Isoniazid Monoresistance: A Precursor to Multidrug-Resistant Tuberculosis?

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Drug-resistant tuberculosis (TB) is a global threat to overall TB control and a World Health Organization high-priority drug-resistant pathogen (1). Annually, 600,000 incident cases of multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB occur (2), a number that has been progressively increasing even as the overall TB epidemic has slowly been brought under control. However, to date, drug-resistant TB epidemiology has focused primarily on rifampin resistance, to the exclusion of other forms of resistance.

In this month's issue of the *AnnalsATS*, Salindri and colleagues (pp. 331–340) use a longitudinal retrospective cohort from Georgia to analyze risk factors for and treatment outcomes of isoniazid monoresistance (IMR) patients compared with drug-susceptible (DS)-TB patients (3). The main finding was that treatment outcomes and all-cause mortality did not significantly differ between IMR and DS-TB patients treated during this time. Strengths of the study include a relatively large size, careful analysis including sensitivity analyses, and availability of molecular fingerprinting to assess for effect modification resulting from TB outbreaks. The study may have been strengthened with more detail on the treatment course, including drug regimens for IMR-TB, duration of regimens, and reasons for prolonged treatment duration. The study's overall contribution strengthens our understanding that when IMR-TB is recognized early and treated appropriately, treatment outcomes comparable to DS-TB with few microbiologic failures are achievable. It is important to note,

however, that the comparative efficacy of treatment regimens for IMR-TB have not been established.

Isoniazid is a critically important first-line TB drug, and resistance isoniazid and rifampicin define MDR-TB. Isoniazid is a prodrug that, after activation, acts to inhibit mycolic acid synthesis and mycobacterial cell wall formation. Isoniazid monoresistance is the single most common TB drug resistance mutation, estimated to occur in between 6.4% and 33.5% of new TB cases from 1994 to 2009 (4). Resistance is most frequently caused by mutations in genes coding for a bacterial catalase-peroxidase enzyme or a enoyl-acyl carrier protein reductase, although multiple other genes are implicated in isoniazid resistance (5). Although common, until recently, IMR has not received the same attention as rifampicin resistance because isoniazid resistance is more complex to diagnose using molecular testing, and the clinical implications of isoniazid resistance are uncertain.

Modern experience with the treatment of IMR was initially described in a 1986 summary report of British Medical Research Council TB treatment trials performed in Africa, Hong Kong, and Singapore (6). In this report, 72/72 (100%) IMR patients achieved treatment success (notably, all were treatment-naïve) when treated for at least 6 months with 4 or more antimycobacterial drugs. A more contemporary retrospective study from San Francisco essentially confirmed these results, showing rates of treatment failure with IMR that were not different than DS-TB when treated with at least 6 months

of four-drug therapy (7). However, other studies, primarily retrospective, from high-burden, lower-resource settings have shown increased risk for treatment failure with IMR treatment compared with DS-TB (8, 9). A limitation of these retrospective studies is the incomplete description of treatment regimen and confounding by indication (i.e., drug-susceptibility testing performed preferentially in patients failing treatment).

More recently, TB genomics researchers have attempted to understand the evolution of the development of MDR-TB drug resistance through whole-genome sequencing of *Mycobacterium tuberculosis* (MTB) isolates. In whole-genome sequencing studies performed in South Africa (10), Argentina (11), and Russia (12), researchers used genetic clock analysis and experimentally derived mutation rates (13) to estimate timing of phylogenetic acquisition of drug resistance mutations in MTB genomes from clinical isolates. In these studies, mutations conferring resistance to isoniazid were found to occur before other drug resistance-conferring mutations in MTB isolates that went on to develop into MDR-TB. A larger whole-genome sequencing study (14) using a dataset containing 5,310 MTB genomes extended these results by showing the priority of catalase-peroxidase enzyme-conferring and non-catalase-peroxidase enzyme isoniazid-conferring mutations in the development of MDR-TB. The authors excluded the hypothesis that the priority of isoniazid-conferring mutations was a function of isoniazid coming into clinical use before rifampin by looking sequentially

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at the likelihood of emergence of mutations sequentially in the years between 1971 and 2000 and finding no effect modification by year, suggesting that even during years when isoniazid and rifampin were coadministered, isoniazid resistance predated rifampin resistance. The implication of this research is that the phenotype of IMR may be highly clinically significant and more appropriately conceptualized as a precursor to MDR-TB, and as such, requires intensified diagnostic and therapeutic approaches.

The most likely answer to the apparent contradiction between Medical Research

Council and U.S.-based clinical studies demonstrating high rates of successful IMR-TB treatment, and phylogenetic studies of MDR-TB evolution showing IMR as a key driver of emergent resistance, is that, in the high-burden, low-resource settings in which MDR-TB arises, isoniazid resistance testing is not routinely performed, and inadequate treatment for unrecognized IMR is, therefore, common (15). In the setting of underdiagnosis, IMR-TB may be properly considered pre-MDR-TB, and it is unsurprising that evolutionary studies have identified IMR as a precursor to further drug resistance.

Paradoxically, the broad global rollout of the real-time polymerase chain reaction platform, Gene Xpert MTB/RIF, may potentially lead to further selection for isoniazid-resistant MTB isolates and emergent MDR-TB, as GeneXpert MTB RIF diagnoses rifampin but not isoniazid resistance. Routine testing of MTB isolates for all relevant drugs should not be regarded as costly extras but, rather, as critical steps for overall drug-resistant TB control. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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