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Challenges in the clinical assessment of novel tuberculosis drugs☆

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ABSTRACT

To tackle the global TB epidemic effectively, novel treatment strategies are critically needed to shorten the duration of TB therapy and treat drug-resistant TB. Drug development for TB, stymied for decades, has enjoyed a renaissance over the past several years. However, the development of new TB regimens is hindered by the limitations in our understanding and use of preclinical models; the paucity of accurate, early surrogate markers of cure, and challenges in untangling the individual contributions of drugs to multidrug regimens in a complex, multi-compartment disease. Lack of profit motive, advocacy, and imagination has contributed mightily to the dearth of drugs we have on the shelf to treat this ancient disease. Areas that will speed the development of new regimens for TB include novel murine and *in vitro* pharmacodynamics models, clinical endpoints that are not culture-based, innovative clinical trial designs, and an infusion of much-needed funding.

Contents

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1. Introduction[1]

Tuberculosis (TB) has now surpassed HIV as the number one cause of infectious disease-associated death worldwide. Novel treatment strategies are critically needed to shorten the duration of TB therapy and treat drug-resistant TB, an emerging global health threat. Drug development for TB, stymied for decades, has enjoyed a renaissance over the past several years. However, development of new TB regimens is hindered by the limitations in our understanding and use of preclinical models; the paucity of accurate, early surrogate markers of cure; historic use of trial outcome variables that are relatively uninformative with poor statistical properties (e.g. mid-treatment sputum culture conversion); and challenges in untangling the individual contributions of drugs to multidrug regimens in a complex, multi-compartment disease. Lack of imagination (by investigators and industry), profit motive, and advocacy has also contributed mightily to the dearth of drugs we have on the shelf to treat this millennia-old disease.

2. Tuberculosis: still not controlled?

2.1. Drug-sensitive TB: prolonged multidrug treatment for a widely lethal foe

Among bacteria, *Mycobacterium tuberculosis* is the single greatest killer on the planet. The World Health Organization (WHO) estimates that there were over 9 million new cases and 1.5 million deaths due to TB in 2013 [1]. TB control efforts are hampered by the lengthy, complex treatment regimens necessary for cure without relapse. Although the current regimens and drugs have been very successful in controlled clinical trials with cure rates up to 95%, in practice treatment completion and outcomes vary widely by setting. Currently, under ideal conditions, TB is treated for six months, though in practice, treatment completion often takes longer. So-called "short course" TB therapy includes isoniazid, rifampicin, pyrazinamide, and ethambutol given during the intensive phase (first two months) of therapy followed by isoniazid and rifampicin given during the continuation phase (last four months). The full application of the directly observed therapy short course (DOTS) strategy is becoming more and more difficult in resource-limited settings where TB incidence is high, as these countries are also battling to control the HIV epidemic. There is a need for highly potent TB treatments that can cure disease in substantially fewer than the six months currently required. Shorter treatment duration can decrease the logistical burden and expense of prolonged treatment (given in large part under direct observation), improve adherence, and help prevent the emergence of acquired drug resistance. An urgent research priority is thus to evaluate new drugs and new combination regimens that can shorten treatment duration for drug-sensitive TB, both for the benefit of individual patients and to improve TB control from a public health standpoint.

2.2. Drug-resistant TB: ushering in the post-antibiotic era—can't we do better?

Multidrug resistant (MDR) TB, TB resistant to isoniazid and rifampicin, is a growing public health threat, with an estimated 480,000 cases in 2013. Extensively drug-resistant (XDR) TB, TB that is resistant to isoniazid, rifampicin, fluoroquinolones, and injectable anti-TB drugs, has been found in every country in which it has been sought [2]. Additional resistance to drugs beyond those included in the definition of XDR has also been reported, coined by some as "totally drug-resistant (TDR) TB", threatening a return to the pre-antibiotic era of TB management [3–6]. In general, therapeutic options for drug-resistant TB are limited in availability, acceptability, and efficacy. Currently, only 1 in 5 patients diagnosed with MDR-TB is started on treatment [2]. Current treatment for MDR-TB requires ≥20 months of multidrug therapy, including ≥8 months of an injectable agent [7], and yet is successful in only 48% of patients [2], not very different from the cure rates in the pre-antibiotic era—30% for sputum smear positive and 80% for sputum smear-negative, culture-positive TB [8]. In some settings though, higher success rates have been achieved with intensification of resources and/or enhancement of the treatment regimen [9–11]. Furthermore, MDR-TB treatment regimens are poorly tolerated and have significant toxicities. A common standard regimen, for example, may include kanamycin or amikacin (ototoxicity, which can be irreversible), a fluoroquinolone, ethionamide or prothionamide (dose-limiting gastrointestinal toxicity), pyrazinamide (hepatotoxicity and risk of resistance, as this drug is a standard part of first-line regimens), cycloserine/terizidone (central nervous system toxicity), and ethambutol (ophthalmologic toxicity risk and risk of resistance, as this drug is a standard part of first-line regimens). Having effective new anti-TB drugs and regimens is, thus, not only important to improve cure rates and reduce risk of acquired resistance but also to reduce suffering related to common and severe side effects of standard MDR-TB regimens.

3. Preclinical models of TB disease—the translational gap

3.1. Traditional mouse model of TB disease and its treatment

The mouse model of TB disease has been used for more than 50 years for the development and evaluation of new TB drugs and regimens [12]. Although it has been criticized for not recapitulating the clinicopathological manifestations of TB in humans [13], the mouse model of experimental chemotherapy has been instrumental in testing drug combinations and in predicting agents and combinations with treatment-shortening potential. Mice are infected via aerosol or intravenous route, and after 2–3 weeks of infection, bacillary burden approaches that seen in human TB pulmonary cavities. Treatment efficacy is assessed by measuring colony-forming units in lung and spleen homogenates at various intervals during treatment, and relapse is assessed 3–6 months after discontinuation of a test regimen. The mouse model successfully discriminates between drugs with good bactericidal but limited sterilizing activity (isoniazid and streptomycin) and those with treatment-shortening potential (rifampicin and pyrazinamide) [14]. The model is simple, inexpensive, tractable, and has the highest predictive value for clinical efficacy of combination regimens of any preclinical model [15]. Every drug regimen tested clinically for TB treatment in the 21st century has been tested first in the mouse model. It is important, though, to understand the strengths and limitations of this model, lest we overestimate its translational value.

3.2. Recognizing the strengths and limitations of the mouse model—optimizing its translational value

The mouse model is an important tool for TB drug development. In particular, it is useful for creating early knowledge about exposure–response (or pharmacokinetic/pharmacodynamic) relationships, for determining the pharmacodynamic driver of individual drug activity (e.g. does the drug display time-dependent or concentration-dependent killing), and for identifying combination regimens with promising bactericidal and sterilizing activity that merit clinical testing. However, the model has limitations that

[1] TB: tuberculosis
WHO: World Health Organization
DOTS: directly observed therapy short course
MDR: multidrug resistant
XDR: extensively drug resistant
TDR: totally drug resistant
EBA: early bactericidal activity

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