Letter to the Editor: From Min Gong et al: "Risk for Infections During Treatment With Denosumab for Osteoporosis: A Systematic Review and Meta-analysis"

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To the editor:

We read with great interest the systematic review by Diker-Cohen et al (1) about the risk of infection under the treatment of denosumab for osteoporosis. This is a well-conducted systematic review that provided us with valuable information about the safety of denosumab. We would like to point out some concerns about the analytic methods used in the systematic review.

We noticed that the main outcome of this systematic review was the serious adverse events of infections (SAEIs), and the authors reported the results measured by risk ratio (RR) and risk difference (RD). The authors claimed that they used RD with the Mantel-Haenszel method to deal with studies with no events in both arms. We totally agree with this. However, for RR, they failed to use a valid method to deal with studies with no events; instead, they discarded such studies in the meta-analysis. This is problematic as such studies generally indicate no difference for treatment effects for balanced trials, and discarding them is expected to result in an overestimate of the effects (2). In their systematic review of SAEI outcome, 9 out of 34 studies had no events in both arms, and 5 of them had balanced sample size in treatment and control arms.

One valid and easy-to-implement method to pool studies with no events in both arms could be the generalized linear mixed model (GLMM) (2). By assigning different random terms for GLMM, we can obtain several models to analyze the data. We used 2 standard GLMMs: the random intercept GLMM (fixed-effect) and the random intercept and slope GLMM (random-effect), both as examples to re-analyze the data (denosumab treatment and risk of SAEI). Our result of fixed-effect model (RR = 1.23; 95% confidence interval [CI], 1.05-1.43; P = .008) was consistent with the Diker-Cohen et al result; however, the random-effect model showed no statistically significant difference (RR = 1.20; 95% CI, 0.76-1.87; P = .44).

Another concern is the reporting of the results. The authors reported the results of RR and RD, however they failed to explain why they choose RR instead of odds ratio (OR) as an effect estimator. We used the same method (fixed-effect based on Mantel-Haenszel) by Diker-Cohen et al while replaced RR as OR in the analysis and again found no statistically significant difference (OR = 1.23; 95% CI, 0.94-1.62; P = .13). Actually, if we used the same method but employed a random-effect model as sensitivity analysis, the results based on RD and RR would also change to statistically insignificant. The reporting of the results seems uninformative and incomprehensive, which may mislead the clinical practice.

Therefore, based on the unstable results by our "sensitivity analysis," we think the conclusion of current systematic review should be treated with caution.

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Abbreviations: CI, confidence interval; GLMM, generalized linear mixed model; OR, odds ratio; RD, risk difference; RR, risk ratio; SAEI, serious adverse events of infection.

Additional Information

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