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Efficacy of fexuprazan compared with rebamipide in Korean patients with gastritis: A matching-adjusted indirect comparison

Gwang Ha Kim, Hang Lak Lee

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Gwang Ha Kim, Department of Internal Medicine, Pusan National University School of Medicine and Biomedical Research Institute, Pusan National University Hospital, Busan 49241, South Korea

Hang Lak Lee, Department of Internal Medicine, Hanyang University College of Medicine, Seoul 04763, South Korea

Corresponding author: Gwang Ha Kim, MD, PhD, Professor, Department of Internal Medicine, Pusan National University School of Medicine and Biomedical Research Institute, Pusan National University Hospital, 179 Gudeok-ro, Seo-gu, Busan 49241, South Korea.
doc0224@pusan.ac.kr

Abstract

BACKGROUND

Gastritis is one of the most frequently diagnosed diseases requiring medical treatment in South Korea. Fexuprazan, a novel potassium-competitive acid blocker, has been approved for treating gastritis and erosive esophagitis. Meanwhile, rebamipide is the most commonly used mucoprotective agent for acute and chronic gastritis in real-world settings in South Korea. However, there have been no studies comparing the efficacy of these two drugs yet.

AIM

To compare the efficacy of fexuprazan with that of rebamipide for acute and chronic gastritis.

METHODS

This was a matching-adjusted indirect comparison. Individual patient data from a phase III study of fexuprazan (10 mg BID) were compared with cumulative data from two matching studies of rebamipide (100 mg TID). Erosion improvement and healing rates were compared between two weeks of fexurapan, two weeks of rebamipide, and four weeks of rebamipide. The two main outcome variables were presented as percentages, and the risk differences (RD) and 95% confidence intervals (CI) were calculated for the relative treatment effects.

RESULTS

In the primary analysis, the erosion improvement and healing rates after a two-week treatment with fexuprazan were 64.5% and 53.2%, respectively, while a two-week treatment with rebamipide resulted in erosion improvement and healing

rates of 43.6% (RD: 21.0%; 95%CI: 9.6-32.3; $P < 0.01$) and 35.6% (RD: 17.6%; 95%CI: 6.1-29.2; $P = 0.003$), respectively. In the additional analysis, the erosion improvement and healing rates for the two-week fexuprazan treatment (64.2% and 51.2%, respectively) were similar to those obtained during a four-week treatment with rebamipide (60.6%; RD: 3.6%; 95%CI: -9.8, 17.0; $P = 0.600$ and 53.5%; RD: -2.3%; 95%CI: -16.1, 11.5; $P = 0.744$, respectively).

CONCLUSION

The two-week fexuprazan treatment was superior to the two-week rebamipide treatment and similar to the four-week rebamipide treatment for patients with gastritis.

Key Words: Gastritis; Erosive gastritis; Fexuprazan; Rebamipide; Matching-adjusted indirect comparison; Indirect treatment comparison

Core Tip: In a matching-adjusted indirect comparison, the effectiveness of fexuprazan, a novel potassium-competitive acid blocker, was compared with that of rebamipide, one of the most commonly used mucoprotective agents for acute and chronic gastritis in a real-world setting in South Korea. We conclude that a two-week fexuprazan treatment is superior to a two-week rebamipide treatment and similar to a four-week rebamipide treatment for patients with gastritis.

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INTRODUCTION

Gastritis, an inflammation of the gastric mucosa confirmed histologically or diagnosed based on endoscopic findings, is one of the most common gastrointestinal disorders reported worldwide[1]. In South Korea, gastritis is the most common digestive disorder and one of the most frequently diagnosed diseases in adult patients; its prevalence has increased over time[2].

Unfortunately, no established causal treatment for gastritis exists; hence, a symptomatic approach aimed primarily at symptom control and facilitated healing of gastric lesions remains routine practice[3]. The aims of empirical therapy include the suppression of gastric acid secretion, protection of the gastric mucosa, and modulation of gastrointestinal motility[4].

Gastric acid is an important factor in the pathogenesis of gastric mucosal erosions, which explains why acid suppression therapies are effective in healing erosions and improving related symptoms[1]. Potassium-competitive acid blockers (P-CABs) are a novel class of gastric acid-reducing agents that inhibit H^+, K^+-ATPase through reversible potassium-competitive ionic binding without acid activation. P-CABs have a longer half-life than proton pump inhibitors, a group of drugs commonly used for gastric acid suppression, and show acid-inhibiting activity regardless of the medication time (after meals *vs* before meals)[5].

