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Monitoring for Tuberculosis Drug Hepatotoxicity: Moving from Opinion to Evidence

Jussi J. Saukkonen, M.D.,
Pulmonary Center, Boston University School of Medicine, Boston, Massachusetts

Krista Powell, M.D., M.P.H.,
Division of Tuberculosis Elimination, Centers for Disease Control, Atlanta, Georgia

John A. Jereb, M.D.
Division of Tuberculosis Elimination, Centers for Disease Control, Atlanta, Georgia

The treatment of tuberculosis (TB) is complicated by drug-induced hepatotoxicity, with reported rates ranging widely, from approximately 3 to 25%, depending on the hepatotoxicity definitions, the regimens, the methodologies, and the study populations (1). Several recent studies utilizing American Thoracic Society (ATS) or similar transaminase criteria for hepatotoxicity place the rate at about 3 to 13% (2–5). However, not all increases in serum alanine aminotransferase concentration (ALT) indicate true drug-induced liver injury (DILI). Hepatic adaptation (i.e., temporary stress or mild injury to the liver) occurs in 20% or more of patients treated with anti-TB medications (1, 6). Current recommendations (1, 7) are to obtain baseline biochemical testing in all patients being treated for TB, and then to target those deemed to be at risk for drug-induced liver injury for serial ALT monitoring. Because we lack a robust evidence base, these recommendations are based on observational studies and expert opinion. We need more data—and could readily generate a wealth of data—to help guide TB drug hepatotoxicity monitoring strategies.

In this issue of the *Journal*, Singanayagam and colleagues from Imperial College London (ICL) (pp. 653–659) provided a fresh look at monitoring for hepatotoxicity during anti-TB treatment (8). In a single-center retrospective cohort study, they monitored 288 patients for hepatotoxicity. They compared the utility of a uniform scheme of measuring the baseline and the 2-week serum ALT concentrations to that of the ATS recommendations, which target only patients with putative hepatotoxicity-predictive factors for serial biochemical monitoring after a baseline test (1, 7). Intensive early ALT monitoring in the ICL study detected DILI within 2 weeks in about 4% of patients, but was poor at predicting who would be among the 3% of patients having DILI later (8). The forecasting ability of the ATS putative predictive clinical factors for DILI (1, 7) was similarly mediocre.

Despite the study's limitations—a small sample size, enrollment of patients at a single TB program, nonuniform and infrequent use of directly observed therapy, and an asymmetrical

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ALT sampling frequency—the ICL study draws attention to the need for a better evidence base for hepatotoxicity monitoring strategies and for distinguishing true DILI from hepatic adaptation. The ICL strategy did detect early large increases in ALT concentration (i.e., more than five times the upper limit of normal) in asymptomatic patients. However, both ICL and ATS schemes presumably should detect symptomatic patients at the same time. The authors postulated that universal retesting shortly after treatment initiation might predict subsequent DILI incidence better than relying on clinical risk factors. This raises intriguing questions about the kinetics of ALT changes in predicting DILI.

Measuring ALT more frequently during treatment probably would detect more episodes of increasing ALT, but this brings us to the dilemma: our present assays and evidence base do not help us to distinguish between hepatic adaptation and DILI. The low sensitivity of the ICL scheme also does not afford a means of doing so. In the ICL study, most patients who had treatment interrupted because of ALT elevations tolerated reintroduction of the standard regimen, suggestive of hepatic adaptation instead of DILI. Under current recommendations, treatment is interrupted simply when safety thresholds are reached to avoid serious DILI (1, 7). Both testing strategies might be interrupting treatment too early, suggesting that the ALT safety thresholds are too low or perhaps ALT is not the right measure. Unfortunately, in the absence of hepatic symptoms or of an increasing serum bilirubin concentration, we still do not know how to predict severe DILI from initial ALT changes. Modifying long-held safety thresholds will require additional compelling data.

The evaluation provided by Singanayagam and coworkers of their alternative monitoring scheme and of the ATS scheme found both to be suboptimal. The need to avoid life-threatening DILI efficiently while limiting treatment interruptions is intensified in high–TB-burden countries, because the entire endeavor of biochemical monitoring, treatment interruption, evaluation of hepatotoxicity, and medication re-challenge is resource intensive. We need larger, multicenter studies to determine the following:

1. What is the optimal testing strategy or schedule for biochemical monitoring?
2. Can the kinetics of serum ALT concentration distinguish between impending DILI and inconsequential hepatic adaptation?
3. Would any biochemical indicators besides ALT be more useful for detecting DILI early, thus arresting its progress?
4. Which patients should—or should all patients—be evaluated for hepatotoxicity in the strategies to be employed?
5. What lessons regarding safety, hepatic adaptation, and DILI can be learned from studying rechallenge following treatment interruption for significant hepatotoxicity?

As we begin to understand how to separate hepatic adaptation from true DILI, the nomenclature to describe the full spectrum of liver abnormalities seen during TB treatment will need to be revised. Lastly, it is hoped that the burgeoning pipeline of TB drugs under development will yield treatments that can avoid causing hepatotoxicity altogether.

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