Author's response to reviews

Title:  Insulin Versus Oral Agents in the Management of Cystic Fibrosis Related Diabetes: A Case Based Study

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Editors
BMC Endocrine Diseases

Dear Editors,

This is a re-submission of the manuscript “Insulin versus oral agents in the management of cystic fibrosis related diabetes: a case based study” that has incorporated the revisions suggested by reviewers 1, 2 and 3. I encourage that feedback on this revised manuscript continue to be directed toward the corresponding author at the following address.

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The following involves the point-by-point description of changes that were made. Reviewer 1 made no major compulsory revisions recommendations, rather recommended a rewrite and re-title to “The effect of TZDs and studies of TZDs on respiratory function in CF patients”. After making statistical revisions recommended by Reviewer 3, the editors should find the rewriting of this manuscript is no longer relevant.

The body of the manuscript was reformatted as referenced in the formatting document. As a result of this formatted change some text editing was made.

Specific changes as recommend by the reviewer 2 and 3 were made. Reviewer 2 recommended softening criticism of CF Foundation policy. My original manuscript was written to commend the CF Foundation for developing their treatment guidelines, with the intent to imply that CFF guidelines need to be stringent due to the high prevalence of glucose intolerance associated with CF. I did reward this section using phrasing that was advised by Reviewer 2, and hope this introduction reflects a more positive tone. I further rearranged sections from Methods and Results as guided by Reviewer 2, with the intent of cleaning up overlap between these two sections. The numbers of patients reviewed and their eligibility and exclusion for this study were further clarified. Inclusion of change of weight and details as to weight measurements were further detailed, especially in light of the changes in statistical methods advised by Reviewer 3. Statistical significance was further clarified as recommended by Reviewer 2, by incorporating P values into the Tables. Discussion was further softened as advised by Reviewer 2 such that statements would not infer proof. Minor essential revisions regarding missing labels and errors in use of terms were further addressed from Reviewer 1, 2 and 3 recommendations.

Clarification as to how long patients in the study received treatment as recommended by Reviewer 3 were detailed in the Key to Table 1, where the statement “Rx Course (Yrs), represents the number of years that a patient received consecutive therapy with a specific class of agent,” has been added. The methods section was edited and expanded as recommended by both Reviewers 2 (see above paragraph) and 3. My statistical consultant, Adrienne Stolfie [referenced in the Acknowledgements section of the revised manuscript], stated that non-parametric test would not be the most appropriate method of analysis, as the numbers were less reflective of the best choice of statistical measure, but more related to the comparisons made to the insulin standard of care. She advised that changes/year as appropriately identified by Reviewer 3, were best to be compared between groups with either one-way ANOVA or Welch ANOVA. All data was therefore recalculated using these methods on rates/year outcomes which significantly changed some of the conclusions made in the original manuscript. These changes were rewritten in the appropriate Methods and Discussion sections of this revised manuscript.
The use of a healthier metformin group was further added to the discussion as advised by Reviewer 3. Reviewer 3 additionally recommended BMI rather than weight be used as a baseline statistic; however, my statistical advisor noted that in a population that has reached maximal height, weight would be appropriate to use as a baseline statistic since the height used in calculating BMI becomes a constant. Doses, dose ranges and compliance evaluation of all agents used in this study were added to the Methods section as advised by Reviewer 3. Additionally, minor essential revisions recommended by Reviewer 3 were also made with the attempt to shorten sentences, clarification statements and correct grammar and spelling errors that were missed in the original manuscript and was identified by this reviewer.

The reviewers’ comments were very helpful, and I apologize if this manuscript did not appear tight in the original form. I did have the original document proofed by four other individuals for grammatical corrections prior to making the original submission. I hope reviewers and editors find an improved quality within this revised manuscript and still find merit as stated by Reviewer 2 as “an article of importance in its field” and “The paper deals with an important and unanswered question in cystic fibrosis – what is the optimal treatment for diabetes in these patients?” as stated by Reviewer 3.

I truly agree with all three reviewers that this retrospective review is not the optimal study to prove the utility of using the data reported for these agents. But it is the only data that currently exists for oral agents with anti-inflammatory activity. The experience gained by working through this preliminary study will be of considerable value for the next phase of study that will focus on only one of the anti-inflammatory agents reported in this study in a larger multi-center trial. I do appreciate that the editors consider this as a preliminary report that helps in guiding a larger study design in a multi-center setting to include patient numbers that will provide more statistical power.

Sincerely,

Gary M. Onady MD, PhD
Dayton Adult Cystic Fibrosis Program Director