Randomized Control Trials

Green tea extracts for the prevention of metachronous colorectal polyps among patients who underwent endoscopic removal of colorectal adenomas: A randomized clinical trial

Cheol Min Shin\textsuperscript{a}, Dong Ho Lee\textsuperscript{a,}\textsuperscript{*}, A. Young Seo\textsuperscript{a,}\textsuperscript{b}, Hyun Joo Lee\textsuperscript{a}, Seong Beom Kim\textsuperscript{a}, Woo-CHAN Son\textsuperscript{c}, Young Kyung Kim\textsuperscript{d}, Sang Jun Lee\textsuperscript{d,}\textsuperscript{e}, Sung-Hee Park\textsuperscript{d}, Nayoung Kim\textsuperscript{a}, Young Soo Park\textsuperscript{a}, Hyuk Yoon\textsuperscript{a}

\textsuperscript{a}Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do, South Korea
\textsuperscript{b}Health Promotion Center, Samsung Changwon Hospital, Sankyunkwan University School of Medicine, Changwon, South Korea
\textsuperscript{c}Department of Pathology, Asan Medical Center, College of Medicine, University of Ulsan, Seoul, South Korea
\textsuperscript{d}Beauty in Longevity Science Research Division, AmorePacific Co., R&D Center, Yongin, Gyeonggi-do, South Korea
\textsuperscript{e}Holistic Bio Co., Gyeonggi-do, South Korea

\textbf{ARTICLE INFO}

\textbf{Article history:}
Received 27 September 2016
Accepted 23 January 2017

\textbf{Keywords:}
Green tea
Epigallocatechin gallate
Colon polyps
Recurrence risk

\textbf{SUMMARY}

\textbf{Objectives:} To determine the preventive effect of green tea extract (GTE) supplements on metachronous colorectal adenoma and cancer in the Korean population.

\textbf{Materials and methods:} One hundred seventy-six subjects (88 per each group) who had undergone complete removal of colorectal adenomas by endoscopic polypectomy were enrolled. They were randomized into 2 groups: supplementation group (0.9 g GTE per day for 12 months) or control group without GTE supplementation. The 72-h recall method was used to collect data on food items consumed by participants at baseline and the 1-year follow-up during the past 48 h. Follow-up colonoscopy was conducted 12 months later in 143 patients (71 in control group and 72 in the GTE group).

\textbf{Results:} Of the 143 patients completed in the study, the incidences of metachronous adenomas at the end-point colonoscopy were 42.3% (30 of 71) in control group and 23.6% (17 of 72) in GTE group (relative risk [RR], 0.42; 95% confidence interval [CI], 0.21–0.87). The number of relapsed adenoma was also decreased in the GTE group than in the control group (0.7 ± 1.1 vs. 0.3 ± 0.6, \( p = 0.010 \)). However, there were no significant differences between the 2 groups in terms of body mass index, dietary intakes, serum lipid profiles, fasting serum glucose, and serum C-reactive protein levels (all \( p > 0.05 \)).

\textbf{Conclusion:} This study of GTE supplement suggests a favorable outcome for the chemoprevention of metachronous colorectal adenomas in Korean patients (ClinicalTrials.gov number, NCT02321969).

\textcopyright 2017 Published by Elsevier Ltd.

\textbf{1. Introduction}

Colorectal cancer (CRC) is the third most commonly diagnosed cancer, and the fourth most common cause of cancer-related death in the world [1,2]. In Korea, colorectal cancer has the second and the third highest incidences among men and women respectively in 2011 [3]. Especially, the incidence showed a rapid increase with an annual change of 5.6% in men and 4.3% in women between 1999 and 2012 [4]. The increase in CRC might be associated with environmental factors including westernized lifestyle and economic development in recent decades.

