

Article Type: Original Article

**Title: Efficacies of a tailored eradication strategy based on the presence of a 23S ribosomal RNA point mutation *versus* empirical bismuth-containing quadruple therapy as first-line eradication for *Helicobacter pylori* infection in Korean patients: A prospective, comparative, open trial**

Running Title: Tailored eradication therapy vs empirical bismuth based quadruple therapy as first line eradication for *Helicobacter pylori*

## **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)	Changes done on page number and line number
<p>The manuscript, 51677, reports the results of comparative studies, conducted with over 150 Hp-positive patients, on the efficacy of TR strategy based on the presence of a 23S ribosomal RNA point mutation that causes CAM resistance with those based on the empirical bismuth-based quadruple therapy (EBQT). The findings revealed that the efficacy of TR was similar to that of</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>Even though there have been limited reports in which tailored regimen vs EBQT regimen were compared in terms of costs effectiveness, cost problem of TR regimen should be evaluated as compared to EBQT design for the first line treatment in helicobacter eradication. Cho et al. reported that a tailored <i>H. pylori</i> eradication strategy based on the presence of a 23S ribosomal RNA point mutation that causes CAM resistance in patients with <i>H. pylori</i> infection is more cost effective than empirical treatment [27]. In this study, different from ours, researchers choose PAC regimen as the empirical treatment. Cho et al demonstrated that the average costs per patient for tailored therapy were \$307.37, and compared with triple therapy, the incremental cost-effectiveness</p>	<p>Whole text</p>

EBQT. However, the side effect profile of TR was significantly better than that of EBQT. Based on the obtained results, it is suggested that TR should be considered as an effective tool in designing therapies for Hp eradication which do not require the use of difficult to comply bismuth-based quadruple therapy.

Obvious concern is that the TR design would increase the costs of treatment.

ratios of tailored therapy were \$3.96 per patient for first-line treatments. Since the failure rate of PAC regimen for helicobacter eradication has been increasing in Korea, the overall medical costs for PAC regimen might over those of EBQT designs, the medical costs issue should be further evaluated.

We would like to add aforementioned paragraph on discussion session as below (in red).

**<After revision>**

## **Discussion**

In this prospective, open-label, comparative study, we compared the efficacies and safety profiles between the TR strategy, based on the presence of a 23S ribosomal RNA point mutation (n = 50), and the EBQT strategy (n = 100) as first-line eradication strategies for *H. pylori* infection in Korea. The efficacy of TR was similar to that of EBQT (96.0% vs. 95.7%,  $P = 0.9$ ), and the side effect profile of TR was significantly better than that of EBQT (12% vs. 43.0%,  $P < 0.001$ ). Given that the eradication rate of the empirical triple regimen (PPI +

AMX + CAM) has decreased to less than 70% in Korea, the DPO-PCR-based TR may be an effective first-line eradication therapy with fewer treatment-related side effects compared to EBQT.

To our knowledge, this is the first study to make a head-to-head comparison of the efficacy and safety level of the TR and EBQT regimens.

In this study, we did not consider PPI-based triple therapy as an eradication option, because the CAM resistance rate has surpassed 15% in Korea, and the efficacy of empirical triple therapy is minimal. The latest version of the Korean Clinical Practice Guidelines for *H. pylori* recommend either triple therapy with a PPI, AMX, and CAM, or a bismuth-based quadruple regimen if CAM resistance is suspected. In addition, several reports suggest that 9.6% of the strains in Korea have dual resistance to CAM and MTZ<sup>[20, 22, 23]</sup>; thus, it may be prudent to avoid choosing an empirical conventional triple regimen as a first-line eradication strategy. Therefore, we did not choose the triple regimen in this study.

	<p>Both the Maastricht V/Florence and Korean guidelines recommend bismuth-based quadruple therapy as the policy for failed first-line therapy, or even as an option for first-line therapy. However, several reports have indicated treatment-related side effects of bismuth quadruple therapy, which may directly lead to poor patient compliance. Given that treatment-related side effects might lead to treatment failure, and imperfect eradication is closely associated with increased antibiotic resistance, treatment-related side effects are important factors when considering <i>H. pylori</i> treatment. A multicenter study from Italy, where CAM resistance rates are above 15%, reported that 46.6% of patients who received bismuth-based quadruple therapy complained of at least one side effect, including nausea, diarrhea, and vomiting, among 209 patients<sup>[7]</sup>, which was similar to the rate observed in the present study. Daniela et al. conducted a randomized control trial in Israel, where CAM resistance rates are increasing, and the patients who took the bismuth-containing regimen reported significantly more treatment-related complications (84.0%),</p>	
--	---	--

such as gastrointestinal discomfort, with less compliance<sup>[24]</sup>. Although there has been a wide range of complication rates for bismuth-containing quadruple therapy, the complication rates are not negligible, which can lead to poor compliance.

