Author's response to reviews

Title: Use of Case Reports and the Adverse Events Reporting System in Systematic Reviews: Overcoming Barriers to Assess the Link between Crohn's Disease Medications and Hepatosplenic T-Cell Lymphoma

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Author's response to reviews: see over
Author Response to Comments

Manuscript Title: Use of Case Reports and the Adverse Events Reporting System in Systematic Reviews: Assessing the link between Crohn’s Disease Medications and Hepatosplenic T-Cell Lymphoma

We thank the editors and the reviewers for their thoughtful comments on our manuscript. We appreciate the opportunity to revise and resubmit the manuscript.

Below find the reviewer’s comments with responses. All changes in the manuscript are highlighted in yellow.

Sincerely,
Saranya Selvaraj, on behalf of the authors

REVIEWERS’ COMMENTS (SEE BELOW); Authors’ response in bold:

REVIEWER 1:

1. The question posed by the authors of “Use of Case Reports and the Adverse Events Reporting System in Systematic Reviews: Assessing the Link between Crohn’s Disease Medications and Hepatosplenic T-Cell Lymphoma” appears to be new and clearly defined.

2. And I believe that their conclusions about the uneven reporting of data from case reports is consistent with published reports in other medical specialties.

3. I was surprised that there was no references to the work of Jeffrey Aronson who has written extensively on this topic: “The tenets of evidence-based medicine include a hierarchy of evidence with systematic reviews of randomized clinical trials at the top and anecdotes near the bottom. Our observations show that anecdotes can, under the right circumstances, be of high quality and can serve as powerful evidence.” Or Diaz and Neuhauser (Qual Saf Health Care 2005;14:140-3). Have the authors considered Aronson’s extensive work in this area? Particularly in the area of causality assessment. (This point should be addressed in a minor revision by the authors.)

We have reviewed Aronson’s work in this area and have included a reference to his editorial “Anecdotes as Evidence” into our revised discussion, mentioning both his assessment of the quality of case reports and his call for a standardized guideline for case reporting.

4. The method of data extraction and analysis appear to be sufficient and their attention to identify duplicate publications in the FDA AER and the published medical literature.

5. This article is an important contribution to the need for reporting guidelines for case reports so that systematically reported data (e.g. Meaningful Use 2 in the United States) become routinely collected and is available for analysis.
6. I do not have extensive experience using the causality assessment tools they described. I have delved into causality in the area of case reports. (This reference may prove useful to the authors as a background article rather than a specific tool.)

7. I believe that information from the point of care and published case reports will become increasingly used to assess adverse events and this article points out the importance of a checklist for case reports. Case report guidelines will be presented at the Peer Review and Biomedical Publication Congress this fall sponsored by JAMA and the BMJ.

In the conclusion, we have included a sentence stating that our findings support the development and adaptation of case report guidelines, which will be discussed at the next Peer Review and Biomedical Publication Congress.

8. The writing of this article was clear, understandable and balanced.

We thank the reviewer for his interest and suggestions.

REVIEWER 2:

Major Compulsory Revisions

1. I believe that within the substance of this submission, but not properly developed or discussed, is an important message for both clinicians and researchers who access this journal -- the pressing need, within systematic reviews, to consider methods to improve the process of data collection on drug adverse events that would increase the quality of the evidence of harms associated with a given pharmacological therapy – especially for rare, unexpected, and serious/fatal AE’s…… so that, with improved quality of evidence, the risk/harm side of a benefit-risk assessment can properly support a strong recommendation for treatment. Without a major revision of the article’s discussion section to further identify, develop and suggest methods of case report data quality improvement -- the key message to the general reader, I cannot recommend publication of the article as written. The study’s stated result, “Consistent with FDA safety warnings, we confirmed that anti-metabolites, anti-TNFas, and cyclosporine have a possible causal association with HSTCL” is information already well recognized and previously published.

We agree with the reviewer that the call for improved case report quality is a key message of our manuscript, as inconsistent reporting limits case report utility in providing information on rare adverse events for systematic reviews. We thank the reviewer for his suggestions for revising the discussion portion of the manuscript and have revised our title, abstract, discussion, and conclusion section to make sure that this important message is highlighted.