The world’s second most popular beverage is tea. Among them, green tea contains high concentrations of catechins; in contrast, high amounts of theaflavins and thearubigins were found in black tea. A previous metaanalysis of epidemiologic studies on the effect of green tea on CRC including both case–control studies and prospective cohort studies showed a significant reduction in colorectal cancer risk by 20% [5]. However, a recent metaanalysis that...
2. Methods

2.1. Subjects

The present study is a single-center prospective randomized open-labelled study. Between 2011 and 2015, patients who had undergone endoscopic polypectomy for the complete removal of colorectal adenomas were enrolled from Seoul National University Bundang Hospital. The inclusion criteria were as follows: 1) subjects were men or women between the ages of 19–85 years; 2) colorectal adenoma(s) were removed by endoscopic polypectomy or endoscopic mucosal resection at the time of enrollment; and 3) adequate bowel preparation (Boston Bowel Preparation Score ≥ 2 in all 3 segments) was performed. The followings were the exclusion criteria: 1) suspicious hereditary CRC (such as familial adenomatous polyposis and hereditary non-polyposis colorectal cancer); 2) personal history of any cancer; 3) presence of inflammatory bowel disease (such as ulcerative colitis and Crohn's disease); 4) previous history of a resection of the small or large intestine; 5) co-administration of aspirin or any NSAIDs; 6) previous history of a major organ transplantation or co-administration of immunosuppressive drugs; and 7) poor bowel preparation in the initial colonoscopy. The subjects were randomized into 2 groups using a blocked randomization method (block size = 4) as follows: a treatment group with GTE supplementation (0.9 g GTE per day for 12 months) and a control group without GTE supplementation. A priori power analysis determined that a sample size of 176 patients (88 per each group) was required to give the study 80% power to detect a difference assuming a two-sided significance test at the 0.05 level. Among these subjects, 143 (71 in the control group and 72 in the GTE group) completed the study protocol (Fig. 1). The study participants were checked every 3 months to evaluate adverse effects and compliance. In addition, co-administration of aspirin or NSAIDs was checked at each follow-up. A follow-up colonoscopy was conducted at 12 months to observe the occurrence of any new colorectal polyps. The endoscopists were not informed on which group the study participants belonged to which excluded any potential bias. In addition, the study subjects underwent well-taken endoscopy tests, answered a questionnaire which included their habitual tea and coffee consumption (at baseline only), and for the dietary assessment, a structured 3-day recall questionnaire was given at baseline and 1-year follow-up. The Ethics Committee at Seoul National University Bundang Hospital approved the study protocol (B-1006-103-00).

2.2. Green tea extract tablet formulation

The green tea extract tablets (both water and ethanol extracts) were provided by the AmorePacific R&D Center (Gyeonggi-do, Korea). Fresh green tea leaves (Camellia sinensis) harvested in 2009 from 3 tea-growing areas in the Jeju island (south Korea) were used to manufacture the tablets. One GTE tablet (500 mg) contained 225 mg of GTE consisting of 51.5 mg (-)-epigallocatechin gallate (EGCG), 11.6 mg (-)-epicatechin, 65.5 mg (-)-epigallocatechin, 5.7 mg (-)-epicatechin gallate, and 10.9 mg caffeine, which is approximately equivalent to 2 Japanese-size cups (approximately 400 mL) of green tea. The GTE supplementation group received two GTE tablets 30 min after a meal twice a day for 12 months, which is equivalent of 0.9, 0.6 and 0.2 g/day GTE, catechin, and EGCG, respectively.

2.3. Blood testing

For all the study participants, blood was drawn by venipuncture at baseline and at the 1-year follow-up. Laboratory testing included liver enzymes [alanine transaminase (ALT)/aspartate transaminase (AST)], lipids [total cholesterol, triglyceride, low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C)], C-reactive protein (CRP), and fasting serum glucose level.

2.4. Evaluation of the rectal mucosal proliferation index

Additionally, to evaluate the rectal mucosal proliferation index (RMI) using a known proliferation marker (Ki-67), at least two random biopsies of rectal mucosa were taken. Among the study participants, 30 patients (30 pairs at baseline and after 1 year) were analyzed to select well-stained and the tissue sections showing well-oriented, U-shaped crypts that were open from the apical lumen to the base. Formalin-fixed, paraffin-embedded tissue blocks of polyp were cut (3 μm thickness) and mounted on coated glass slides. Immunohistochemistry was done with an automated slide preparation system Benchmark XT (Ventana Medical systems Inc, Tucson, AZ). EZ prep, CC1 (cell conditioning solutions 1), and the BMK ultraVIEW diaminobenzidine (DAB) detection system (Ventana Medical Systems) were used for deparaffinization, epitope retrieval, and staining according to the manufacturer’s instructions. Sections were stained with Ki-67 (ab15580, 1:700). Ultra-VIEW copper was used to amplify the positive signals. Hematoxylin and blueing reagent were used to counterstain the sections. Microscopic examinations were performed (OLYMPUS BX53). Images were captured (CellSens, Olympus, ×200) for all slides, and positively stained cells in the crypts were counted with the IMT i-Solution software (version 10.1). All the % values in one patient were averaged to produce an average % of Ki-67 stained cells.

