Reviewer's report

Title: Peroxisome Proliferators-Activated Alpha Agonist Treatment Improves Hepatic Damage in Rats with Obstructive Jaundice: An Experimental Study

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Reviewer: Olivier Barbier

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In this manuscript, Cindoruk and colleagues report that a fenofibrate treatment for 6 days reduces the cholestatic effects of bile duct ligation in rats. They suggest that short-term administration of fenofibrate to bile-duct ligated rats exerts beneficial effects on hepatocellular apoptosis. This is an interesting study reporting significantly novel observations. However, a number of important questions (listed below) may be addressed prior publication.

1) The clinical relevance of this study is unclear. How the observations reported here may be extrapolated to the human situation? Indeed, fibrates, as peroxisome proliferators, have significantly different effects in rodents and humans. Are there any situations in which human patients may profit of such a short-term treatment with fibrates?

2) In accordance with the present study, the beneficial effects of fenofibrate for cholestatic patients with asymptomatic PBC as already been reported (Ohira H et al. Am J Gastroenterol 2002). However, the observation that fenofibrate reduces apoptosis and increases bile duct number in livers of BLD animals is truly original. Nevertheless, the authors do not discuss neither the significance nor the mechanism of the increased number of bile ducts. This is an important issue since this observation is the most original result from this study.

3) While the fenofibrate treatment significantly reduces the serological parameters analysed, most remains drastically high when compared to the Sham control animals. This means that fenofibrate only partially corrects the effects of bile-duct ligation. Do the authors believe that longer exposure to the drugs may further improve the response and restore the liver functions? This should be discussed.

4) The authors state that “decreasing the synthesis of bile acids, and thus affecting the bilirubin levels indirectly” (page 8). There is no reference to support this statement and to the best of our knowledge there are no evidence that the level of bilirubin is directly or indirectly related to bile acid synthesis. Could the authors indicate what the evidences of such a statement are?

5) Fibrates are known to induce bilirubin conjugation with a glucuronide group, the major eliminating pathway for this pigment. Therefore, the authors should discriminate whether the reduction of total bilirubin in fenofibrate-treated animals reflects a reduction of the conjugated or non conjugated bilirubin.

6) The authors indicate that “BLD is associated with intrahepatic bile acid overload”. Did they measure the bile acid content in the liver of BLD and BLD-treated animals? This is required to assess the importance of bile acid reduction as a mediator of the beneficial effects of fenofibrate in their study.

7) A large number of approximations and inconsistencies are found all along the manuscript. This manuscript should be extensively edited, or at least carefully read and corrected by the authors themselves. Below are some examples of the most important discrepancies:
   a. The authors mix the terms apoptosis/necrosis. However, these are 2 different biological processes. They should use the appropriate term in their sentences.
   b. In the last sentence of the introduction, they indicate that they aim at measuring also the effects of fenofibrate on oxidative stress. However, no data are presented for this parameter.
   c. As presented in the discussion the true effects of fibrates on NFkB activity is very confusing. In the 3rd paragraph the authors indicate that “PPARalpha agonists activate NFkB”, while in the 4th one they mention that “anti-inflammatory effects of fibrates on human CRP expression in hepatocytes is based on up-regulation of IkBa resulting in reduced NFkB activity.” This should be clarified.
   d. All along the discussion the author mention that the beneficial effects of fenofibrate are PPARalpha-mediated. However, they cannot exclude the possibility that fenofibrate exert PPARalpha-independent effects. To state that PPARalpha is truly responsible for the change observed the
authors need to compare with similar treatments in KO animals. It would be more appropriate to discuss the
effect of fenofibrate rather than those of the receptor.
e. What is tissue MDA level in table 1? How was it determined?
f. In fig. 2 authors indicate a p value lower than 0.05, while in the corresponding result section, they mention
a p<0.001.
Numerous grammatical and orthography errors have to be corrected.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests