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Efficacy of *Rikkunshito* for Functional Heartburn: A Prospective Pilot Study

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Background: Although *rikkunshito* was reported to be effective for treatment-resistant nonerosive gastroesophageal reflux disease (NERD), it is unclear which Rome IV subgroups of NERD patients benefit from *rikkunshito*. This study investigated the efficacy of *rikkunshito* in patients with functional heartburn.

Methods: Ten patients with functional heartburn who experienced symptoms of dyspepsia were enrolled and received *rikkunshito* for 8 weeks. The Frequency Scale for Symptoms of GERD (FSSG), the Japanese translation of the Quality of Life in Reflux and Dyspepsia (QOLRAD-J) questionnaire, and the Hospital Anxiety and Depression Scale (HADS) before, and 4 and 8 weeks after, administration were evaluated. Overall treatment efficacy (OTE) was evaluated at 8 weeks after administration.

Results: One patient voluntarily withdrew from treatment at 4 weeks. Total FSSG score was significantly (P = 0.039) lower 8 weeks after treatment or at discontinuation (13.2 ± 8.0) than before treatment (18.3 ± 10.7). Although QOLRAD-J score was higher 8 weeks after treatment or at discontinuation than before treatment, the difference was not significant different. HADS score was not significantly lower 8 weeks after treatment or at discontinuation, as compared with before treatment. However, total FSSG and HADS anxiety scores were positively correlated (correlation coefficient: 0.684, P = 0.027).

Conclusions: The findings from this first study of the efficacy of *rikkunshito* for functional heartburn suggest that it might be effective in such patients. (J Nippon Med Sch 2022; 89: 56–65)

Key words: *rikkunshito*, functional heartburn, nonerosive gastroesophageal reflux disease, potassium-competitive acid blocker-resistant, multichannel intraluminal impedance-pH monitoring

Introduction

Approximately 60% of patients with gastroesophageal reflux disease (GERD) have nonerosive GERD (NERD). According to the Rome IV criteria (the most recent international criteria for classifying functional gastrointestinal disorders), NERD is classified as true NERD (excessive esophageal acid exposure), reflux hypersensitivity (normal esophageal acid exposure and reflux-related symptoms), and functional heartburn (normal esophageal acid exposure and symptoms unrelated to reflux)[1]. Functional heartburn is a cause of proton pump inhibitor (PPI)-resistant NERD, and approximately 20% to 50% of patients with PPI-resistant NERD have functional heartburn[2–5]. Additionally, about half of NERD patients who are resistant to treatment with a potassium-competitive acid blocker (P-CAB) (a novel and potent acid secretion inhibitor), and whose symptoms do not improve, have functional heartburn[6–8]. Although the pathophysiology of functional heartburn is unclear, symptom onset is not triggered by reflux. Rather, symptoms are believed to be caused by visceral hypersensitivity, abnormal recognition processing in the brain, and changes in esophageal perception due to psychological factors such as stress and anxiety[1,9–11]. Functional heartburn was also reported to overlap with functional dyspepsia and irritable bowel syndrome[12–14].

According to the Rome IV criteria, antidepressants such as tricyclic antidepressants, serotonin reuptake in-

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hibitors, serotonin noradrenergic reuptake inhibitors, and other neuromodulators (eg, pregabalin or gabapentin) may relieve symptoms of functional heartburn[1]. Furthermore, a psychological approach is effective in some patients. However, overall therapeutic satisfaction is low, and symptoms are refractory in many patients with functional heartburn. In practice, treating functional heartburn in patients with GERD is a challenge. Japanese clinical practice guidelines for GERD describe the use of the Japanese herbal medicine *rikkunshito* as a treatment option for refractory GERD[15]. *Rikkunshito* exerts many pharmacological actions, such as promoting gastric emptying[16,17] and gastric adaptive relaxation[18–20] and suppressing upper gastrointestinal hypersensitivity[21,22]. Moreover, *rikkunshito* was reported to be effective for PPI-resistant NERD. However, no reports have comprehensively examined the effectiveness of *rikkunshito* in relation to Rome IV NERD subgroup. The objective of this pilot study was therefore to explore the efficacy of *rikkunshito* for patients with functional heartburn.

