Rigor in the Design of Observational Noninferiority Trials

TO THE EDITOR—Fernández-Hidalgo and colleagues report an important observational active-comparator study to address the need for an aminoglycoside antibiotic in the treatment of enterococcal endocarditis [1]. The study is essentially designed to test the noninferiority hypothesis that ampicillin with ceftriaxone is not meaningfully less effective than ampicillin plus gentamicin while being better tolerated than the prevailing standard of care. Unfortunately, a clinically acceptable noninferiority margin was not explicitly specified [2]. As a result, it cannot be determined whether the analysis was sufficiently powered to exclude a clinically relevant difference in efficacy between the treatment arms. Although the point estimates for the key outcome variables appear similar, the 95% confidence intervals for the between-treatment differences are not presented. Without this information, the reader cannot readily determine how less efficacious the β-lactam combination might be relative to the standard regimen in a worst-case scenario based on the lower bound of the confidence interval [3].

Deciphering the similarity of therapeutic interventions mandates more than comparison of point estimates [4]. Confidence intervals speak to the precision of the estimates and are required for assessing the intrinsic variability in measurements of between-treatment differences (particularly when the sample size is small). Perhaps it is too much to expect as much rigor in an observational study as in randomized control trials [5]. However, the failure to appropriately test a noninferiority (or equivalence) hypothesis erodes confidence in the conclusion. For now, based on the limited available database, I would only routinely recommend an aminoglycoside-sparing double β-lactam regimen to treat Enterococcus faecalis native-valve endocarditis when the causative isolate displays high-level aminoglycoside resistance but is susceptible to ampicillin and/or either nephrotoxicity or ototoxicity is anticipated or becomes evident.

Note
Potential conflicts of interest. M. J. D. is an employee of Merck and owns stock and stock options in the company. Per standard policy, this article underwent formal review by the company. Merck distributes aminoglycoside antibiotics in several markets outside the United States. The opinions expressed herein represent the views of the author and do not necessarily reflect the formal position of Merck.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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