July 6, 2015

Dear Professors and Editors:

RE: Manuscript NO. 19423

"One-week and two-week moxifloxacin-containing triple therapies for second-line eradication of *Helicobacter pylori* infection after non-bismuth quadruple sequential and concomitant treatment failure"

Coauthored by Ji Hyun Lim, Seong Tae Lee, Nayoung Kim, Young Soo Park, Cheol Min Shin, and In Sung Song

Thank you very much for giving us an opportunity to revise our manuscript. Accurate and kind comments have proved very useful in revising this paper. The revisions are based on the comments of the reviewers and we respond to them point-by-point. We believe that these comments improved our manuscript and hope that these changes now make this paper acceptable for publication. The changes have been made by changing the color to RED in the revised manuscript, tables and figure legends to avoid any confusion.

I anticipate good response.

Thank you!

Sincerely,

Dong Ho Lee, M.D., Ph.D.

General:

We carefully revised our manuscript according to the guidelines and requirements for manuscript revision (retrospective study) and the editor's suggestions in the edited manuscript file. After that, our manuscript was proofread by the native speakers in a professional institution. Thank you!

Reply to reviewer's Comments

Reviewer 1. (No. 183445) :

Comment to the Author

1. Data on moxifloxacine resistance should be more widely presented in the Discussion.

Answer: Thank you for the kind comment. We are entirely in agreement with your advice. We reviewed and added the references regarding the moxifloxacin resistance associated with moxifloxacin-based regimen and corrected the "Discussion" section (page 11, line 11-23) as follows:

"…The high prevalence of moxifloxacin resistance in our region may explain the lower efficacy observed in our study. Although we did not perform antibiotic susceptibility testing, a recent study of 162 patients from our center (2009–2012) showed that 34.6% of *H. pylori* isolates were resistant to moxifloxacin[27]. This rate was substantially higher than the 18.7% reported by the Taiwanese study described above. The authors reported eradication rates of 92% and 33% for levofloxacin-susceptible and levofloxacin-resistant strains, respectively, by PP analysis. Similarly,

in the study by Liao *et al*.[28], treatment success was remarkably influenced by fluoroquinolone susceptibility. With the levofloxacin-containing triple therapy, the success rate was 97.3% in the susceptible group and 37.5% in the resistant group. A study conducted in our hospital showed borderline significance for the effect of moxifloxacin resistance on eradication failure (P = 0.056)[29]…."

27 Lee JW, Kim N, Kim JM, Nam RH, Chang H, Kim JY, Shin CM, Park YS, Lee DH, Jung HC. Prevalence of primary and secondary antimicrobial resistance of Helicobacter pylori in Korea from 2003 through 2012. *Helicobacter* 2013; **18**(3): 206-214 [PMID: 23241101 DOI: 10.1111/hel.12031]

28 Liao J, Zheng Q, Liang X, Zhang W, Sun Q, Liu W, Xiao S, Graham DY, Lu H. Effect of Fluoroquinolone Resistance on 14-day Levofloxacin Triple and Triple Plus Bismuth Quadruple Therapy. *Helicobacter* 2013; **18**(5): 373-377 [PMID: 23581720]

29 Yoon K, Kim N, Nam RH, Suh JH, Lee S, Kim JM, Lee JY, Kwon YH, Choi YJ, Yoon H. Ultimate eradication rate of Helicobacter pylori after first, second, or third-line therapy in Korea. *J Gastroenterol Hepatol* 2015; **30**(3): 490-495 [PMID: 25363555]

The authors really appreciate the kind and accurate comments. The revision based on these comments made this manuscript more accurate and the quality improved. Thank you again.

Dong Ho lee , M.D., Ph.D.

Ji Hyun Lim, M.D.

Reviewer 2. (No. 503535) :

Comments to the Author

1. As the authors discussed, clarithromycin and moxifloxacin resistant rates were

very important and interesting.

