Shortened multidrug-resistant tuberculosis treatment in settings with a high prevalence of ofloxacin resistance

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TEXT:

We have read with interest the research letter by Javaid et al. in a recent issue of the European Respiratory Journal.[1] The authors aptly note some uncertainty in current World Health Organization (WHO) guidelines.[2] Nevertheless, we question the authors' main assertion that "high prevalence of ofloxacin resistance should not limit the applicability of the new shorter regimen". The shortened regimen has indeed produced promising results in a number of settings, in populations carefully selected for their limited exposure and resistance to second-line drugs.[3–5] That this should be extended to settings with high prevalence of fluoroquinolone resistance, without individual, rapid molecular testing for fluoroquinolone resistance, is not supported by data or WHO.

The present sub-national, cross-sectional study shows worryingly high levels of resistance to ofloxacin and other drugs contained in the shortened multidrug-resistant tuberculosis (MDR-TB) regimen. We concur with the authors on the importance of strengthening the public-health response to the various sources of fluoroquinolone-resistant TB in Pakistan. Nevertheless, the presence of ofloxacin resistance, tested at 2 $\mu g \cdot mL^{-1}$, in 48.6% of patients does not support widespread applicability of the shortened regimen in this population. More than 50% of the patients in Bangladesh with "high-level" resistance to ofloxacin by this definition had unfavorable treatment outcomes on the shortened regimen.[3] Moreover, it is noteworthy that the present study did not report overlapping resistance among these drugs to further inform estimates of the population eligible for the shortened regimen. Since rapid, reliable pyrazinamide testing is not available routinely, any use of the shortened regimen in the presence of high population levels of ofloxacin resistance needs to consider the frequency of concurrent pyrazinamide resistance: according to results from meta-analyses that supported the development of WHO recommendations, the probability of

favorable outcomes on the shortened regimen is reduced from 90.3 (95% CI: 87.8-92.4%) among all patients to 67.9% (95% CI: 47.5-84.1%) among patients with isolates resistant to both drugs.[6] The authors assertion that "it is not recommended to base decision-making on the basis of resistance to pyrazinamide and ethambutol" is at odds with these findings and with WHO guidance. The latter recommends avoiding the shortened treatment in patients with "documented or likely resistance to medicines in the regimen" and "in patients infected with strains known or strongly suspected of being resistant to one or more drugs in the shorter MDR-TB treatment regimen (e.g. pyrazinamide) …".[6]

The authors propose to increase the applicability of the shortened regimen in this and similar settings by: a) increasing the clinical breakpoint for ofloxacin from 2 to 4 $\mu g \cdot mL^{-1}$, b) administering moxifloxacin at high dose, and c) considering resistance to moxifloxacin/gatifloxacin, rather than ofloxacin, as an exclusion criterion for the short course treatment. However, these changes neither resolve the uncertainty in the guidelines nor strengthen the case for the shortened regimen in populations with high prevalence of fluoroquinolone resistance. First, rationale for the proposed increase of MIC for ofloxacin, presumably to serve as a better proxy for resistance to later-generation fluoroquinolones, is not presented; this cut-off is higher than that used for both the national survey and the observational study that demonstrated different clinical outcomes of the shorter regimen in strains with low-level versus high-level fluoroquinolone resistance.[3,7] Second, moxifloxacin/gatifloxacin are already prescribed at high dose (400 to 800 mg/day according to weight group) in some applications of the shortened regimen, so the results showing reduced effectiveness in the presence of resistance to fluoroquinolones and pyrazinamide already factor in this reinforcement.[6] Third, while we agree in principle that usefulness of late-generation fluoroquinolones is best guided by drug susceptibility testing (DST) to those

drugs—and not by DST to earlier-generation class members[8]—the proposed modification to guidance to rule out moxifloxacin/gatifloxacin resistance is problematic from an operational standpoint; DST to these drugs is infrequently available in high-burden settings (including Pakistan, according to the authors). More practically, rapid molecular tests will be used to assess eligibility. Their careful interpretation to identify individual patients eligible for the shortened regimen will be especially important in settings with known high population levels of fluoroquinolone resistance. Existing data from sequencing suggest that resistance caused by mutations in the QRDR region of *gyrA* (except 94Ala) is associated with an important increase in poor outcomes on the shortened regimen.[9] Fortunately, there are other options: the advent of delamanid and bedaquiline,[10] as well as other "core" MDR-TB drugs used in conventional regimens offer alternatives to using the shortened regimen in patients in whom its success is likely compromised. Multiple new studies of shortened regimens containing these drugs (Nix-TB [NCT02333799], TB-PRACTECAL [NCT02589782], endTB [NCT02754765]) may generate palatable and effective alternatives.

In conclusion, we recommend caution in the introduction of the shortened MDR-TB treatment in settings with high prevalence of resistance to ofloxacin or pyrazinamide; eligibility for shortened treatment should be evaluated individually according to rapid molecular testing and available DST results.

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