Methods

Patients

The enrollment period was September 2017 through December 2018, and 10 patients (mean age: 54.3 ± 17.2 years, four men) diagnosed with functional heartburn who experienced symptoms of dyspepsia were enrolled. This was a prospective, single-arm, open-label study (UMIN000029668). Patients with symptoms of dyspepsia and GERD such as heartburn and regurgitation despite administration of a P-CAB (20 mg/day vonoprazan) for ≥2 weeks and with a score of ≥8 points on the Frequency Scale for Symptoms of GERD (FSSG) (including ≥1 point in acid-related dysmotility symptom [ARD] score [dyspepsia-related symptom score]) were examined by esophagogastroduodenoscopy and high-resolution manometry (HRM), to exclude the possibility of organic disease and primary esophageal motility disorders. After excluding these conditions, multichannel intraluminal impedance-pH (MII-pH) monitoring was performed during P-CAB therapy to examine the relationship between reflux and symptoms. Functional heartburn was diagnosed when esophageal acid exposure was normal (percentage of time with an esophageal pH <4 was <4%) and symptom index (SI) was <50%. The Starlet ver. 8.1-15.3 (Starmedical, Inc., Tokyo, Japan) HRM system was used and diagnosis was determined according to the Chicago Classification v3.0—an HRM-based classification of esophageal motility disorders[23]. The exclusion criteria were as follows: grade A or worse reflux esophagitis (as determined by the modified Los Angeles classification), eosinophilic esophagitis, peptic ulcer, malignant tumors, primary esophageal motility disorders, abnormal esophageal acid exposure, SI of ≥50% in MII-pH monitoring, prior surgery of the upper gastrointestinal tract, other organic digestive disorders, pregnancy or lactation, and administration of Japanese herbal medicines within 4 weeks before administration of *rikkunshito*.

Study Protocol

The patients received *rikkunshito* 7.5 g/day for 8 weeks and FSSG (including total score and reflux symptom [RS], and ARD scores) was evaluated as the primary endpoint before, and 4 and 8 weeks after, administration[24]. As secondary endpoints, the Japanese translation of the Quality of Life in Reflux and Dyspepsia (QOLRAD-J) questionnaire (including total score and emotional distress, sleep disturbance, eating/drinking disorders, physical/social functioning, and vitality scores)[25] and the Hospital Anxiety and Depression Scale (HADS) (including total score and anxiety and depression scores)[26] were evaluated before, and 4 and 8 weeks after, administration. Overall treatment efficacy (OTE) was evaluated before and 8 weeks after administration. Additionally, correlations between primary and secondary endpoints were evaluated.

Concomitant use of the following drugs was prohibited during the study period: gastric acid secretion inhibitors (PPI/histamine-2 receptor antagonist/P-CAB), Japanese herbal medicines, anxiolytics, antipsychotics, antidepressants, mood stabilizers, psychostimulants, neuromodulators (eg, pregabalin or gabapentin), and nonsteroidal anti-inflammatory drugs. Furthermore, the following drugs were permitted to be used in combination as concomitantly restricted drugs throughout the study period, although changes in administration method or dose or new administration were forbidden: prokinetic drugs, gastrointestinal motility inhibitors, stomachics/digestants, and corticosteroids (excluding topical drugs). To assess safety, blood testing (aspartate aminotransferase, alanine transferase, gamma-glutamyl transpeptidase, alkaline phosphatase, total bilirubin, potassium, creatinine, and blood urea nitrogen) was performed before and 8 weeks after administration, and edema and adverse events were confirmed at 4 and 8 weeks after administration.

This study was performed in accordance with the provisions of the Declaration of Helsinki and was approved by the Ethics Committee for Human Research of Nippon

Medical School. All patients provided written informed consent.

FSSG

The FSSG is a questionnaire for diagnosing GERD and assessing treatment response. The FSSG can assess reflux- and dyspepsia-related symptoms and consists of 12 items. Seven concern reflux symptoms, and five concern dyspeptic symptoms. The total score is calculated by summing the RS and ARD scores, and a total score greater than 8 indicates probable GERD, as previously validated[24].

QOLRAD-J Questionnaire

The QOLRAD-J is a disease-specific quality of life (QOL) assessment instrument that consists of 25 questions across five domains: emotional distress, sleep disturbance, eating/drinking disorders, physical/social functioning, and vitality. The QOL of each domain is represented by a score from 1 to 7. Lower QOLRAD-J scores indicate poorer GERD-related QOL[25].

HADS

The HADS is used to assess anxiety and depression and is divided into anxiety and depression subscales. Each subscale contains seven items that are scored from 0 to 3; the total subscale score thus ranges from 0 to 21. Higher HADS scores indicate a greater tendency toward anxiety and depression. The recommended cutoff score for diagnosing anxiety and depression is ≥8 for each subscale[26].

OTE

The OTE questionnaire is a seven-point scale that rates changes in symptoms as highly improved, improved, slightly improved, unchanged, slightly aggravated, aggravated, or highly aggravated.

HRM

HRM studies were performed after a fast of at least 6 h. The Starlet HRM system has a catheter with 36 solid-state sensors at 1-cm intervals (Unisensor AG, Attikon, Switzerland). The catheter was placed transnasally and positioned to record from the hypopharynx to the stomach. The manometric protocol included a 5-min period to assess basal lower esophageal sphincter pressure and 10 swallows of 5 mL of water at 30-s intervals in the supine position. The presence or absence of primary esophageal motility disorders was diagnosed based on the Chicago Classification v3.0[23]. The normal cutoff value of each parameter of the Starlet system was determined by referring to examination values from healthy subjects.