Fexuprazan is a novel P-CAB developed by Daewoong Pharmaceutical Co. Ltd. (Seoul, South Korea). The drug exhibits promising pharmacokinetic and pharmacodynamic properties such as rapid action, long elimination half-life, and high effectiveness, similar to or greater than other P-CABs, regardless of medication time, and is sustained throughout the night[6]. Preclinical data obtained from healthy volunteers were confirmed in a phase III randomized clinical trial in Korean patients with acute or chronic gastritis[3]. In that study, fexuprazan showed a significantly higher erosion improvement rate than placebo, and no differences were observed in the incidence of adverse drug reactions between 10 mg fexuprazan and placebo. Based on the clinical trial results, fexuprazan has been approved for the treatment of gastritis in South Korea.

The gastric mucoprotective agent rebamipide is the most commonly prescribed drug for acute and chronic gastritis according to Health Insurance Review & Assessment Service database. Rebamipide promotes gastric mucosal healing by enhancing prostaglandin and mucous glycoprotein synthesis, inhibiting the generation of reactive oxygen species and inflammatory cytokines, and suppressing leukocyte activity[7].

The present study aimed to analyze the effectiveness of fexuprazan against rebamipide using matching-adjusted indirect comparison (MAIC). This is in line with the regulations of the Health Insurance Review & Assessment Service in South Korea regarding the detailed assessment criteria for pricing negotiations for new drugs, which determine which drug should have the highest market share among all comparable drugs. The two drugs belong to different therapeutic groups, and their effectiveness has never been the subject of a head-to-head comparison, which constitutes the rationale for the present MAIC analysis. Based on evidence from previous studies on fexuprazan, we hypothesized that this agent might produce better outcomes in gastritis than rebamipide, and hence might become a mainstream therapeutic option for this indication.

MATERIALS AND METHODS

Individual patient data for fexuprazan

Individual patient data (IPD) were obtained from the aforementioned phase III study of fexuprazan, a double-blind, placebo-controlled, double-dummy, randomized, multicenter study conducted in South Korea from May 2020 to August 2021[3]. This study included individuals with symptomatic acute or chronic gastritis accompanied by one or more gastric erosions confirmed by esophagogastroduodenoscopy (EGD). A total of 327 patients were randomized to receive fexuprazan 20 mg once a day (QD), fexuprazan 10 mg twice a day (BID), or placebo for two weeks, and the primary endpoint was the erosion improvement rate, defined as the percentage of patients with an erosion score improved by 50% or more at two weeks after treatment. As the approved fexuprazan regimen for the treatment of gastric erosion in South Korea is 10 mg BID, IPD data from 102 patients who were randomized to the fexuprazan 10 mg BID group and included in the efficacy analysis set were extracted for MAIC analysis.

Systematic literature reviews

A systematic literature review (SLR) was conducted to identify studies reporting the efficacy results of fexuprazan and/or rebamipide, following the recommendations of the PRISMA guidelines[8]. As a comparator to fexuprazan, rebamipide was selected as it is the most frequently prescribed drug for patients with gastritis[4]. The eligible studies included randomized controlled clinical trials conducted in patients with acute or chronic gastritis who had one or more gastric erosions published up to the date of the search (March 6, 2023). An efficacy endpoint related to erosion improvement was included as an outcome measure. The language of the articles was restricted to English or Korean. The complete inclusion and exclusion criteria are listed in Supplementary Table 1.

Two reviewers (GHK and HLL) independently extracted the data according to predefined selection criteria from KoreaMed (http://www.koreamed.org), Korean Studies Information Service System (KISS, https://kiss.kstudy.com/), PubMed, and Cochrane Library databases. The MeSH search terms were gastritis and rebamipide (supplementary concept). Free-text terms were gastritis, fexuprazan, DWP14012, abeprazan, rebamipide, and OPC*12759. Data on the target disease, interventions, study design, report type, outcome measures, and notes were extracted.

Selection of comparator data and outcome measures

Among the articles identified from the SLR, those reporting the efficacy results of rebamipide administered at a dose of 100 mg thrice a day (TID) in a randomized comparative study setting were considered for MAIC analysis.

