

Article Type: Original Article

Title: Tailored eradication strategy *versus* concomitant therapy for *Helicobacter pylori* eradication treatment in Korean patients

Running Title: Tailored eradication therapy vs concomitant regimen for *Helicobacter pylori* eradication

Reply to the reviewers' comments

Dear Editor and Reviewers,

I would like to thank the editor and reviewers of *World journal of gastroenterology* for their review of our article.

The reviewers' comments enabled us to revise and improve the manuscript. All changes are summarized below:

Reviewer #1

Original comments of the reviewer	Reply by the author(s)
<p>Comment 1.</p> <p>This article is original in its content, well designed (except for adverse events evaluation), interesting to read.</p> <p><u>In the title I would suggest to delete "a comparative study", because it is easy to understand this is a comparison.</u></p>	<p>Thank you very much for your careful comments.</p> <p>We are willing to revise our title as below.</p> <p><Before revision></p> <p>Title:</p> <p>Tailored eradication strategy versus concomitant therapy for Helicobacter pylori eradication treatment in Korean patients: A comparative study</p> <p><After revision></p> <p>Tailored eradication strategy versus concomitant therapy for Helicobacter pylori eradication treatment in Korean patients</p>

Comment 2.

I believe that **TT and CT should be better defined in the abstract** (eg: a bismuth-containing quadruple combination versus the standard triple regimen).

We sincerely appreciate your valuable comments, and agree reviewer's opinion that definition of TT and CT should be further defined, and are willing to revise our manuscript as below (in red).

<Before revision>

Abstract

BACKGROUND

Antibiotic resistance to *Helicobacter pylori* (*H. pylori*) infection, which ultimately results in eradication failure, has been an emerging issue in the clinical field. Recently, to overcome this problem, an antibiotic sensitivity-based tailored eradication strategy (TT) for *H. pylori* infection has received attention.

AIM

To investigate the efficacy and safety profiles of TT for *H. pylori* infection treatment compared to a concomitant regimen (CT).

METHODS

We included patients (>18 years) with an *H. pylori* infection and without a history of *Helicobacter* eradication who visited the Gil Medical Center between March 2016 and October 2020. After being randomly assigned to either the TT or CT treatment group in 1 to 1 manner, patient compliance, eradication success rate, and patient-reported side effects profiles were assessed and compared between the two groups. *H. pylori* infection was diagnosed using a rapid urease test, Giemsa stain, or dual priming oligonucleotide polymerase chain reaction (DPO-PCR). For the TT group, a DPO-PCR test, which detected A2142G and/or A2143G point mutations, and a clarithromycin resistance test were performed. Patients in the clarithromycin-resistant group were treated with a bismuth-containing quadruple combination therapy, while those with sensitive results were treated with the standard triple regimen.

<After revision>

Abstract

BACKGROUND

Antibiotic resistance to *Helicobacter pylori* (*H. pylori*) infection, which ultimately results in eradication failure, has been an emerging issue in the clinical field. Recently, to overcome this

problem, an antibiotic sensitivity-based tailored eradication strategy (TT) for *H. pylori* infection has received attention.

AIM

To investigate the efficacy and safety profiles of TT for *H. pylori* infection treatment compared to a **non-bismuth quadruple therapy**, concomitant regimen (CT).

METHODS

We included patients (>18 years) with an *H. pylori* infection and without a history of *Helicobacter* eradication who visited the Gil Medical Center between March 2016 and October 2020. After being randomly assigned to either the TT or CT treatment group in 1 to 1 manner, patient compliance, eradication success rate, and patient-reported side effects profiles were assessed and compared between the two groups. *H. pylori* infection was diagnosed using a rapid urease test, Giemsa stain, or dual priming oligonucleotide polymerase chain reaction (DPO-PCR). **Tailored eradication strategy based through the presence of a 23S ribosomal RNA point mutation.** For the TT group, a DPO-PCR test, which detected A2142G and/or A2143G point mutations, and a clarithromycin resistance test were performed. Patients in the clarithromycin-resistant group were treated with a bismuth-containing quadruple combination therapy, while those with sensitive results were treated with the standard triple regimen.

