ever, this remains a clinical decision based on limited data and many variables.

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The Best Approach to Reintroducing Tuberculosis Treatment after Hepatotoxicity Is Still Open to Debate

To the Editor—The best approach of reintroducing tuberculosis drugs after hepatotoxicity is still open to debate. Sharma et al [1] suggested that simultaneous reintroduction of isoniazid, rifampin, and pyrazinamide after drug-induced hepatotoxicity did not yield statistically significantly different results from sequential reintroduction with regard to the risk of recurrent hepatotoxicity. An editorial attempted to attribute the negative finding to mere hepatic adaptation or incidental liver function derangement for many of the initial events and to noncompliance during reintroduction [2]. We would like to share slightly different views in the interpretation of the findings.

The statistical power of the study by Sharma et al [1] was probably suboptimal. If a superiority trial design was used to prove a difference between arm 1 (simultaneous reintroduction) and either arm 2 or arm 3 (sequential reintroduction), and if the risk of recurrent hepatotoxicity was assumed to be 24% for arm 1 [3] and 7% for arms 2 and 3 [4], then 68 cases per arm would be sufficient. However, a difference as big as 3–4-fold might be partly due to different patient profiles associated with different cohorts. If a noninferiority trial design was used to prove a lack of difference, a sample size of 256 cases per arm, as suggested by the investigators [1], would be sufficient, but the margin of noninferiority in such an estimation would be unrealistically close to 0. Using a more realistic margin of 8.5%, which is one-half of the difference between 24% and 7%, the study would require 212 subjects per arm. Thus, the study was grossly underpowered.

Sharma et al [1] found a significant association between pretreatment serum albumin levels and recurrence of hepatotoxicity. Pretreatment albumin levels were significantly different between the 3 arms, with higher mean levels in arm 1. Had the mean pretreatment albumin levels been comparable, the difference in the risk of recurrent hepatotoxicity between arm 1 and arms 2 and 3 could have been even bigger. This further casts doubt on the lack of difference between simultaneous and sequential drug reintroduction.

A risk of recurrent hepatotoxicity of 13.8% during simultaneous drug reintroduction, as shown by Sharma et al [1], is by no means low, taking into account of its highly variable course that may culminate in irreversible liver failure and death. Thus, there is still a dire clinical need for caution in the drug reintroduction process.

The ultimate aim of drug reintroduction is to establish an effective regimen in a safe and speedy fashion. Sequential reintroduction may help identify the cause of hepatotoxicity [2] only if the first reintroduced drug causes a hepatotoxic event, but often not if hepatotoxicity occurs in the presence of several drugs. It might be overly simplistic to attribute hepatotoxicity to the last added drug.

Drug reintroduction over an excessively prolonged period may delay effective treatment and even invite the emergence of resistance. Reintroduction of drugs in escalating doses might reduce the risk of recurrent hepatotoxicity through hepatic adaptation. Because rifampin given alone rarely causes hepatotoxicity [5], and because rifampin and isoniazid are ~3 times less hepatotoxic in the absence of pyrazinamide [6], it might be a reasonable compromise to consider giving full-dose rifampin and isoniazid together, followed by pyrazinamide in escalating dosages.
...randomly with the use of computer-generated random numbers, blocked in groups of 3 that were kept in sealed opaque envelopes. The envelopes were in the possession of an individual who was not involved in the conduct of study. Each arm had a different reintroduction protocol for anti-tuberculosis drugs. Because the allocation of the patients to each of the 3 arms was purely by “chance,” and because the mean pretreatment serum albumin level was within the normal range in all the 3 arms, these intergroup differences occurred purely by chance.

Therefore, the issue of the best reintroduction regimen is still open for future research. Chang and Leung [1] also suggest that giving full-dose rifampicin and isoniazid together, followed by pyrazinamide in escalating doses, may be a reasonable compromise. The idea seems interesting, but the efficacy and safety of this protocol must be established by a prospective study with sufficient power and a large sample size.

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Reply to Chang and Leung

To the Editor—We thank Chang and Leung [1] for their comments on our article [2]. We agree with their statement that, in the absence of quality trials with sufficient numbers of subjects, the best approach to reintroducing antituberculosis drugs after hepatotoxicity is still open for debate. We tend to agree with them that the statistical power is inadequate if the noninferiority margin is 8.5%. According to this threshold, 212 subjects would be required per arm, and this would translate to 636 patients with antituberculosis drug-induced hepatotoxicity (DIH). It took us 5 years to achieve the sample size of 175 patients with DIH. Here, we would like to point out that directly observed treatment has become an integral part of TB treatment in India, where thrice-weekly, intermittent treatment is administered. Given the low risk of DIH associated with this regimen (authors’ unpublished data) along with the observed exclusion criteria, such a large sample size, would be difficult to attain in a specified time. We fully understand the limitations of the noninferiority trial design for estimating the sample size and reiterate what we mentioned in the Discussion section of our article: we noted that our study lacked sufficient power to detect a difference between the 3 arms and suggested the need for a multicenter trial in situations where TB is endemic to address this important issue.

Chang and Leung [1] mention that the mean pretreatment albumin levels were significantly different between the 3 arms. However, to say that the difference in the risk of recurrent hepatotoxicity among the 3 arms could have been bigger, had the mean pretreatment albumin levels been similar, is a bit far fetched. When we looked for the recurrent hepatotoxicity among the 3 groups, with adjustment for baseline albumin level, the recurrence rates among the 3 groups were still statistically not significant (odds ratio for group 1 vs group 2, 0.50 [95% confidence interval, 0.15–1.65]; P = .26); odds ratio for group 1 vs group 3, 0.39 [95% confidence interval, 0.11–1.39]; P = .15). Thus, the postulation that the risk of recurrent hepatotoxicity among the 3 arms would have been bigger may not be true. We would like to point out here that, although the mean pretreatment serum albumin level (± standard deviation) was higher in arm 1 (4.03 ± 0.66 g/dL) than in arm 2 (3.77 ± 0.60 g/dL) and arm 3 (3.75 ± 0.59 g/dL; P = .03), the values were within the acceptable level for serum albumin (ie, >3.5 g/dL). Furthermore, allocation of patients to each of the 3 arms was performed...