The chosen outcome measures were the erosion improvement and healing rates, defined as the percentage of patients with an erosion score that improved by 50% or more and the percentage whose erosion lesions disappeared, respectively. Erosion improvement and healing rates were, respectively, the primary and secondary efficacy endpoints in the current MAIC and in the phase III study of fexuprazan[3]. Both endpoints were based on EGD findings two weeks after treatment.

For the primary analysis, studies documenting these two endpoints were selected if the definition of the endpoints and their assessment time points matched those stated above. Studies reporting results of the same endpoints assessed at different time points were used for additional analyses.

Selection of matching variables and population matching

Given the absence of a common comparator between fexuprazan and rebamipide, the present analysis used an unanchored MAIC approach. In this approach, both effect modifiers and prognostic variables must be identified and reflected during population matching[9]. Therefore, all available outcome confounding factors such as smoking history, alcohol consumption, EGD findings on erosion, edema, redness, hemorrhage, and symptom score were included as matching variables in addition to demographic and anthropometric characteristics such as age, male sex, and body mass index (BMI). In particular, high BMI and smoking history were treated as major prognostic factors because they were identified as significant risk factors for erosive gastritis in a study by Yamamoto *et al*[10]. Trial population matching was performed using a propensity score-weighted model. Specifically, the IPD from the fexuprazan phase III study were weighted to match the baseline characteristics of the rebamipide aggregate data using a logistic regression method. The propensity score was estimated using the generalized method of moments. This study aimed to achieve an exact balance in the weighted mean baseline characteristics between the populations of the weighted IPD and aggregate data. Any imbalance between the studies was tested using a standardized mean difference, and a threshold of 10% was used to determine the imbalance in a specific factor between the studies. Several scenarios were created by varying the combinations of matching variables, and the effective sample size was calculated for each scenario. The two risk factors of erosive gastritis, smoking and BMI, as well as the erosion score from EGD findings, were included in all scenarios. The best scenario was selected if it included a higher number of major matching variables while maintaining a greater effective sample size than the other scenarios.

Statistical analysis

All statistical analyses were performed using the R Statistical Software (version 4.2.2z; R Foundation for Statistical Computing, Vienna, Austria). Propensity score weighting and effective sample size were calculated using the R package MAIC[11]. The two main outcome variables were presented as percentages, and the risk difference (RD) with its 95% confidence interval (CI) was calculated to express the relative treatment effects for the probability of achieving erosion improvement or erosion healing using the R package fmsb[12]. Statistical significance was set at $P < 0.05$.

RESULTS

Systematic literature review results

The SLR confirmed that the only available data source regarding fexuprazan was the aforementioned phase III study[3]. No additional studies or sources of information on fexuprazan were identified during the review process. Five studies providing data on rebamipide were identified. The number of studies identified from each database and the study selection process used in the SLR are presented in the PRISMA flowchart (Supplementary Figure 1).

Results from the matching-adjusted indirect comparison

Selection of the studies: While the IPD were available from the study by Kim *et al*[3], only aggregate data were available from the five studies that provided rebamipide data. As shown in Supplementary Table 2, no head-to-head studies compared rebamipide and fexuprazan directly. Therefore, the MAIC was conducted to compare the efficacy and outcomes of the two treatments.

All five studies on rebamipide were randomized, comparative clinical trials that satisfied the study quality criteria. However, three studies by Du *et al*[13], Han *et al*[14], and Jeong *et al*[15] were excluded from the MAIC based on the following rationale. First, the endpoints reported by Du *et al*[13] and Han *et al*[14], such as patient-reported symptom score, endoscopic inflammation score, and endoscopic scoring using different criteria, did not match the outcome measures targeted in the current MAIC analysis. Second, the treatment duration and efficacy evaluation time points of the studies by Du *et al*[13] and Han *et al*[14] were 8 wk and 26 wk, respectively, which differed significantly from those of the fexuprazan study by Kim *et al*[3]. Furthermore, both studies were conducted in China, resulting in different patient characteristics such as older age (only in the study by Han *et al*[14]), higher prevalence of male sex, and a higher positivity rate of *Helicobacter pylori* (Supplementary Table 2). Considering the potential effect on the outcome measures by such differences in patient demographics and possible discrepancies in clinical practice, combined with different efficacy endpoints, these two studies[13,14] were excluded from MAIC analysis. The study by Jeong *et al*[15] was excluded because of its small sample size (n = 37) and the outdated nature of the results obtained in 2004.