<p>Comment 3.</p> <p>The rest of the abstract is very appropriate. The findings are adequately and appropriately described, highlighting the key points concisely.</p>	<p>Thank you very much for your comments.</p>
<p>Comment 4.</p> <p>I could not confirm the following references (no free text available): 4, 6, 8, 10, 17, 20, 22, 23, 24, 26, 27, 28, 29, 31, 32, 33, 34, 38, 42, 44, 46, 49, 51, 52, 53, 54, 55, 56. Could you please send them for the final revision?</p>	<p>Thank you very much for your review comments.</p> <p>However, we are worried how we could send aforementioned articles to reviewers. Could you let us know your personal e-mail address?</p>

Reviewer #1's comments on world file

<p>Reviwer #1's attached comments</p> <p>1. Abstract session</p>	<p style="text-align: center;"><Pre revised manuscript and reviewer #1's comments(highlighted in yellow)></p> <p>After being randomly assigned to either the TT or CT treatment group in 1 to 1 manner, patient compliance, eradication success rate, and patient-reported side effects profiles were assessed and compared between the two groups. <i>H. pylori</i> infection was diagnosed using a rapid urease test, Giemsa stain, or dual priming oligonucleotide polymerase chain reaction (DPO-PCR).</p> <p><Reviewer's comment></p> <p>In methods you have 1 to 2 manner</p> <p style="text-align: center;">→ Author reply</p> <p>We appreciate your comments. 1:1 manner is right in our study. We should correct method session as below in accordance with Abstract session.</p> <p><After revision> (in red)</p> <p>Method</p>
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	<p><i>Enrolled study population</i></p> <p>We enrolled patients (>18 years) with evidence of an <i>H. pylori</i> infection who were treatment naïve for <i>H. pylori</i> eradication that visited the Gil Medical Center (Incheon, Korea) between March 2016 and October 2020. Exclusion criteria for this study were as follows: 1) patients under 18 years of age; 2) patients with a history of previous eradication; 3) patients with a history of an allergy to any medication used in this study; 4) patients with any operation history regarding the stomach; 5) patients with critical medical history (heart failure [\geq New York Heart Association class II], severe respiratory illness, decompensated liver cirrhosis, terminal stage of malignancy, etc.); 6) patients who could not afford to revisit the hospital for follow-up after medication; and 7) patients who could not take medication orally.</p> <p>Enrolled patients were randomly assigned to either the TT group or the CT group in a 1 to 1 manner and their compliance rates, eradication success rates, and treatment-related side effect rates were assessed (Figure 1).</p>
<p>Reviwer #1's attached comments</p> <p>1. Abstract session</p>	<p><Pre revised manuscript and reviewer #1's comments(highlighted in yellow)></p> <p>RESULTS</p> <p>Of the 217 patients with a treatment naïve <i>H. pylori</i> infection, 110 patients (mean age: 58.66±13.03, men, n=55(50.00%)) were treated with TT, and 107 patients (mean age: 56.67±10.88, men, n=52(48.60%)) were treated with CT. The compliance (TT vs. CT, 100% vs. 98.13%, p=0.30), and</p>

follow-up loss rates (8.18% vs. 9.35%, $p=0.95$) were not significantly different between the groups. The eradication success rate after treatment was also not statistically different between the groups (TT vs. CT, 82.73% vs. 82.24%, $p=0.95$). However, the treatment-related and patient-reported side effects were significantly lower in the TT group than in the CT group (22.77% vs. 50.52%, $p<0.001$).

Reviewer's comment

I would suggest: $n=55$ [50%])

Same thing

→ Author's reply

Thank you very much for reviewer's careful comments.

We are willing to revise our manuscript as reviewer's recommendation.

