Secondary Outcomes and Peto OR in Meta-analysis

To the Editor:

The recent article in CHEST (June 2014) by Dong et al. on a systematic review and meta-analysis of randomized controlled trials on the use of inhaled corticosteroids in patients with COPD and the risk of TB and influenza was an interesting read. The article summarizes the odds of TB and influenza in patients with COPD exposed to inhaled corticosteroids. The resultant Peto OR of 2.29 is significant (95% CI, 1.04 - 5.03).

Do we need to take the results at face value or with a certain skepticism? The primary outcome of none of the studies included in the meta-analysis was to ascertain the risk of TB and influenza. The sample size calculated for the primary outcome in the selected studies has been used in the present study to answer a question for which the sample size may have been inadequate. The authors have not brought out the rationale addressing this aspect in their article.

The Peto OR was stated to have been used for analyzing OR without continuity correction in view of better CI coverage in rare events. However, the use of Peto OR is subject to the fulfillment of three conditions, viz, a rare event, OR should be close to 1, and both the groups should have similar numbers, out of which only the first condition has been fulfilled by the authors.

Weight of individual studies greatly influences the outcome in meta-analysis. In the present study, for the risk of TB, a study by Calverley et al. has a 76.55% weight, thus influencing the OR.

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Response

To the Editor:

We thank Drs Khera and Ramakrishnan for their attention and comments regarding our recent article. The aim of this study was to conduct a systematic review and meta-analysis of randomized controlled trials to examine the risk of TB and influenza associated with use of inhaled corticosteroids (ICSs) in patients with COPD. As noted in the viewpoints of Drs Khera and Ramakrishnan, trials recruited in our study were primarily designed for efficacy evaluation, and none of them included TB or influenza as a predefined outcome. This may raise the concerns of underdetection or misclassification of TB or influenza cases and reflect inherent challenges of assessing drug safety in clinical trials. However, as per the discussion in our article, given that trial participants were under regular follow-up and close monitoring, trial reports of serious adverse events still potentially provided valuable and complete information on TB case ascertainment. Furthermore, because all of the recruited trials were double-blind, misclassification of TB or influenza cases would be likely to be nondifferential, and the direction of bias may be toward the null.

In our study, we mainly estimated the risk estimates with the Peto OR given that it does not require a continuity correction and has the advantage of providing the best CI coverage when events are rare. To account for the potential imbalance of sample size between treatment groups within trials and inherent limitations that relative statistics are not...
easily defined for trials with zero events, we also applied the Mantel-Haenszel (M-H) and the Bayesian approaches. Each meta-analytic approach yields similar results.

With different meta-analytic methods, weights assigned to individual trials were various in our study, which could prove the robustness of our results and clarify the impacts of influential trials, such as the study by Calverley et al. Based on the pooled M-H risk difference, ICS treatment was still associated with a nonsignificantly increased risk of TB vs non-ICS treatment (M-H risk difference, 0.09%; 95% CI, −0.03%-0.21%), in which the weight of the study by Calverley et al was 27.57%.

Our meta-analysis quantitatively summarized available scientific evidence, which facilitated to provide pooled-risk estimates with better precision as compared with individual recruited trials. We recognize that drug safety assessment using trial data should be performed carefully. A detailed prespecified protocol for study inclusion, evaluation of the risk of bias across studies, and appropriate statistical methods are necessary to offer valid and complementary safety information.

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