MII-pH Monitoring

A Sleuth multichannel intraluminal impedance ambulatory system (Sandhill Scientific, Inc., Highlands Ranch, CO, USA) was used for 24-h MII-pH monitoring. At the end of the 24-h recording period, data were transferred and analyzed manually using dedicated software (BioView analysis; Sandhill Scientific, Inc.). Meal periods were marked and excluded from the analysis. Liquid-containing reflux episodes (liquid only and mixed gas-liquid) were identified based on previously described criteria as a retrograde 50% decline in impedance from baseline in at least two sites[27]. Similarly, gas-only reflux episodes were identified as a simultaneous increase in impedance of >5,000 ohms in at least two esophageal-measuring segments[27]. Reflux episodes were characterized on the basis of pH measurements as acidic, weakly acidic, or weakly alkaline according to a published consensus report on detection and definition of gastroesophageal reflux[28]. Symptoms were considered to be associated with liquid reflux if an episode of liquid reflux was detected 5 min before the symptom occurred. Association of gas-only reflux with symptoms were investigated for each reflux and symptom episode. The SI was calculated for each patient in relation to liquid or gas reflux and was defined as the number of symptoms associated with reflux divided by the total number of symptoms[29]. SIs were assessed for each individual symptom if patients recorded different types of symptoms.

Statistical Analysis

Age; body mass index; acid exposure time; number of reflux episodes; SI; distal contractile integral (DCI), distal latency, and integrated relaxation pressure (IRP) values; and FSSG, QOLRAD-J, and HADS scores are presented as mean ± SD. Statistical analysis of therapeutic effects was performed using the paired t-test or Wilcoxon signed rank test for changes in measured values obtained at each evaluation point. The relationship between primary and secondary endpoints was examined by using Pearson or Spearman rank correlation coefficients. $P < 0.05$ was considered statistically significant.

Results

Clinical and Demographic Characteristics

The clinical and demographic characteristics of the 10 patients with functional heartburn are shown in **Table 1**. One patient voluntarily withdrew at 4 weeks after administration of *rikkunshito*. No patient experienced adverse events. On MII-pH monitoring, mean esophageal acid exposure time was 0.01 ± 0.03%, and most reflux episodes on administration of vonoprazan 20 mg/day were weakly acidic reflux. Mean SI was 3.8% ± 9.30. On

Table 1 Clinical and demographic features of patients with functional heartburn

Number of patients	10
Age, years	54.3 ± 17.2
BMI	21.2 ± 2.6
Sex, male/female	4/6
Current alcohol use, n	2
Current smoking, n	3
H. pylori infection, n	4
Modified LA classification, grade M/N	3/7
MII-pH monitoring parameters	
Esophageal acid exposure time (%)	0.01 ± 0.03
Total number of reflux episodes	21.9 ± 16.54
Number of acid reflux episodes	0.7 ± 1.57
Number of weakly acidic reflux episodes	20.8 ± 15.23
Number of weakly alkaline reflux episodes	0.5 ± 1.27
SI (%)	3.8 ± 9.30
HRM parameters	
DCI (mm Hg-s-cm)	1,278.73 ± 1,303.40
DL (seconds)	6.43 ± 0.98
IRP (mm Hg)	11.92 ± 6.02

Data presented as mean ± SD
BMI: body mass index, *H. pylori*: *Helicobacter pylori*, LA: Los Angeles, MII-pH: multichannel intraluminal impedance-pH, SI: symptom index, HRM: high-resolution manometry, DCI: distal contractile integral, DL: distal latency, IRP: integrated relaxation pressure

