SUPPLEMENT ARTICLE

The Hollow Fiber System Model in the Nonclinical Evaluation of Antituberculosis Drug Regimens

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Tuberculosis remains a serious public health challenge, with the global prevalence of active disease estimated at 8.6 million and the mortality rate at 1.3 million deaths per year [1]. In 2012, the Centers for Disease Control and Prevention reported approximately 10 000 cases in the United States, of which approximately 1% were resistant to both rifampin and isoniazid [2]. These epidemiologic data highlight the need for new antituberculosis drugs, encompassing novel mechanisms of action, improved safety profiles, and fewer drug–drug interactions. New combination regimens will be of particular importance in improving the management and control of tuberculosis globally. A pathway for bringing new antituberculosis drugs and drug combinations efficiently and promptly into later-stage clinical trials is a critical public health goal.

Among recent advances in drug therapy for tuberculosis, shortened treatment regimens have had a dramatic public health impact. Instead of the mid-20th-century practice of administering single- or dual-drug treatments for 1 year or longer, the standard of care today for patients with susceptible tuberculosis is the 6-month 2HRZE/4HR regimen, consisting of 2 months of treatment with isoniazid (H), rifampin (R), pyrazinamide (Z), and ethambutol (E) followed by 4 months of isoniazid and rifampin. The 2HRZE/4HR regimen was developed, primarily by the British Medical Research Council [3], during 1970–1982, through many early-stage phase 2 clinical trials, in which multiple variations of combination drug regimens were investigated. This development process was highly laborious, underscoring the need for tools to inform regimen development, including more efficiently designed, later-stage phase 2 clinical trials.

In this supplement of *Clinical Infectious Diseases*, authors from the Critical Path to TB Drug Regimens (CPTR) and academia present an in vitro model to evaluate drug activity against *Mycobacterium tuberculosis*; specifically, the authors posit that the hollow fiber system model of tuberculosis (HFS-TB) might be used to identify promising regimens appropriate for testing in later-stage phase 2 clinical trials. The HFS-TB can be used to simulate many pharmacokinetic characteristics of antimycobacterial drugs and allows for the exploration of concentration–effect relationships potentially relevant to the treatment of tuberculosis in the clinical setting. In contrast, the clinical identification of such relationships (ie, prior to later-stage clinical trial evaluations) may take several years. In addition, the HFS-TB can model the emergence of resistance by reiterating microbial dynamics (eg, dormancy of bacilli subpopulations).

The effective use of the hollow fiber system model (HFS) in the course of developing individual antibacterial drugs has allowed investigators to predict pharmacodynamic characteristics and thereby determine dosing regimens for clinical trials more efficiently. For example, it was used to predict exposure and efficacy of amoxicillin for the prophylaxis of inhalational anthrax in children and pregnant women [4]. In concert with mathematic

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modeling, the HFS guided the selection of dosing of an investigational β-lactamase inhibitor, in combination with an antibacterial drug, against a clinical isolate of *Klebsiella pneumoniae* [5]. The HFS has also been used for the selection of investigational drug dosing regimens intended to minimize on-therapy drug resistance amplification [6].

Like other useful in vitro pharmacokinetic/pharmacodynamic models, the HFS-TB must be used appropriately, and limitations of the system must inform data interpretation and prediction. Correlations between drug concentration and pathogen survival that are based on in vitro models cannot be expected to reiterate all aspects of in vivo antimycobacterial treatment. For example, the HFS-TB does not directly account for the potential binding of drug to plasma proteins [7], and it cannot address antibacterial efficacy in the context of host defense mechanisms, intracellular localization of microorganisms, or other distributional complexities that may be encountered with tubercular lesions [7, 8].

Introduction of the HFS into antibacterial drug development has been valuable. The use of HFS-TB may contribute to increased efficiency in assessing drug regimens relative to other early-stage phase 2 investigations. The use of the HFS-TB to evaluate a combination of antimycobacterial drugs is a novel approach, and we congratulate the authors in this supplement for their critical path approach to the development of new drug regimens for tuberculosis. Although the HFS-TB model cannot replace later-stage phase 2 trials, it should help select regimens with a greater likelihood of success. Sponsors interested in the development of a new investigational drug regimen identified by HFS-TB should continue to be mindful of the value of animal studies and the regulatory importance of nonclinical safety and toxicology studies (see, eg, US Food and Drug Administration [FDA]'s guidance documents, including the International Conference on Harmonization guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*, and the FDA guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* [www.fda.gov]).

We welcome scientific advancement in approaches to identify investigational drug regimens so that later-stage phase 2 clinical trial development can be as efficient as possible. The results from HFS-TB studies, combined with data from nonclinical toxicology studies and early-stage clinical studies, should help to inform the selection of antimycobacterial drug regimens for late-stage testing. Efforts by the CPTR to identify new investigational drug regimens contribute to the public health goal of improving the management of tuberculosis.

Notes

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