POINT-BY-POINT RESPONSE TO THE REVIEWERS' COMMENTS

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Manuscript Number : 88707, Clinical Trials Study

Manuscript Title : Optimized sequential therapy versus 10 and 14-day concomitant therapy for eradicating Helicobacter Pylori: A randomized clinical trial

GENERAL COMMENTS :

My co-authors and I thank you for your time and effort in reviewing our manuscript. The feedback has been invaluable in improving the content and presentation of our paper.
Many thanks to the editorial office as well for the opportunity to address the reviewers' comments and revise the manuscript accordingly.

COMMENTS FROM REVIEWER 1 :

Comment 1 :

For inicial diagnostics authors used morphology and took biopsies according to the recommended Sydney system. Unfortunately they didn't use the OLGA/OLGIM system for description of gastritis, thich would be important.

Response :

Staging of operative link on gastritis assessment (OLGA) and operative link on gastric intestinal metaplasia (OLGIM) systems are important tools for risk assessment of early gastric cancer. Therefore, we agree with you that they should be in included in the conclusion of histology reports, combined with the presence of Helicobacter Pylori. Helicobacter Pylori eradication therapy reduces the incidence of gastric cancer. However, the aim of our study was mainly focused on comparing an optimized sequential therapy with the standard non-bismuth quadruple therapies of 10 and 14 days, in terms of efficacy, incidence of adverse effects (AEs) and cost. That is the reason why we did not include data relative to gastritis in our study.

Comment 2 :

As authors described previous local data: the eradication rate of 10 days therapy was 83%. I'm not sure if it was ethical to prescribe 10-days regimen of therapy in one of the randomised groups. At that period the Maastricht V consensus had recommended the only 14-days regimen.

Response :

We gave considerable thought to prescribing the 10-days regimen. If the optimized sequential therapy was not as efficient as the 14-days quadruple therapy, we wanted to establish whether it was still a better option than the 10-days regimen. All patients included in the study provided a written informed consent before being enrolled in the trial. They were closely monitored, and we had many means to contact them and offer an alternative therapy in case of treatment failure.

Comment 3 :

I would recommend improving statistical analysis. In tables 1 and 2 shown 4 and 3 groups of patients and the only one p-value.

Response :
We are afraid we did not understand your comment and would very much like further clarification. We thank you in advance. Qualitative variables (eradication rates of the three groups) were compared using Chi-square test and Fisher's exact test. Continuous variables were compared between the three groups using one-way ANOVA test.
The eradication rate in the OST-14 group was higher compared to the QT-10 group in the ITT analysis (p=0.04) and in the PP analysis (0.03), however there was no statistically significant difference between the eradication rate of OST-14 and QT-14 groups (in ITT analysis: p=0.34, in PP analysis p=0.35). The treatment tolerance was better in the OST-14 group, with an incidence of AEs of 24.7% compared to 42.7% and 39% in the QT-14 and QT-10 respectively (p=0.03).

Reviewer 2 :
Comment 1 :
In present study, the eradication rates of ITT and PP in the OST-14 group were all higher than those in the OT-14 group. Although there was no significant statistical difference between the two groups, it is recommended to explore the possible mechanisms by which the OST regimen improves efficacy in the discussion section of the article.

Response :
Thank you for pointing this out. We revised the discussion section accordingly.
In fact, the last Maastricht consensus states that switching Omeprazole 20 mg twice daily to Rabeprazole 20 mg bid or Esomeprazole 40 mg bid may increase eradication rate by 8-12% [7]. the advantage of PPIs lies in the fact that the majority of proposed regimens are PH dependent and become less effective when the intragastric PH is low [27], hence the use of higher dose of PPIs and second-generation substances. A possible explanation for the superiority of second-generation PPIs (Rabeprazole and Esomeprazole) can be their metabolism, which is less dependent on CYP2C19 genetic variables and their higher acid inhibition power [28]. A further metanalysis by McNichol et al confirmed that both Esomeprazole and Rabeprazole lead to higher eradication rates compared to first generation PPIs (Omeprazole, Lansoprazole and Pantoprazole) [29]. High doses of PPIs also improve the efficacy of the eradication therapy. In stains resistant to clarithromycin, the eradication rate can be increased using PPI-amoxicillin dual therapy [30].
Comment 2 :
The author mentioned in the article that Vonoprazan can be used instead of PPI to improve the efficacy of Helicobacter pylori eradication. With the increasingly serious issue of antibiotic resistance in Helicobacter pylori, especially the impact of clarithromycin resistance on treatment, whether the author consider exploring the application of Vonoprazan in the treatment of Helicobacter pylori in future study?

Response :
Many studies showed that the use of Vonoprazan increases the Helicobacter Pylori eradication rate. We would very much like to conduct a clinical trial using Vonoprazan. At the time being, it is unfortunately not available in Morocco. In accordance with your suggestion,

we added a reference to Vonoprazan and why we could not include its use in our study. Thank you.