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EDITORIAL

Advancing the science in clinical trials for new TB drugs

In this issue of the *Journal*, a remarkable report appears.[1] Its authors include Professor Denis Mitchison, who continues a distinguished career of work at the leading edge of tuberculosis research. The Oflotub Phase 2B trial report details several novel findings, each of which may have important effects in the development of new drugs for the treatment of tuberculosis. These findings include:

1 the potential predictive value of two new quantitative bacteriologic endpoints for Phase 2B trials of new anti-tuberculosis agents—serial sputum colony counts (SSCC) and time to culture conversion;
2 that two newer fluoroquinolones (gatifloxacin and moxifloxacin) may have the ability to safely shorten the requisite duration of therapy for pulmonary tuberculosis;
3 that sophisticated statistical modeling methods for the analysis of SSCC data may lead to new insights regarding the biologic effects of treatment regimens and increase the power of such studies; and,
4 that 2-month culture conversion, especially in liquid medium culture, was surprisingly low in this southern African setting; this finding needs further exploration and may offer useful clues to biological variation among populations of patients and bacilli.

1 For the first time in more than 30 years, we have multiple promising new agents for TB treatment being evaluated in clinical trials.[2] Phase 2B trials, the initial step at which the efficacy of a new regimen is evaluated, are a critical point in new drug development. Very large sample sizes are required for the definitive Phase 3 evaluation of a new regimen for drug-susceptible disease, because the key outcome, relapse, is an uncommon event. Furthermore, detection of relapse requires prolonged follow-up (12–24 months) after the completion of therapy. Approximately 2–5% of patients treated with current 'short-course' therapy fail during treatment or relapse after therapy. A similar proportion develop serious toxicity attributed to TB therapy, most often drug-induced hepatitis.[3,4] A new shorter treatment regimen for drug-susceptible TB will not result in revised guidelines and major changes in TB control program activities unless there is persuasive evidence that the clinical outcomes of the new regimen are comparable to those of standard therapy. Furthermore, trials supporting a change must be large enough to ensure that the benefits of a new treatment regimen are comparable among key subgroups (e.g., HIV-infected persons). Such evidence and assurance require large sample sizes. Phase 3 trials will therefore remain expensive and lengthy, even in high-prevalence settings where enrollment can be rapid.

Phase 2B is the key step in deciding which of the many new regimens that have activity in animal models of TB treatment are sufficiently promising to warrant the time and expense of a Phase 3 trial. Several recent Phase 2B trials have used the 2-month sputum culture status as an endpoint.[5] This marker has displayed significant association with eventual relapse in many Phase 3 trials, particularly those of the British Medical Research Council.[6] It is believed—but not yet proven—that a regimen with higher rates of 2-month sputum conversion (compared to standard therapy) will allow substantial shortening of treatment.[7] However, this marker is statistically inefficient—comparisons of 2-month culture conversion, a dichotomous outcome at a fixed time point, require relatively large sample sizes (in the order of 100–200 patients per arm, depending on the assumptions made). In addition, there are uncertainties about whether the addition of broth culture techniques, now increasingly used throughout the world, changes the predictive value of 2-month culture status. Unless a new endpoint is found for Phase 2B and/or much more funding becomes available for TB clinical trials, the sample-size implications of the standard endpoint of 2-month culture status are that the evaluation of the new promising TB treatment regimens will be delayed.

2, 3 This issue of the *Journal* includes the initial evaluation of two proposed new endpoints—change in quantitative sputum mycobacterial load (SSCC)[8] and time to culture conversion—and the novel application of statistical methods for these comparisons. The authors use these new endpoints to demonstrate that two newer fluoroquinolones achieve more rapid sputum conversion than standard therapy, and suggest that their use may allow therapy to be shortened. They illustrate the greater statistical efficiency of SSCC and time-to-culture-conversion analyses, which are essentially continuous measures, compared to standard 2-month culture conversion.[9] Perhaps more importantly, these analyses focus on different features of the regimens' bactericidal activity. Employing a nonlinear mixed effects model with biologically relevant parameters, they are able to distinguish between effects on 'early' and 'late' phase activity. The estimated parameters are interpretable in terms of rate of decline of colony counts. The incorporation of random effects reduces bias in parameter estimates, allows for individual variability in response, and accounts for

within-patient correlation to accurately reflect the variability of the estimates.

Their results are credible and impressive. Their approach demands fewer patients, and can thus be less costly than traditional Phase 2B approaches. However, this approach also demands highly skilled and reliable quantitative bacteriologic capacity, which exists in few sites. The authors' work suggests the potential to use more widely available techniques and markers (e.g., time to positivity in solid or liquid culture), but the validation of such markers also demands additional study.