<After revision> (in red)

RESULTS

Of the 217 patients with a treatment naive *H. pylori* infection, 110 patients (mean age: 58.66 ± 13.03 , men, $n=55$ [50%]) were treated with TT, and 107 patients (mean age: 56.67 ± 10.88 , men, $n=52$ [48.60%]) were treated with CT. The compliance (TT vs. CT, 100% vs. 98.13%, $p=0.30$), and follow-up loss rates (8.18% vs. 9.35%, $p=0.95$) were not significantly different between the groups. The eradication success rate after treatment was also not statistically

	different between the groups (TT vs. CT, 82.73% vs. 82.24%, p=0.95). However, the treatment-related and patient-reported side effects were significantly lower in the TT group than in the CT group (22.77% vs. 50.52%, p<0.001).
Reviwer #1's attached comments 2. Method session	<p style="text-align: center;"><Pre revised manuscript and reviewer #1's comments(highlighted in yellow)></p> <p><Before revision></p> <p>Enrolled study population</p> <p>We enrolled patients (>18 years) with evidence of an <i>H. pylori</i> infection who were treatment naïve for <i>H. pylori</i> eradication that visited the Gil Medical Center (Incheon, Korea) between March 2016 and October 2020. Exclusion criteria for this study were as follows: 1) patients under 18 years of age; 2) patients with a history of previous eradication; 3) patients with a history of an allergy to any medication used in this study; 4) patients with any operation history regarding the stomach; 5) patients with critical medical history (heart failure [≥ New York Heart Association class II], severe respiratory illness, decompensated liver cirrhosis, terminal stage of malignancy, etc.); 6) patients who could not afford to revisit the hospital for follow-up after medication; and 7) patients who could not take medication orally.</p>

Enrolled patients were randomly assigned to either the TT group or the CT group in a 1 to 2 manner and their compliance rates, eradication success rates, and treatment-related side effect rates were assessed (Figure 1).

Reviewer's comment 1)

MALT lymphoma patients were excluded? If so, that should be listed here too. Some of these patients are treated exclusively with antibiotics (those with localized disease and responsive).

I can see now that you put that info in the table only. That should be listed here too.

→ Author's reply:

Thank you very much for your comments. Korean *Helicobacter* guidelines recommend MALToma patients to take *Helicobacter* eradication treatment for their disease remission. In this regard, MALT lymphoma patients who were indicated *Helicobacter* eradication for treating their diseases were enrolled in this study. MALT lymphoma patient was not excluded. Therefore, our opinion is that it is not necessary to emphasize MALToma disease in our study on method session since aim of this study was to focus on the eradication

success rate of CT and TT regimen among patients who were recommended *Helicobacter* eradication , and not focused on efficacies of two regimen in MALToma patients.

Reviewer's comments 2) :

I would replace for “relevant”. This exclusion criteria is based on the author's opinion.

→ Author's reply:

We appreciate reviewer's careful comments. However, the word 'critical' we used in our manuscript did not mean 'important' but 'seriously ill patients' such as 'critical care medicine'. We are willing to revise our term 'critical medical disease' to 'critical medical disease, seriously ill patients'.

Reviewer's comments 3):

Patients in supportive care? : terminal disease or supportive care patients were all not enrolled in our study

→ Author's reply:

: We did not enroll terminal stage of malignancy along with supportive care patients. We are willing to add aforementioned information on our manuscript as below.

Reviewer's comment 4):

In the abstract you have 1 to 1 manner

→ Author's reply

: 1 to 1 manner is right. We are willing to revise our manuscript as below.

<After revision> (in red)

Enrolled study population

We enrolled patients (>18 years) with evidence of an *H. pylori* infection who were treatment naïve for *H. pylori* eradication that visited the Gil Medical Center (Incheon, Korea) between March 2016 and October 2020. Exclusion criteria for this study were as follows: 1) patients under 18 years of age; 2) patients with a history of previous eradication; 3) patients with a history of an allergy to any medication used in this study; 4) patients with any operation history regarding the stomach; 5) **seriously ill patients with critical medical history** (heart failure [\geq New York Heart Association class II], severe respiratory illness, decompensated liver cirrhosis, **terminal or supportive care stage of malignancy**, etc.); 6) patients who could not afford to revisit the hospital for follow-up after medication; and 7) patients who could not take medication orally.