2.5. Statistical analysis

Data on food intake obtained from the 3-day recall questionnaires were analyzed by the Computer Aided Nutritional Analysis version 3.0 (CAN-pro 3.0, Nutritional Assessment Program, 2006, The Korean Nutrition Society, Seoul, Korea) [10]. To evaluate whether any significant difference was present in demographic or clinical features between controls and GTE group, univariate analysis with Student’s t-test or χ2-test was performed. The paired t-test and Spearman’s rank correlation test were used to analyze the paired samples. For the comparison in the changes in body weight,
body mass index, dietary factors, laboratory findings, and RMPI from baseline to the 1-year follow-up between the 2 groups, a general linear model was applied. All statistical analyses were done with SPSS (version 17.0, SPSS Inc, Chicago, IL, USA). All statistical tests were 2-sided, and $p$-values less than 0.05 were considered statistically significant.

3. Results

In the baseline characteristics, there was no significant difference between the control group and GTE supplementation group in terms of age, gender, body mass index, comorbidity, smoking and alcohol intake, coffee and tea consumption, laboratory findings, and baseline colonoscopic findings (Table 1).

After the 1-year follow-up, however, metachronous polyps occurred in 60.6% (43 of 71) and 27.8% (20 of 72) in the control group and GTE supplementation group, respectively (relative risk [RR], 0.25; 95% confidence interval [CI], 0.12–0.51), which is statistically significant ($p < 0.001$, Table 2). The GTE supplementation group had a significantly small number of recurrent polyps compared to the control group (1.5 ± 2.0 vs. 0.5 ± 0.9 in controls and GTE group, respectively, $p < 0.001$). Occurrences of metachronous adenoma also showed a decrease in GTE group (23.6%, 17 of 72) compared to control group (42.3%, 30 of 71; RR, 0.42; 95% CI, 0.21–0.87, $p = 0.018$, Table 2). The number of relapsed adenomas was also lower in the GTE supplementation group than in the control group (0.7 ± 1.1 vs. 0.3 ± 0.6 in the control and GTE groups, respectively, $p = 0.010$). The size of the largest relapsed adenomas was smaller in the GTE supplementation group than in the control group, although it was not statistically significant (5.6 ± 2.2 vs. 4.5 ± 1.9 in the control and GTE groups, respectively, $p = 0.092$).

Additionally, changes in body weight, body mass index and waist circumference were not statistically significant between the 2 groups (Table 3). For example, body mass index showed a slight decrease in the GTE group (delta = −0.4 kg/m²) and a slight increase in the control group (delta = 0.4 kg/m²), which was not statistically significant ($p = 0.689$). There were no significant differences between the 2 groups in terms of dietary intake. Moreover, serum fasting glucose, lipid and CRP levels were not significantly different (all $p$-values > 0.05).

We performed random rectal mucosal biopsies at baseline and at the 1-year follow-up to evaluate whether there was a difference between the 2 groups in terms of the rectal mucosal proliferation index (RMPI) evaluated by Ki-67 staining. Fourteen subjects in the control group and 16 in the GTE supplementation group were compared (Fig. 2). However, there were no significant changes observed in the percentage of Ki-67 stained cells between the rectal biopsy specimens taken at baseline and at the 1-year follow-up in the GTE supplementation group as well as the control group (all $p > 0.05$); there was no significant difference between the 2 groups when analyzed by a general linear model ($p > 0.05$).

Self-reported compliance to the GTE capsule was excellent (99.3%). There were no serious adverse reactions reported by the study participants related to the GTE supplementation. In terms of the liver function test abnormalities, any study participants in both groups did not have a serum alanine transaminase (ALT) level more than 5 times the upper limit of the normal range (UNL) at baseline and at the 1-year follow-up. However, five of the 72 subjects (6.9%) in the GTE group had a serum ALT level more than twice the UNL.

