

Reply to the reviewer's comments

Manuscript NO: 44654

Title of the paper : **Efficacy of Detoxsan[®] powder on diarrhea caused by gastrointestinal neuroendocrine tumors**

02441744

Conclusion: Minor revision
Scientific Quality: Grade C (Good)
Language Quality: Grade A (Priority publishing)

This is a very interesting manuscript assessing a new product to help control NET induced diarrhoeas. It seems that more studies are needed to get clear conclusions but in any case, what I cannot understand is if a proper diet was recommended to all patients taking this medication or if they could have access to a professional to guide in dosages or continuation rather than making decisions by themselves. Then, you mentioned that all patients had standard treatment but it would be better to be more specific regarding the dose and intervals of either Octreotide or Lanreotide (were the intervals between injections shorter trying to control diarrhoea?). Were those patients using some Loperamide for example or Codeine at the same time to reduce bowel movements?. Were all of them in first line of treatment?, etc. Where the metastases? A Table with all these characteristics would be helpful (may be adding some columns to the table you have included already)

Reply:

Dear reviewer, thank you very much for your helpful remarks. Regarding the diet and medication instructions, all patients included in this study received a consultation by a professional nutritionist during the first admission to our center. Moreover, there is a close, interdisciplinary cooperation between the internal medicine/gastroenterology and surgical department since we are a certified ENETS Center of Excellence. For this purpose we added an additional Table and included 'Nutrition consultation'.

The same comes true for the other remarks like treatments with somatostatin analogs, dosage, metastases etc. Thus, we added a new Table (Table 2) according to the reviewer's recommendation. All patients suffered from diarrhea refractory to standard treatments like loperamide, 19 of 20 patients had been treated with octreotide or lanreotide on 3-6 weeks interval. Furthermore, details of treatment line, localization of the primary tumor and metastasis were added to the patient characteristics in Table 2, too.

02861617

Conclusion: Major revision
Scientific Quality: Grade D (Fair)
Language Quality: Grade A (Priority publishing)

The paper is original and well written and deals with an interesting issue of NETs treatment. I, however, urge the authors to clarify some aspects: 1. The authors report that patients did not respond to standard treatment. I would like to see in Table 1 the dose and schedule of treatment with somatostatin analogues that was employed. This would help discussing about possible refractoriness to Tx. 2. Functional NETs (midgut carcinoid) tend to cause symptoms only if metastatic. The authors should report on disease stage. If they were disease-free after surgery for the primary lesion the diarrhea is most likely NOT due to the syndrome (serotonin). 3. Serotonin dosing in the blood is not a good marker; 24 hours urinary 5HIAA is far better. Comment or data on this. 4. Most patients might have diarrhea due to small intestine bacterial overgrowth which is a common complication of this kind of surgery. Did they receive treatment for this? Please comment and add data.

Reply:

Dear reviewer, thank you very much for your helpful remarks.

1.+2. Patient characteristics were updated according to the aspects you mentioned. All patients included in this study were in stage IV according to WHO 2017 when starting to use Detoxsan, none of them were tumor-free at this timepoint (patterns of metastasis are listed in a new Table, Table 2). 19 of 20 patients had been treated with octreotide or lanreotide with a 3-6 weeks interval prior to Detoxsan, however, a potential overlap to a short bowel syndrome after resection of the primary tumor cannot be entirely ruled out.

3. We commonly follow up patients for restaging as outpatient patients with a commonly long travel time to our center. Urine collections are cumbersome for the patient and impact on their daily activities; they are consequently often poorly performed, leading to over- or under-collection of urine and inaccurate 5-HIAA excretion results. In our experience, serum serotonin monitoring appears much more feasible in daily practice than collecting 24-hours-urine and showed a good correlation between 5HIAA vs. serum serotonin level for long-term follow-up. Nevertheless, we agree that urinary 5HIAA level would be important to follow up as well, since it's the more widely used biomarker and it is the more stable compound in comparison to serotonin.

4. All treatment decisions were supervised by a multidisciplinary board of specialist of internal medicine, surgery, oncology etc., patients with suspicion of a postoperative short bowel syndrome and related complications (like suspicion of small intestine bacterial overgrowth) were referred to our gastroenterology department for supervision. None of the patients included in this study received any antibiotics due to small intestine bacterial overgrowth. Nutritional advices for weight loss or vitamin and mineral deficiencies, were given, e.g. supplementation of vitamin B12 and fat-soluble vitamins, calcium or magnesium. Additionally, dietary restrictions were advised.

00506481 **Conclusion:** Accept (High priority)
 Scientific Quality: Grade A (Excellent)
 Language Quality: Grade A (Priority publishing)

A well conducted pilot study showing interesting findings to be shared with the scientific community

We thank the reviewers again for the valuable suggestions.