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Clarity with INHindsight: High-Dose Isoniazid for Drug-Resistant Tuberculosis with *inhA* Mutations

Isoniazid has been a cornerstone of tuberculosis treatment and prevention since clinical introduction in the early 1950s and remains a key drug in the standard, first-line regimen. Its utility is threatened by expansion of drug-resistant tuberculosis; isoniazid monoresistance, estimated at 10% globally (although in some regions of the world as many as 27% of *Mycobacterium tuberculosis* strains have isoniazid resistance [1]), is associated with substantially worse treatment outcomes even with rifamycin-containing regimens (2). Multidrug resistance (MDR; resistance to at least isoniazid plus rifampin) requires longer and less-effective therapy, threatening the prospects of the global goal to end tuberculosis in the next decade (3). Although new and repurposed agents have shifted the treatment landscape for drug-resistant tuberculosis, none rival the potent early bactericidal activity (EBA) of isoniazid. The possibility of leveraging isoniazid, a safe and widely accessible antituberculosis drug with few pharmacokinetic interactions, is therefore appealing.

After activation by KatG (catalase-peroxidase), isoniazid-derived radicals bind InhA, a fatty acid synthase, potently inhibiting the ability of *M. tuberculosis* to synthesize mycolic acids (4). This results in rapid killing of replicating bacilli at drug concentrations achieved with standard isoniazid dosing at 4 to 6 mg/kg, even for individuals with "fast acetylator" genotypes (5). Mutations in the *inhA* active site or promoter region, causing reduced target affinity or overexpression, respectively, lead to moderate minimum inhibitory concentration (MIC) elevations (0.25–2 μg/ml) (6) and are responsible for approximately 7% of isoniazid resistance globally (1). Because isoniazid displays dose-dependent EBA (7), higher doses may result in exposures that overcome *inhA*-mediated resistance and translate into efficacy.

This is the postulated mechanism for observed clinical benefit of high-dose isoniazid added to conventional agents in MDR-tuberculosis (8, 9). A randomized controlled trial conducted in India (9) and a retrospective cohort study in Haiti (8) both reported reduced time to culture conversion and improved outcomes with inclusion of isoniazid 16 to 18 mg/kg in MDR-tuberculosis regimens, despite most measured isoniazid MICs exceeding the critical concentration of 0.2 μg/ml. High-dose isoniazid has also been studied as part of successful treatment-shortening regimens for MDR-tuberculosis (10, 11), leading to endorsement for this indication as part of a seven-drug combination regimen by the World Health Organization (12, 13). However, there is major uncertainty about the independent effect of isoniazid on *M. tuberculosis* killing and optimal dosing in the context of INH-resistance mutations, leading the World Health Organization to call for more research in this area (12, 13).

In this issue of the *Journal*, Dooley and colleagues (pp. 1416–1424) report findings from the INHindsight study, a phase IIA dose-ranging trial of isoniazid for patients with pulmonary MDR-tuberculosis and *inhA* mutations (14). Participants were recruited at a single site in South Africa and randomized to receive isoniazid at standard (5 mg/kg) or higher (10 or 15 mg/kg) doses. Another group of participants with drug-susceptible tuberculosis was provided isoniazid

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at the standard dose as a form of internal control. The trial was powered for a conventional primary outcome of change in daily colony-forming unit count over 7 days for each arm and not for formal comparisons across dosing strategies. Other outcomes included change in time to culture positivity, an established pharmacodynamic measure of bacillary load and growth, and safety. The trial cohort included 43 participants with drug-resistant tuberculosis and *inhA* mutations and 16 participants with drug-susceptible disease; overall, 20% were HIV positive. Isoniazid MIC distributions overlapped but were higher in the resistance groups, with a median of 1 μg/ml (range, 0.05–4 μg/ml) for strains with *inhA* mutations and 0.2 μg/ml (range, 0.2–1 μg/ml) for drug-susceptible strains.

The key finding was that, at doses of 10–15 mg/kg, isoniazid had measurable bactericidal activity in participants with low-level phenotypic isoniazid resistance at a similar magnitude to standard doses in participants with drug-susceptible tuberculosis. Isoniazid exposures were roughly dose proportional, indirect evidence of an exposure–response relationship. These findings demonstrate independent antituberculosis activity of high-dose isoniazid against *inhA* mutant strains and provide compelling justification to evaluate efficacy in treatment regimens for both MDR and isoniazid monoresistant tuberculosis where the isoniazid resistance mutation is known.