4 The study is also the second published report of an observation that has now been made in several studies—that 2-month culture conversion is lower than had been expected among patients with pulmonary TB in Africa. The authors suggest that this is due to the use of on-site mycobacterial culture, whereas in previous trials the sputum specimens were shipped to a central laboratory. However, the reproducibility of the low 2-month sputum culture conversion among African patients suggests that specimen shipping is not the sole explanation for this difference.[5,10] Furthermore, the difference between culture conversion as measured on solid media vs. that measured by broth culture was greater than had been expected. These differences need to be further evaluated in current and future clinical trials. Possible explanations for these differences may include host factors (differences in genetic susceptibility, in immunologic response, in severity of disease, in absorption of medications, in concomitant infections), bacillary characteristics (differences in virulence of strains, adaptation to host populations, or tolerance), or something else.

Overall, these are exciting results and presage a change to a more efficient continuous measure of outcome in Phase 2B trials. Three similar trials, though, have produced conflicting results.[5,11,12] Thus, the predictive value of these more sensitive measures for identifying regimens that allow shortening of treatment must be validated in Phase 3 clinical trials with clinical outcomes. It is possible that the added activity of these newer fluoroquinolones is detectable using these sensitive measures and statistical techniques, but is not great enough to permit TB treatment to be shortened. Fortunately, this Phase 2B trial is partnered with a large Phase 3 trial of gatifloxacin (also called 'Oflotub'), which is already well underway. A second Phase 3 trial testing the potential of moxifloxacin ('Remox TB') to shorten the treatment duration of drug-sensitive disease is just beginning in different sites.[2] We should know within 2–3 years, if these new methods for Phase 2B trials are valid predictors. If so, these techniques should accelerate TB drug development.

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References

1 Rustomjee R, Lienhardt C, Kanyok T, et al., and the Gatifloxacin for TB (OFLOTUB) study team. A Phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacins in pulmonary tuberculosis. Int J Tuberc Lung Dis 2008; 12: 128–138.
2 Ginsberg A M, Spigelman M. Challenges in tuberculosis drug research and development. Nat Med 2007; 13: 290–294.
3 Yee D, Valiquetee C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. Am Rev Respir Crit Care Med 2003; 167: 1472–1477.
4 Teleman M D, Chee C B E, Earnest A, Wang Y T. Hepatotoxity of tuberculosis chemotherapy under general programme conditions in Singapore. Int J Tuberc Lung Dis 2002; 6: 699–705.
5 Burman W J, Goldberg S, Johnson J L, et al. Moxifloxacin versus ethambutol in the first 2 months of treatment for pulmonary tuberculosis. Am J Respir Crit Care Med 2006; 174: 331–338.
6 Fox W, Ellard G A, Mitchison D A. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications. Int J Tuberc Lung Dis 1999; 3 (Suppl 2): S231–S279.
7 Mitchison D A. Assessment of new sterilizing drugs for treating pulmonary tuberculosis by culture at 2 months. Am Rev Respir Dis 1993; 147: 1062–1063.
8 Brindle R, Odhiambo J, Mitchison D A. Serial counts of *Mycobacterium tuberculosis* in sputum as surrogate markers of the sterilizing activity of rifampicin and pyrazinamide in treating pulmonary tuberculosis. BMC Pulm Med 2001; 1: 2–9.
9 Davies G R, Brindle R, Khoo S H, Aarons L J. Use of nonlinear mixed-effects analysis for improved precision of early pharmacodynamic measures in tuberculosis treatment. Antimicrob Agents Chemother 2006; 50: 3154–3156.
10 Joloba M L, Johnson J L, Namale A, et al. Quantitative sputum bacillary load during rifampin-containing short course chemotherapy in human immunodeficiency virus-infected and non-infected adults with pulmonary tuberculosis. Int J Tuberc Lung Dis 2000; 4: 528–536.
11 Dorman S, Johnson J, Padayatchi N, Goldberg S, Bozeman L, Chaisson R. Moxifloxacin vs. isoniazid in the first 2 months of treatment for pulmonary tuberculosis. 47th ICAAC, 2007: Abstr. L-736b.
12 Chaisson R E, Conde M, Efron A, et al. A randomized, placebo-controlled trial of moxifloxacin vs. ethambutol in the initial phase of tuberculosis therapy in Brazil. 47th ICAAC, 2007: Abstr. L-736a.