	<p>Enrolled patients were randomly assigned to either the TT group or the CT group in a 1 to 1 manner and their compliance rates, eradication success rates, and treatment-related side effect rates were assessed (Figure 1).</p>
<p>Reviwer #1's attached comments</p> <p>2. Method session</p>	<p><Pre revised manuscript and reviewer #1's comments(highlighted in yellow)></p> <p><i><pre-revision></i></p> <p><i>Follow up strategy, and outcome interpretation (efficacy and safety profiles)</i></p> <p>Four weeks after taking the eradication medication, patients were recommended to visit the Gil Medical Center and undergo the ^{13}C-ure breath test (UBT; UBiTkit; Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) with a cut-off value of delta $^{13}\text{CO}_2 < 2.5\%$ to evaluate eradication success. During this visit, the patients reported treatment-related side effects and drug compliance rates were recorded by the physician.</p> <p><i>Definition for treatment compliance</i></p> <p>Treatment compliance was defined according to the status of the consumption of the prescribed drugs through personal interviews at the follow-up visit. Patients who consumed >80% of the scheduled prescription were classified as having good compliance.</p> <p><i>Statistics</i></p>

Treatment outcomes (efficacy profiles and safety profiles) were analyzed using an ITT analysis and PP analysis. In the ITT analysis, after excluding patients meeting the exclusion criteria, all of the enrolled study population were included. In PP analyses, patients who were lost to follow-up or those with poor compliance (< 80%) were excluded. Categorical variables were analyzed as percentiles and compared between the TT and CT groups using the χ^2 test. Continuous variables are represented as mean \pm standard deviation and were compared between groups using Student's t-test. Statistical significance was set to $P < 0.05$. The Statistical Package for the Social Sciences (SPSS) software (version 22.0; IBM Corp., Armonk, NY, USA) was used for statistical analyses.

Reviewer's comment 1) :

Four weeks after the last treatment day? When was the proton pump inhibitor stopped?
(that can cause false negative results)

→ **Author's reply:** Thank you very much for reviewer's careful comments.
: We should amend our manuscript to "four week after finishing their eradication medication".

Reviewer's comment 2):

Poor information about adverse events reporting. Was there any group of questions to enquire in each patient? When did you consider a complain relevant? According to CTCAE (Common terminology of criteria for adverse events for their events)? If so, above each grade? That must be written.

→ Author's reply

We sincerely appreciate your valuable comments. We followed common terminology of criteria for adverse events for adverse events. We should clearly describe the adverse events during study periods.

Physicians interviewed enrolled patients regarding treatment-related adverse events at follow up. Patients were asked for their treatment-related adverse effects type as both of open-ended, and closed-ended questions. Items for closed-ended questions regarding treatment-related side effect types were as follows: 1) taste disturbance, 2) nausea/vomiting, 3) diarrhea/loose stool/constipation, 4) abdominal discomfort, dyspepsia, 5) general weakness, myalgia, 6) dizziness, head ache, 7) skin rash.

The degree of treatment-related side effect were classified as 'mild', 'moderate', and 'severe'

events according to the degree of tolerance of patients' daily activities as follows: no adverse events; mild (without limitation in daily activities); moderate (partly limited daily activities); and severe (completely limited daily activities). Patients were instructed to visit hospital immediately when any severe adverse events occurred.

Reviewer's comment 3):

Was there any document for patients to take a note every time they took the pill? Was there any other mechanism to confirm the treatment adherence correctly? If not, this was only based on patient's statement...

→ Author's reply

We should describe more clearly on our study design especially the definition of compliance as below.

The compliance level was investigated through patients' self-reported questionnaire, and defined as the consumed, and remained medication pill counts. Degree of compliance was designated as 'good' if more than 80% of prescribed medication was taken by patients.

Reviewer's comment 4) : X2 test-> Chi-square

→ Author's reply : we should amend our manuscript.

Reviewer's comment 5) :Are-> Were. (as in the previous sentence)

→ Author's reply : we should amend our manuscript.

Reviewer's comment 6): P-> Small P (p)

→ Author's reply : we should amend our manuscript.

<After revision>(in red)

Follow up strategy, and outcome interpretation (efficacy)

Four weeks after finishing the eradication medication, patients were recommended to visit the Gil Medical Center and undergo the ^{13}C -ure breath test (UBT; UBiTkit; Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) with a cut-off value of delta $^{13}\text{CO}_2 < 2.5\%$ to

evaluate eradication success. During follow-up visit, the patients' reported treatment-related side effects and drug compliance rates were also recorded by the physician.