4. Discussion

To date, several chemopreventive drugs have been suggested to reduce colorectal cancer including aspirin, NSAIDs, antioxidants and statins. However, no agents have been recommended for the prevention of colorectal cancer in the general population [11]. Therefore, further research is still necessary to find new chemopreventive agents, including green tea and other phytochemicals. Among the green tea catechins, (−)-epigallocatechin gallate (EGCG) is the most abundant one, which accounts for more than 50% of the total polyphenols in green tea [12]. To date, both in vitro and in vivo studies have evaluated the molecular mechanisms of cancer chemoprevention by EGCG, and several molecular mechanisms have been suggested [13, 14]. Briefly, it targets specific cell signaling pathways to promote inflammation and cellular proliferation, or to inhibit apoptosis. In colorectal carcinogenesis, through the
inhibition of COX-2 expression and the activation of EGFR family of receptor tyrosine kinases, the cell growth is inhibited and apoptosis is induced [15–17]. In one study, EGCG attenuated COX-2 expression through the AMPK signaling pathway, which leads to apoptosis in colon cancer cells [18]. EGCG inhibited the activation of the IGF-1 receptor [19]. In the APcmin mouse model, EGCG attenuated intestinal tumors by decreasing nuclear β-catenin, phospho-Akt, and phospho-ERK1/2 [20]. In addition, a synergistic effect of EGCG and NSAIDs on apoptosis has been reported in the human lung cancer cell line PC-9, which might be attributed to an up-regulation of growth arrest and DNA damage-inducible gene 153 (GADD153) and p21. [14] In a xenograft mouse model, the combination of EGCG and either paclitaxel or docetaxel showed a complete elimination of the human prostate cancer cell line PC-3ML [21].

Previously, there have been a few clinical studies on whether GTE could reduce metachronous colorectal polyps [8,22]. All these studies have reported positive results. However, some of them had limitations including a small sample size and/or the enrollment of patients who had undergone an operation due to colorectal cancer. Thus, further studies are necessary to clarify this. In the present study, we studied the effect of 0.9 g/day of GTE (0.6 g/day catechin, 0.2 g/day EGCG) supplementation for one year on colorectal polyps in patients who had undergone endoscopic removal of colorectal adenomas without a history of colorectal surgery. We also observed a dramatic decrease in metachronous adenomatous polyps in the GTE supplementation group (Table 2); the number of new adenomatous polyps also showed a significant decrease in the GTE group. Our findings are consistent with previous results. When the results from a recent prospective clinical trial (MIRACLE) are published, the effect of long-term GTE supplementation on colorectal adenomatous polyps should be clarified [9].

Next, this study investigated the underlying mechanisms for these findings. Unfortunately, we could not find any significant results. According to our data, the changes in body weight, body mass index, waist circumference, serum fasting glucose level, serum lipid profile, and inflammatory marker such as C-reactive protein were not meaningful enough to explain our positive results. Previous reports have shown that short-term administration of GTE could lead to a decrease in body weights and/or improvement in serum lipid profiles [23,24]. In this long-term GTE supplementation study, however, the patients who had undergone endoscopic removal of colorectal adenomatous polyps (premalignant lesions of colorectal cancer) might have changed their lifestyles such as drinking, smoking, dietary habits and exercise, which was able to modify the clinical outcomes. Alternatively, the effect of GTE to attenuate colorectal adenomatous polyps might be attributed to an intrinsic mechanism.

Previous studies have reported that the rectal mucosal proliferation index (RMPI) using proliferation markers such as proliferating cell nuclear antigen (PCNA) or Ki-67 could be a good methodology to evaluate rectal mucosal proliferation which is a good marker for colorectal cancer risk [25]. Thus, we also did Ki67 immunohistochemical staining of the rectal mucosal biopsy specimens in a subset of the study participants (n = 30, Fig. 2). However, we did not found any significant results (p > 0.05). It might be attributed to the small sample size. Thus, further study is necessary to clarify this issue.

