

## EDITORIAL



## Shortening Treatment for Tuberculosis — Back to Basics

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With approximately 8 million incident cases and 1.3 million deaths each year, increasing drug resistance, and exacerbating coexisting conditions such as the human immunodeficiency virus–acquired immunodeficiency syndrome and diabetes, tuberculosis continues to pose a massive threat to global health. In the absence of a vaccine to provide long-term protection, control of drug-susceptible tuberculosis is largely dependent on a standard 6-month chemotherapy regimen that has been in use for more than three decades. Any experimental therapy designed to modify this short-course regimen — which comprises a 2-month intensive phase with four drugs (rifampin, isoniazid, pyrazinamide, and ethambutol) followed by a 4-month continuation phase with two drugs (isoniazid and rifampin) — must not increase the rate of recurrence due to relapse. Where the aim is to reduce the duration of treatment — a critical transformation to improve patient adherence and reduce costs — the challenge is significant: demonstration of noninferiority with fewer months of therapy. Three trials reported in this issue of the *Journal*<sup>1-3</sup> offer a sobering reminder of the enormity of this task, while providing some insight into the factors that are likely to determine the success of new, treatment-shortening regimens.

Each trial was designed to test whether the inclusion of a fluoroquinolone in a modified regimen could shorten the duration of treatment for drug-susceptible tuberculosis. The Rapid Evaluation of Moxifloxacin in Tuberculosis (REMoxTB) Consortium<sup>1</sup> investigated two regimens in which either ethambutol or isoniazid was replaced by moxifloxacin in a single 4-month combination therapy. In the trial conducted by the OFLOTUB/

Gatifloxacin for Tuberculosis Project,<sup>2</sup> gatifloxacin was substituted for ethambutol in the intensive phase and was maintained in a novel three-drug combination with rifampin and isoniazid in a 2-month continuation phase. The RIFAQUIN Trial Team<sup>3</sup> tested two regimens in which moxifloxacin replaced isoniazid in an intensive phase that was followed by either 2 months of standard-dose rifapentine and moxifloxacin twice weekly or 4 months of high-dose rifapentine and moxifloxacin once weekly. In all three studies, observed culture conversion rates at 2 months were consistent with phase 2 data indicating that fluoroquinolone-containing regimens were likely to be superior. However, this property did not reliably predict sterilizing activity and risk of relapse: the shortened regimens were not noninferior.

Phase 3 trials require enormous financial investment. Although the studies described here have established the capacity for large, multicenter trials across disease-endemic countries, the design and selection of future experimental regimens will need to incorporate a triage process that can mitigate risks while enabling the accelerated development of much-needed treatment-shortening therapies. The disconnect between the phase 2 data that motivated these trials<sup>4</sup> and the phase 3 results reinforces the idea that small sample sizes limit the utility of short trials in predicting the success of treatment-shortening regimens.<sup>5</sup> In the meantime, innovative approaches, such as a “multi-armed, multi-stage” trial design<sup>5</sup> and a meta-regression model that uses sputum-culture status at month 2 and treatment duration to predict relapse rates,<sup>6</sup> appear promising.

What about advances in basic tuberculosis biology that could be used to inform the process? All three trials were grounded in evidence obtained from mouse models of tuberculosis that suggested a treatment-shortening role for fluoroquinolones. Although the trial results appear to reaffirm concerns about the role of standard mouse models in regimen design, alternatives such as the “Kramnik” mouse,<sup>7</sup> rabbits, and non-human primates, all of which better recapitulate key pathologic features of tuberculosis in humans, hold considerable promise: for example, the results of a recent phase 2a study on clofazimine-containing regimens are corroborated by observations in the Kramnik mouse model.<sup>7</sup> Moreover, nonhuman primates are amenable to advanced imaging and analytic techniques that enable the real-time monitoring of disease progression,<sup>8</sup> and distributions of antituberculosis drugs have been quantified in lung tissue and lesions from rabbits.<sup>9</sup> Notably, the concentrations of moxifloxacin are markedly lower in the caseum of caseating granulomas — where persisting bacilli are found to lurk<sup>10</sup> — than in the cellular regions of granulomatous lesions. Whereas current drugs were introduced into clinical use without consideration of the pharmacokinetic–pharmacodynamic properties that might influence drug efficacy, the incorporation of information about lesion penetration and distribution will be critical in future regimen design.<sup>9</sup>

In summary, although the urgency of the medical need may justify additional clinical trials of experimental tuberculosis drugs and drug regimens, there must be a considerable increase in investment in fundamental research if we are to develop and validate correlates of durable

cure. As these three trials have confirmed, our understanding of the science underlying positive clinical outcomes remains rudimentary. It’s time to go back to basics.

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