Definition for treatment-related adverse events

Physicians interviewed enrolled patients regarding treatment-related adverse events at follow up. Patients were asked for their treatment-related adverse effects type as both of open-ended, and closed-ended questions. Items for closed-ended questions regarding treatment-related side effect types were as follows: 1) taste disturbance, 2) nausea/vomiting, 3) diarrhea/loose stool/constipation, 4) abdominal discomfort, dyspepsia, 5) general weakness, myalgia, 6) dizziness, head ache, 7) skin rash.

The degree of treatment-related side effect were classified as 'mild', 'moderate', and 'severe' events according to the degree of tolerance of patients' daily activities as follows: no adverse events; mild (without limitation in daily activities); moderate (partly limited daily activities); and severe (completely limited daily activities). Patients were instructed to visit hospital immediately when any severe adverse events occurred.

Definition for treatment compliance

Treatment compliance was defined according to the status of the consumption of the prescribed drugs through personal interviews at the follow-up visit. The compliance level was investigated through patients' self-reported questionnaire, and consumed/ remained medication pill counts. Patients who consumed >80% of the scheduled prescription were classified as having good compliance.

Statistics

Treatment outcomes (efficacy profiles and safety profiles) were analyzed using an ITT analysis and PP analysis. In the ITT analysis, after excluding patients meeting the exclusion criteria, all of the enrolled study population were included. In PP analyses, patients who were lost to follow-up or those with poor compliance (< 80%) were excluded. Categorical variables were analyzed as percentiles and compared between the TT and CT groups using the chi-square test. Continuous variables were represented as mean \pm standard deviation and were compared between groups using Student's t-test. Statistical significance was set to $p < 0.05$. The Statistical Package for the Social Sciences (SPSS) software (version 22.0; IBM Corp., Armonk, NY, USA) was used for statistical analyses.

Reviewer #2

Original comments of the reviewer	Reply by the author(s)
<p>Reviewer's comment 1.</p> <p>This is an interesting and well-described study that investigated the efficacy and safety profiles of a tailored therapy (TT; PCR-guided clarithromycin AST) regimen compared to those of concomitant therapy (CT) in patients with treatment-naïve H. pylori infections in Korea, where the clarithromycin resistance rate is high (>15%).</p> <p>While there was no significant difference in the efficacy of the treatments, the safety profile was better for the TT regimen, most</p>	<p>We sincerely appreciate your comments.</p>

likely due to the lower number of antibiotics prescribed.	
<p>Reviewer's comment 2.</p> <p>The authors should <u>provide an explanation for the different treatment durations used in the study.</u></p>	<p>We all appreciate your review and comments.</p> <p>At first, we followed Korean <i>Helicobacter</i> eradication guidelines. In Korea, guidelines recommended CLR based triple regimen with 14 days rather than 10 days. As for bismuth based quadruple regimen, either option is acceptable prescribing 10 days or 14 days. Concomitant regimen is generally prescribed for 10 days in Korea. Therefore we prescribed CLR-based triple regimen for 14days, bismuth based quadruple regimen for 10 days, and concomitant regimen for 10 days.</p> <p>We are willing to add aforementioned information to more clearly describe our study design on method session as below (in red).</p> <p><After revision></p> <p><i>Eradication regimen for TT group, and CT group</i></p> <p>For the TT group, after the DPO-PCR test, patients who were deemed CLR resistant were administered a bismuth-containing quadruple combination (PBMT), and those who were CLR sensitive with a standard triple regimen (PAC) (Figure 1). The bismuth-containing quadruple</p>

	<p>regimen consisted of 30 mg of lansoprazole twice daily + 500 mg MTZ twice daily + 300 mg bismuthate four times daily + 500 mg tetracycline four times daily for 10 days. The PAC regimen consisted of 30 mg lansoprazole + 500 mg CLR + 1000 mg amoxicillin (AMX), administered twice daily for 14 days.</p> <p>The CT regimen consisted of 30 mg lansoprazole twice a day + 1 g AMX twice a day + 500 mg MTZ twice a day + 500 mg CLR twice a day for 10 days.</p>
<p>Reviewer's comment 3.</p> <p><u>They should further discuss the implementation of PCR-guided treatment clinically and whether it is likely that this approach could be recommended for widespread clinical use in Korea considering cost, staff training etc</u></p>	<p>Thank you very much for your comments. We are willing to further discuss the possibility of tailored treatment in <i>Helicobacter pylori</i> infection in real-world clinical practice in Korea as below (in red). We would like to add paragraph and proper references regarding cost problem of tailored therapy in discussion part.</p> <p><After revision> (in red)</p> <p>Recently, to overcome the aforementioned problems of empirically chosen eradication policies, the concept of 'tailored therapy (TT)' has been introduced in the eradication policy for <i>H. pylori</i> infection¹²⁻¹⁸. TT for <i>H. pylori</i> eradication is based on a pre-treatment antibiotic resistance test using stool or stomach biopsy samples^{18,19}. However,</p>