In addition to the treatment-related complications of the bismuth-based quadruple regimen, too many antibiotics have been used to eradicate *H. pylori*. Because the empirical bismuth-based quadruple regimen includes MTZ and tetracycline, and inappropriate antibiotic use leads to antibiotic resistance, antibiotics should be prescribed more carefully in Korea considering the high CAM (>5%), and MTZ (>30%) resistance rates. As *H. pylori* culture and antibiotic sensitivity testing is not always available in a clinical setting, DPO-PCR-based tailored therapy is a realistic option for eradication in a region with increasing antibiotic resistance.

Several studies have indicated favorable outcomes of DPO-PCR-based tailored therapies in line with our results, even though there are no published

comparisons between tailored therapy and bismuth-based quadruple therapy<sup>[15, 16]</sup>. Zhou et al. reported that tailored therapy achieved significantly higher eradication rates (88.7% vs. 78.3%) and fewer side effects (22.0% vs. 31.7%) than a concomitant therapy<sup>[25]</sup>.

Park et al. reported that personalized tailored therapy based on 23S rRNA genotypes can increase eradication success rates in patients with *H. pylori* infection compared to empirical CAM-based triple therapy, as the 2143G point mutation in the 23S rRNA of *H. pylori* was found to be an independent risk factor for eradication failure in CAM-based triple therapy<sup>[26]</sup>. Furthermore, Cho et al. reported that a tailored *H. pylori* eradication strategy based on the presence of a 23S ribosomal RNA point mutation that causes CAM resistance in patients with *H. pylori* infection is more cost effective than empirical treatment<sup>[27]</sup>. Kim et al. also conducted an economic modeling study comparing TR based on DPO-PCR and empirical treatment.

**Even though there have been limited reports in which tailored regimen**

vs EBQT regimen were compared in terms of costs effectiveness, cost problem of TR regimen should be evaluated as compared to EBQT design for the first line treatment in helicobacter eradication. Cho et al. reported that a tailored *H. pylori* eradication strategy based on the presence of a 23S ribosomal RNA point mutation that causes CAM resistance in patients with *H. pylori* infection is more cost effective than empirical treatment [27]. In this study, different from ours, researchers choose PAC regimen as the empirical treatment[27]. Cho et al demonstrated that the average costs per patient for tailored therapy were \$307.37, and compared with triple therapy, the incremental cost-effectiveness ratios of tailored therapy were \$3.96 per patient for first-line treatments[27]. Since the failure rate of PAC regimen for helicobacter eradication has been increasing in Korea, the overall medical costs for PAC regimen might over those of EBQT designs, the medical costs issue should be further evaluated.

Apart from medical cost problem of TR regimen, given that issues on increased prevalence of drug resistance helicobacter infection in worldwide,



**tailored approaches in treating *H. pylori* infection should be considered further.**

The possible reasons for treatment failure in their TR group are as follows [28, 29]. First, although *H. pylori* has traditionally been regarded as a homogenous organism, there is increasing evidence that populations of *H. pylori* in humans show wide diversity<sup>[29]</sup>. The quasi-species development of *H. pylori* in a single host might result in treatment failure even after a tailored eradication strategy based on the presence of a 23S ribosomal RNA point mutation<sup>[28]</sup>. Second, a DPO-PCR-based evaluation is limited to detecting mutations in A2142G or A2143G on 23S rRNA, and other mutations, such as the A2144G or A2142C genes in *H. pylori*, cannot be detected<sup>[20, 30]</sup>.

This study had several limitations. First, because of the relatively small sample size, the results of this study should be interpreted cautiously. A further, larger sample-sized, randomized trial should be conducted to verify our results. Second, as this study was conducted at the GMC, a tertiary center

in Korea, it may have been subject to selection bias. Third, we did not culture the *H. pylori* of enrolled patients for antibiotic sensitivity testing, but DPO-PCR was performed for CAM.