There have been several studies to evaluate the toxicity of GTE or \( \chi^2 \)-test (for categorical variables). Bold style indicates clinical significance. GTE, green tea extract; SD, standard deviation.
one study, 108 healthy volunteers were administered 2.25 g/day of GTE for 6 months, and only mild to moderate adverse effects were reported including epigastric discomfort, heartburn, diarrhea and insomnia, which was probably attributed to the caffeine contained in the extract; most of the volunteers (78%) had no adverse effects during the study period [26]. Another phase I study in patients with advanced lung cancer showed that even a high dose of 3.0 g/m² per day of GTE was well tolerated without grade 3 or 4 toxicities such as diarrhea, nausea and hypertension (maximal tolerated dose) [27]. In the present study, the daily dose of GTE was 0.9 g/day, which was less than that in previous studies, and the daily dose of caffeine was 43.6 mg/day, which was comparable to that in a previous Japanese clinical trial (47.1 mg/day) that showed no serious adverse reactions during the follow-up [8]. Our data also showed that no adverse reactions related to the GTE supplementation were reported.

There are some concerns on liver toxicity related to green tea catechins based on several animal studies [28,29]. Thus, we carefully evaluated the serum ALT levels before and after GTE supplementation. We defined serum ALT levels more than 5-times the ULN as a serious adverse reaction. After one year, five of the 72 (6.9%) subjects in the GTE supplementation group had abnormal serum ALT levels more than 2-times the UNL, but less than 5-times the ULN. We defined serum ALT levels more than 5-times the UNL, but less than 5-times the ULN as a serious adverse reaction. After one year, five of the 72 (6.9%) subjects in the GTE supplementation group had abnormal serum ALT levels more than 2-times the UNL, but less than 5-times the ULN.

Table 3

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 71)</th>
<th>GTE (n = 72)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 1 yr</td>
<td>1 yr</td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>65.8 ± 9.8</td>
<td>66.0 ± 9.9</td>
<td>1.2 ± 7.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.8 ± 5.4</td>
<td>23.9 ± 2.7</td>
<td>0.4 ± 2.7</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>81.1 ± 7.2</td>
<td>80.9 ± 9.3</td>
<td>1.0 ± 11.2</td>
</tr>
<tr>
<td>Calories (kcal/day)</td>
<td>1470 ± 520</td>
<td>1385 ± 403</td>
<td>−82.4 ± 614.6</td>
</tr>
<tr>
<td>Fat (g/day)</td>
<td>34.7 ± 33.8</td>
<td>30.0 ± 16.7</td>
<td>−4.7 ± 36.2</td>
</tr>
<tr>
<td>Dietary fiber (g/day)</td>
<td>17.9 ± 7.4</td>
<td>17.8 ± 5.9</td>
<td>−0.2 ± 8.9</td>
</tr>
<tr>
<td>Vitamin B6 (mg/day)</td>
<td>1.3 ± 0.5</td>
<td>1.3 ± 0.4</td>
<td>−0.1 ± 0.6</td>
</tr>
<tr>
<td>Calcium (g/day)</td>
<td>409.6 ± 198.6</td>
<td>419.2 ± 213.8</td>
<td>9.6 ± 289.7</td>
</tr>
<tr>
<td>Folate (µg/day)</td>
<td>431.6 ± 163.2</td>
<td>451.7 ± 202.1</td>
<td>20.1 ± 225.8</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>23.3 ± 10.1</td>
<td>30.2 ± 13.4</td>
<td>6.9 ± 13.6</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>23.8 ± 13.9</td>
<td>28.5 ± 14.2</td>
<td>4.3 ± 13.5</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>105.3 ± 30.4</td>
<td>96.5 ± 12.9</td>
<td>−8.4 ± 26.8</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>187.8 ± 29.9</td>
<td>191.7 ± 41.3</td>
<td>3.7 ± 36.3</td>
</tr>
<tr>
<td>Fasting triglyceride (mg/dL)</td>
<td>160.7 ± 102.4</td>
<td>142.4 ± 108.0</td>
<td>−22.7 ± 82.8</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>52.3 ± 12.7</td>
<td>53.6 ± 15.0</td>
<td>1.7 ± 12.7</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>109.0 ± 27.3</td>
<td>120.4 ± 26.9</td>
<td>11.5 ± 22.4</td>
</tr>
<tr>
<td>hs-CRP (mg/dL)</td>
<td>0.12 ± 0.13</td>
<td>0.14 ± 0.33</td>
<td>0.02 ± 0.30</td>
</tr>
</tbody>
</table>

P-values were calculated using general linear model. GTE, green tea extract; BMI, body mass index; AST, aspartate transaminase; ALT, alanine transaminase; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; hs-CRP, highly-sensitive C-reactive protein.