We chose two studies on rebamipide for the MAIC against fexuprazan based on the time point of the primary endpoint assessment and the sample size. Specifically, the study by Kim *et al*[4] was chosen for the primary analysis for MAIC based on the similarity in patient characteristics, treatment duration (two weeks), and the time point for the evaluation of the erosion improvement[3]. The study by Moon *et al*[16] generally satisfied the comparability criteria; however, the efficacy outcomes were evaluated four weeks after treatment, and the availability of treatment effect-modifying factors or prognostic factors was relatively limited compared with the study by Kim *et al*[4]. Nevertheless, the study by Moon *et al*[16] was used for additional analysis, as it was assumed that the clinical outcome of erosive gastritis was unlikely to change much within 2-4 wk.

Primary MAIC analysis for outcome measures at week 2

Among the selected matching variables, which included the treatment effect modifier and prognostic factors, sex, alcohol consumption status, patient-assessed symptom score, and EGD findings, the standardized mean difference was greater than 10%. In the base-case scenario, all four factors of EGD findings and patient factors, such as sex, BMI, and smoking, were also included, and the effective sample size was the largest among the scenarios tested. The baseline characteristics before and after population matching compared with the rebamipide group in the study by Kim *et al*[4] are summarized in Table 1. Similar baseline characteristics were observed in other scenarios tested in the sensitivity analysis (Supplementary Table 3).

After the matching-adjustment of the confounding factors, the erosion improvement rate of the fexuprazan group was calculated as 64.5%, resulting in a between-group difference of 21.0% (95%CI: 9.6-32.3; P < 0.01). The erosion healing rate was also significantly better with fexuprazan than with rebamipide, with a risk difference of 17.6% (95%CI: 6.1-29.2; P = 0.003) (Table 2). Data are expressed as percentages of patients, unless specified otherwise. Matching variables included in the scenario are indicated in bold.

Additional MAIC analysis for outcome measures at week 4

Additional MAIC analysis was performed with data from the study by Moon *et al*[16] by adjusting for the erosion factors of EGD findings and patient factors such as age and sex (Table 3). The baseline characteristics of the other scenarios tested in the sensitivity analysis also resembled those of the base case (Supplementary Table 4). In this additional MAIC analysis, no significant risk difference was found in terms of erosion improvement rate (risk difference = 3.6%; 95%CI: -9.8, 17.0; P = 0.600) or erosion healing rate (risk difference = -2.3%; 95%CI: -16.1, 11.5; P = 0.744) between fexuprazan and rebamipide (Table 4).

DISCUSSION

In the present study, the primary analysis conducted within the framework of MAIC demonstrated that a two-week treatment with fexuprazan, a novel P-CAB (10 mg BID), produced superior clinical outcomes for the treatment of gastritis than a two-week treatment with rebamipide (100 mg TID), the most commonly prescribed mucoprotective agent in South Korea. Additional analysis revealed that the two-week treatment with fexuprazan was as effective as the twice-as-long, four-week administration of rebamipide at the same dose (100 mg TID).

Table 1 Patient characteristics for the primary analysis

		Fexuprazan 10 mg BID[3], before matching (*n* = 102)	Fexuprazan 10 mg BID[3], after matching (*n* = 44.5[1])	Rebamipide 100 mg TID[4] (*n* = 225)
Age, yr		46.4	-	46.8
Male		35.3	**41.8**	41.8
Body mass index (kg/m^2)		23.7	**24**	24
Smoking	Non-smoker	77.5	**77.3**	77.3
	Smoker	11.8	**14.2**	14.2
Alcohol drinking	Non-drinker	28.4	-	39.1
	Drinker	57.8	-	57.3
Erosion	2 (1-2 erosions)	56.9	**34.7**	34.7
	3 (3-5 erosions)	24.5	**33.3**	33.3
	4 (≥ 6 erosions)	18.6	**32**	32
Edema	1 (none)	29.4	**42.7**	42.7
Redness	1 (none)	47.1	**16.9**	16.9
	2 (mild)	38.2	**52**	52
	3 (moderate)	10.8	**27.1**	27.1
Hemorrhage	1 (none)	83.3	**60.4**	60.4
	2 (1 lesion)	8.8	**16.4**	16.4
	3 (2-5 lesions)	5.9	**16.9**	16.9
	4 (6-10 lesions)	1	**4.9**	4.9
Patient-assessed symptom score		20.5	-	9.1

[1]Effective sample size was computed as the square of the summed weights divided by the sum of the squared weights.
Data are expressed as percentages of patients, unless specified otherwise. Matching variables included in the scenario are indicated in bold.

