False-positive Xpert(®) MTB/ RIF assays and previous treatment

Although patients with bacilli resistant to any drugs were excluded from the trial, the 6-month regimen would be particularly appropriate for the treatment of patients with INH-resistant TB. In contrast to Europe, RIF is licensed for the treatment of TB in the USA, and there has been a recent substantial price reduction. We would therefore encourage consideration of this RIF and MFX intermittent regimen for the treatment of patients with INH intolerance or drug resistance in the USA, and for further implementation studies to evaluate its utility in other settings.

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In reply

I agree with Phillips and Lipman that the performance of the recently published 6-month rifapentine (RIF) and moxifloxacin (MFX) containing regimen in the RIFAQUIN trial is very encouraging news. Despite once-weekly dosing for the final 18 weeks with MFX plus high-dose RIF, the outcomes for the 212 patients in the experimental 6-month arm were similar to those for the standard 6-month regimen with daily dosing throughout.[1] The enthusiasm of Phillips and Lipman for more research into the treatment of isoniazid (INH) resistant tuberculosis is very welcome.

While the RIFAQUIN results are very promising, it is likely that more research will be needed before this regimen will be considered standard therapy to replace the poorly tolerated regimen used in the United States for INH resistance.[2] The currently approved RIF dose of 600 mg twice weekly during the intensive phase of tuberculosis treatment and the recommended 600 mg once-weekly regimen for selected patients during the continuation phase is rarely used. As most patients with INH resistance or intolerance will likely have received rifampin (RMP) during initial therapy, recommendations will need to address whether it is reasonable to transition patients to once-weekly RIF and MFX without the full 8 weeks of daily dosing with RIF, MFX, pyrazinamide and ethambutol used.

The more important potential application of the RIFAQUIN study is on the global scale, where 9.5% of nine million cases are estimated to be due to INH-resistant but RMP-susceptible *Mycobacterium tuberculosis*.[3] Caution will be in order in many countries, as only 49 of the patients were human immunodeficiency virus infected, most with CD4 cell counts well over 200 cells/mm^3, and pregnant women were excluded from the study. Caution should not be a barrier, however, to timely completion of the necessary research, given the evidence of acquired RMP resistance with the current regimens used to treat INH-resistant tuberculosis.[4]

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False-positive Xpert® MTB/RIF assays and previous treatment

We thank Steingart et al. for their reply to our case series and welcome their further analysis.[1] It is reassuring that the performance of Xpert® MTB/RIF does not seem to be substantially affected by the phenomenon we described when one looks at a broad group of patients being investigated for tuberculosis (TB). However, there is a signal that specificity may be lower in patients with a history of previous TB, in that specificity is 100% in cohorts where only 2% of

patients have a history of TB but declines to 92% when that proportion increases to 55%.

It is unfortunate that only 36% of studies reported 'percentage of patients with a history of TB', and we suggest that future studies clearly state the treatment history of all patients and report separately on specificity for those with previous treatment. Ideally this would be stratified into those within 6 months, 1 year and 2 years of completing TB treatment. We have requested access to the data from the two largest studies[2,3] in order to determine specificity separately for those with a history of TB treatment. Our request was declined on the basis that it would be a post hoc analysis of a question the trials were not designed to answer. We repeat our request to the owners of the data to provide this analysis, despite the limitations, in order to provide a clearer picture of the use of Xpert MTB/RIF in re-treatment cases.

Data from Friedrich et al. suggest that specificity may be poor soon after TB treatment is completed but may improve with time;[4] in addition, inter-current lower respiratory tract infection may lead to false-positive Xpert MTB/RIF years later, as in our index case.[5] We believe the priority for prospective study is patients being investigated for active TB who completed treatment within 2 years in order to determine the specificity, positive predictive value and positive likelihood ratio for Xpert MTB/RIF in this cohort.

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