Fig. 2. Changes in rectal mucosal proliferation index (RMPI) evaluated by Ki-67 immunohistochemical staining in control group (A) and GTE supplementation group (B). GTE, green tea extract. P-values were calculated using paired t-test and general linear model.
of UNL (range: 83–112 IU/L). Four of these five patients had a baseline ALT level more than UNL. Therefore, more attention should be paid to those with an abnormal LFT before the administration of GTE. According to our data, GTE supplementation at 0.9 g/day appears to be safe and tolerable in those with normal LFT.

This study has the following limitations. First, it was a single-center, randomized, open-label study. That is, there was no placebo provided to the control group because of some ethical issues, namely for the controls to take placebo capsules for such a long time. However, the endoscopists who performed the follow-up colonoscopy did not know whether he or she was allocated to the GTE supplementation group to minimize any bias. Second, the duration of the GTE supplementation was 1-year, which was a short time to evaluate the chemopreventive effect of GTE capsules in colorectal carcinogenesis. Third, only 30-paired samples from 30 subjects (14 from the control group and 16 from the GTE group) were available for the RMPI analysis. Fourth, the 72-h recall appears to have a limited value for the evaluation of dietary intake of individuals. Fifth, we evaluated smoking, alcohol-drinking, and tea drinking habits only at baseline, and not at the 1-year follow-up. Thus, we could not identify whether the changes in these lifestyle factors affected the clinical outcome. However, any lifestyle modifications in the controls, including regular exercise, smoking cessation, reduced alcohol intake, and increased intake of green tea, would act to reduce the strength of any observed associations. Furthermore, unlike Japanese people, more than 80% of the Koreans do not drink green tea regularly, and most Koreans who drink green tea regularly have no more than 2 cups per day (Table 1). Thus, if some of the subjects in the control group might have started drinking green tea regularly during the follow-up, the amount of EGCG intake in these patients should be much lower than in the subjects in the GTE supplementation group. Sixth, the drop-out rate in this study was relatively high (19.3% and 18.1% in the control and the GTE groups, respectively). However, between those who completed the study protocol and those who did not, the baseline characteristics showed no significant differences. Seventh, even though the co-administration of aspirin, COX-2 inhibitors, or NSAIDs was strictly prohibited, statin use could not be restricted. Eighth, the adenoma detection rate in the control group at the 1-year follow-up colonoscopy was relatively high (42.3%). This is higher than that in a previous Japanese study (31%) [8]. However, many of the study participants were regarded as a high risk group for the development of metachronous adenomas. All the polyps detected during the 1-year follow-up colonoscopy were less than 1 cm in size. Furthermore, information about the study groups was not given to the endoscopists who performed the follow-up colonoscopy, thus, the missing polyp rate was not different between the groups. Possibly, EGCG might have a role in the regression of pre-existing tiny polyps that were not detected during the first colonoscopy.

To conclude, our study showed that long-term GTE supplementation might be effective for the chemoprevention of metachronous adenomas in the Korean population. GTE in the prevention of colorectal cancer is safe and well tolerated. Further studies are warranted to confirm this issue.

Q3 Statement of authorship

CMS enrolled the study subjects, analyzed the data, and made the manuscript, tables, and figures. DHL designed the study, enrolled the subjects, and supervised the manuscript. AVS, HJJ and SBK performed endoscopy and collected the data. WCS performed the RMPI analysis and supervised the manuscript. YKK and SJL conceptualized the study and supervised the manuscript. SHP supervised the study protocol, performed statistical analyses, and reviewed the draft. NK advised the entire study protocol and supervised the manuscript. YSP and HY enrolled the study subjects, performed endoscopy, and supervised the manuscript.

Conflict of interest

Authors YKK and SHP are employees of AmorePacific Corporation; SJL was an employee of AmorePacific Corporation. The other authors have any conflict of interest or financial arrangement that could potentially influence the presented research.

Acknowledgements

This study was supported by AmorePacific R&D Center.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2017.01.014.

References


