Author’s response to reviews

Title: Impact of Tumor Necrosis Factor Inhibitors and Methotrexate on Diabetes Mellitus Among Patients with Inflammatory Arthritis

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Author’s response to reviews:

Dear editorial board,

We would like to thank the reviewers for their thoughtful comments in the review of our manuscript. We have addressed each of the comments in a point-by-point manner below. We hope that we have been able to fully address these concerns.

Reviewer 1

The paper try to determine the role of TNFi, MTX, or metformin in patients with inflammatory arthritis and DM. This is a great idea. The methodology is robust and the strengths and limitations are appropriate. The primary outcome was the absolute change in HbA1c after initiation of a TNFi, MTX, or metformin. But it would be ideal if C-Peptide was included as a secondary outcome. It is also acceptable for publication if such information is not available.

Response: We thank the reviewer for the supportive comments. Unfortunately, we do not have c-peptide in this administrative database. We agree that would be very interesting and something that should be considered in a future study.

Reviewer 2

Thank you for the opportunity to review your paper. It was interesting and well-written. I have the following comments:
1. Abstract

- Is there a reason that the p-values have not been reported in the abstract?

Response: We had not included the p-values in the abstract because we have included the confidence intervals (CI) which provide more information than a p-value. A p-value is by definition not significant if the 95% confidence interval for a beta-coefficient includes zero. The width of the CI provides information about the confidence (or power) around the estimate. However, we have now included the p-values in the abstract.

- I may be missing something, but the abstract states that patients with a diagnosis of DM AND/OR a HbA1c of ≥7% were included while the methods section states that patients with a diagnosis of DM AND a HbA1c of ≥7% were included?

Response: Thank you for raising this discrepancy. We have corrected this in the methods. Patients in the primary analysis were not required to have a diabetes code because they by definition have diabetes based on the HbA1c alone. However, almost all (95%) did in fact have a code for diabetes.

2. What was the mean/median HbA1c at baseline in the DM criteria group vs. the primary analysis group?

Response: Thank you for identifying this omission. We have now added to this to Table 1 and Suppl Table 1.

3. Is there a reason why the primary analysis was not conducted in patients who met "DM criteria" and had an inadequately controlled HbA1c? What proportion of the "DM criteria" patients had a HbA1c that was ≥7%?

Response: As noted above, while the majority of patients with a HbA1c≥7 had a code for diabetes, by definition, they have diabetes so we did not feel it was necessary to separately run the model in those with a code for diabetes. Among those with a code for diabetes, 51% had a HbA1c ≥7 overall. This has now been added to Supplemental Table 1.

4. Is there a reason that baseline PNL was not included as a covariate in the primary analysis as an effect modifier?

Response: Because glucocorticoid use is on the pathway between treatment for the diseases of interest and development of diabetes and can be a cause of diabetes or elevated glucose, adjusting for glucocorticoids would not be appropriate and could influence the results of the model, even inducing a false relationship. We have included this in the limitations: “Accounting for glucocorticoid use is challenging given that it is likely on the causal pathway between treatment and HbA1c values. For this reason, we did not adjust for prednisone use nor account
for prednisone use in time varying models.” Instead of adjusting, we instead ran the model in patients who had not used glucocorticoids during the baseline period and found that the results were similar.

5. "These findings support the concept that modulating inflammation associated with inflammatory arthritis may have off target benefits regardless of the therapy" "This study found no compelling evidence for a difference in the effect between TNFi and MTX, suggesting similar treatment effects."

Response: We agree that there was not a meaningful difference between TNFi and MTX. We meant to suggest that modifying the immune system (through initiation of either TNFi or MTX) may have off target benefits. However, we understand the reviewer’s concern. We have changed this to “These findings potentially support the concept that modulating inflammation associated with inflammatory arthritis may have off target benefits regardless of the therapy. We acknowledge the changes seen in this study were small and were not observed among all patients with diabetes when including patients with normal HbA1cs at baseline. Thus, additional studies are needed to confirm these results.”

- The fact that there was no change in the TNF and MTX groups when those on PNL were excluded, particularly given the high numbers of patients on PNL in the former groups is concerning.

Response: Overall, the estimates in this sensitivity analysis were quite similar. In the final model excluding those with baseline glucocorticoid use, the estimates for TNFi vs MTX and Metformin vs MTX were -0.04 (-0.18, 0.10) and -0.34 (-0.46, -0.22). This is very similar to the primary analysis. The confidence intervals are wider given that 40% of patients were dropped for this analysis.

- The fact that prednisolone use has not been accounted for in the analysis probably warrants highlighting in the abstract + discussion + conclusion, as this would temper the suggestion/the risk of the reader assuming that the effects seen in the TNFi and MTX group are related to TNF/MTX.

Response: This is already mentioned in the limitations of the discussion. We have added this to the abstract, methods and conclusions per the request of the reviewer.

6. Re: supplementary material, table 1: All pts in the Metformin group were already on a baseline drug for their diabetes?

Response: Yes, by definition, patients on metformin were taking it in the baseline period.

7. Was there a consideration re: comparing the MTX and TNF groups to a group of patients with IA and DM that had NO change in their treatment? Were the numbers too small?
Response: This is a challenging study design because it’s less clear when to sample those patients. This is a good point, overall, because it’s possible that there is generally regression to the mean when you have a higher HbA1c. We have added a sentence to the limitations to address this concern: “Similarly, patients with elevated HbA1c may have improved even without a therapy change. We did not examine patients not changing therapy in this study as it was not part of the original study question but may be one way to address the concern for regression to the mean.”

Thank you for considering our manuscript and the enclosed revisions.

Sincerely,

Alexis Ogdie, MD MSCE on behalf of the co-authors