In conclusion, this study showed that TR is a first-line eradication regimen with non-inferior efficacy and a favorable safety profile compared to bismuth-based quadruple therapy. A future eradication regimen could potentially be designed based on these results for areas where CAM resistance rates are increasing.

## Reviewer #2

Original comments of the reviewer	Reply by the author(s)	Changes done on page number and line number
<p><i>Helicobacter pylori</i> infection is increasingly difficult to treat mainly due to antibiotic resistance, especially to clarithromycin resistance.</p> <p>The authors have compared the efficacies, safety profiles, and compliance rates between a TR strategy based on the presence of a 23S ribosomal RNA point mutation and the empirical bismuth-based quadruple</p>	<p>Thank you very much for your careful comments.</p> <p>According to Korean <i>H. pylori</i> management guidelines, either 7 days or 14 days PAC regimen are acceptable. In our study, in tailored group, 36 patients received PAC regimen and 17 patients were allocated to 7day regimen and 19 patients to 14 day regimen. It is also randomly assigned. No any patient with either 7 day PAC regimen or 14 day PAC regimen showed adverse events.</p> <p>We would like to add aforementioned sentences in method session.</p> <p><b>&lt;After revision&gt;</b>  <b>Eradication regimens for <i>Helicobacter</i></b></p> <p>The PAC regimen consisted of 30 mg lansoprazole + 500 mg CAM + 1,000 mg AMX, administered twice daily for 7 or 14 days. <b>PAC regimen with 7-day or 14-day regimen was randomly allocated.</b></p>	<p>Whole text</p>

<p>therapy (EBQT) as first-line eradication for H. pylori infection in Korean patients. They found the first-line eradication rate did not statistically differ between the two groups. However, the rate of side effects was significantly lower in TR than EBQT strategy. Although the sample size of this study was not big, but it can suggest that the TR strategy is worth further exploring. There are some problems: <b><u>1. About the eradication regimens:</u></b> <b><u>"The PAC regimen consisted of 30 mg</u></b></p>	<p>The EBQT regimen consisted of 30 mg lansoprazole twice daily + 500 mg MYZ twice daily + 300 mg bismuthate four times daily + 500 mg tetracycline four times daily for 14 days.</p>	
---	---	--

<p><u>lansoprazole + 500 mg</u>  <u>CAM + 1,000 mg AMX,</u>  <u>administered twice daily</u>  <u>for 7 or 14 days.” How to</u>  <u>determine whether the</u>  <u>course of treatment is 7</u>  <u>days or 14 days?</u></p>		
<p>2. How many patients who reported adverse events were treated with the BQT regimen or with the PAC regimen in RT group, respectively?</p>	<p>Thank you very much for your comments</p> <p>In tailored group, 36 patients were treated with the PAC regimen and 14 patients with BQT regimen. No patients with PAC regimen in tailored group reported adverse events. Two patients with BQT regimen in tailored group showed eradication related adverse events.</p> <p>We are willing to add aforementioned sentences on the result session as below (in red).</p> <p><b>&lt;After revision&gt;</b></p> <p><b>Result</b></p> <p><b>Treatment related adverse events</b></p>	

	<p>In ITT analysis, total of 154 <i>H. pylori</i> infection patients, 12.0% (6/50) of the TR recipients and 43.7% (45/104) of those treated with EBQT reported at least one adverse event during eradication therapy. In tailored group, 36 patients were treated with the PAC regimen and 14 patients with BQT regimen. <b>In tailored group, no patients with PAC regimen (0/36) reported adverse events and two patients with BQT regimen (2/14) showed eradication related adverse events.</b> EBQT exhibited statistically significantly higher frequencies of overall adverse events than TR group (43.7% vs 12.0%; <math>P = &lt;0.01</math>) (Table2).</p>	
<p>3. In paragraph 1 of the discussion section: “In this prospective, open-label, comparative study, we compared the efficacies and safety profiles between the TR strategy, based on the presence of a 23S ribosomal RNA point mutation (n = 100), and the EBQT strategy (n = 50) as</p>	<p>We appreciate your careful comments</p> <p>We are willing to revise our manuscript as bellows (in red).</p> <p><b>&lt;After revision&gt;</b></p> <p><b>Discussion</b></p> <p><b>In this prospective, open-label, comparative study, we compared the efficacies and safety profiles between the TR strategy, based on the presence of a 23S ribosomal RNA point mutation (n = 50), and the EBQT strategy (n = 100) as first-line eradication strategies for <i>H. pylori</i> infection in Korea.</b></p>	

first-line eradication strategies for H. pylori infection in Korea.” <b>Whether the numbers are right ? The word “stratefy” is misspelled?</b>		
---	--	--

