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Reply to letter to the editor from Dr. Boers re: Rheumatoid arthritis disease activity and hospitalized infection in a large U.S. registry

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To the Editor:

We thank Dr. Boers for his interest and comments [1] on our recently published study evaluating the association between disease activity and hospitalized infection among patients with rheumatoid arthritis in the CorEvitas registry [2]. Dr. Boers raised an important question, and we are pleased to have the opportunity to respond.

As Dr. Boers mentioned, disentangling the independent effects of glucocorticoids (GC) on disease activity and subsequent adverse events is fraught with challenges. For this reason, we used marginal structural models to address the confounding that may blur the indication for glucocorticoid use and downstream effects [3, 4]. This method can account for the time-varying interrelationship between disease activity, RA medication use (including biologics and glucocorticoid dose), and censoring. Marginal structural models incorporate not only current disease activity and glucocorticoid dose, but also previous disease activity and other treatments. While Dr. Boers raises concerns that patients on glucocorticoids may have “hidden” disease activity, incorporating previous disease activity and treatments should help address this concern.

Dr. Boers astutely suggests that there should be a lagged period associated with GC dose, and in fact this is the temporal sequence of how information was captured in the CorEvitas registry and the analysis was conducted. At each visit, both patients and physician were required to document their medication use (including GC dose) prior to the visit and record their disease activity measured at that visit. Serious infections requiring hospitalization were captured using linked Medicare data, occurring after the visit.

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The possibility of introducing an interaction term (GC dose*disease activity) to account for their interdependence was also suggested, but we believe that the interpretation of such an interaction term might be problematic. In particular, since our main independent variable of interest is disease activity, interpreting the main effect in the presence of a significant interaction term would be challenging. Additionally, since the purpose of the current study was to evaluate whether disease activity was associated with hospitalized infection, after introducing an interaction term, the research question would become whether the association between disease activity and infection was different for patients with or without steroid use. Finally, because only 253 patients (<10%) in this analysis used glucocorticoids at a dose of >5–10 mg/day, this interaction term may have been underpowered.

We appreciate the findings from trial that Dr. Boers and his colleagues summarized and contrasted to our work. In GLORIA [5], the relative risk for serious infection in the glucocorticoid users (vs. placebo) was 1.62, almost identical to the risk of 1.61 observed in our study. Several other points of commonality deserve mention. Mean age was 72 years in GLORIA versus 69 years in our analysis; the average patient in the GLORIA trial began in moderate disease activity (mean DAS28 4.4 units); we required all patients at baseline to begin in moderate disease activity (CDAI 10–22). Notably, the rate of serious infections was similar in both studies: GLORIA, 7.3/100 patient years and in our registry-based analysis, 7.9/100 patient years.

We agree with Dr. Boers that randomized clinical trials remain the gold standard for evidence, but it is impractical to randomly assign patients to different disease activity groups and not possible to conduct an RCT to address every clinical question, especially in the setting of rare outcomes as demonstrated by the lack of statistical significance for serious infection in GLORIA. While even advanced causal inference methods such as marginal structural models may be affected by unmeasured confounding, the similar results in our study and in the GLORIA trial lend additional credibility to our work and help justify the ability of rigorous analyses with large datasets to provide information to help guide clinical care.

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LH: is an employee and shareholder of CorEvitas LLC; a consultant to AbbVie, Bristol Myers Squibb and Roche; speakers bureau for Bristol Myers Squibb.

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