Early Biomarkers and Regulatory Innovation in Multidrug-Resistant Tuberculosis

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Biomarkers play an essential role in accelerating drug development. Sputum culture conversion using solid medium is the best-characterized tuberculosis biomarker, having been examined at the patient and trial levels in studies with thousands of subjects, and having recently been validated using data from 3 unsuccessful phase 3 trials. We presently are poised at the threshold of regulatory innovation for antibacterials to treat drug-resistant infections, in which Special Medical Use authorization restricted to patients with limited options could be based on the results of small clinical trials. Patients worldwide would be well served by licensing of new regimens for multidrug-resistant tuberculosis based on biomarker evidence commensurate with the urgency of the current global crisis.

Keywords. tuberculosis; drug resistance; biomarkers; sputum culture; regulatory innovation.

Major unmet medical needs exist for all forms of Mycobacterium tuberculosis infection. All patients need shorter regimens that do not increase the risk of relapse; to date, these have proven elusive [1–3]. In addition, patients with multidrug-resistant (MDR) tuberculosis urgently require treatments that quickly eradicate active infection while preventing emergence of additional resistance, which otherwise causes treatment failure and death. Failure and relapse occur via different pathogenic mechanisms in distinct microbial subpopulations (see Knight et al in this supplement). Failure (the inability to eradicate viable M. tuberculosis from sputum) is the main unsatisfactory outcome in MDR tuberculosis. It occurs from the genetic selection of drug-resistant mutants among replicating mycobacteria in the presence of inadequate chemotherapy. In contrast, relapse, the main unsatisfactory outcome in drug-sensitive tuberculosis, occurs from epigenetic persistence of susceptible mycobacteria despite otherwise effective treatment. Failure, by definition, precludes the possibility of relapse [4]. As a result, relapse is presently a minor concern in MDR tuberculosis [5]. Relapse will become increasingly important in MDR tuberculosis, however, as regimens become more effective and shorter durations are considered.

Biomarkers are measurable characteristics that indicate normal or pathogenic biological processes, or pharmacological responses to therapeutic intervention [6]. Biomarkers can accelerate drug development by serving as surrogates for clinical endpoints (trial-level surrogacy); they can also directly improve outcomes by informing therapeutic decisions for individual patients (patient-level surrogacy). Tuberculosis biomarkers are therefore best considered in a 2-dimensional matrix, according to clinical outcome (failure vs relapse) and level of surrogacy (trial vs patient).

Sputum culture conversion using solid medium is the best-characterized tuberculosis biomarker, having been examined in many studies either as a simple measure (eg, month 2 culture status) or in more complex forms requiring subsequent negative cultures (eg, "stable" culture conversion). In 2002, Benator et al examined culture status at month 2 as a patient-level predictor in a clinical trial of 1004 drug-sensitive tuberculosis patients [7]. The study found 20% of patients to be culture positive at month 2, 1% failing after month 4, and 6% relapsing after completing treatment. The odds ratio (OR)
Kurbatova et al recently examined sputum culture conversion as a patient-level predictor of end-of-treatment success (vs failure or death) in 1712 patients with MDR tuberculosis [8]. Stable culture conversion occurred by month 2 in 29%, and success at the end of treatment in 79%. The 2 parameters were significantly associated, with an OR of 3.6 (95% CI, 2.5–5.2) and PPV of 80% (95% CI, 79%–81%) (Figure 1). However, overall biomarker accuracy was only 46%, because many patients still positive at month 2 were ultimately cured. Some of these cures may have resulted from treatment changes initiated due to positive month 2 cultures; if so, true biomarker accuracy would be higher than that reported. Odds ratios improved after month 2; however, at later time points, conversion becomes less a prognostic biomarker and more a fait accompli. The bar thus is set high if culture conversion is to perform well as a patient-level predictor, whether for relapse or failure.

The biomarker performance of month 2 culture status at the trial level, however, is another matter. Mitchison in 1993 first proposed a role for month 2 culture status in the evaluation of new tuberculosis regimens [9]. Two independent analyses of regimen pairs of equal duration confirmed the relationship between sputum culture status and relapse [10, 11]. In 2013, meta-regression modeling of 58 diverse regimens of various durations studied in 7793 patients identified month 2 culture status and duration as independent predictors of relapse [12]. At that time, 5 phase 2 trials of 6 gatifloxacin or moxifloxacin-containing regimens had reported month 2 conversion rates of

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**Figure 1.** Time to sputum culture conversion among 1712 patients with multidrug-resistant tuberculosis according to treatment outcome (success vs failure or death). Adapted from Kurbatova et al [8] with permission.

