Author's response to reviews

Title: Bone Growth during Rapamycin Therapy in Young Rats

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Author's response to reviews: see over
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Scott Edmunds, PhD
Senior Editor
BMC-Series Journal
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RE: Revised Version of Manuscript #9764537292074621

Dear Dr. Edmunds:

Attached with this letter is the second revised version of the original manuscript entitled “Bone Growth during Rapamycin Therapy in Young Rats” and the point-by-point answers to the reviewers’ critiques. The revised text is underlined. We would like to thank the reviewers for their careful evaluation of our paper.

Hopefully, this version is acceptable for publication in the open access journal BMC Pediatrics. Thank you for your attention to this matter.

Sincerely,

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ANSWERS TO REVIEWERS’ CRITIQUES:

Reviewer #1:
(1) Page 4, line 4. The changed sentence provided here for this revision is confusing, and should be reworked to indicate clearly the equivalent bone ages in rats versus in children.

This sentence has been revised and underlined.

(2) Page 11, Fig. 2: This figure could be better labeled to reduce confusion between the microscopic effects of rapamycin on collagen II expression (upper left panel), versus on H-4 protein expression (middle left panel), and on mTOR expression (lower left panel), by labeling each panel in larger letters at the top of each panel. For example, the upper left panel would say "Type II collagen expression" written at the top of it and the left middle panel would say "H-4 protein expression", written over the top of it, etc. The same labeling pattern could easily be used with the analytical panels on the right of Fig. 2. Page 11, third paragraph, Fig. 3: The same pattern of labeling as suggested for Fig. 2 could be used to clarify Fig. 3, and also Figs. 4, 5, 6 and 7.

The figures have been labeled.

(3) Page 13, paragraph 3, Fig. 7, lower left panel. These microscopic images, that are said to show a decreased number of TRAP-staining chondro/oosteoclasts in rapamycin-treated animals at 2 and 4 weeks of age, are not convincing, and do not support the numerical, osteoclast count data presented in the lower right panel. In fact the photomicrographs seem to suggest that there are more TRAP-positive osteoclasts in growth plates and metaphyses of the rapamycin-treated rats.

The pictures have been changed and re-checked. Low power is the best way to show the number of TRAP positive chondro/oosteoclasts in the chondro-osseous junction however, the pictures do not show well and quite difficult to differentiate, so we have opted to change the pictures for the different groups. The 2 weeks Control group was mislabeled as 4 weeks Rapamycin.

Reviewer #2:
(1) The statement added to the conclusions in the abstract is not true and should be modified because growth retardation persisted in a similar degree after 4 weeks of rapamycin administration.

This has been revised according to the reviewer’s suggestion.

(2) Femur lengths are reported on Table 1 and in the text of the Results section but the authors do not state in this version of the manuscript that the femurs were extracted from the rats.

The femur length measurements were not included in the manuscript so the values have been removed in the Table as well.

(3) The amount of food ingested by the animals is still missing. This information should be added.

The total amount of food ingested at the time of sacrifice has been included in Table 1 as suggested. There was no significant difference between the 2 weeks and 4 weeks Rapamycin and Control groups.
(4) The authors should comment in the discussion on the limited value of immunohistochemistry and in situ hybridization to accurately estimate quantitative changes in protein and mRNA expression, respectively.

A statement has been included in the Conclusion section of the revised paper.

Reviewer #3:

(1) Anthropomorphic is not the appropriate term. Anthro refers to human.

As suggested, the term has been changed in the Table and text sections.

Reviewer #4:

No comments.