## Reviewer #3

Original comments of the reviewer	Reply by the author(s)	Changes done on page number and line number
<p>The authors have written an important paper regarding treatment of HP infection. They show that treatment based on the detection of 23S rRNA mutations improves the success rate of HP eradication on a older regimen with less side-effects. The authors address the small sample number and the limitation to a specific population. The study is well</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>Even though there have been limited reports in which tailored regimen vs EBQT regimen were compared in terms of costs effectiveness, cost problem of TR regimen should be evaluated as compared to EBQT design for the first line treatment in helicobacter eradication. Cho et al. reported that a tailored <i>H. pylori</i> eradication strategy based on the presence of a 23S ribosomal RNA point mutation that causes CAM resistance in patients with <i>H. pylori</i> infection is more cost effective than empirical treatment [27]. In this study, different from ours, researchers choose PAC regimen as the empirical treatment. Cho et al demonstrated that the average costs per patient for tailored therapy were \$307.37, and compared with triple therapy, the incremental cost-effectiveness</p>	<p>Whole text</p>



<p>conceived and the methodology is robust. <b>My only comment is that I think there should be a discussion of the cost effectiveness of this approach. Ultimately this will have an effect on its adoption.</b></p>	<p>ratios of tailored therapy were \$3.96 per patient for first-line treatments. Since the failure rate of PAC regimen for helicobacter eradication has been increasing in Korea, the overall medical costs for PAC regimen might over those of EBQT designs, the medical costs issue should be further evaluated.</p> <p>We would like to add aforementioned paragraph on discussion session as below (in red).</p> <p><b>&lt;After revision&gt;</b></p> <p><b>Discussion</b></p> <p>In this prospective, open-label, comparative study, we compared the efficacies and safety profiles between the TR strategy, based on the presence of a 23S ribosomal RNA point mutation (n = 50), and the EBQT strategy (n = 100) as first-line eradication strategies for <i>H. pylori</i> infection in Korea. The efficacy of TR was similar to that of EBQT (96.0% vs. 95.7%, <math>P = 0.9</math>), and the side effect profile of TR was significantly better than that of EBQT (12% vs. 43.0%, <math>P &lt; 0.001</math>). Given that the eradication rate of the empirical triple regimen (PPI +</p>	
--	---	--

AMX + CAM) has decreased to less than 70% in Korea, the DPO-PCR-based TR may be an effective first-line eradication therapy with fewer treatment-related side effects compared to EBQT.

To our knowledge, this is the first study to make a head-to-head comparison of the efficacy and safety level of the TR and EBQT regimens.

In this study, we did not consider PPI-based triple therapy as an eradication option, because the CAM resistance rate has surpassed 15% in Korea, and the efficacy of empirical triple therapy is minimal. The latest version of the Korean Clinical Practice Guidelines for *H. pylori* recommend either triple therapy with a PPI, AMX, and CAM, or a bismuth-based quadruple regimen if CAM resistance is suspected. In addition, several reports suggest that 9.6% of the strains in Korea have dual resistance to CAM and MTZ<sup>[20, 22, 23]</sup>; thus, it may be prudent to avoid choosing an empirical conventional triple regimen as a first-line eradication strategy. Therefore, we did not choose the triple regimen in this study.

	<p>Both the Maastricht V/Florence and Korean guidelines recommend bismuth-based quadruple therapy as the policy for failed first-line therapy, or even as an option for first-line therapy. However, several reports have indicated treatment-related side effects of bismuth quadruple therapy, which may directly lead to poor patient compliance. Given that treatment-related side effects might lead to treatment failure, and imperfect eradication is closely associated with increased antibiotic resistance, treatment-related side effects are important factors when considering <i>H. pylori</i> treatment. A multicenter study from Italy, where CAM resistance rates are above 15%, reported that 46.6% of patients who received bismuth-based quadruple therapy complained of at least one side effect, including nausea, diarrhea, and vomiting, among 209 patients<sup>[7]</sup>, which was similar to the rate observed in the present study. Daniela et al. conducted a randomized control trial in Israel, where CAM resistance rates are increasing, and the patients who took the bismuth-containing regimen reported significantly more treatment-related complications (84.0%),</p>	
--	---	--

such as gastrointestinal discomfort, with less compliance<sup>[24]</sup>. Although there has been a wide range of complication rates for bismuth-containing quadruple therapy, the complication rates are not negligible, which can lead to poor compliance.