tissue culture based antibiotic resistance testing for *H. pylori* is not ideal in that it is costly, time consuming, and not all of the antibiotics used in the regimen can be tested. Instead, dual priming oligonucleotide polymerase chain reaction (DPO-PCR) has been used²⁰⁻²². DPO-PCR tests are cost effective and less time consuming than tissue culture based tests^{23,24}. However, DPO-PCR test is currently only available for clarithromycin (CLR) resistance testing, as a method for rapid metronidazole (MTZ) resistance testing for *H. pylori* has been invented clinically. However, Korea is a region with high CLR resistance. In fact, the resistance rate has gradually increased, from 22.9% in 2003–2005 to 37.0% in 2007–2009, with the major barriers for *H. pylori* eradication success being CLR resistance, prompting clinical data to be accumulated using DPO-PCR tests in *H. pylori* eradication regimens^{9,25}.

Even efficacy of TT regimen in treating *H. pylori* infection has been evaluated, and proved to be efficacious, cost effectiveness of TT regimen should be evaluated to be widely used in clinical practice in Korea. Tailored regimen needs additional diagnostic procedure of antibiotic resistance test such as DPO-PCR. Even it varies depending on insurance coverages, DPO-PCR costs approximately \$55.24 more than rapid urease test in Korea^[23]. In this regards, several previous studies investigated medical costs of *H. pylori* tailored eradication strategy as compared to empirical first line eradication strategy (CLR based triple regimen) in Korea^[23]. Cho et al. reported that it is acceptable level of predictive additional costs (only an extra \$3.96 per eradicated patient) for tailored *H. pylori* eradication strategy with DPO-CPR as compared to CLR based conventional triple therapy^[23]. In our study, we compared efficacy and safety level of TT vs CT regimen, and

	<p>should discuss the medical cost effectiveness of TT vs CT regimen. However, there has been little data to investigate medical cost of TT strategy as compared to CT regimen. One would say medical cost of TT regimen might be much higher than that of CT regimen, since eradication success rate of empirical CT regimen is generally much higher than empirical CLR based triple regimen. Not just considering each patient's medical cost during <i>Helicobacter</i> eradication, but also given that worrisome issues on increased prevalence of drug resistance bacteria in worldwide, tailored approaches in treating <i>H. pylori</i> infection should be considered following the major principle of antibiotic use guidelines, antibiotic sensitivity result-based treatment.</p>
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Science editor

Original comments of the reviewer	Reply by the author(s)
1 Scientific quality: The manuscript describes a retrospective cohort study of the tailored eradication strategy versus concomitant therapy for <i>Helicobacter pylori</i> eradication treatment in Korean patients.	Thank you very much for your review.
The topic is within the scope of the WJG.	Thank you very much for your review.
(1) Classification: Grade B and Grade B; (2) Summary of the Peer-Review Report: The authors found an interesting and well-described study that investigated the efficacy and safety profiles of a tailored therapy. However, the questions	Thank you very much for your review.

