Author’s response to reviews

Title: A Randomized, Controlled, Crossover Pilot Study of Losartan for Pediatric Nonalcoholic Fatty Liver Disease

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Author’s response to reviews:

Reviewer 1:

1) The authors should be more specific in the results section of the abstractly including numbers/percentage to justify their conclusion (as they did in the results section of the manuscript body).

Response: The results section in the abstract was changed to be more specific including percentages.

2) The authors should provide more information about the liver biopsy quality/execution. What was the technique? Mean+SD length and mean+SD number of portal tracts should be reported. Was the pathologist a single reader were there more than one pathologist involved?
Response: In this pilot, patients were included who already had a liver biopsy as part of their past medical history. At our center, the pathologists have created a uniform approach to scoring the clinical biopsies so we were able to use the clinical reports as the inclusion criteria. However, no information on length and portal tracts was routine included in the reports. There was more than one pathologist.

More specific information was added to the methods section about the liver biopsies including the following: “The liver biopsies were obtained during routine clinical care and assessed by one of several hospital pathologists.”

3) Beside transaminases, the researchers should report changes in non-invasive liver fibrosis tests. If no transient elastography or other imaging technique was available, they should include simple fibrosis biomarkers, which have been also validated in the paediatric setting: APRI, FIB-4 (see for example, Yang et al, WJG 2012).

Response: We recently published a validation study of non-invasive markers including APRI and FIB-4 that show no utility of these markers in children. Further, fibrosis is a slowly changing feature of NASH and would not be expected to improve over 8 weeks. This is a helpful suggestion for a future, larger trial.

4) Table 1 showing demographic is quite scarce in terms of information given. Platelets? GGT? Medications the children are on? Coffee and alcohol intake?

Response: We have added more descriptive variables to the table. Coffee intake was not assessed. None of the children consumed alcohol.

5) There is no mention of collecting data about alcohol intake and at what threshold of alcohol intake patients were excluded.

Response: These are young children and do not typically consume alcohol. At the time of clinical diagnosis, alcohol use was an exclusionary criteria.

6) Can the authors provide a flow chart of participants selection with those excluded, even as a supplemental figure?

Response: Yes, this figure has now been added as a supplemental figure.
Comments from Editor

I agree with reviewers suggestions for improvement and would also like additional material for clarification. For Table 1, as there are only 9 subjects, means and SD should be supplemented with median and range.

Response: Yes, additional data was added to table 1 as requested, including medians in variables that are skewed.

Could the results be presented in terms of responder status. Are their values for the outcomes that indicate clinical important response? Then response to intervention and response to placebo could be summarized in terms of positive response to both, response only to intervention, only to placebo or neither.

Response: The ALT is the most important indicator of clinically important response. However, the amount of response that is clinically important (to indicate response) is variable depending on the baseline ALT. The best would be normalization of ALT but that is not expected in a short trial like this. To add this concept to the paper, we added a sentence to the abstract showing the percent that responded to losartan and the percent that responded to placebo. This information is also in the results section.