standards. In addition, we will seek foundation and government support to begin the site development process at these sites. In this we hope to forestall delays in treatment advances that might otherwise result from a shortage of trial sites.

Moreover, because trials for prevention of MDR-TB in contacts of patients with MDR-TB are an essential part of the RESIST-TB strategy for controlling the MDR-TB epidemic worldwide, clinical trial capacity for household contact studies will need to be assessed and augmented. In some cases, such trials can be performed in sites that are already carrying out treatment trials; such co-location will maximize benefits from investments in laboratory, data and operations. However, not all treatment sites will be able to perform contact studies, and we will undertake a separate evaluation for this capacity.

The importance of an overall MDR-TB Treatment Trial Strategy

To ensure prevention of emergence of resistance, new drugs should be given in regimen with at least two other drugs to which the individual's isolate is susceptible. In initial trials, when new drugs are being given in combination with existing drugs and drug susceptibility of patient isolates will often not be known at the time of initiation of therapy, a four drug regimen is preferred. This gives some protection against the presence of unrecognized resistance to one of the drugs in the regimen, as well as a margin of safety if one of the drugs is not tolerated by the patient. Some individualization of regimens will likely be required in the first trials, when only one new drug is available. As more new drugs become available to replace existing drugs, increasing standardization may become possible. In addition to developing a regimen that can achieve a high rate of cure, the goal of an MDR-TB treatment study must be to examine the optimal duration of therapy, as therapy for too short a time will reduce cure rates, while therapy for too long creates unneeded toxicity and wastes scarce program resources.

We anticipate that the first new drug, TMC-207, will be available through the "conditional approval" process in 2011. Animal studies of TMC-207 indicate that TMC-207 has bactericidal activity equal or superior to isoniazid (INH) or rifampin (RIF),⁶ and combination of TMC-207 with moxifloxacin or high-dose levofloxacin (HFQ) and pyrazinamide (PZA) or an aminoglycoside for treatment of drug-susceptible *M. tuberculosis* has a high cure rate with a relapse rate equivalent to that of the standard 6-month 2HRZ/4HR regimen.⁷ Therefore, TMC-207 should be studied in combination with at least three drugs likely to be effective in MDR-TB patients. Companion drugs currently under consideration are: HFQ, PZA and kanamycin (KAN). Recent results from a Phase 2B trial in patients with MDR-TB showed that addition of TMC-207 to a similar background regimen resulted in a two-month culture conversion rate (in liquid medium) of 47.5%, compared to only 8.7% in patients receiving the background regimen plus placebo.⁸ If, as expected, the second stage of the TMC-207 Phase 2B trial again reveals a substantial benefit associated with TMC-207, it will be neither ethical nor practical in future studies to have a study arm that does not contain TMC-207. Consequently, we believe that a trial that compares two durations of a regimen containing TMC-207 will be the next step. The optimal duration of such a regimen is unknown, but by analogy with the regimen of INH, PZA and streptomycin in patients with drug-susceptible TB, 9 months duration might well achieve a 95% cure rate.⁹ Animal studies to define the likely optimal treatment duration of this regimen will be needed, however, before the durations to study in human trials are finalized, and these animal studies should be initiated expeditiously.

It will also be essential to include children in such trials, since many children have MDR-TB. Although it is not necessary or desirable to perform independent efficacy trials in children with MDR-TB, pediatric regimens must have been demonstrated to have similar pharmacokinetic characteristics to those of adults, while being free of unacceptable toxicity. If pediatric formulations and dosing schedules are not available at the start of

the proposed trials, then the trial designs will include addition of children as soon as the necessary background studies have been performed.

Additional new agents—such as SQ-109, PA-824 and OPC-67683—may also become available for potential study relatively soon after TMC-207. Deciding which agent to study next and in what combination will require both animal studies examining efficacy and drug interaction studies in man; these studies need to be planned as soon as possible. We recommend first replacing the injectable agent with one of the new agents, followed by replacement of PZA with another new agent. This will result in a regimen with three new agents, so that there will no longer be a need for additional second-line drugs to prevent emergence of resistance.

In addition, a series of sequential trials (e.g. arm 1 versus arm 2, followed by a trial of the best arm from that study versus arm 3, etc.) will take so long, even with rapid enrollment, that the optimal regimen might not be identified until the completion of two or more 4-year cycles. If the drugs come out as quickly as is currently hoped, they may be in widespread use by the completion of the second cycle, and the opportunity for ethically acceptable comparative studies will have been lost. Therefore, RESIST-TB is advocating substantial development of site capacity for MDR-TB clinical trials, so that rapid accrual will allow prompt identification of optimal new MDR-TB treatment regimens. Exploratory studies (using surrogate endpoints) to discriminate among regimens that are likely to be the most efficacious can also be a useful strategy for accelerating development.

To ensure uptake and utilization of effective MDR-TB regimens by TB treatment programs, regimens should ideally be completely oral, relatively free of toxicity, and of as short duration as possible, while ensuring a high cure rate and low relapse rate. When an optimal regimen is identified, we will seek to have it compounded and licensed as a combination pill, so that one agent in the regimen cannot be administered without the others. This will minimize emergence of drug resistance through failure to take one or more of the components of the regimen.

Clinical Trials for Prevention of MDR-TB

Regimens for treatment of latently infected contacts of MDR-TB patients must also be developed to prevent secondary cases of MDR-TB. Therefore, we anticipate a second series of trials to examine the efficacy of new drugs for prevention of MDR-TB disease among household or other close contacts of persons with infectious pulmonary MDR-TB. Although the mycobacterial load is low in persons with infection but not disease and single-agent therapy is not expected to lead to the emergence of drug resistance, combinations have two advantages for treatment of contacts: first, they may allow shorter durations of treatment, and second, they offer protection against emergence of resistance if a contact with unrecognized incipient disease is administered the regimen.

As with the MDR-TB treatment trial plan above, the biggest challenge will be deciding which regimens and durations to study and whether to study them sequentially, together in one large trial, or in a staggered fashion. In studying preventive regimens, the sequential strategy would require very large sample sizes after the first study. Only in the first trial would there be an arm containing a new drug (or drugs) with established activity against MDR-TB and an arm with no activity against MDR-TB.¹¹ Subsequent trials would require as the comparator the best regimen from the initial trial, with a resulting sample size increase of thousands of participants per arm. Thus, we recommend a single trial with multiple arms, each being compared for superiority to the control arm.

In vitro studies have suggested that at least three of the agents that are on track to come out in the next 5 years act against both replicating and non-replicating *M. tuberculosis* organisms. Therefore, regimens including these agents, particularly in combination, may be effective for treatment of latent TB in less than 6 months. This is important, because 6-9 month regimens for TB prophylaxis are completed by fewer than 50% of patients who start them. Selecting the optimal drugs and combinations to study and the durations they are to be given will require animal studies, which have been useful in predicting the duration of preventive treatment.¹² Pharmacokinetic studies of compatibility of the new agents with each other and with antiretroviral agents will also be needed.

Conclusions

Substantial progress has been made in improving the cure and survival of patients with MDR-TB through the efforts of the Green Light Committee and intensive community-based treatment programs. However, there is great room for improvement. Major steps forward will require new drugs and clinical trials to determine how to best use them. As new classes of anti-TB drugs are developed, trials need to be carefully planned and quickly implemented. Ideally, multisite trials are needed to assure rapid enrollment and avoid undue delay in obtaining trial results, which will then be used to plan subsequent trials. RESIST-TB is developing such a network by bringing together sites from around the world with requisite patient populations and adequate clinical trial infrastructure.

Rapid development of knowledge about how to best use new drugs in combination to cure MDR-TB and prevent XDR-TB will require testing agents from multiple developers and should commence as soon as the drugs have obtained initial regulatory approval. RESIST-TB has developed a plan to move forward rapidly on several fronts to undertake the requisite trials and address the critical issues facing MDR-TB treatment and prevention. This plan directly focuses on clinical trials, one of the primary research priorities for programmatic scale-up of MDR-TB treatment, as formulated by the MDR-TB Working Group of the Stop TB Partnership. This plan also includes essential animal studies to identify drug combinations and treatment durations that should be carried forward into human trials. In addition, negotiations with drug developers, WHO and regulatory agencies to agree on acceptable trial designs will be essential to ensure that trial results

are widely accepted and rapidly translated into practice. Commitments for pediatric formulations and studies of compatibility of new TB drugs with antiretroviral agents will need to be essential features of this process.

A historic opportunity for vastly improved treatment of MDR-TB will soon be upon us. If a detailed yet flexible plan is not implemented to identify the optimal way to use the new drugs before they become widely available, this opportunity will be lost, and we will be faced with sequential emergence of resistance to the new agents. As a collaborative effort between TB drug developers, TB clinical trials experts and multinational TB control program directors, RESIST-TB is well qualified and ready to design and implement such a plan.

Citations

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