<p>raised by the reviewers should be answered; and (3) Format: There are 4 tables and 1 figure.</p> <p>(4) References: A total of 56 references are cited, including 21 references published in the last 3 years;</p>	
<p>(5) Self-cited references: There is 1 self-cited reference. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and</p>	<p>Since there are only 3 self-cited references (articles in <i>World journal of Gastroenterology</i>: reference number of 18, 40, and 47) in our article, therefore, we think there is no issue on self-cited reference rate.</p> <p>There is the reason why we used each reference in our manuscript as below (in red).</p> <p>18 Ierardi E, Giorgio F, Iannone A, Losurdo G, Principi M, Barone M, Pisani A, Di Leo A. Noninvasive molecular analysis of Helicobacter pylori: Is it time for tailored first-line therapy? <i><u>World J Gastroenterol</u></i> 2017; 23(14): 2453 [PMID: 28465629 DOI: 10.3748/wjg.v23.i14.2453] : This article is regarding tailored therapy which is key concept of our manuscript.</p> <p>40 Kim SJ, <i><u>Chung JW</u></i>, Woo HS, Kim SY, Kim JH, Kim YJ, Kim KO, Kwon KA, Park DK. Two-week bismuth-containing quadruple therapy and concomitant therapy are effective</p>

	<p>first-line treatments for Helicobacter pylori eradication: A prospective open-label randomized trial. World J Gastroenterol 2019; 25(46): 6790-6798 [PMID: 31857780 PMCID: PMC6920663 DOI: 10.3748/wjg.v25.i46.6790]</p> <p>: This article is regarding concomitant treatment, and which is also key concept of our manuscript.</p> <p>47 Choi YI, Chung JW, Park DK, Kim KO, Kwon KA, Kim YJ, Seo JY. Tailored eradication vs empirical bismuth-containing quadruple therapy for first-line Helicobacter pylori eradication: A comparative, open trial. World J Gastroenterol 2019; 25(46): 6743-6751 [PMID: 31857776 PMCID: PMC6920661 DOI: 10.3748/wjg.v25.i46.6743]</p> <p>: This article is regarding tailored treatment, and which is also key concept of our manuscript.</p>
<p>(6) References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer</p>	<p>We did not have been requested any suggestions from peer reviewers to cite their articles.</p>

<p>reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately.</p>	
<p>2 Language evaluation: Classification: Grade B and Grade A. A language editing certificate issued by Editage was provided.</p>	<p>Thank you very much for your review.</p>
<p>3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the STROBE Statement and the Institutional Review Board Approval Form. Written informed consent was waived. No academic misconduct was</p>	<p>Thank you very much your review.</p>

<p>found in the Bing search.</p>	
<p>4 Supplementary comments:</p> <p>This is an unsolicited manuscript. The study was supported by 3 grants. The topic has not previously been published in the WJG.</p>	<p>This is <u>solicited manuscript</u>.</p> <p>Please find attached an email from World Journal of Gastroenterology.</p> <p>This email was sent to our corresponding author, Jun-Won Chung (WJG ID: 03008912). Editorial Board Office <u>accepted our title submission (2021-02-02)</u>, and <u>we submitted our</u> manuscript (this manuscript , manuscript ID: 67692, entitled: <i>Tailored eradication strategy versus concomitant therapy for Helicobacter pylori</i> eradication treatment in Korean patients) on <u>2021-04-29</u>.</p> <p>Therefore, our manuscript is a solicited manuscript from WJG.</p> <p>However, <u>we received an email form WJG on 2021-05-27 that invitation from WJG will withdraw because we did not submit our manuscript on time</u>. We are not able to understand this situation, because we've already submitted our manuscript on 2021-04-29.</p> <p>We are worried that some mistake was happened in this manuscript processing.</p> <p>Please find the history our title submission, and manuscript submission.</p> <hr/> <p>Dear Dr. Chung,</p>

We are very sorry to inform you that we will withdraw our invitation to you to contribute an article to *World Journal of Gastroenterology*, because you failed to submit your manuscript by the due date. We fully understand that you may have many logistical challenges in your professional schedule and therefore cannot fulfill accomplish your promise, and we sincerely hope to have the opportunity to cooperate in the future with your making other contributions to the academic exchanges in our field. The information regarding the manuscript that we invited you to contribute is as follows:

Number ID: 03008912

Publication Name: *World Journal of Gastroenterology*

Author: Jun-Won Chung

Title: Concomitant vs Tailored therapy based on 23S rRNA point mutation in *Helicobacter Pylori* eradication

Abstract:

Manuscript Type: Retrospective Cohort Study

Title Submit Date: 2021-02-02

Title Accepted Date: 2021-02-02

Manuscript Submission Deadline: 2021-04-28

Manuscript Submission Postponed Date:

