Author’s response to reviews

Title: Acute Versus Chronic Methotrexate Poisoning; a Retrospective Study

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Author’s response to reviews:

Dear Editor in Chief:

Thank you for giving us the opportunity to improve our manuscript. We tried to modify our article based on your reviewers’ comments. We hope this new version is acceptable for you. Changes are as follow:

BMC Pharmacology and Toxicology operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Giovanni Tarantino (Reviewer 1): Dealing with a paucity of cases, authors should present detailed data (in a single table) for any patient comprehending age, sex, diagnosis of the basal illness, dose of MTX, period of therapy of MTX before the event and type of event.

RE: We added a new table providing the requested detailed data if available.

Kathleen Job (Reviewer 2):

Abstract:
Page 2 Line 29: The first and second groups have not been defined yet. Consider referring to them as acute and chronic here.

RE: Done

Page 2 Line 26: Are the authors recommending additional treatment?

RE: Recommendation for additional treatments including use of higher leucovorin doses or use of bone marrow stimulants like G-CSF was added to the text.

Introduction:

Page 3 Line 35: Is there a reference to the second to last sentence. Ultimately, will this work be able to suggest more aggressive treatment?

RE: No. We did not find an article confirming our claim. However, managing methotrexate-poisoned patients has shown to us that some patients respond to conservative therapy and follow-up while some other patients need leucovorin (even in high doses) ad G-CSF. This is what we meant to say. We re-phrased our sentence to better show this.

Methods:

Page 4 Line 33: Was the self-made questionnaire filled out as part of standard of care?
RE: No, it was designed at the beginning of this study and was not a part of standard care that patients received. This was added to the text.

Results:

I would recommend including a demographics table. A table showing difference in treatment may also be helpful as this is part of the ultimate conclusions of the manuscript.

RE: Added.

Page 5 Line 19: Please define how total dose was calculated.

RE: In acute toxicities, the total amount was calculated by determination of the number and dose of methotrexate. In chronic toxicities, the dose was calculated by determination of the number of the days and total consumed dose per day. Some of our cases where those who were admitted with vague signs and symptoms, like weakness, and during our work-up we found out that they were using wrong doses of MTX, while patients themselves did not know that they were taking wrong doses. In this case, realizing the exact day from which the patients had started to consume wrong dose (and consequently the ingested dose) was impossible. We were unable to contact
some of our cases to complete and confirm the missing data in their profile. Even when we could contact them, some of them could not remember the duration of their treatment with MTX or the dose that resulted in their toxicity. The MTX toxicity was not only due to consumption of wrong doses but in some cases it was due to the concomitant consumption of other agents like azathioprine. Furthermore, in some other cases it was due to not taking the complementary prescribed medication including folic acid regularly. These reasons made us estimate some of the details and information about our patients like the duration of treatment with MTX based on the patients’ profile.

Page 5 Line 48: This sentence and others may benefit from reorganization. Consider discussing complaints in a similar structure to that in the article with PMID 30146743.

RE: Done.

Discussion:

I would recommend reformatting this section to be what was observed and why the results do or do not align with what is known from the current literature. The Limitations section, particularly the need for better definitions of acute versus chronic methotrexate poisoning, may deserve more attention in the Discussion.

RE: Done.

Conclusion:

The difficulties of differentiating between chronic and acute methotrexate poisoning should be brought up in the discussion, introduction, and/or possibly methods section. I would like a clearer statement on what this work contributes to the field as whole. How do the last two statements fit in to the work described in this manuscript?

RE: Done.

Table 1: I recommend staying consistent and reporting means only. There is an asterisk after pH on the bottom line. I did see further explanation near the table. Please include statistical test information hear and Table 2 as well.

RE: Some variables had normal distribution while some had not. We gave means for those with normal distribution and median for those without it. We insist on giving them

Yours