In addition to the treatment-related complications of the bismuth-based quadruple regimen, too many antibiotics have been used to eradicate *H. pylori*. Because the empirical bismuth-based quadruple regimen includes MTZ and tetracycline, and inappropriate antibiotic use leads to antibiotic resistance, antibiotics should be prescribed more carefully in Korea considering the high CAM (>5%), and MTZ (>30%) resistance rates. As *H. pylori* culture and antibiotic sensitivity testing is not always available in a clinical setting, DPO-PCR-based tailored therapy is a realistic option for eradication in a region with increasing antibiotic resistance.

Several studies have indicated favorable outcomes of DPO-PCR-based tailored therapies in line with our results, even though there are no published

comparisons between tailored therapy and bismuth-based quadruple therapy<sup>[15, 16]</sup>. Zhou et al. reported that tailored therapy achieved significantly higher eradication rates (88.7% vs. 78.3%) and fewer side effects (22.0% vs. 31.7%) than a concomitant therapy<sup>[25]</sup>.

Park et al. reported that personalized tailored therapy based on 23S rRNA genotypes can increase eradication success rates in patients with *H. pylori* infection compared to empirical CAM-based triple therapy, as the 2143G point mutation in the 23S rRNA of *H. pylori* was found to be an independent risk factor for eradication failure in CAM-based triple therapy<sup>[26]</sup>. Furthermore, Cho et al. reported that a tailored *H. pylori* eradication strategy based on the presence of a 23S ribosomal RNA point mutation that causes CAM resistance in patients with *H. pylori* infection is more cost effective than empirical treatment<sup>[27]</sup>. Kim et al. also conducted an economic modeling study comparing TR based on DPO-PCR and empirical treatment.

**Even though there have been limited reports in which tailored regimen**

vs EBQT regimen were compared in terms of costs effectiveness, cost problem of TR regimen should be evaluated as compared to EBQT design for the first line treatment in helicobacter eradication. Cho et al. reported that a tailored *H. pylori* eradication strategy based on the presence of a 23S ribosomal RNA point mutation that causes CAM resistance in patients with *H. pylori* infection is more cost effective than empirical treatment [27]. In this study, different from ours, researchers choose PAC regimen as the empirical treatment[27]. Cho et al demonstrated that the average costs per patient for tailored therapy were \$307.37, and compared with triple therapy, the incremental cost-effectiveness ratios of tailored therapy were \$3.96 per patient for first-line treatments[27]. Since the failure rate of PAC regimen for helicobacter eradication has been increasing in Korea, the overall medical costs for PAC regimen might over those of EBQT designs, the medical costs issue should be further evaluated.

Apart from medical cost problem of TR regimen, given that issues on increased prevalence of drug resistance helicobacter infection in worldwide,

**tailored approaches in treating *H. pylori* infection should be considered further.**

The possible reasons for treatment failure in their TR group are as follows<sup>[28, 29]</sup>. First, although *H. pylori* has traditionally been regarded as a homogenous organism, there is increasing evidence that populations of *H. pylori* in humans show wide diversity<sup>[29]</sup>. The quasi-species development of *H. pylori* in a single host might result in treatment failure even after a tailored eradication strategy based on the presence of a 23S ribosomal RNA point mutation<sup>[28]</sup>. Second, a DPO-PCR-based evaluation is limited to detecting mutations in A2142G or A2143G on 23S rRNA, and other mutations, such as the A2144G or A2142C genes in *H. pylori*, cannot be detected<sup>[20, 30]</sup>.

This study had several limitations. First, because of the relatively small sample size, the results of this study should be interpreted cautiously. A further, larger sample-sized, randomized trial should be conducted to verify

our results. Second, as this study was conducted at the GMC, a tertiary center in Korea, it may have been subject to selection bias. Third, we did not culture the *H. pylori* of enrolled patients for antibiotic sensitivity testing, but DPO-PCR was performed for CAM.

In conclusion, this study showed that TR is a first-line eradication regimen with non-inferior efficacy and a favorable safety profile compared to bismuth-based quadruple therapy. A future eradication regimen could potentially be designed based on these results for areas where CAM resistance rates are increasing.