Table 2 Matching-adjusted indirect comparison of outcome measures at two weeks after treatment

	Fexuprazan 10 mg BID[3], before matching (*n* = 102)	Fexuprazan 10 mg BID[3], after matching (*n* = 44.5[1])	Rebamipide 100 mg TID[4] (*n* = 225)
Erosion improvement rate	65.7	64.5	43.6
Risk difference (95%CI)	22.1 (10.9, 33.4)	21.0 (9.6, 32.3)	
P value	< 0.01	< 0.01	
Erosion healing rate	57.8	53.2	35.6
Risk difference (95%CI)	22.3 (10.8, 33.7)	17.6 (6.1, 29.2)	
P value	< 0.01	0.003	

[1]Effective sample size was computed as the square of the summed weights divided by the sum of the squared weights.
Data are expressed as percentages of patients, unless specified otherwise.

Table 3 Patient characteristics for the additional matching-adjusted indirect comparison analysis

		Fexuprazan 10 mg BID[3], before matching (*n* = 102)	Fexuprazan 10 mg BID[3], after matching (*n* = 87.5[1])	Rebamipide 100 mg TID[16] (*n* = 99)
Age, years		46.4	**49.8**	49.8
Male		35.3	**36.4**	36.4
Erosion	2 (1-2 erosions)	56.9	**45.5**	45.5
	3 (3-5 erosions)	24.5	**23.2**	23.2
	4 (≥ 6 erosions)	18.6	**31.3**	31.3

[1]Effective sample size was computed as the square of the summed weights divided by the sum of the squared weights.
Data are expressed as percentages of patients, unless specified otherwise. Matching variables included in the scenario are indicated in bold.

Table 4 Outcome measures of fexuprazan (2 wk) *vs* rebamipide (4 wk)

	Fexuprazan 10 mg BID[3], before matching (*n* = 102)	Fexuprazan 10 mg BID[3], after matching (*n* = 87.5[1])	Rebamipide 100 mg TID[16] (*n* = 99)
Erosion improvement rate	65.7	64.2	60.6
Risk difference (95%CI)	5.1 (-8.2, 18.4)	3.6 (-9.8, 17.0)	
P value	0.455	0.6	
Erosion healing rate	57.8	51.2	53.5
Risk difference (95%CI)	4.3 (-9.4, 18.0)	-2.3 (-16.1, 11.5)	
P value	0.538	0.744	

[1]Effective sample size was computed as the square of the summed weights divided by the sum of the squared weights.
Data are expressed as percentages of patients, unless specified otherwise.

In the primary analysis, fexuprazan administered at 10 mg BID resulted in an erosion improvement rate of 64.5% and an erosion healing rate of 53.2%, while a two-week treatment with rebamipide (100 mg TID) produced erosion improvement and healing rates of 43.6% and 35.6%, respectively. Additional analysis demonstrated that the erosion improvement and healing rates for fexuprazan 10 mg BID (64.2% and 51.2%, respectively) were similar to those obtained with rebamipide 100 mg TID during the four-week treatment (60.6% and 53.5%, respectively).

A clinical trial of rebamipide that satisfied the inclusion criteria of the present MAIC was the study comparing two formulations of this drug, 150 mg BID and 100 mg TID, in patients with endoscopically proven erosive gastritis[4]. The present analysis included data from patients receiving rebamipide at a dose of 100 mg TID. According to the best matching-adjustment scenario including all the most important prognostic factors, such as sex, BMI, and smoking status, and providing the largest effective sample size, both the erosion improvement and healing rates for the fexuprazan group were significantly higher than those for the rebamipide group by 21.0% ($P < 0.001$) and 17.3% ($P = 0.003$), respectively. Additional analyses included the results of a randomized clinical trial comparing the efficacy of rebamipide (100 mg TID) with another gastroprotective agent, sulglycotide, in patients with endoscopically confirmed erosive gastritis[16]. Regardless of the scenario, no significant differences in erosion healing or improvement rates were found between the fexuprazan and rebamipide groups in the analysis adjusted for the erosion factors of EGD and patient characteristics. In summary, the results of the MAIC analysis suggest that the therapeutic effect of fexuprazan (10 mg BID) could be achieved after two weeks of treatment, whereas comparable effects of rebamipide (100 mg TID) were observed no earlier than four weeks.

