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Reply to Chang and Yew

From the Authors:

We appreciate the letter by Drs. Chang and Yew commenting on the Official Guidelines of the American Thoracic Society (ATS)/CDC/European Respiratory Society (ERS)/Infectious Disease Society of America (IDSA) on the treatment of multidrug-resistant tuberculosis (MDR-TB) (1). Three issues are raised in the letter: first, the certainty of the evidence on the use of linezolid and bedaquiline in the management of fluoroquinolone-sensitive and -resistant MDR-TB; second, the risk of resistance to these two drugs with generalized use, suggesting focused use of these drugs in selected patients might limit this hazard and minimize acquisition of resistance and serious adverse events; and third, that with broadening availability of rapid drug susceptibility testing (DST), optimized longer and existing standardized shorter-course regimens still have value.

On the first issue, we concur that the certainty in the evidence is low. However, until such a time when randomized controlled trials in TB therapeutics are adequately funded, conducted, and completed, the propensity score (PS)-matched individual patient data meta-analysis (IPDMA) of a database of more than 12,000 patient records from 25 countries in support of the ATS/CDC/ERS/IDSA guidelines represents the best available evidence base on which to assess drugs for treatment of drug-resistant TB (1, 2). Our PS-matched IPDMA showed consistently that bedaquiline and linezolid improved treatment success and reduced mortality across all patients with drug-resistant TB (with the greatest impact noted in extremely drug-resistant TB). These benefits were substantial, with absolute reductions in mortality of 5–10% with use of bedaquiline or linezolid (2). Sensitivity analyses were also conducted across subgroups of MDR-TB patients with respect to additional resistance to any fluoroquinolone, and the results remained essentially unchanged within subgroups (1, 2). The potency of linezolid and bedaquiline, when combined with a later-generation fluoroquinolone, allows for the composition of an all-oral regimen for MDR-TB for the first time in patients with fluoroquinolone-susceptible TB. The availability of effective and injectable-free regimens is an advance that we endorse enthusiastically.

On the second issue, we concur that the development and scale-up of rapid genotypic DST for new agents are urgently needed. The ATS/CDC/ERS/IDSA guidelines recommend as a good practice statement that regimens should include only drugs to which the patient's *Mycobacterium tuberculosis* isolate has a documented or a high likelihood of susceptibility. Drugs known to be ineffective based on *in vitro* growth-based or molecular resistance should not be used given consistent findings in the IPDMA that outcomes were worse in patients who received drugs to which their isolates were resistant (2). For the settings in which these guidelines are relevant, molecular methods and, more recently, whole-genome sequencing are increasingly available and can provide information on resistance to all first-line and many second-line drugs.

On the third issue, although we concur that the standardized shorter-course regimens may still have value when susceptibility is documented for all the drugs in the regimen, we found that when applying the eligibility criteria from the World Health Organization for using this regimen (3) for the population included in our PS-matched IPDMA, fewer than 15% of individuals were eligible for the regimen. In Europe, patient eligibility for the shorter-course regimen has ranged from 8% to 17% in surveillance-based studies (4, 5). In the United States, only 10% of MDR-TB patients would have been eligible based on national data from 2011 to 2016 (6). We recommend the conduct of randomized controlled trials evaluating the efficacy, safety, and tolerability of modified

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shorter-course regimens that include newer oral agents, exclude injectables, and include drugs for which susceptibility is documented or highly likely.

The ATS/CDC/ERS/IDSA guidelines provide guidance for settings in which there is capacity to perform both rapid molecular testing and phenotypic DST, to tailor the regimen based on the drug susceptibility pattern identified, and to manage adverse events caused by drugs, including linezolid and bedaquiline (1, 7, 8). Whereas the newer and more potent drugs provide the opportunity to safely use all-oral regimens, we concur with Drs. Yew and Chang that there is still much more work to do on improving safety and tolerability of MDR-TB treatments as well as the development and scale-up of companion genotypic tools to test and monitor for resistance to our newest agents. ■

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Cardiovascular and Chronic Obstructive Pulmonary Disease Therapeutics: Two Paths, One Destination?

To the Editor:

Crim and colleagues tested whether vascular stiffness was affected by inhaled long-acting β_2-agonist, corticosteroid, or combination therapy in patients with moderate chronic obstructive pulmonary disease (COPD) (1). Baseline arterial pulse wave velocity predicted mortality but was unaffected by therapy (1). The authors conclude that inhaled therapy for COPD appeared unlikely to reduce cardiovascular (CV) risk (1). Although aggressive risk factor modification and smoking cessation are pivotal in addressing CV risk in COPD, optimal use of existing drugs and potential avenues for developing novel therapies deserve further discussion.

For the management of hypertension in COPD, limited contemporary data support the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and thiazides (2). In an analysis of clinical trials involving more than 12,000 patients with COPD, treatment with roflumilast, a phosphodiesterase-4 inhibitor with a wide range of antiinflammatory actions, was associated with a 35% relative risk reduction in major adverse CV events (nonfatal myocardial infarction, nonfatal stroke, and CV death) independent of age, sex, smoking status, and concomitant COPD treatments (3). These findings warrant further investigation of the potential CV benefits of roflumilast (3). Endothelial activation earlier in life has been associated with the development

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