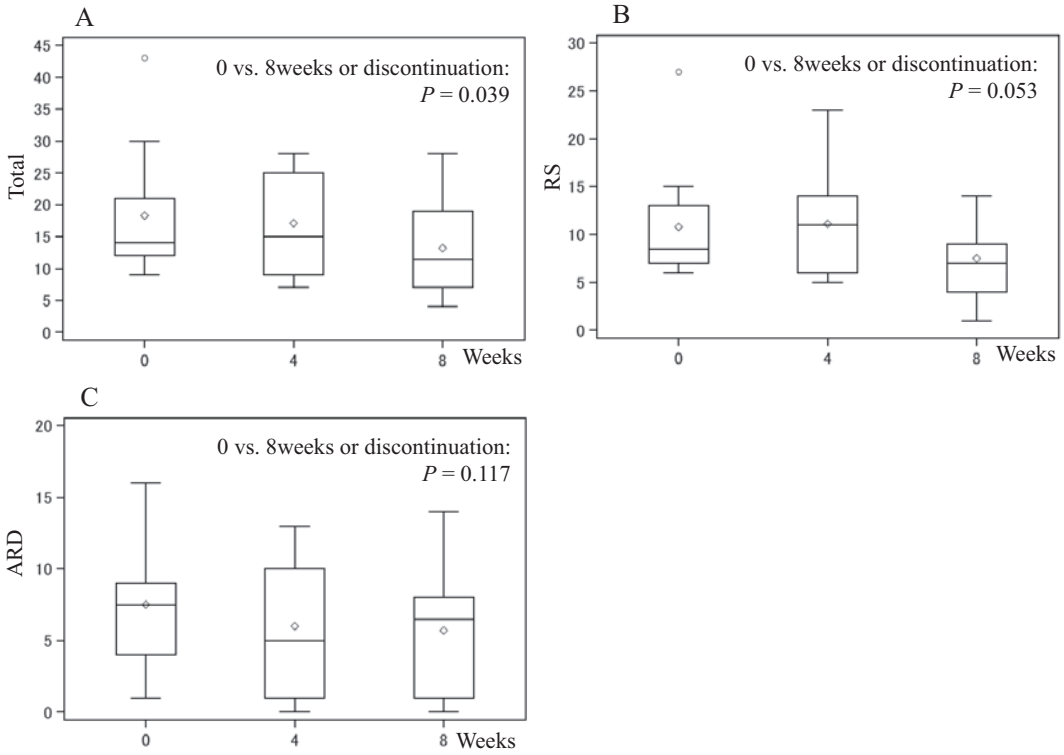

Fig. 1 Frequency Scale for Symptoms of GERD (FSSG) scores before (0 weeks) and 4 and 8 weeks after administration of *rikkunshito*
A: Total, B: Reflux symptoms (RS), C: Acid-related dysmotility symptoms (ARD)

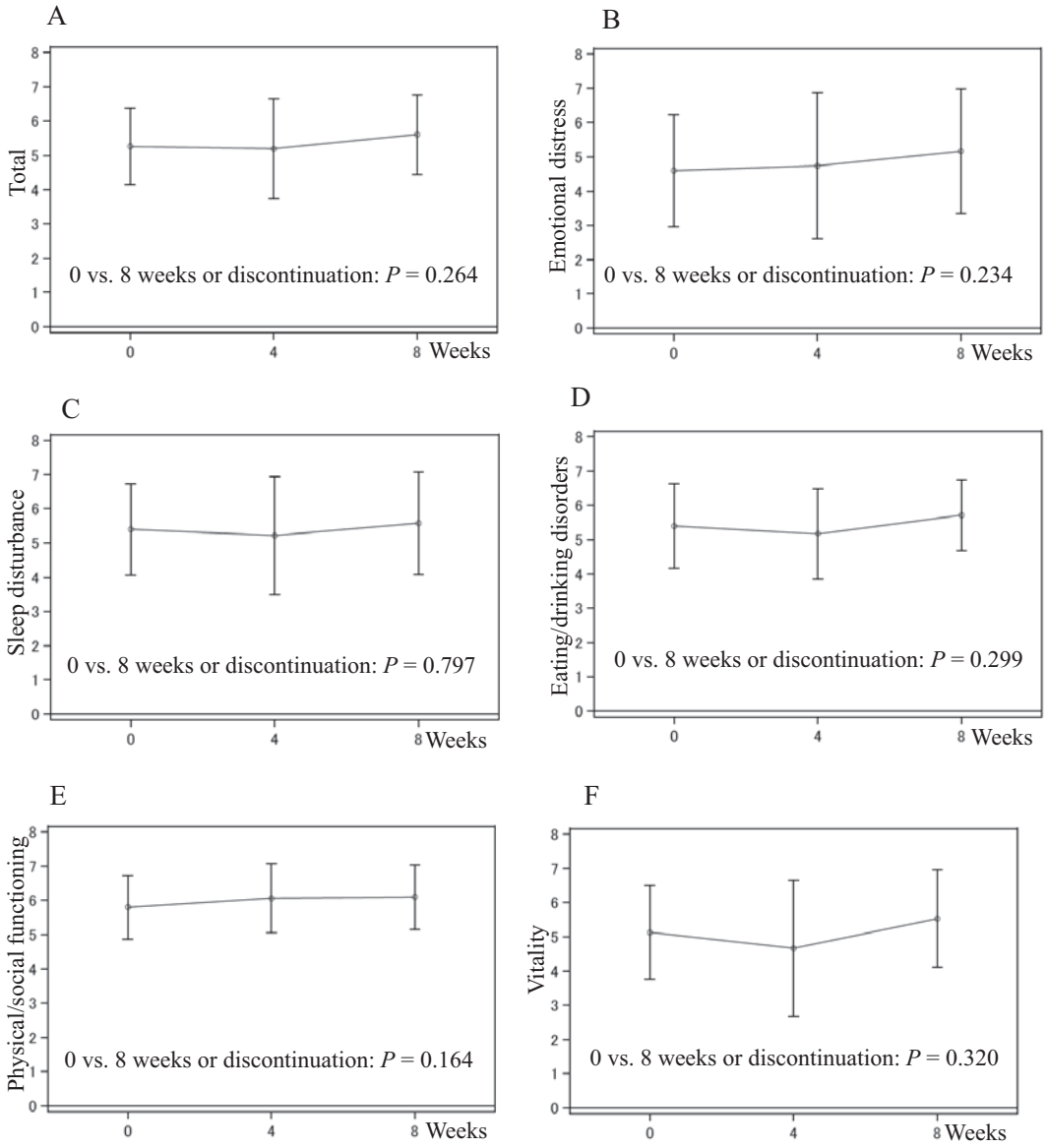

Fig. 2 Japanese translation of Quality of Life in Reflux and Dyspepsia (QOLRAD-J) questionnaire scores before (0 weeks) and 4 and 8 weeks after administration of *rikkunshito*
A: Total, B: Emotional distress, C: Sleep disturbance, D: Eating/drinking disorders, E: Physical/social functioning, F: Vitality

HRM, mean DCI was 1,278.73 ± 1,303.40 mm Hg-s-cm and mean IRP was 11.92 ± 6.02 mm Hg.