There are, however, several important issues the study was unable to address. First, MDR-tuberculosis is mainly diagnosed using rifampicin resistance as a proxy, and genotypic testing for isoniazid resistance is not available in many high-burden settings. It is therefore essential not only to improve access to isoniazid resistance testing but also to understand efficacy of high-dose isoniazid in the presence of more common *katG* mutations, which confer higher-level resistance (15). A second stage of INHindsight will address this question, but it may also be important to understand how high-dose isoniazid performs with strains that have both *inhA* and *katG* mutations, estimated at up to 15% (1). Second, although the absence of severe adverse events in high-dose isoniazid groups is reassuring, the drug was only administered for 7 days, and the trial was not powered to adequately assess safety, a key concern for implementation. Most clinical studies of high-dose isoniazid for MDR-tuberculosis have not systematically ascertained or reported adverse events, and the Indian trial seemed to show more peripheral neuropathy in the high-dose arms (9). Third, isoniazid clearance is largely explained by NAT2 (*N*-acetyltransferase-2) genotype (16), which was not reported in INHindsight. There was an apparent unexplained dose effect on isoniazid clearance (mean clearance, 24.3 L/h in the 5 mg/kg group vs. 14.2 L/h in the 15 mg/kg group), possibly reflecting saturation of first-pass metabolism, which may have been accentuated by slow acetylation. Imbalances of NAT2 genotype across arms may have therefore influenced dose–response effects and interpretation of findings. As acknowledged by the investigators, it will be important to quantify the relationship between isoniazid exposure and EBA, taking into account influential host (NAT2 genotype) and pathogen (MIC) factors. Larger studies with clinical endpoints are clearly required to characterize safety, impact on treatment outcomes, and the role of high-dose isoniazid in new regimens. Such studies should also include groups of individuals who may be at increased risk of isoniazid-related adverse events, including people living with HIV, people with hepatitis B and/or C, people who use alcohol, and people with diabetes mellitus.

For decades, the treatment of drug-resistant tuberculosis has been based on expert opinion and observational cohort studies. Currently, there is a renaissance of high-quality clinical trials for treatment of all forms of tuberculosis, and INHindsight is an important example of how such work can provide more certainty to prescribers and policy makers. Although additional clinical studies are needed, INHindsight has focused our gaze on how isoniazid, one of our most important therapeutic options, can have an ongoing role in efforts to end all forms of tuberculosis. ■

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2019 American Thoracic Society BEAR Cage Winning Proposal: Lung Imaging Using High-Performance Low-Field Magnetic Resonance Imaging

Clinical imaging of the lung is dominated by computed tomography (CT) and X-ray for the assessment of tissue morphology, and by nuclear imaging for the assessment of metabolism and lung function. Magnetic resonance imaging (MRI) allows evaluation of anatomy, function, and physiology during a single exam that is free of ionizing radiation. Significant efforts have resulted in progress toward clinical lung MRI (1, 2), including the development of ultrashort-echo-time imaging for improved depiction of lung structure (3, 4), as well as regional $\dot{V}/Q$ imaging using hyperpolarized gas, oxygen-enhanced imaging, and Fourier decomposition of dynamic lung imaging (5–9). However, proton MRI has suffered from inherent challenges associated with MRI in the lung, and hyperpolarized gas imaging has been hindered by the need for costly specialized equipment and technical expertise. Consequently, lung MRI has not been routinely adopted.

Clinical MRI systems operate with a magnetic field strength of 1.5 T or 3 T, and for many years there has been an impetus to develop systems with higher magnetic field strengths. MRI engineering and imaging methods have improved dramatically in the past several decades, and computational power has become readily available. In light of these advancements, the author's group recently developed a high-performance low-field MRI system that integrates modern technology at 0.55 T and provides superior imaging quality in the lung (10).

This high-performance low-field MRI system configuration, paired with optimal imaging approaches, improves visualization of lung parenchyma, thereby enabling an abundance of new lung imaging applications. This new lung imaging technology, along with its proposed clinical application, received the 2019 American Thoracic Society (ATS) Building Education to Advance Research (BEAR) Cage Innovation Award.

What Does High-Performance Low-Field MRI Offer to Clinical Lung Imaging?

Compared with other imaging modalities, MRI offers the advantage of flexible image contrast. For example, an MRI exam can include assessment of anatomical structure and tissue dynamics, quantification of blood flow, characterization of tissue edema/fibrosis/iron/perfusion/viability, quantification of fat and water, and evaluation of microarchitecture (11, 12). However, in the context of pulmonary diseases, these capabilities been hampered by poor image quality, and comprehensive lung MRI exams have been unattainable.

In the lung, MRI image quality suffers from low water density limiting the available MRI signal, and from air–tissue interfaces causing local magnetic susceptibility gradients (13). High-performance low-field MRI technology can mitigate some of these challenges for the following reasons:

1. A contemporary magnet design operating at lower field produces a more uniform magnetic field, such that the magnetic susceptibility gradients caused by air–tissue interfaces are diminished. The field homogeneity results in reduced image distortion and improves parenchymal visualization.
2. Oxygen performs better as a contrast agent at low field by virtue of increased T1 relaxivity (10, 14). Oxygen-enhanced MRI has been successfully applied on conventional MRI systems for regional ventilation measurements (15, 16), but the signal enhancement will be greater at lower fields, resulting in improved sensitivity.
3. Lower-field MRI technology offers workflow advantages compared with conventional MRI, including reduced acoustic noise and vestibular upset, resulting in improved patient comfort; improved physiological monitoring (e.g., with less

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