The Conundrum of MDR-TB and Combination Therapy

Written by Rita Buckley

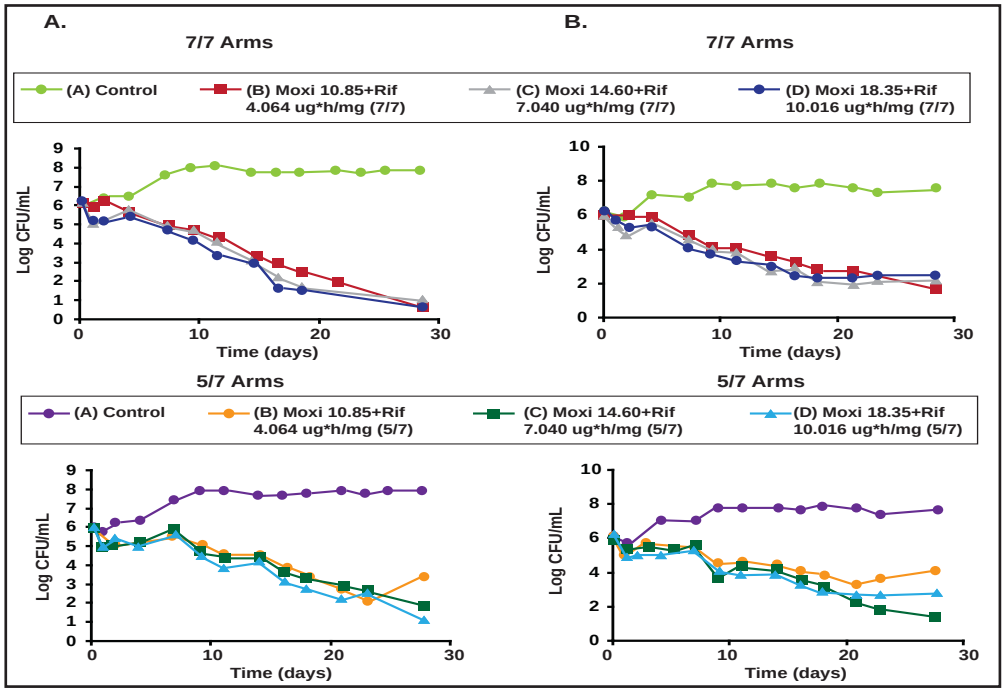
Cases of multidrug-resistant tuberculosis (MDR-TB), defined as TB that is resistant to isoniazid (INH) and rifampin (RMP) and extremely (or extensively) drug-resistant TB [ie, TB that is not only resistant to INH/RMP, but also to quinolone and capreomycin (cyclic peptide) or an aminoglycoside (amikacin or kanamycin)], are increasing. MDR complicates therapy and results in lower success rates and higher mortality, especially in HIV coinfected patients. George L. Drusano, MD, University of Florida, Gainesville, Florida, USA, discussed the conundrum of MDR-TB and combination therapy and ways to address it.

According to Dr. Drusano, combination therapy generally suppresses resistance (Table 1). [Drusano GL et al. *mBio* 2010]. However, when drugs have vastly different half-lives (eg, rifampin and moxifloxacin) and one induces error-prone replication (as with moxifloxacin), resistance can develop with drug holidays (Figure 1) [Drusano GL et al. *mBio* 2011]. "If we wish to shorten therapy," he said, "we have to suppress resistance, pay attention to schedule, and find combinations that are not only antagonistic but, hopefully, synergistic."

Table 1. Resistance Suppression: Log-Phase.

Regimen	AUC/MIC Ratio of Free:		Resistance Suppression
	Rifampin	Moxifloxacin	
600 mg rifampin QD	168.2		Failure
800 mg moxifloxacin QD		177.2	Failure
100 mg rifampin QD + 100 mg moxifloxacin QD	24.2	21.5	Success

Figure 1. Resistance Emergence in Drug Holidays.



Moxi=moxifloxacin; Rif=rifampin.
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Peer-Reviewed Highlights from the

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For the first time in decades, new TB drugs are available. Dr. Drusano stressed the importance of not risking the emergence of resistance to these agents and questioned the use of a study design in which these drugs are being evaluated against MDR-TB in an optimized background. Lack of knowledge of the detailed susceptibility pattern of the isolate prior to initiation of therapy increases the risk of creating resistant mutants. The question then becomes how to test the drugs in clinical trials.