FSSG, QOLRAD-J, and HADS Scores and OTE

Regarding the FSSG, total score was significantly (P = 0.039) lower 8 weeks after treatment or at discontinuation (13.2 ± 8.0) than before treatment (18.3 ± 10.7). RS and ARD scores were lower at 8 weeks after treatment or at discontinuation (RS: 7.5 ± 4.2, ARD: 5.7 ± 4.7) than before treatment (RS: 10.8 ± 6.4, ARD: 7.5 ± 4.9), although the differences were not significant (RS: P = 0.053, ARD: P = 0.117) (**Fig. 1**).

Regarding the QOLRAD-J, total score and scores for emotional distress, sleep disturbance, eating/drinking disorders, physical/social functioning, and vitality were higher at 8 weeks after treatment or at discontinuation than before treatment. However, no significant differences were observed (before treatment vs. 8 weeks after treatment or at discontinuation, total: 5.26 ± 1.12 vs. 5.61 ± 1.16, P = 0.264; emotional distress: 4.60 ± 1.63 vs. 5.17 ± 1.81, P = 0.234; sleep disturbance: 5.40 ± 1.33 vs. 5.58 ± 1.49, P = 0.797; eating/drinking disorders: 5.40 ± 1.24 vs. 5.72 ± 1.04, P = 0.299; physical/social functioning: 5.80 ± 0.93 vs. 6.10 ± 0.94, P = 0.164; vitality: 5.13 ± 1.36 vs. 5.53 ± 1.43, P = 0.320) (**Fig. 2**).

Regarding the HADS, total score and depression score were lower at 8 weeks after treatment or at discontinu-

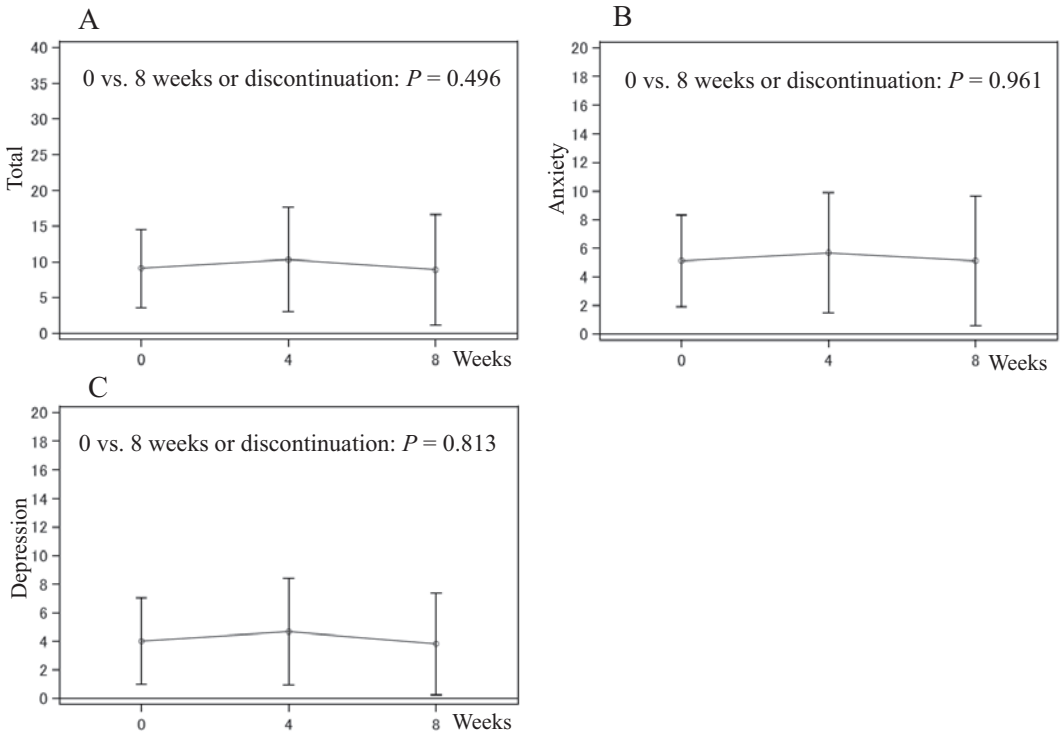

Fig. 3 Hospital Anxiety and Depression Scale (HADS) scores before (0 weeks) and 4 and 8 weeks after administration of *rikkunshito*
A: Total, B: Anxiety, C: Depression

