March 10, 2018

Dr. Damián García-Olmo
D**r.** Stephen C Strom
Dr. Andrzej S Tarnawski
Editors-in-Chief, World Journal of Gastroenterology

Dear Drs. García-Olmo, Strom and Tarnawski,

Thank you for the opportunity to revise our manuscript (Manuscript NO: 38048), entitled "**Thiopurines are negatively associated with anthropometric parameters in pediatric Crohn's disease**", for consideration for publication in ***World Journal of Gastroenterology***.

Below, please find a point-by-point response to each of the reviewers.

Reviewer's Code: 03538272
Reviewer's Country: Australia

Critique A

The article is well written and the overall concept of the effect of current therapies on anthropometry is an interesting component of treatment and this research highlights areas where further research is required.

Response A

Thank you

Critique B

Are you able to give further breakdown of disease severity as per the Montreal classification (fistulating and stricturing phenotypes) and account for this in the modeling?

Response B

8 patients (9.8%) developed a stricture and 16 patients (19.5%) developed a fistula. 2 patients (0.02%) developed both a stricture and fistula.

Results did not change when stricturing disease or penetrating disease were included in the adjusted models. We added the description and results of these adjusted analyses to the statistical methods (page 9) and results (page 11), respectively.

We thank the reviewer for the opportunity to discuss this point.

Critique C

Were there any more direct markers of bowel inflammation available such as endoscopic assessment, fecal calprotectin and cross-sectional imaging? Could these be used to support your impression that the findings are due to differences in efficacy of therapies? Serum biomarkers are not as good at correlating with disease activity hence further measurements are needed.

Response C

Although we did not collect results of endoscopic assessment, fecal calprotectin and cross-sectional imaging, we agree that this information would be helpful in supporting our theory that the findings are due to differences in efficacy of therapies and have added discussion about the importance of including these measures in future studies on page 17 (Limitations).

We thank the reviewer for the opportunity to add these points to the manuscript.

Critique D

Can you separate patients who are on anti-TNF with methotrexate or thiopurines as co-immunomodulator therapy from patients treated with monotherapy in the analysis?

Response D

We have added the frequency of monotherapy versus combination therapy to the Results section (page 10). Because of the small numbers in each category, we do not have sufficient power to analyze monotherapy versus combination therapy. We have added discussion about the importance of examining monotherapy versus combination therapy in future studies (page 17).

We thank the reviewer for the opportunity to discuss this point.

Critique E

The associations for infliximab should be presented (even if not significant) at least in the text.

Response E

We thank the reviewer for the opportunity to discuss this point. The associations between infliximab and anthropometric parameter CA z-scores are reported below.

In an unadjusted analysis, for patients on infliximab therapy, mean subscapular skinfold CA z-scores were 0.14 units lower (95% CI= -0.57 to 0.28; p=.50), mean triceps skinfold CA z-scores were 0.23 units lower (95% CI= -0.62 to 0.15; p= .23), mean mid-arm circumference CA z-scores were 0.28 units higher (95% CI = -0.44 to 0.99; p = .44), mean weight CA z-scores were 0.24 units higher (95% CI = -0.32 to 0.80; p = .40), and mean BMI CA z-scores were 0.16 units lower (95% CI = -0.69 to 0.37; p = .55) than patients not on infliximab therapy.

In an adjusted analysis, for patients on infliximab therapy, mean subscapular CA z-scores were 0.13 units lower (95% CI = -0.57 to 0.31; p = .56), mean triceps skinfold CA z-scores were 0.28 units lower (95% CI = -0.68 to 0.12; p = .17), mean mid-arm circumference CA z-scores were 0.18 units higher (95% CI = -0.55 to 0.92; p = .62), mean weight CA z-scores were 0.12 units higher (95% CI = -.42 to 0.66; p = .67), and mean BMI CA z-scores were 0.22 units lower (95% CI = -0.76 to 0.32; p = .42) than patients not on infliximab therapy.

We added the following sentence to page 11:

“Infliximab was not statistically significantly associated with mid-arm circumference, triceps skinfold, subscapular skinfold, weight or BMI CA z-scores (data not shown).”

We will add the detailed results if you prefer. Thank you.

Critique F

How do the authors explain the lack of association between infliximab and anthropometric markers (other than height)?

Response F

The available data on the impact of biologic agents on body composition and growth are conflicting. Some studies suggest biologic agents improve body composition or growth and some studies do not detect any relationship between biologic agents and body composition or growth. In this study, we detected a positive relationship between infliximab and standardized height in girls, but no relationship in boys. We did not detect any relationship between adalimumab and standardized height in boys or girls. Our findings in combination with the existing literature raise an intriguing question: does TNF-α play an important role in compromising body composition in CD males but statural growth in females? It's important to further examine these findings longitudinally, assessing the impact of medications (and trough levels) on change in standardized anthropometric measurements (clarified in Limitations); (please see Discussion/Limitations/Summary and Conclusions).

We thank the reviewer for this question.

Critique G

Are data available on the prior duration of therapy with each medication and correlation with BA/CA z-scores?