The present primary MAIC analysis included a study comparing rebamipide 100 mg TID with 150 mg BID[4]. After two weeks of treatment, the erosion improvement and healing rates in the 150 mg BID arm were 39.7% and 34.5%, respectively, which were not significantly different from those in the 100 mg TID arm ($P = 0.387$ and $P = 0.786$, respectively)[4]. Meanwhile, in the additional study included, rebamipide 100 mg TID was compared with sulglycotide 200 mg TID, with sulglycotide producing erosion improvement and healing rates of 52.0% and 43.9%, respectively, at four weeks; these rates were also not significantly different from the results obtained for rebamipide 100 mg TID ($P = 0.113$ and $P = 0.175$, respectively)[16]. Thus, one may speculate that the results documented herein for fexuprazan 10 mg

BID might also have been superior to the outcomes of a two-week treatment with rebamipide 150 mg BID[4] and comparable with the results of a four-week therapy with sulglycotide 200 mg TID[16]. In this context, it is also worth emphasizing that, unlike rebamipide, sulglycotide, and other drugs prescribed for this indication, fexuprazan demonstrated superiority over placebo in a randomized clinical trial involving Korean patients with erosive gastritis[3], thus satisfying the principal efficacy criterion.

The unavailability of head-to-head studies comparing the effectiveness of fexuprazan and rebamipide could be considered a potential limitation of the results presented herein. Without a direct comparison, one can hardly speculate on the superiority of one treatment over the other. The conclusions are further limited because of the inability to conduct an anchored MAIC owing to the lack of eligible placebo-controlled studies for rebamipide. Another potential limitation was the small number of studies eligible for unanchored MAIC. The shortage of eligible studies may introduce some uncertainty into the results and hinder their generalizability. Furthermore, while information on *Helicobacter pylori* infection rates was available for the fexuprazan study[3], it was not reported in the two studies of rebamipide[4,16]. The lack of data on this important factor modifying treatment effects precluded its adjustment during MAIC, potentially influencing the validity of the comparative efficacy estimates.

These limitations were at least partially counterbalanced by the strengths of this study. First, the matching-adjustment scenarios considered during the analysis had large effective sample sizes, which positively affected the robustness and reliability of the results. Second, the primary MAIC analysis and additional analysis consistently produced similar outcomes, supporting the validity of the comparative efficacy estimates obtained. Finally, it must be stressed that the efficacy and safety of fexuprazan have already been confirmed in Korean patients[3]. Thus, despite the potential limitations, the present study provides valuable insights into the comparative efficacy of fexuprazan and rebamipide based on available evidence and rigorous analytical methods.

CONCLUSION

The findings of the primary MAIC analysis suggest that a two-week treatment with fexuprazan (10 mg BID) provides better clinical outcomes than a two-week treatment with rebamipide (100 mg TID) in patients with gastritis. Additional analysis showed that the outcomes of the two-week treatment with fexuprazan were comparable with the results obtained after a four-week administration of rebamipide (100 mg TID). Thus, the beneficial effects of fexuprazan (10 mg BID) can be expected to occur earlier than those of rebamipide (100 mg TID). Collectively, the results of the present study imply that fexuprazan may be an attractive therapeutic option and a potential alternative to rebamipide, a commonly prescribed drug for Korean patients with gastritis.

FOOTNOTES

Author contributions: Kim GH conceived and designed the study; Kim GH and Lee HL collected data and performed data analysis; Kim GH and Lee HL wrote the draft of this manuscript; Kim GH edited the manuscript.

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Country of origin: South Korea

ORCID number: Gwang Ha Kim 0000-0001-9721-5734; Hang Lak Lee 0000-0002-2825-3216.

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