

EDITORIALS



Unorthodox Approach to the Development of a New Antituberculosis Therapy

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The development of TMC207 represents an important advance in the chemotherapy of tuberculosis. It is perhaps most amazing because of the defiantly unconventional nature of the effort. At virtually every step, from the original discovery of the diarylquinolines by screening for compounds that would kill *Mycobacterium smegmatis*, a saprophytic distant relative of *M. tuberculosis*, through the phase 2 study by Diacon et al. reported in this issue of the *Journal* (ClinicalTrials.gov number, NCT00449644),¹ this effort flouted conventional wisdom about how to develop new drugs for tuberculosis.

It is also a humbling case study that is worth some reflection. Those of us in the tuberculosis field turned up our noses at looking for compounds that killed anything less than the real human pathogen, and until recently, the whole notion of screening drugs for their ability to provide activity against whole organisms was somewhat anachronistic. Surely we have advanced in the decades since streptomycin was isolated by Selman Waksman after he performed such a screen. Give us a nice, isolated enzyme with a high-resolution x-ray crystallographic structure, and we will use the armamentarium of modern drug discovery to treat the hard-to-treat tuberculosis. The problem, summed up recently by Payne et al.,² is that this approach does not work for bacteria. The truly disturbing fact is that we do not understand why. We can develop exquisitely potent and selective inhibitors of virtually any target we choose, but these inhibitors rarely translate into anything with activity useful against whole cells.

The study by Diacon et al. is important for three distinct reasons. First, the diarylquinolines are a new class of drugs that increase the therapeutic options for patients who have multidrug-

resistant or extensively drug-resistant tuberculosis, for whom treatment options are often sparse, largely ineffective, and often highly toxic. These patients often have little recourse, and their physicians turn as a last resort to agents such as linezolid that have considerable adverse events after prolonged administration. TMC207 appears not to be associated with serious adverse events, at least during the initial 8 weeks of therapy. Longer-term data, of course, are essential, but for now this is encouraging.

The second reason this is an important study is because of the design. The current four-drug regimen for treating persons with drug-susceptible tuberculosis is overwhelmingly effective. Most trials of new agents have involved swapping out one of the four for a new candidate and measuring the difference. These are large, expensive undertakings because of the numbers required to power such a study. Sentiment has been growing that the inherently poor response of patients to second-line tuberculosis drugs means that a small cohort of patients with multidrug-resistant tuberculosis could provide meaningful outcomes.^{3,4} In fact, an earlier report by Diacon et al.⁵ was perhaps the first controlled clinical trial conducted in a population with multidrug-resistant tuberculosis. The phase 2 study of TMC207 reported here is an important step that I hope will serve to dispel the following two prevailing wisdoms: patients with multidrug-resistant tuberculosis are too heterogeneous for such studies because of highly variable regimens of background chemotherapy, and a trial involving patients with multidrug-resistant tuberculosis will limit use of the drug to that population.

It is important to appreciate the distinction between drug development for patients with

multidrug-resistant or extensively drug-resistant tuberculosis and a trial involving patients with multidrug-resistant or extensively drug-resistant tuberculosis that is used as a stepping-stone to a larger trial involving patients with drug-susceptible tuberculosis. A trial offers many important lessons for understanding how to formulate large, expensive phase 3 efficacy studies in patients with drug-susceptible tuberculosis and how to determine whether agents are worth that investment. In the field of oncology, testing experimental chemotherapeutic agents in patients who have advanced disease is a standard prelude to efficacy in the target population. Other ongoing studies (ClinicalTrials.gov numbers, NCT00727844, NCT00425113, and NCT00685360) conducted by several different teams of investigators have embraced this concept, but this trial of TMC207 seems to be the first completed study.

The third reason this is an important study is that one of the largest barriers to the development of new drugs for tuberculosis is the paucity of targets that, when their function is inhibited by drugs, have a positive therapeutic effect in patients. Of the agents currently in use, we have multiple complex prodrugs that have multiple effects, such as isoniazid and pyrazinamide, but designer prodrugs are a tall order (although a rational approach to optimizing prodrugs is emerging with the nitroimidazoles⁶). Among the highly active drugs are very few known targets: rifampin targets RNA polymerase, the aminoglycosides target the bacterial ribosome, and the fluoroquinolones target DNA gyrase. The target of TMC207 is ATP synthase, which the current study by Diacon et al. validates. Efforts are already under way to create other drugs against this target.

The drug and the trial are very encouraging, but there are some reasons to be circumspect regarding the transition of TMC207 into a mainstream drug for the treatment of persons with drug-susceptible tuberculosis. First, the available safety data are still limited and urgently need to be expanded. Second, there are unresolved prob-

lems with the metabolism of TMC207 by a cytochrome P-450 system (CYP3A4) that is strongly induced by rifampin, making it unclear whether TMC207 and rifampin could be effectively coadministered. Rifampin is the most active of the front-line tuberculosis agents, and the choice between it and TMC207 will be difficult if the regimen requires only one of the two. Finally, there are still challenges in addressing the pharmacokinetics of TMC207, which has an unusually long half-life. None of these points detract from the overall value of the current study; they may simply impede the development of TMC207 beyond the population with multidrug-resistant or extensively drug-resistant tuberculosis.

In retrospect, there was a considerable element of luck in the discovery of TMC207 and its target, but there was also a refreshing sense of forward movement. This experience shows that there is always a chance of discovering a new class of molecules, a new therapeutically useful target, and of adopting a new trial design that shows convincing efficacy with the involvement of only 47 patients.

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Interleukin-1 β and the Autoinflammatory Diseases

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Interleukin-1 is a highly active proinflammatory cytokine that causes not only fever, anorexia, and other constitutional symptoms but also tissue damage and remodeling. All these effects — in-

cluding joint destruction, tissue remodeling, and elevated levels of markers of systemic inflammation — can be reversed or reduced by specific blockade of interleukin-1 activity.