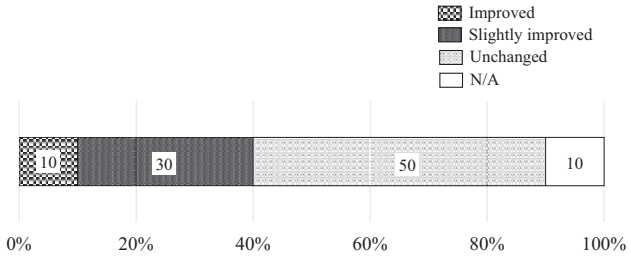

Fig. 4 Overall treatment efficacy (OTE) at 8 weeks after treatment
N/A: Not available

ation, although no significant differences were observed, and anxiety score did not change (before treatment vs. 8 weeks after treatment or at discontinuation, total score: 9.10 ± 5.49 vs. 8.90 ± 7.77, P = 0.496; anxiety: 5.10 ± 3.21 vs. 5.10 ± 4.56, P = 0.961; depression: 4.00 ± 3.02 vs. 3.80 ± 3.58, P = 0.813) (**Fig. 3**).

Regarding the OTE at 8 weeks after treatment, one patient improved, three slightly improved, five were unchanged, and one was not assessed because of discontinuation (**Fig. 4**).

Correlation of Changes in FSSG with QOLRAD-J Scores

Analysis of correlations of changes in FSSG with QOLRAD-J scores from 8 weeks after treatment or discontinuation to before treatment revealed correlations of total FSSG score with total QOLRAD-J, emotional distress, and sleep disturbance scores (total FSSG vs. total QOLRAD-J: correlation coefficient (r) = −0.669, P = 0.032; total FSSG vs. QOLRAD-J emotional distress: r = −0.738, P = 0.012; total FSSG vs. QOLRAD-J sleep disturbance: r = −0.652, P = 0.039). FSSG RS was correlated with total QOLRAD-J, emotional distress, and sleep disturbance scores (FSSG RS vs. total QOLRAD-J: r = −0.639, P = 0.045; FSSG RS vs. QOLRAD-J emotional distress: r = −0.731, P = 0.014; FSSG RS vs. QOLRAD-J sleep disturbance: r = −0.669, P = 0.032), and FSSG ARD score was correlated with total QOLRAD-J, emotional distress, eating/drinking disorders, and vitality scores (FSSG ARD vs. total QOLRAD-J: r = −0.728, P = 0.014; FSSG ARD vs. QOLRAD-J emotional distress: r = −0.659, P = 0.036; FSSG ARD vs. QOLRAD-J eating/drinking disorders: r = −0.753, P = 0.010; FSSG ARD vs. QOLRAD-J vitality: r = −0.861, P = 0.001) (**Fig. 5**).

Correlation of Changes in FSSG with HADS Scores

Analysis of correlations of changes in FSSG with HADS scores from 8 weeks after treatment or discontinuation to before treatment showed a correlation between total FSSG and HADS anxiety scores (r = 0.684, P = 0.027) (**Fig. 6**) but no correlation between FSSG RS and

