Author’s response to reviews

Title: Abatacept Induced Granulomatous Hepatitis with a Sarcoidosis-like Reaction: A Blinded Trial in Mice

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To : Benjamin Ragen
Editor
BMC Pharmacology and Toxicology

From : Dr. Sultan Al Mogairen
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Re : Resubmission of manuscript to BMC Pharmacology and Toxicology

Editor Comments:

I am pleased to inform you that it is potentially acceptable for publication in BMC Pharmacology and Toxicology, once you have carried out some essential revisions suggested by our reviewers.

Reply:

Dear Editor

I would like to thank you for your positive comments. Considering your respected suggestions and reviewer’s comments, the manuscript was carefully modified and improved.
Reviewer reports:

Jack Uetrecht (Reviewer 1):

Comment (a):

On the one hand I applaud the authors for treating....

Reply (a):

Dear Dr. Jack

Thank you for your comments.

I agree with you, but in presence of granuloma it is more likely that the liver injury occurs over weeks rather than hours or days. The latent period for drug induced granuloma is two to six weeks and might extends to several months in humans (Iqbal U et al, J Investig Med High Impact Case Rep. 2017; Tong D et al, Intern Med J. 2012).

Comments (b&c):

(On the other hand there are several problems with the study...... it does not appear that this is a model of abatacept liver injury in humans) (The authors should more clearly indicate the contrast between the limited liver injury in humans and the findings of this study).

Reply (b&c):

Thank you for the valuable comment.

So far, no evidence in the literature to indicate that abatacept causes granulomatous hepatitis in humans, but probably because majority of patients with drug induced hepatic granuloma are asymptomatic and 60% of them are reported to have elevated transaminases but did not meet the criteria for liver biopsy. These will indicate the contrast between the limited liver injury in humans discovered by high transaminases and the findings of the current study (Iqbal U et al, J Investig Med High Impact Case Rep. 2017; McMaster KR 3rd and Hennigar GR, Lab Invest. 1981; Yu YC et al, Hepatol Int. 2017). Previous literature does not reflect the magnitude of drug–induced granulomatous hepatic disease and that many cases reported as “granulomatous hepatitis consistent with “sarcoidosis” as well as many “undiagnosed” cases have a drug etiology. There have recently been reports of hepatic granulomas induced by drugs that had not previously been considered to be causal of this condition, and we therefore believe that many more drugs may potentially play a role in the development of hepatic granuloma (Coash M et al, J Formos Med Assoc. 2012; Culver EL et al, Clin Liver Dis. 2016; Abe M et al, J Gastroenterol. 2002).
Discussion has been modified. Please see Discussion, Lines 2-13, para 3, page 9.

Comment (d):
Furthermore, it is possible that because abatacept is an immunosuppressant….. animal facility the results could be different

Reply (d):
Necrotizing granulomas in infectious disease processes often do not respect the architecture of the liver and may destroy adjacent structures. Necrotizing epithelioid granulomas quite frequently have an infectious etiology, and associated with Supportive inflammation. On the other hand necrotizing granuloma rarely induced by drugs. So it is unlikely that hepatic granuloma in Abatacept treated group is due to infection in immunocompromised mice. (Lamps LW, Arch Pathol Lab Med. 2015 )

Discussion has been modified. Please see Discussion, Lines 1-6, para 1, page 10

Comment (e):
It is a shame that when the authors…

Reply (e):
Absolutely I agree with your comments.

It’s unfortunate this happened however this pilot study budget was tight to the degree that we couldn’t do other important tests such as transaminases levels.

Comment (f):
Overall, this work is interesting….

Reply (f):
Thanks for your nice comments and your previous valuable suggestions.
Giovanni Tarantino (Reviewer 2):

Comment:

Interesting research.

Reply:

Dear Dr. Giovanni

Thanks for your positive comment & appreciated.