0.60 [95% CI, .50–.71]). Second, among the five most common individual statins, only pravastatin was found to be significantly associated with lower risk of active TB in this study. Although our findings support Dutta and colleagues' study [1] that pravastatin may be a better choice than other statins in the management of TB, the exact mechanistic difference between pravastatin and other statins in preventing TB still requires further investigation.

In conclusion, this real-world study provides further evidence that statins can reduce the risk of active TB, particularly for pravastatin.

Notes

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Reply to Lai et al

To the Editor—We read with interest the letter by Lai et al [1] in response to our article on adjunctive host-directed therapy with statins for tuberculosis in preclinical models [2]. The authors have sought to assess potential differences among various statins, including atorvastatin, simvastatin, rosuvastatin, fluvastatin, and pravastatin, in their ability to prevent tuberculosis. They performed a population-based, nested case-control study of patients with active tuberculosis as case patients and healthy individuals as controls. Case patients and controls were matched by age, sex, and time of study recruitment. The authors performed regression analysis with very rigorous methods to control for all potential confounders.

Lai et al found that current statin use (ie, statin prescription filled within 30 days of the index date) was associated with a reduced risk of active tuberculosis, with an adjusted rate ratio of 0.79 (95% confidence interval [CI], .68–.92) [1]. When stratified by the type of statin used, only pravastatin use was associated with a significant reduction in the risk of active tuberculosis (adjusted rate ratio, 0.54; 95% CI, .30–.98). Although the other statins did not show a significant reduction in the risk of new-onset tuberculosis, the analysis did not have adequate power to compare tuberculosis incidence among the different statin groups due to a very low prevalence of statin use among cases and controls.

The findings of Lai et al [1] are largely consistent with those of systematic reviews based on observational studies by Duan et al [3] and Li et al [4], which showed that statin use reduces the risk of active tuberculosis disease with pooled risk ratios of 0.78 (95% CI, .63–.95) and 0.6 (.45–.75), respectively. This conclusion remained unchanged irrespective of subgroup analyses based on sex, diabetes status, and study design during meta-analysis. Neither of these meta-analyses stratified outcomes based on the type of statin used.

We have shown that statins have host-directed, antitubercular activity and that their use as adjunctive agents enhances *Mycobacterium tuberculosis* killing by the standard regimen in mice [2, 5]. Findings of our preclinical studies also suggest that this activity represents a class effect [6] mediated by cholesterol-driven autophagy via the AMP-activated protein kinase (AMPK)-mechanistic target of rapamycin complex 1 (mTORC1)-Transcription factor EB (TFEB) axis in macrophages [7].

To our knowledge, to date only one clinical study, by Chen et al [8], has evaluated the effect of statin use on outcomes of patients with tuberculosis. Although this population-based cohort study found that tuberculosis treatment completion rates did not improve after statin therapy, its conclusions were limited, in that the data were derived from an insurance database. Furthermore, no previous study has evaluated the effect of statin use on important clinical outcomes, such as mortality or long-term lung function, or on microbiological outcomes following tuberculosis treatment. Based on the available evidence, and given the favorable safety profile of statins, we believe randomized clinical trials are warranted to determine their potential utility in reducing tuberculosis incidence among latently infected individuals at high risk for tuberculosis reactivation, such as those with human immunodeficiency virus coinfection, and in improving clinical and microbiological outcomes in patients treated for active tuberculosis.

Notes

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Further Considerations on the Natural History of Anal Dysplasia in Response to Jongen et al and Barroso

To the Editor—The Consortium for Anal Cancer Screening is a forum for regional high-resolution anoscopy (HRA) providers to discuss and collaborate on clinical and research questions related to anal dysplasia. In a recent journal club, we reviewed the article by Jongen et al on the natural progression of low-grade squamous intraepithelial lesions (LSILs) of the anus and the accompanying editorial by Barroso [1, 2]. We were somewhat concerned about the low prevalence of high-grade squamous epithelial lesions (HSILs) on initial diagnosis (17.8%; 298/1678) in this high-risk cohort and wondered whether this is an error, as a previous publication regarding this cohort listed the baseline HSIL prevalence as 29.6% (497/1678) [3]. It is generally thought that experienced HRA providers detect HSIL in 40%–50% of human immunodeficiency virus (HIV)-positive men who have sex with men (MSM) in a first HRA, and any missed HSIL diagnosis at baseline may be erroneously assessed as progression at follow-up [4]. The editorial by Barroso also sparked an interest to review recent reports supporting or disputing direct LSIL to HSIL progression. Two publications by a group at the Icahn School of Medicine at Mount Sinai took a similar longitudinal approach to that of Jongen et al to determine HSIL progression in HIV-positive MSM with baseline LSIL diagnosis. The 2 studies were conducted with a follow-up HRA within 5 to 35 months [5, 6]. HSIL progression rates were 36% and 41%, respectively, slightly higher than that described by Jongen et al; p16 staining of histologic samples and persistent human papillomavirus (HPV)-16/18 obtained from cytology swabs, but not from tissue, were identified as predictors of progression. All examinations in these 2 studies were performed by a single HRA provider and a single pathologist, reducing intraobserver variability during HRA or pathology evaluations, which was correctly identified by Barroso as a major impediment to the interpretation of longitudinal studies of anal dysplasia. In addition, lesions detected at follow-up in octants adjacent to the ones of the original lesion were included in the analyses to account for mucosal shifts between procedures; this practice was not described in the study by Jongen et al and its impact on the accuracy of the findings is not known. Although these 3 studies seem to support direct LSIL to HSIL progression, molecular detection of HPV types in laser capture microscope-dissected anal and cervical lesions has demonstrated that HPV types and different grades of dysplasia can be in close proximity to each other, which might be impossible to distinguish in routine biopsy specimens [7]. Furthermore, recent evidence in the cervix has shown that certain cells do not support permissive HPV infection so that high-risk HPV infection can directly lead to transformative infection and HSIL [8]. With regard to the virus, specific HPV16 sublineages have been associated