

January 8, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 8046-review.doc).

Title: *Helicobacter pylori* Eradication with Moxifloxacin-Containing Therapy Following Failed First-Line Therapies in Korea.

Author: Kyu Keun Kang, Dong Ho Lee, Dong Hyun Oh, Nayoung Kim, Young Soo Park, Cheol Min Shin, Hyuk Yoon, Hyun Chae Jung

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 8046

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

(1) Reviewer 00503535

a. How about other fluoroquinolon antibiotic based therapy? For example triple therapy with PPI, amoxicillin, and sitafloxacin for one week might be an effective regimen for *H. pylori* as the third- line therapy.

Answer: Thank you for your incisive comments. In case of sitafloxacin, it is not yet available in Korea. In future we are planning to try it. In response to this comment, we added statement about this quinolone to the Discussion as follows (eighth paragraph, line 4-8): "Sitafloxacin also a fluoroquinolone has a low minimum inhibitory concentration, and *H. pylori* demonstrates low resistance to its effects; therefore; it has recently been used in Japan. Triple therapy with sitafloxacin, PPI, and amoxicillin as third-line treatment has demonstrated high eradication rates of approximately 70-90%^[25,26]. However, it is not yet available in Korea."

Added reference is as follows;

25. **Murakami K**, Furuta T, Ando T, Nakajima T, Inui Y, Oshima T, Tomita T, Mabe K, Sasaki M, Saganuma T, Nomura H, Satoh K, Hori S, Inoue S, Tomokane T, Kudo M, Inaba T, Take S, Ohkusa T,

Yamamoto S, Mizuno S, Kamoshida T, Amagai K, Iwamoto J, Miwa J, Kodama M, Okimoto T, Kato M, Asaka M; Japan GAST Study Group. Multi-center randomized controlled study to establish the standard third-line regimen for *Helicobacter pylori* eradication in Japan. *J Gastroenterol*. 2013; **48**:1128-1135 [PMID: 23307042 DOI: 10.1007/s00535-012-0731-8]

26. **Furuta T**, Sugimoto M, Kodaira C, Nishino M, Yamade M, Uotani T, Sahara S, Ichikawa H, Yamada T, Osawa S, Sugimoto K, Watanabe H, Umemura K. Sitafloxacin-based third-line rescue regimens for *Helicobacter pylori* infection in Japan. *J Gastroenterol Hepatol*. 2013 Nov 13. doi: 10.1111/jgh.12442

b. *H. pylori* eradication rate of moxifloxacin triple therapy in peptic ulcer patients was higher than that in non-ulcer patients. Why?

Answer: Thank you for your extremely important advice. We added statement to Discussion as follows (the third paragraph, line 1-8); "The eradication rate in patients with PUD was higher than in the non-ulcer patients in our study. Although strong evidence is lacking to support expectations of higher eradication rates in PUD, there are several hypotheses that may explain greater success in PUD. *H. pylori* strains with high virulence factors were more likely to cause PUD and had a higher eradication rate than those of low virulence. PUD results in moderate to severe inflammation of the antrum, and this may play an important role in the success of *H. pylori* eradication. Inflammation degrades the mucus and epithelial layers and alters the vascular and epithelial permeability; these effects may result in better penetration and delivery of drugs."

Added reference is as follows;

9. **Domingo D**, Alarcón T, Vega AE, García JA, Martínez MJ, López-Brea M. Microbiological factors that influence the eradication of *Helicobacter pylori* in adults and children. *Enferm Infecc Microbiol Clin*. 2002 ;**20**:431-4 [PMID: 12425876]

10. **Gisbert JP**, Marcos S, Gisbert JL, Pajares JM. *Helicobacter pylori* eradication therapy is more effective in peptic ulcer than in non-ulcer dyspepsia. *Eur J Gastroenterol Hepatol*. 2001; **13**:1303-1307 [PMID: 11692055]

c. Misspellings and grammatical errors should be corrected by the native English copyeditors.

Answer: Thank you for your comments. It was done.

d. Figure and table legends should be more precise

Answer: Thank you for your comments. It was done.

e. In the tables 4 and 6, the rates of 95% CI are no inserted

Answer: Thank you for your comments. It was done.

(2) Reviewer 00183445

a. How often the therapy containing-moxifloxacin is used in the treatment of *H. pylori* infection and what is their effectiveness?

Answer: Thank you for your comments. There were no available data about how often moxifloxacin-containing therapy prescribes. However, moxifloxacin prescription rate as rescue treatment in our center was about 50% until 2010. Eradication rate was up to 90% in 2004-2005, but it was decreasing to 79.9% in 2008 because of increasing resistance.

b. Are there certain data available on moxifloxacin first-line therapy?

Answer: Thank you for the kind and accurate advice. The eradication rate of moxifloxacin-containing triple therapy as first-line treatment is from 84.1 to 89%, and it results in a higher eradication rate compared to standard triple therapy. We add this statement to Discussion, fourth paragraph, line 2-5. Added reference is as follows;

11. **Wenzhen Y**, Kehu Y, Bin M, Yumin L, Quanlin G, Donghai W, Lijuan Y. Moxifloxacin-based triple therapy versus clarithromycin-based triple therapy for first-line treatment of *Helicobacter pylori* infection: a meta-analysis of randomized controlled trials. *Intern Med.* 2009; **48**:2069-2076 [PMID: 20009394]

12. **Nista EC**, Candelli M, Zocco MA, Cazzato IA, Cremonini F, Ojetti V, Santoro M, Finizio R, Pignataro G, Cammarota G, Gasbarrini G, Gasbarrini A. Moxifloxacin-based strategies for first-line treatment of *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* 2005; **21**: 1241-1247 [PMID: 15882245 DOI: 10.1111/j.1365-2036.2005.02412.x]

c. Are there data on the scale of *H. pylori* resistance to this antibiotic?

Answer: Thank you for your kind advice. We mentioned in Discussion part that the primary resistance rate to moxifloxacin in 2004 was low (5.6%); however, the rate of resistance dramatically increased to 28.2% over the following 4 years. In recent data, the documented resistance rate was as high as 34.6% in 2009-2012.

(3) Reviewer 00068278

a. Why the authors wanted to see if the first- line treatment regimens affect the response to moxifloxacin-containing triple therapy as a second-line treatment? Do they have a hypothesis?

Answer: Thank you for your comments. As mentioned in Discussion, moxifloxacin-containing triple

therapy has good compliance and simple dose schedule compared with bismuth-containing quadruple therapy as second-line treatment. We added statement to the Introduction as follows (the third paragraph, line 10-13); "In addition, rescue regimens have not been well established after failed sequential and concomitant therapy as first-line treatments, and both regimens included metronidazole, which creates challenges in using bismuth-containing triple therapy as second-line treatment." These reasons were aim to investigate our study.

b. Consolidation of the tables or elimination of the tables (table 3, 4) would not compromise the readability of this manuscript.

Answer: Thank you for this advice which helped us improves our manuscript. We removed table 3 and 4 for avoiding the overlapping messages.

3. References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in black ink, appearing to read "Lee Dong Ho". The signature is fluid and cursive, with the first name "Lee" being the most prominent.

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