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**Figure 2.** A, Observed and predicted proportions of subjects with tuberculosis recurrence in the 8 arms of 3 phase 3 fluoroquinolone treatment-shortening trials [1–3]. Recurrences were predicted using the original mathematical model as described in 2013 [12]. Axes indicate logit-transformed recurrence risk, with insets indicating corresponding proportions. Red symbols indicate 4-month regimens; blue symbols indicate 6-month regimens. Error bars indicate 80% confidence intervals (10%–90%). B, Predicted proportion of patients with recurrence based on the proportion positive after 2 months of treatment, for regimens of 4 and 6 months’ duration. Solid and dotted lines indicate updated and original model predictions, respectively. Shading indicates 80% confidence intervals for the updated estimates. Adapted from Wallis et al [18], with permission. Abbreviation: CI, confidence interval.
71%–92% [13–17]. The model predicted these regimens would yield unsatisfactory relapse rates (10%–19%) if administered for only 4 months [12]. The predicted rates are highly consistent with those subsequently reported in the four 4-month arms of 3 unsuccessful phase 3 fluoroquinolone treatment-shortening trials (13%–18% in a per-protocol analysis of patients at risk of recurrence at end of treatment) [1–3, 18]. Across all 8 arms in these trials, there was a high correlation between observed recurrence rates and those predicted based on month 2 cultures ($R^2 = 0.86$; Figure 2A). Using the prespecified threshold of 10% recurrences as the maximum likely to be judged acceptable to tuberculosis control programs, the original model correctly predicted all 4 six-month regimens as satisfactory, and 3 of 4 four-month regimens as unsatisfactory (PPV = 80%; overall accuracy = 88%). A revision of the regression model based on the full dataset of 66 regimens and 11 181 patients resulted in only minimal changes to its predictions (Figure 2B). The main effect of the revision was to increase to 10% the predicted recurrence rate in the sole 4-month regimen incorrectly predicted to yield acceptable results. A corresponding meta-analysis of culture conversion as a trial-level predictor of failure will not be possible until results of multiple phase 3 trials of new MDR tuberculosis regimens have been reported. However, the high PPV of month 2 conversion for patient-level success in MDR tuberculosis (80%) indicates a high likelihood that improved activity of new regimens at 2 months will translate into superior long-term outcomes. The criteria proposed by Chau et al for biomarker validation classify culture conversion as “probable valid” for failure, and “known valid” for relapse, the latter based on independent replication in multiple studies [19]. Several limitations must be acknowledged. Sputum biomarkers are unlikely to be satisfactory in young children, due to the difficulty in obtaining adequate specimens. Culture conversion is a poor predictor of survival in human immunodeficiency virus type 1 (HIV-1)-infected patients with MDR tuberculosis, apparently reflecting deaths due to other HIV-related causes [8]. Nonetheless, these findings confirm an important role for month 2 culture conversion in the development of shorter, more effective MDR tuberculosis regimens. The gap separating this body of knowledge from those for other candidate tuberculosis biomarkers is large. Early changes in $^{18}$F-fluorodeoxyglucose positron imaging, for example, have been examined as a patient-level predictor of failure in a total of only 31 patients with MDR tuberculosis [20, 21]. Early changes in gene expression profiles have been described to date in 2 studies in a total of 44 patients with drug-sensitive tuberculosis, but in neither study were these examined in relation to clinical outcome [22, 23]. Substantial research will be required in larger cohort studies and randomized controlled trials to understand the relationship between changes in these markers, treatment duration, and likelihood of cure or relapse, if they are to be used to assess new tuberculosis regimens.

Regulatory agencies attempt to balance risk against benefit in their assessment of new therapies. In most cases, risk reflects an incomplete understanding of a new drug, and benefit reflects its potential impact on unmet medical need. An imbalance of these factors 25 years ago in HIV led to biomarker-facilitated accelerated approvals (subpart H 21CFR314) by the US Food and Drug Administration (FDA), and conditional market authorizations (EC 507/2006) by the European Medicines Agency. At that time, the substitution of a biomarker (plasma HIV RNA) for a clinical endpoint (survival) relieved an unacceptable bottleneck in antiretroviral drug development. We presently face a similar therapeutic crisis for drug-resistant bacterial infections [24], and as a result are poised at the threshold of further regulatory innovation. Testing of new antimicrobials currently requires large noninferiority studies conducted in patients readily treated with other agents, in the hope that a small number with highly resistant infections will be enrolled into the experimental arm. The recent Presidential Executive Order Combating Antibiotic-Resistant Bacteria [25], and the report of the President’s Council of Advisors on Science and Technology on which it is based [26], create a new testing paradigm (small trials in patients with highly resistant infections) and a new approval mechanism (Special Medical Use, restricted to patients with limited therapeutic alternatives). The PATH Act [27] formally mandates the creation of the Special Medical Use mechanism at the FDA. Its implementation could be a major departure from current accelerated approvals, removing the requirement to conduct large phase 3 trials in hard-to-recruit patient populations, and potentially substituting enhanced reporting of clinical outcomes.

MDR tuberculosis was not likely first or foremost in the minds of legislators when these regulatory changes were first considered. Yet it is difficult to imagine a better exemplar with which to test their feasibility and impact. Unlike other drug-resistant pathogens, MDR tuberculosis offers rapid diagnostics, validated biomarkers, specially trained physicians, dedicated treatment facilities, globally accepted reporting mechanisms, and the normative and advisory roles of the multiple national and international organizations. The interests of patients worldwide would be well served by efforts on the part of all these agencies to facilitate the early adoption and postlicensing evaluation of new MDR tuberculosis regimens based on limited biomarker evidence that is commensurate with the urgency of the current global MDR tuberculosis crisis.

Notes

**Supplement sponsorship.** This article appears as part of the supplement “Advances in Tuberculosis Research: A Blueprint for Opportunities.” This article was sponsored by the Aurum Institute.

**Potential conflict of interest.** Both authors: No potential conflicts of interest.
Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References