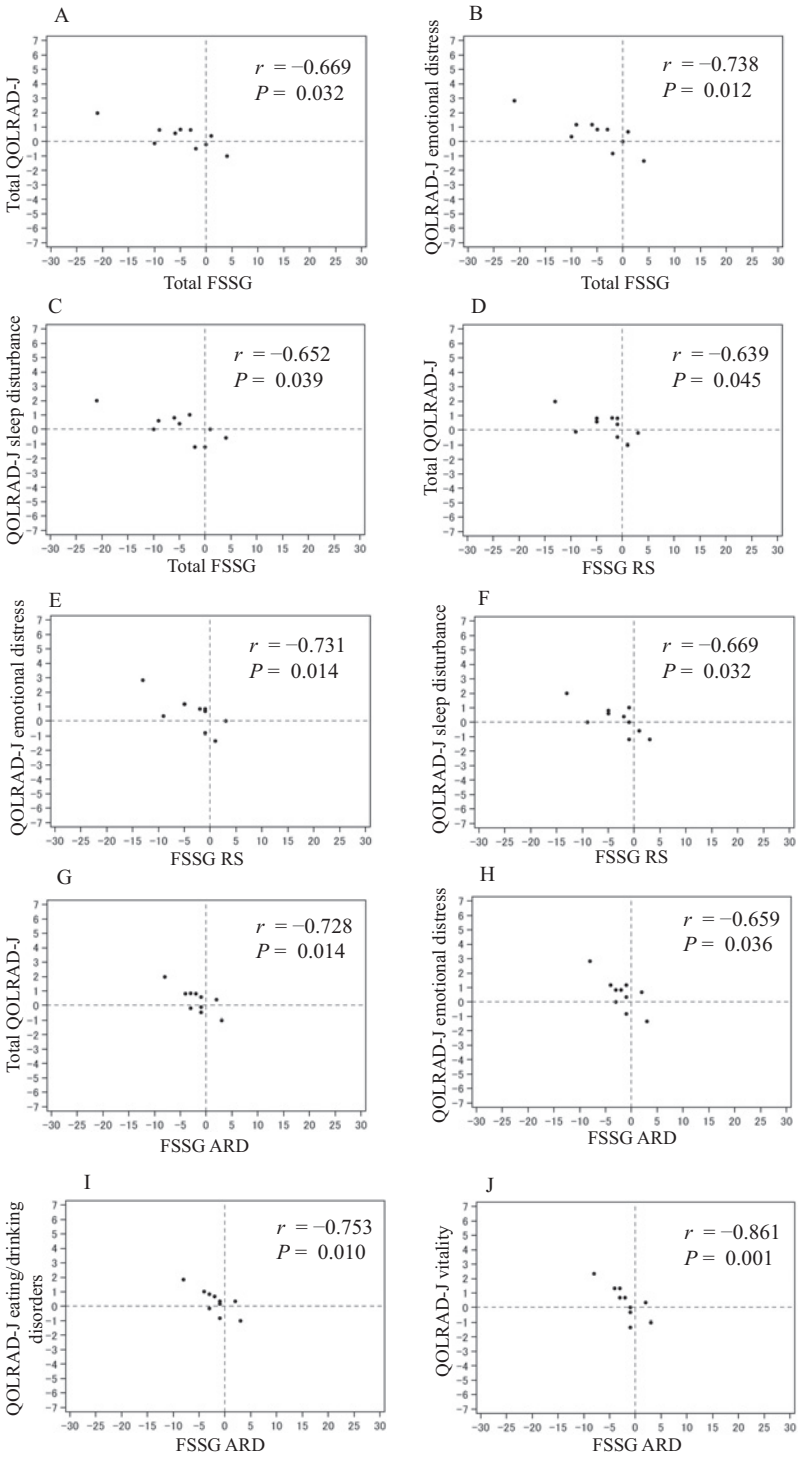

Fig. 5 Correlation of changes in Frequency Scale for Symptoms of GERD (FSSG) with Japanese translation of Quality of Life in Reflux and Dyspepsia (QOLRAD-J) questionnaire scores

A: Total FSSG vs. total QOLRAD-J, B: Total FSSG vs. QOLRAD-J emotional distress, C: Total FSSG vs. QOLRAD-J sleep disturbance, D: FSSG reflux symptom (RS) vs. total QOLRAD-J, E: FSSG RS vs. QOLRA-J emotional distress, F: FSSG RS vs. QOLRAD-J sleep disturbance, G: FSSG acid-related dysmotility symptom (ARD) vs. total QOLRAD-J, H: FSSG ARD vs. QOLRAD-J emotional distress, I: FSSG ARD vs. QOLRAD-J eating/drinking disorders, J: FSSG ARD vs. QOLRAD-J vitality

r: correlation coefficient

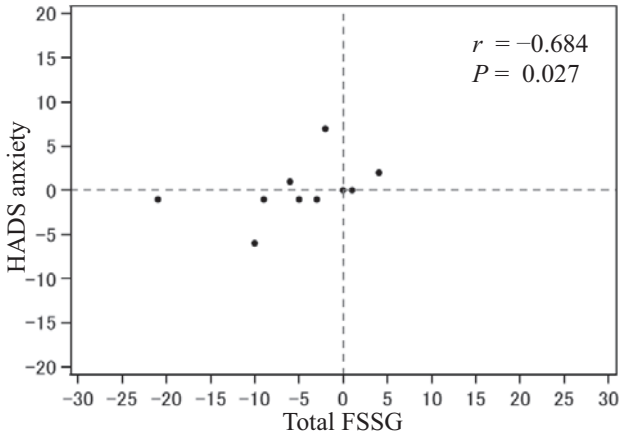

Fig. 6 Correlation of changes in total Frequency Scale for Symptoms of GERD (FSSG) with Hospital Anxiety and Depression Scale (HADS) anxiety scores
r: correlation coefficient

HADS scores or between FSSG ARD and HADS scores.

Correlation of Changes in FSSG Score with OTE

Analysis of correlations of changes in FSSG score from 8 weeks after treatment or discontinuation to before treatment with OTE revealed correlations between total FSSG score and OTE and between FSSG RS score and OTE (total FSSG vs. OTE: $r = 0.857$, $P = 0.0017$; FSSG RS vs. OTE: $r = 0.857$, $P = 0.0017$) (**Fig. 7**).

Discussion

This is the first report to examine the efficacy of *rikkunshito* in patients with functional heartburn. Prior studies examined the efficacy of *rikkunshito* in patients with PPI-resistant GERD and NERD. Tominaga et al. compared administration of rabeprazole (RPZ) 10 mg/day plus *rikkunshito* with administration RPZ 20 mg/day in patients with PPI-resistant GERD and found significant decreases in total FSSG scores in both groups after 4 weeks[30]. In another study, they compared administration of RPZ 10 mg/day plus *rikkunshito* with administration of RPZ 10 mg/day plus placebo in patients with PPI-resistant NERD and found that patients receiving RPZ plus *rikkunshito* had significantly greater improvements in mental QOL score than did those given RPZ plus placebo[31]. However, those studies were conducted in patients with GERD and NERD of various causes, and no subgroup analysis included patients with functional heartburn. No study has evaluated patients with functional heartburn.