Answer: Thank you for the kind comment. We are entirely in agreement with your opinion. As mentioned above, we additionally stated the resistance data and corrected the "Discussion" section (page 11, line 11-23) as follows:

"…The high prevalence of moxifloxacin resistance in our region may explain the lower efficacy observed in our study. Although we did not perform antibiotic susceptibility testing, a recent study of 162 patients from our center (2009–2012) showed that 34.6% of *H. pylori* isolates were resistant to moxifloxacin[27]. This rate was substantially higher than the 18.7% reported by the Taiwanese study described above. The authors reported eradication rates of 92% and 33% for levofloxacin-susceptible and levofloxacin-resistant strains, respectively, by PP analysis. Similarly, in the study by Liao *et al*.[28], treatment success was remarkably influenced by fluoroquinolone susceptibility. With the levofloxacin-containing triple therapy, the success rate was 97.3% in the susceptible group and 37.5% in the resistant group. A study conducted in our hospital showed borderline significance for the effect of moxifloxacin resistance on eradication failure (P = 0.056)[29]…."

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line therapy in Korea. *J Gastroenterol Hepatol* 2015; **30**(3): 490-495 [PMID: 25363555]

2. Did CYP2C19 genotypic status affect the eradication rates in the first and second line eradication therapies?

Answer: Thank you for your accurate comment. Our study has a limitation that we did not evaluate the CYP2C19 genotype, although, to give some help to our result, we added another references and stated the CYP2C19 genotype data of our center in the "discussion" section (page 11, line 8th from the bottom to page 12, line 5th)

"…Resistance to antibiotics appears to be the most important contributory factor to treatment failure, although *CYP2C19* polymorphism could influence the eradication rate of PPI-based therapy for *H. pylori* eradication. The frequency of the *CYP2C19* polymorphism varies among different ethnic populations. The poor metabolizer genotype is relatively more common in Asians than in Caucasians and African Americans. Although we did not evaluate the *CYP2C19* genotype in our study population, a recent study of 2,202 patients from our center (2003–2013) evaluated the effect of *CYP2C19* genotype on eradication rates[30]. The proportions of extensive metabolizer and poor metabolizer genotypes were 86.0% and 14.0%, respectively. The poor metabolizer genotype was associated with a high eradication rate compared with the extensive metabolizer genotype (86.8% *vs*. 78.2%, P = 0.035). However, the rabeprazole-based regimen used in our study is known to be less affected by the *CYP2C19* polymorphism[31]…."

30 Lee JY, Kim N, Kim MS, Choi YJ, Lee JW, Yoon H, Shin CM, Park YS, Lee DH, Jung HC. Factors affecting first-line triple therapy of Helicobacter pylori including CYP2C19 genotype and antibiotic resistance. *Dig Dis Sci* 2014; **59**(6): 1235-1243 [PMID: 24599773]

31 Kuo C-H, Lu C-Y, Shih H-Y, Liu C-J, Wu M-C, Hu H-M, Hsu W-H, Yu F-J, Wu D-C, Kuo F-C. CYP2C19 polymorphism influences Helicobacter pylori eradication. *World journal of gastroenterology: WJG* 2014; **20**(43): 16029 [PMID: 25473155]

3. Were the eradication rates different among patients with atrophic gastritis, gastric ulcers, and duodenal ulcers?

Answer: Thank you for the accurate comment. The presence of gastric or duodenal ulcer did not influence the eradication rate, though we did not evaluate the effect of atrophic gastritis on the eradication rate. In turn, we corrected the "Abstract" section (page 3, line 19-21), "Result" section(page 9, , line 1st ~ 3rd from the bottom), and "Table 3" as follows:

"…Clinical factors such as age, sex, alcohol and smoking habits, comorbidities, and presence of gastric or duodenal ulcer did not influence the eradication therapy efficacy.…"

"…Clinical factors such as age, sex, alcohol and smoking habits, comorbidities, and presence of gastric or duodenal ulcer did not influence the efficacy of eradication therapy. …"

Clinical factor	No. patients	Eradication rate	P-value
Gastric ulcer			
No	92	64.1%	1.000
Yes	6	66.7%	
Duodenal ulcer			
No	83	63.9%	0.834
Yes	15	66.7%	

The authors really appreciate the kind and accurate comments. The revision based on these comments made this manuscript more accurate and the quality improved. Thank you again.

Dong Ho lee , M.D., Ph.D.

Ji Hyun Lim, M.D.