Reviewer’s report

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

Version: 0 Date: 21 Aug 2018

Reviewer: Jack Uetrecht

Reviewer's report:

On the one hand I applaud the authors for treating the animals for an extended period of time. I see many animal studies that claim to be an animal model of some human idiosyncratic reaction, but the injury in the animals occurs after just a few hours while the injury in humans only occurs after a month or more. On the other hand there are several problems with the study. As far as I know there is no evidence that abatacept causes granulomatous hepatitis in humans. It can cause an increase in ALT in ~1% of patients, but the closest I can find to granulomatous hepatitis is one report of autoimmune hepatitis in humans. Therefore, it does not appear that this is a model of abatacept liver injury in humans. Furthermore, it is possible that because abatacept is an immunosuppressant, the granulomas are caused by a pathogen that has been unmasked by the immunosuppression. If that is the case, if the study were done in another animal facility the results could be different. It is a shame that when the authors did the study they did not determine ALT so that any hepatocyte necrosis could be more readily quantified. It will be more difficult to repeat the study to find out the degree of hepatocyte injury. Overall, this work is interesting but of limited importance. The authors should more clearly indicate the contrast between the limited liver injury in humans and the findings of this study.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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