Invitation Withdrawal Date: 2021-05-27

Best regards,

Lian-Sheng Ma, Founder and Chief Executive Officer

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Online Submission: <https://www.f6publishing.com/>

<https://www.wjgnet.com>

5 Issues raised: (1) The title is too long, and it should be no more than 18 words;	<p>We sincerely appreciate your comments.</p> <p>We are willing to amend our title as below.</p> <p><After revision></p> <p>Tailored eradication strategy <i>versus</i> concomitant therapy for <i>Helicobacter pylori</i> eradication treatment in Korean patients</p>
(2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);	<p>We sincerely appreciate your comments. We are willing to re-upload our approved grant application forms.</p>
(3) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;	<p>We sincerely appreciate your comments. We should have prepared original figure documents, and are willing to resubmit our original figure documents.</p>
(4) PMID and DOI numbers are missing in the reference list.	<p><After revision></p>

Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout; and

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	<p>YW, Kim JJ, Kim SY, Korean College of H, Upper Gastrointestinal R. Nationwide antibiotic resistance mapping of <i>Helicobacter pylori</i> in Korea: A prospective multicenter study. <i>Helicobacter</i> 2019; 24(4): e12592 [PMID: 31111572 DOI: 10.1111/hel.12592]</p> <p>56 Kwon YH, Jeon SW, Nam SY, Lee HS, Park JH. Efficacy of tailored therapy for <i>Helicobacter pylori</i> eradication based on clarithromycin resistance and survey of previous antibiotic exposure: A single-center prospective pilot study. <i>Helicobacter</i> 2019; 24(4): e12585 [PMID: 30969459 DOI: 10.1111/hel.12585]</p>
<p>(5) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text.</p>	<p>Thank you very much for your careful comments.</p> <p>We would like to add paragraph and proper references regarding cost problem of tailored therapy.</p> <p><After revision></p> <p>Article Highlight</p> <p>Research background</p> <p>Antibiotic resistance to <i>Helicobacter pylori</i> (<i>H. pylori</i>) infection has been an emerging issue in the clinical field. Recently, to overcome this problem, an antibiotic sensitivity-based tailored eradication strategy (TT) for <i>H. pylori</i> infection has got attention.</p>

Research motivation

However, there is limited data regarding efficacy of TT strategy in treatment of *H. pylori* infection in Korea as compared to that of concomitant regimen (CT).

Research objectives

To investigate the efficacy and safety profiles of TT for *H. pylori* infection treatment compared to a non-bismuth quadruple therapy, CT.

Research methods

We included treatment naive *H. pylori* infection patients (>18 years) who visited the Gil Medical Center between March 2016 and October 2020. After randomly assigned to either the TT or CT treatment group in 1 to 1 manner, patient compliance, eradication success rate, and patient-reported side effects profiles were compared between the two groups. For the TT group, a DPO-PCR test, which detected A2142G and/or A2143G point mutations, and a clarithromycin resistance test were performed. Patients in the clarithromycin-resistant group were treated with a bismuth-containing quadruple combination therapy, while those with sensitive results were treated with the standard triple regimen.

Research results

Of the 217 patients with a treatment naive *H. pylori* infection, 110 patients (mean age: 58.66±13.03, men, n=55[50%]) were treated with TT, and 107 patients (mean age: 56.67±10.88, men, n=52[48.60%]) were treated with CT. The compliance (TT vs. CT, 100% vs. 98.13%, p=0.30), and follow-up loss rates (8.18% vs. 9.35%, p=0.95) were not significantly different between the groups. The eradication success rate after treatment was also not statistically different between the groups (TT vs. CT, 82.73% vs. 82.24%, p=0.95). However, the treatment-related and patient-reported side effects were significantly lower in the TT group than in the CT group (22.77% vs. 50.52%, p<0.001).

Research conclusions

The DPO-based TT regimen shows promising results in efficacy and safety profiles as a first-line *Helicobacter* eradication regimen in Korea, especially when physicians are confronted with increased antibiotic resistance rates.

Research perspectives

The DPO-based TT regimen might role as a first-line *Helicobacter* eradication regimen with similar efficacy and safety profiles as compared to CT regimen.

Company editor-in-chief

Original comments of the reviewer	Reply by the author(s)
	Thank you very much for your careful review.