In the present study, significant improvement in total FSSG score was observed after administration of *rikkunshito*, indicating it may be effective in patients with functional heartburn. In the DREAM study, which compared *rikkunshito* with placebo in patients with functional dyspepsia, those given *rikkunshito* showed significant improvement in modified-FSSG score, as compared with those given placebo. Furthermore, total HADS and anxiety scores decreased in the group receiving *rikkunshito*, indicating an association between improvement in psychiatric symptoms and improvement in GERD symptoms in response to *rikkunshito*[32]. *Rikkunshito* was reported to suppress increases in serum adrenocorticotropic hormone and cortisol under stress conditions[33] and might improve disturbance of autonomic nerves caused by psychological stress. In patients with functional heartburn, stress and anxiety may increase esophageal hypersensitivity and induce symptoms. Therefore, *rikkunshito* was expected to improve psychiatric symptoms in the present patients with functional heartburn. However, no significant improvements in HADS scores were observed after its administration, although total FSSG was positively correlated with HADS anxiety score, and improvement in GERD symptoms was associated with psychiatric symptoms. A possible explanation for the lack of significant improvement in HADS scores in the present study (unlike in the DREAM study) is that pretreatment mean total HADS, anxiety, and depression scores were low: 9.1, 5.1, and 4.0 points, respectively.

Although no significant changes were observed in QOLRAD-J scores after administration of *rikkunshito*, correlations were observed between changes in total FSSG and RS scores, and total QOLRAD-J, emotional distress, and sleep disturbance scores. Regarding the association of GERD with sleep disorders, reflux at night causes sleep disorders, and sleep disorders cause esophageal hypersensitivity[34]. Our results show an association between GERD symptoms and sleep quality in patients with functional heartburn.

In the present study of functional heartburn, patients with NERD resistant to treatment with P-CAB (20 mg/day vonoprazan) were selected rather than those with PPI-resistant NERD because the latter might experience symptoms caused by acid reflux induced by insufficient gastric acid suppression on administration of PPI. In contrast, in a previous study, no patients had symptoms caused by acid reflux while receiving a P-CAB[6]. Therefore, patients with functional heartburn can be more reliably selected from those with P-CAB-resistant NERD. Administration of vonoprazan 20 mg for 2-4 weeks may be useful in determining whether symptoms are caused by acid reflux (P-CAB test).

This study is limited by the fact that it was a single-

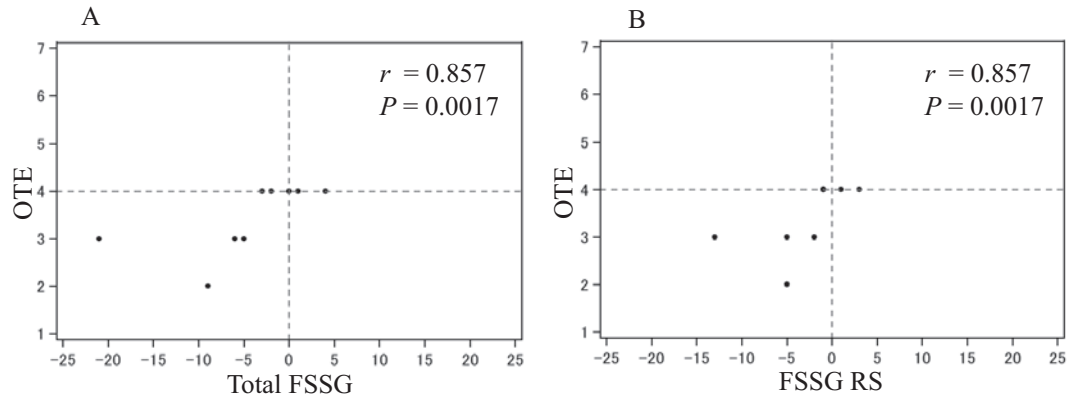

Fig. 7 Correlation of changes in Frequency Scale for Symptoms of GERD (FSSG) score with overall treatment efficacy (OTE)
OTE scale results were classified as follows: 1: highly improved, 2: improved, 3: lightly improved, 4: unchanged, 5: lightly aggravated, 6: aggravated, 7: highly aggravated.
A: Total FSSG vs. OTE, B: FSSG reflux symptom (RS) vs. OTE
r: correlation coefficient

arm study of a small number of patients, and because it was unclear why *rikkunshito* was effective in patients with functional heartburn. However, our results are valuable for newly exploring the efficacy of *rikkunshito* in patients with functional heartburn. Larger-scale placebo-controlled comparative studies are needed in order to further validate our results. In addition to patients with functional heartburn, the efficacy of *rikkunshito* should be studied in patients with true NERD, ie, those who experience excessive esophageal acid exposure, and in patients with reflux hypersensitivity with symptom onset triggered by reflux.

In conclusion, to our knowledge, this is the first study to investigate the efficacy of *rikkunshito* in patients with functional heartburn. The results suggest it may be effective in these patients.

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Conflict of Interest: Dr. Iwakiri received lecture fees from Otsuka Pharmaceutical Co., Ltd. and Takeda Pharmaceutical Co., Ltd. There are no other conflicts of interest to declare.

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