Author’s response to reviews

Title: Effect of imatinib on plasma glucose concentration in subjects with chronic myeloid leukemia and gastrointestinal stromal tumor. A retrospective cohort study

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Author’s response to reviews:

Mexico City, Mexico, August 2018.

Dear

Editorial Team

BMC Endocrine Disorders
Thank you for giving us the opportunity of resubmission after this minor revision. We have tried to amend and improve the paper according to the reviewer’s comments. The point-by-point response to each comment suggested by the reviewers is given on the next page. We hope that the revised version will fulfill the requirements for publication in BMC Endocrine Disorders.

We are looking forward to your response.

Sincerely,

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RESPONSE TO THE REVIEWERS

Reviewer #1.

Comment #1

“It is recommended that the ethnicity of the study group is discussed. It may be that the divergent reported effects of imatinib are due to differences in ethnicity.”

Response:

Thank you for your suggestion. We specify that our subjects were Hispanic and added in the discussion a section where we talk about ethnicity and imatinib response.

“Ethnicity could affect imatinib’s treatment response. Several studies compared the difference of imatinib therapy response between different ethnic groups, but few studies have enough Hispanic subjects to compare against other ethnic groups. Lee et al performed a study with more Hispanic subjects with CML compared to non-Hispanics [60.9% vs 39.1%, respectively], and concluded
that Hispanic subjects achieved better treatment responses to imatinib when compared to non-Hispanic subjects.”

Discussion section, page 13, line 5-11.

Comment #2

2. Some of the T2D patients had normal fasting blood glucose and normal HbA1c before start of imatinib treatment. These patients did not respond to imatinib, which is not very surprising. This should be discussed.

Response:

Thank you for this suggestion. We included a short paragraph explaining the lack of response of T2DM subjects with normal fasting glucose and HbA1c.

“Is important to recall that some of the T2DM subjects had normal FG and normal HbA1c before imatinib treatment. These subjects did not respond to imatinib. This lack of response to imatinib could be due to a low impaired insulin secretion from the β-cells of pancreatic islets and other pathways; thus, acting like normal FG patients.”

Discussion section, page 12, line 15-19.

Comment #3

3. HbA1c should be described statistically and discussed better. It looks like imatinib reduces HbA1c in patients with high starting HbA1c values.

Response:

We included in the results section the statistical analysis of HbA1c between groups, thank you for your recommendation.

“HbA1c decreased from 7.48 (±1.82) to 6.2 (±0.57), with a significant reduction at 1 and 6 months after imatinib treatment (p = 0.040).” Results section, page 11, line 7-9.
“HbA1c reduction indicates that FG was reduced, especially in subjects with high-starting HbA1c values. Imatinib inhibits the phosphorylation of proteins which may result in better signaling, better function of effectors, or both, with improvement in insulin sensitivity; thus, decreasing HbA1c levels in patients with high-starting values. Therefore, we can assume there is a therapeutic benefit in patients with T2DM.”

Discussion section, page 12, line 7-12.

Comment #4

4. Can other metabolic markers (cholesterol, CRP…) be added to the results?

We thank you for this suggestion, but sadly, this study was retrospective and not all patients had all data available.

Comment #5

5. The text needs linguistic revision.

Thank you for your suggestion, linguistic revision was performed.

Reviewer #2.

“This is a small, minor-impact retrospective study of the effects of the tyrosine kinase inhibitor imatinib mesylate on fasting plasma glucose (FPG) levels (and other diabetes associated metrics). The statistical methods employed seem to be appropriate and are well described. The results are discussed appropriately and placed within the context of previous work in this area. The figure is clear and informative. In summary, this is a reasonably well written study on a small patient population that may be of some interest to specialists in the field.”

Comment #1:

“The main issue is the small number of patients included, especially in the subgroup analysis. Otherwise, it is fairly well written, with some minor grammatical errors. Clear meaning is sometimes hampered by assuming that the reader has specific knowledge in this area, and the
appeal could be broadened by including more exposition of the nature of the disease under investigation. The tables are a little unwieldly but otherwise informative.”

Response:

Thank you for your suggestion, we included a brief summary of imatinib effects in fasting plasma glucose concentration.

“We reviewed the pathophysiology of T2DM and several animal and human studies that aimed to establish the mechanism by which imatinib lowers FPG concentration. T2DM derives from the abnormal metabolism of carbohydrates, fats and proteins which leads to hyperglycemia and hyperlipidemia. Within time, high levels of glucose and lipids induce changes in the metabolic pathways of insulin causing impaired insulin secretion from the β-cells of pancreatic islets, insulin resistance and decreased glucose use in peripheral tissues, and abnormal hepatic glucose production. Imatinib has shown to interfere in these pathways”.

Discussion section, page 13, line 12-19.

Dear Reviewers; we want to thank you for your comments on our manuscript. We hope that this new submission fulfills BMC Endocrine Disorders requirements to be published.