Methods of case report quality improvement that we have suggested in the discussion include the creation of a universal, standardized checklist for case reporting including but not limited to detailed medication dosage and timing information,
dechallenge/rechallenge data, and detailed reporting of confirmatory testing of the adverse event. As many of these elements are important for causality assessment and requested by reporting systems, but inconsistently reported, we also suggest modification of the Adverse Event Reporting System (AERS) so that certain data fields are required to be completed for submission. The presence of a universal checklist will allow journals to encourage similar standards for published case reports. An additional suggestion that we provide in the revised manuscript is that reporters are prompted to provide additional patient history when the suspected adverse event is HSTCL or another malignancy, whether submitting a report to AERS or a journal.

2. Although mentioned rather obliquely in their discussion section, the authors do arrive at this key (poor data quality in case reports) message by reporting almost incidentally as a secondary study finding that the poor quality of the data available to them in case study reports, from both the published literature and the FDA AERS reports … the lack of standardization of data elements necessary for evaluating the association between the HSTCL adverse event and the drug therapies…… prevents adequate assessment of harm or risk. However, this key message is neither reflected in the title of the study or the abstract, nor have the authors developed this insight in the discussion or conclusion sections.

As discussed previously, we agree with the reviewer that this message is a key part of our manuscript and have revised our title, abstract, discussion, and conclusion section to make sure that this important message is emphasized.

3. I do not believe that the study design/methods, a literature review with identification of 37 unique cases of HSTCL in patients with Crohn’s disease and application of causality assessment tools to those cases represents significant new information not already available in published literature to readers. As a stand alone result, without the further development of discussion/conclusions as described above, this case series would not merit approval for publication.

In compiling the case series and applying the causality assessments to the case, we identified numerous deficiencies in the information contained in the case reports. Previous case series have not highlighted these deficiencies. We agree with the reviewer that the unique aspects of our manuscript lie in our exploration of what information is lacking and how these reports can be improved, as well as our suggestions for improved reporting in clinical trials and other observational study designs. In the revised manuscript, we have incorporated the reviewers’ comments to make sure these findings and suggestions for improving case reports are emphasized.

4. I do not believe that the authors use of the Naranjo causality scale and related instruments is generally recognized in 2013 as a preferred method for reaching more certainty about causality for this type of serious/fatal, but rare ADR. As noted in their Chou et al. reference (36), the basis for the AHRQ methodology guide, case reports are considered as hypothesis-generating, or perhaps hypothesis-strengthening, data sources, with more rigorous observational studies used to achieve more certainty of a causal
relationship between drug and adverse outcome. For me, the results described – all three tools generating a “possible” causality score for all treatment drugs - would not merit approval for publication.

We agree with reviewer about limitations of the causality scales, which are substantiated by the “possible” association result using each scale. However, these are the causality scales available at this time. We have explained in our results section the process by which all of the medications received a “possible” association using the causality assessment scales. In the revised discussion, we expand upon ways to improve both case reports and modify causality assessments to make the results more meaningful. As discussed in other parts of the letter, improving the data contained within the case reports will help improve causality assessment.

The causality assessments also proved difficult to apply because of their reliance on rechallenge and dechallenge data, which are not possible to obtain for a fatal adverse event. We suggest that once routine reporting of demographic and medical risk factors is established for adverse events such as fatal malignancies, that causality assessments be modified for use with such events by incorporating questions related to the biology and epidemiology of these malignancies.

5. In an attached document, I have provided a few comments on my perspective on directions that these authors might develop in the discussion section ….. suggestions for improvement in the quality of the data in case series sources that would support future systematic reviews.

We thank the reviewer for his suggestions. In the revised discussion, we have expanded on our suggestions for improving the quality of data in case reports and case series. These suggestions take into consideration the data requested by the MedWatch 3500 forms, the checklist proposed by Aronson in “Anecdotes as Evidence,” and the guidelines for case reports on liver injury available on the NIDDK website. When discussing additional information such as family history, details on past medical history and past medication use that can help identify additional risk factors for HSTCL, we have also suggest that this information be collected as part of the FDA’s existing enhanced safety surveillance efforts.

We also call for reports from clinical trials, observational studies, and registries to provide detailed information on any adverse events and just as importantly, the absence of adverse events of interest. Such an effort will improve the ability to calculate a rate of HSTCL occurrence by medication use.

Minor Essential Revisions
I would only suggest the minor factual correction in the Background section……….”a black box warning was issued in 2006 for the anti-TNFa’s and HSTCL”…………more accurately, I believe, a warning about the observed association between HSTCL and use of Remicade/infliximab was added to the Boxed Warning for Remicade in May 2006.

We have revised the introduction to reflect this correction.

Discretionary Revisions – none
EDITORIAL REQUESTS
Please include a Conclusions section as the last section of the text. This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance.

We have included a brief conclusions section.
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End