ANSWERING REVIEWERS

May 3, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS-2208-edited.doc).

Title: Therapeutic efficacy of baclofen in refractory gastroesophageal reflux-induced chronic cough

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Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer and highlighted in red color in the revised text.

Reviewer 1

(1) dose?
R: We add the dose of baclofen which can be seen in Abstract section, page 2 line 7.

(2) Add-on to what?
R: "to omeprazole" is added to Abstract section, page 2 line 7.

(3) Please define C2
R: We rewrite about C2 which can be seen in Abstract section, page 2 line 17-18.

(4) Please define C5
R: Just the same as (3)

(5) Reference needed
R: We add the reference to the text, page 3 line 21 (Ref 6)

(6) Please define intensified anti-reflux regimen. The patient characteristics need to be much better described. What kind of intensified regimen had they been on previously, and how did they respond? Also, if the cough improves or disappears with intensified regimen, what then is the motivation for looking for alternative therapies?
R: We revise the manuscript according to the reviewer suggestions, which can be seen in Material and Methods section, page 5 line 28- page 6 line 6.

(7) Reflux?
R: We correct the typesetting mistake.

(8) There is no information on when the MII-pH measurement was done, let alone the measurement time. Please provide this information
R: MII-pH was performed prior to the beginning of the anti-reflux therapy. The revision can be seen in Material

and Methods section, page 4 line 26-27.

(9) How was the position of the LES determined?
R: We determined the position of the LES manometrically. The revision can be seen in Material and Methods section, page 5 line 2.

(10) I cannot find any information about the baclofen dose anywhere. Was the dose gradually increased as is most often the case? This information MUST be given.
R: We add the dose of baclofen to the text, which can be seen in Material and Methods section, page 5 line 20-21.

(11) Dose?
R: We add the dose of omeprazole to the text, which can be seen in Material and Methods section, page 5 line 21.

(12) Dose?
R: We add the dose of ranitidine to the text, which can be seen in Material and Methods section, page 6 line 3.

(13) SD? SEM?
R: It is not SD or SEM, but 25%-75% interquartile

(14) Reference required.
R: We add the reference to the text, page 8 line 23 (Ref 24)

(15) This is a misconception. Dog studies have shown that TLESRs can be abolished by higher doses (cite Lehmann et al., Gastroenterology, 1999). However, such high doses cannot be administered to humans due to side-effects. Please modify the discussion and insert the appropriate reference
R: We modify the discussion and insert the appropriate reference. The revision can be seen in Discussion section, page 9 line 9-11 (Ref 31).

(16) Here, it has to be mentioned that in humans, baclofen and the GABAB agonist lesogaberan have consistently been demonstrated to increase basal LES pressure in humans. Please also insert relevant references.
R: We revised the manuscript as the reviewer 1 suggested. The revision can be seen in Discussion section, page 9 line 14-17 (Ref 33).

(17) I don't understand what you mean by this
R: We revised the manuscript as the reviewer 1 suggested. The revision can be seen in Discussion section, page 9 line 23.

(18) This sentence has to be re-written to reflect that fact that the dose of baclofen is gradually increased in clinical practice for the treatment of spasticity.
R: We revise the manuscript as the reviewer 1 suggested. The revision can be seen in Discussion section, page 9 line 24-25.

Reviewer 2

(1) Abstract: What is meant by number of acid reflux in result section ? What is the definition of refractory cough ?
R: We mean that is the number of acid reflux episodes, which can be found in page 2 line 22. Furthermore, the definition of refractory GERC is added to page 2 line 3-4.

(2) Introduction:Authors should clearly define the refractory GER cough. How much time should pass on maximum treatment. What about nocturnal GER induced cough? What is the standard therapy (PPIs twice daily before meals) and adding H2blockers at night.

R: We have clearly defined the refractory GERC and the standard therapy in page 3 line 13-15. However, we did not add H2blockers at night as a standard therapy.

(3) Material and methods: A.Very small sample size. Is there statistical power; B. What is meant by (disappears or improves with the consequent intensified anti-reflux regimen); C. Is there any follow up after stoppage of treatment?

R: A. It is true that sample size was small. However, there is statistical power (56.3% vs 30%, t=2.29. $P<0.05$) even though the total controlled rate for refractory GERC with the effect of placebo is assumed as 30% (Vertigan HK, et al. Thorax 2006; 61: 1065-9), not to mention that the total controlled rate for refractory GERC may be less with the placebo. B. It can be found how to judge disappearance or improvement of cough with the subsequent intensified anti-reflux regimen (Material and Methods section, page 5 line 25- page 6 line 6); C. No patients stop the treatment. In contrast, they are given the lowest maintenance dose of baclofen 20mg daily.

(4) Results: A. In the first paragraph: For the remaining 7 patients withdrawing baclofen (n=4) or resistant to treatment (n=3), cough was resolved by the consequent therapies combining ranitidine with omeprazole in 2 patients or by doubling dose of omeprazole in 5 patients. This means that these patients were not refractory as they were not on maximum antireflux therapy from the beginning. B. In the last paragraph: …. However, The number of acid reflux was higher in the responders than in the non-responders (Z=-2.277, P=0.023). what is meant by acid reflux number (episodes, exposure time , amount,….?)

R: A. We defined refractory GERC as cough due to reflux unresponsive to the standard anti-reflux therapy as recommended by ACCP cough guideline, which did not include doubling dose of omeprazole or combining the ranitidine with the double dose of omeprazole in the usual treatment. Instead, we consider the later two regimen as intensified acid suppression therapy for refractory GERC. B. We mean that is the number of acid reflux episodes, which can be found in the revised part of the manuscript (page 7 line 12).

(5) Discussion: In the paragraph: In addition, proton pump inhibitors are useless for non-acid (weak acid or weak alkaline) reflux. Studies proved some efficacy of PPIs in non acid reflux through reduction of gastric juice

R: We revise it as the reviewer 2 suggested. The revision can be found in page 8 line 14.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology.*

Sincerely yours,

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