Response G

We do not have data available on duration of therapy. We have added the importance of including this information in future studies (page 17). We thank the reviewer for the opportunity to discuss this point in the manuscript.

Critique H

By convention, a $p<.05$ (not $\leq .05$) is considered significant.

Response H

We thank the reviewer for pointing this out. We had made the change accordingly (page 9).

Critique I

Consider removing Table 3 and just using Table 4

Response I

Our rational for including Table 3 is that we believe it is useful for readers to have this information to compare to Table 4 (adjusted analysis) and Table 5 (z scores calculated based on BA rather than CA). We thank the reviewer for the opportunity to discuss this point.

We will remove Table 3 if you prefer that we do.

Critique J

The headings for the tables need to provide further description of the analysis performed, as it can be confusing to readers working out the differences between the tables given that they are all presenting similar data.

Response J

We have attempted to clarify the headings and have added additional detailed footnotes to clarify the results presented in the Tables (Tables 3-7). We thank the reviewer for the opportunity to improve the Tables.

Critique K

Socioeconomic status could potentially confound these results given it affects access to biologic treatment and nutrional status. Is data available on the proportion of patients who are insured/uninsured available or do all patients have equal access to medications.

Response K

We do not have data on socioeconomic status but believe all patients in the study had similar access to medications. We thank the reviewer for this question.

Reviewer's Code: 00004011
Reviewer's Country: Greece

Critique L

Very interesting well written and documented review

Response L

Thank you

Reviewer's Code: 00058695
Reviewer's Country: Denmark

Critique M

With a small number of patients, e.g. a group of n=17, nonparametric statistics is recommended. Thus, such observations are not Gaussian distributed, which is actually a pre-requisite for parametric statistics. Accordingly, the statistical data provided here need to be interpreted with caution

Response M

Choice of parametric vs non-parametric statistical methods depends on actual distribution of the residual, not the sample size. We conducted normality tests for the residual for each regression model we presented in this manuscript. The test for normality supports the validity of using linear regression in our analyses. We thank the reviewer for the opportunity to discuss this point.

Critique N

It might be suggested that severely diseased patients are exposed for long-term thiopurines and in this way it might not be the drug per se, but rather the underlying condition which influence the anthropometric parameters provided. The authors need to make a detailed comment on this matter.

Response N

The relationships between medications and anthropometric parameters may reflect efficacy of medications, side effects of medications, or confounding by indication. Since body

composition measurements were obtained as part of a study protocol and not standard of care, it is unlikely these relationships reflect confounding by indication since these body composition measurements were not available to the care provider. A negative association between thiopurines and anthropometric measurements suggests suboptimal disease control by thiopurines (since anthropometric measurements are markers of disease status/inflammatory burden). Our results suggest methotrexate, infliximab and adalimumab are more effective than thiopurines for treating pediatric CD because these medications are positively associated with specific anthropometric parameters, suggesting more optimal disease control.

Please see Discussion (pages 15-16).

Critique O

Did the authors account for how long time thiopurines or biologics were administrated for the individual patients investigated?

Response O

We do not have data available on duration of therapy. We have added the importance of including this information in future studies (page 17). We thank the reviewer for the opportunity to discuss this point in the manuscript.

Critique N

It is of importance to know whether patients were treated with concomitant thiopurines and infliximab, a combo widely used in adult IBD care.

Response N

We have added the frequency of monotherapy versus combination therapy to the results section (page 10). Because of the small numbers in each category, we do not have sufficient power to analyze monotherapy versus combination therapy. We have added discussion about the importance of examining monotherapy versus combination therapy in future studies (page 17).

We thank the reviewer for the opportunity to discuss this point.

Critique O

It is remarkable that the Results section is very brief (a bit too superficial) of about 1 page with many unadjusted associations stated

Response O

We have expanded the Results section.

Critique P

The Discussion of approximately 5 pages is rather wordy and could easily be shortened by 50% without losing any scientific information.

Response P

We have shortened the Discussion section. We will shorten it further if you prefer.

Critique Q

The data provided are speculative and are not based on validated on a proper statistical basis

Response Q

We conducted normality tests for the residual for each regression model we presented in this manuscript. The test for normality supports the validity of using linear regression in our analyses.

Prospective longitudinal studies are required as a next step to further investigate these findings (please see Discussion/Summary and Conclusions).

We thank the reviewer for the opportunity to discuss these points.

Critique R

The authors should consider giving the manuscript an edit overhaul, so its content became clearer/well-substantiated for the readers.

Response R

We have edited the manuscript. Thank you for the opportunity to do so.

Thank you for your consideration of our manuscript.

Please let us know if we may clarify or add any information.

Sincerely,

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Growth Study Information Sheet: http://goo.gl/tlWffh
Growth Study Information Videos: https://goo.gl/eJZbA2
Alex: Hope for Tomorrow: https://vimeo.com/165915363

Join us for the Sixth Annual Pediatric IBD Research Day at Weill Cornell on Thursday, October 4, 2018 (#PIBDRD18)!