He suggested starting by examining INH, to which the bug must be resistant, to be called MDR-TB. INH kills rapidly, with multilog decline at standard drug exposures with low minimal inhibitory concentration (MIC) values. Doses as large as 1200 mg cannot completely counter-select resistance amplification as monotherapy. Area under the curve/MIC is the pharmacodynamic-linked variable for cell kill. Because of the fast/slow acetylator divide, different populations will respond somewhat differently to INH. Specifically, fast acetylators will obtain suboptimal results at MIC values >0.25 mg/L. Therefore, noted Dr. Drusano, "wouldn't it be nice to know the MIC distributions in different areas of the world?" Unfortunately, such a database does not exist. In the absence of that information, Dr. Drusano noted that he would test the new drugs in standard patients to learn how to optimize them in combination and to suppress resistance. He stressed the risk of generating and spreading a number of resistant isolates if new drugs are used to treat MDR- and extremely drug-resistent-TB patients as single drugs.

"Combination therapy is the key for successful treatment of TB," he said. He stressed the need to learn to use new agents alone and, more importantly, in combination to optimally kill organisms and suppress resistance. He also suggested a dialog with regulatory officials to get these issues out on the table.

The United States Food and Drug Administration's (FDA) Critical Path Initiative is already transforming the way FDA-regulated products are developed, evaluated, and manufactured. One way is by publishing articles on models and approaches for anti-TB drug testing. "The Global Alliance is taking similar actions," said Dr. Drusano.

New Drugs on the Horizon to Treat MDR Pathogens

Written by Eric Butterman

Aminoglycosides are a well-known class of drugs with proven efficacy; however, they are being used less frequently because of resistance, nephrotoxicity, and ototoxicity. George Zhanel, PhD, University of Manitoba, Winnipeg, Manitoba, Canada, discussed plazomicin (formerly ACHN-490), a new aminoglycoside that is used to treat gram-negative infections, which was evaluated against gentamicin, tobramycin, and amikacin. Dr. Zhanel believes plazomicin is a next-generation aminoglycoside that retains its activity against multidrug-resistant gram-negative and gram-positive bacterial strains that express all clinically relevant aminoglycoside-modifying enzymes. It is not active against organisms that harbor rRNA methyltransferases. Plazomicin is synergistic with daptomycin and ceftobiprole against a variety of MRSA phenotypes and with a variety of β-lactams (eg, cefepime, doripenem, imipenem, and piperacillin-tazobactam) and against *P. aeruginosa* (*in vitro*). At 15 mg/kg IV, plazomicin has a C_{max} of 113 µg/mL, an AUC_{0-24} of 239 h·µg/mL, $t_{1/2}$ of 3.0 hr, and V_{ss} of 0.24 L/kg. Animal and human studies have not reported nephrotoxicity or ototoxicity [Zhanel G et al. *Expert Rev Anti Infect Ther* 2011. Submitted; Zhanel G et al. IDSA 2011]. Plazomicin is currently being investigated in a Phase 2 study to treat complicated urinary tract infections and acute pyelonephritis [NCT01096849].

Prabhavathi Fernandes, PhD, Cempra Pharmaceuticals, Chapel Hill, North Carolina, USA, presented information on macrolides and ketolides with improved antibacterial properties. Dr. Fernandes discussed several investigational programs: a novel series of azetidinyl ketolides that mitigate hepatotoxicity by minimizing hepatic turnover and time-dependent inactivation of CYP3A isoforms in the liver [Magee TV et al. *J Med Chem* 2009]; cethromycin, a ketolide antibiotic that has shown potent activity (similar to telithromycin) against macrolide-resistant bacterial strains but failed to obtain United States Food and Drug Administration approval for community-acquired bacterial pneumonia (CABP) and is now being pursued in superiority trials in simple drug-resistant respiratory infections; and modithromycin, a bridged bicyclic macrolide that is also similar in potency to telithromycin that is active against pneumococcal strains with *erm* and *mef* resistance but has a relatively high (8 µg/mL) MIC_{90} for *H. influenzae* and a very long half-life. Dr. Fernandes concluded her presentation with solithromycin (CEM-101), an oral (Phase 2) and intravenous (Phase 1) fluoroketolide that is being evaluated for the treatment of CABP that has shown activity against *S. pneumoniae,* CA-MRSA, *Enterococci*, and *M. avium* and in animal models of malaria. MICs are similar to azithromycin for gram-negatives, but on average, solithromycin is 8 to 16 times more active for the gram-positive organisms and is active against azithromycin-resistant strains. Solithromycin has 67% oral bioavailability, as compared with 38% for azithromycin; is well distributed into tissues