Back to the Future: Where Now for Antituberculosis Drugs?

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A review of the current portfolio of anti-tuberculosis drug candidates beckons us not only to look towards the future and the hope of a new era of tuberculosis (TB) therapy, when promising new drugs are incorporated into shorter, simpler, and less toxic treatment regimens, but also to consider the past for the lessons to be learned from what has gone before. The development of TB drug therapy was a landmark in the fight against TB. Groups such as the British Medical Research Council[1] and the US Public Health Service[2] have studied tuberculosis medications since the discovery of streptomycin in 1944. Since then, the necessary duration of TB treatment has been reduced almost fourfold: from more than 24 months to only 6 months. The roles of multidrug therapy and of adherence to the treatment regimen in the prevention of acquired drug resistance have been elucidated. Worldwide, TB treatment for most patients is now affordable and intermittent (or simplified through fixed-dose combinations), and no longer requires hospitalization. On the other hand, challenges remain: the current standard anti-tuberculosis regimen must still be taken for 6 to 9 months, TB is still a leading infectious disease (with 10 million new cases per year), and the continued spread of multidrug-resistant tuberculosis (MDRTB) endangers the control of TB globally.

In this issue of *Enfermedades Infecciosas y Microbiología Clínica*, Waisman et al[3] add to the body of reports that have evaluated interventions for the control of nosocomial outbreaks of MDRTB, defined as TB due to strains of *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampin. Like the MDRTB nosocomial outbreaks reported previously in the United States, the outbreak in Hospital Muñiz (Buenos Aires) primarily involved patients with advanced human immunodeficiency virus (HIV) infection (the median CD4+ cell count was below 40/μl among the Argentinean patients studied). Like the US outbreaks, the Hospital Muñiz outbreak was initially characterized by delays in diagnosis and delays in institution of effective therapy. And just as in the US, serious deficiencies in infection control led to broad transmission to susceptible persons (including both patients and health care workers) of an individual MDR isolate[4]. However, important differences exist between the two settings. The US-based outbreaks occurred between 1990 and 1992, while the Muñiz outbreak occurred during 1994-2002. The Muñiz outbreak was larger – while the US-based outbreaks involved seven hospitals and approximately 250 patients, the Muñiz outbreak, in a single hospital, involved at least 731 patients. Finally, the human and financial resources available for the implementation of measures to interrupt transmission were different not only in quantity, but also in matters of policy, epidemiology, and health care. Nonetheless, the numerous control measures implemented within a few months for all US hospitals were later adapted effectively in Argentina.

The MDRTB "hot spots" in both North and South America were controlled by a combination of factors that included reduction of the population at risk by very high mortality, introduction of effective anti-HIV treatment, improved infection control, and earlier diagnosis and treatment for TB and MDRTB. However, cure rates are low (60-75%) when the current second-line drugs are used to treat patients with MDRTB. Both drug toxicities and nonadherence to the necessarily lengthy regimens contribute to high rates of treatment failures and thus, promote continued transmission of MDRTB.

In the domain of drugs, we can again learn from the past. The presently recommended treatment regimen (the combined use of the drugs isoniazid [discovered in 1952], rifampicin [1963], pyrazinamide [1954], and ethambutol [1962]) addresses three separate properties of the tubercle bacillus to provide an effective cure: active replication, spontaneous mutation to drug resistance, and persistence[5]. However, the basic science behind these medicines is half a century old. Treatment regimens for MDRTB lack an adequate replacement for rifampin, whose ability to affect nonreplicating persistent bacilli[6] is the mainstay of current short-course (6 month) regimens. Second-line drugs are almost all far more toxic, far less active, far slower to act (requiring longer therapy), and far more costly (about 100 times more) compared to the existing first-line anti-tuberculosis drugs[7]. On the other hand, significant advances in TB and pharmaceutical science – such as sequencing of the *M. tuberculosis* genome, new technologies for drug development (including combinatorial chemistry, high throughput screening, and rational drug design based on knowledge of molecular structures), and improved understanding of the biology of the tubercle bacillus – provide hope that we may soon achieve our goal of shorter and more active therapies for both drug-susceptible and drug-resistant TB[5].

Several antibiotics are currently being evaluated for use as TB drugs. Both moxifloxacin and linezolid have been used successfully in the treatment of MDRTB. Moxifloxacin is a broad-spectrum fluoroquinolone. In several murine studies, moxifloxacin was shown to have dose-dependent bactericidal activity against *M. tuberculosis*[8,9].

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Spontaneous resistance to these drugs is rare; resistance is encountered primarily in patients with MDRTB who have received these drugs in treatment[10,11]. In long-term tolerability studies, moxifloxacin has been well tolerated[12]. Linezolid is an oxazolidinone active against both susceptible and MDR strains of *M. tuberculosis*. It has no cross-resistance with first and other second-line standard TB drugs[13] and it is 100% bioavailable[14]. Its major toxicities include myelosuppression and neurotoxicity. The hematological effects appear to be reversible after dose reduction or discontinuation of the drug, whereas neurotoxicity may persist after drug discontinuation. The risk of myelosuppression increases as duration of therapy increases[15]. Notably, the high cost of linezolid ($100 per day) is a serious limitation to its wider use[16].

Other compounds being developed as TB drugs include TMC-207, a diarylquinoline compound, and SQ-09, a diamine-based compound. Compared to current TB drugs, the diarylquinolone compound TMC 207 acts on a novel target, the ATP synthase of *M. tuberculosis*. It is bactericidal *in vitro* against both susceptible and resistant isolates. In mouse studies, a single 100 mg/kg dose was bactericidal for 8 days, indicating the potential for intermittent dosing. In human studies, the compound was well absorbed after a single oral dose and adverse events were only mild or moderate in severity[17]. Initial testing in humans began in mid-2005: it is the most exciting member in the portfolio of potential new TB drugs. The diamine compound SQ-109 is an ethambutol analog, yet has an intracellular target different from that of ethambutol[18]. *In vitro*, it is also active against drug-resistant isolates. In mouse studies, SQ-109 inhibited bacterial growth in the spleen and lungs in a dose-dependent manner, and was as effective as ethambutol at 1/1000 of the ethambutol dose[19]. To date, SQ-109 is being prepared for entry into Phase I clinical trials.

Multidrug resistant TB in Argentina has decreased (from 4.6% in 1996 to 1.8% in 1999), mostly due to improved isolation and ventilation procedures, improved diagnosis, and greater awareness of the risk to immunocompromised patients in its main epicenter, Hospital Muñiz. The availability and correct implementation of four-drug second-line MDRTB treatment regimens undoubtedly contributed to the control of the epidemic, albeit to a lesser extent. The prior occurrence of numerous MDRTB outbreaks in wealthier countries, and the evolving twin epidemics of HIV and TB, gave rise to studies like that of Weisman et al, assessing which interventions are critical to successful outbreak control and evaluating the need, feasibility, and cost-effectiveness of these approaches in countries with fewer resources. Along with the socioeconomic and host factors that underlie this problem, a fundamental problem that hinders more effective TB control is the ability of *M. tuberculosis* to persist in the host and to develop drug resistance, often as a consequence of poor adherence to lengthy therapy. Within a rational framework for controlling MDRTB, the importance of the development of new sterilizing drugs that target persistent bacteria and shorten TB therapy must not be overlooked. Back to the future.

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