Current Therapeutic Research 84 (2017) 37–41

Contents lists available at ScienceDirect

Current Therapeutic Research

journal homepage: www.elsevier.com/locate/cuthre

Esophageal Motility and Rikkunshito Treatment for Proton Pump Inhibitor-Refractory Nonerosive Reflux Disease: A Prospective, Uncontrolled, Open-Label Pilot Study Trial

Takeo Odaka, MD, PhD[1,*], Shigeru Yamato, MD, PhD[2], Osamu Yokosuka, MD, PhD[3]

[1] Odaka Medical and Gastrointestinal Clinic, Chiba, Japan
[2] Division of Gastroenterology, National Center of Neurology & Psychiatry, Tokyo, Japan
[3] Funabashi Central Hospital, Chiba, Japan

ARTICLE INFO

Article history:
Accepted 28 March 2017

Key words:
proton pump inhibitor
non-erosive reflux disease
high-resolution impedance manometry
esophageal motility
rikkunshito

ABSTRACT

Background: Only a few reports focused on esophageal motility in patients with proton pump inhibitor (PPI)-refractory nonerosive reflux disease (NERD) and there has been no established strategy for treatment.
Objective: To clarify the characteristics of esophageal motility in patients with PPI-refractory NERD, we evaluated esophageal function using combined multichannel intraluminal impedance and esophageal manometry (MII-EM). In addition, we evaluated the efficacy of rikkunshito (RKT), which is a gastrointestinal prokinetic agent.
Methods: Thirty patients with NERD were enrolled and underwent MII-EM. After 8 weeks of RKT (7.5 g/d) treatment, MII-EM was repeated on patients with PPI-refractory NERD. Symptoms were assessed by the Gastrointestinal Symptom Rating Scale.
Results: In patients with PPI-refractory NERD, measures of complete bolus transit, peristaltic contractions, and residual pressure of the lower esophageal sphincter during swallowing deviated from the standard values and esophageal clearance was found to be deteriorated. RKT significantly improved the peristaltic contractions ($P < 0.05$), the complete bolus transit ($P < 0.01$), and the residual pressure of lower esophageal sphincter ($P < 0.05$) in these patients. The overall score ($P < 0.01$) and the subscale scores of acid reflux syndrome ($P < 0.05$), abdominal pain ($P < 0.05$), and indigestion syndrome ($P < 0.01$) in the Gastrointestinal Symptom Rating Scale were significantly improved by the 8-week RKT treatment.
Conclusions: In the pilot study, patients with PPI-refractory NERD had disorders of esophageal and lower esophageal sphincter motility that were improved by RKT. Further studies examining esophageal motor activity of RKT in PPI-refractory NERD are required. University hospital Medical Information Network (UMIN) Clinical Trial Registry identifier: UMIN000003092.
© 2017. The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Gastroesophageal reflux disease (GERD) is a common disorder caused by the reflux of gastric contents into the esophagus.[1] Nonerosive reflux disease (NERD) and reflux esophagitis (RE) represent the most common phenotypic presentations of GERD. A systematic review of the epidemiology and clinical characteristics of GERD in a Japanese population showed that 58.6% (2944 out of 5022) patients had NERD.[2] GERD is associated with a significant decrease in health-related quality of life (QOL) and imparts higher burden on work, daily productivity, and economic costs, especially when persistent.[3] The mainstream therapeutic strategy for GERD is inhibition of acid secretion by proton pump inhibitors (PPIs).[4] In fact, mucosal damage in most cases with RE can be improved by PPI. However, in clinical practices, troublesome GERD symptoms have been reported to persist in 20% to 30% of patients despite daily treatment with a standard PPI dose.[5] In particular, patients with NERD had higher PPI resistance rate (40%–50%) than patients with RE.[6]

Various underlying mechanisms have been shown to contribute to the failure of PPI treatment. Patients who did not respond to PPI

* Address correspondence to: Takeo Odaka, MD, PhD, Odaka Medical and Gastrointestinal Clinic, 2F MF Bldg, 1-12-3 Kanadenomori, Narashino-shi, Chiba, Japan 275-0028.
E-mail address: odk-tmrd@car.ocn.ne.jp (T. Odaka).

http://dx.doi.org/10.1016/j.curtheres.2017.03.007
0011-393X/© 2017. The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

treatment were reported to be more likely to have psychosocial comorbidity than those who were successfully treated with PPIs.[7] In a study using combined multichannel intraluminal impedance and pH monitoring, Iwakiri et al[8] revealed that persistent reflux symptoms in patients with PPI-refractory NERD were more likely to be primarily associated with nonacid reflux. Indeed, psychosocial comorbidity and nonacid reflux (ie, weak acid reflux and duodenogastroesophageal reflux) were proposed to be the underlying mechanisms for persistent heartburn despite treatment with PPIs.[9]

Problems in the treatment of GERD are usually attributed to pathologic conditions of PPI-refractory NERD. Therefore, understanding the gastroesophageal function in these patients is imperative. However, only few reports studies have focused on esophageal motility and there is no established treatment strategy for PPI-refractory NERD.

The traditional medication rikkunshito (RKT) (product No. TJ-43; Tsumura & Co, Tokyo, Japan), has been an approved for use by the Ministry of Health and Welfare in Japan, and has been widely prescribed for patients with upper-gastrointestinal (GI) symptoms.[10] RKT acts as a prokinetic agent that enhances gastric emptying[11] and improves deteriorated gastric accommodation.[12] A randomized, parallel comparative study showed that similar to a double dose of rabeprazole (RPZ), RKT combined with standard-dose RPZ decreased the frequency scale for the symptoms of GERD score in PPI-refractory GERD patients.[13] In addition, the Gastroenterology groups-Treatment for PPI-refractory GERD with Rikkunshito: A Multicenter, Randomized, Placebo-controlled, Double-blinded Trial (G-PRIDE) study showed that RKT may be useful in improving mental QOL and dyspeptic symptoms in patients with PPI-refractory NERD, especially in the elderly and women.[14] However, the mechanism of action of RKT in PPI-refractory NERD has not been well understood. Combined MII and esophageal manometry (MII-EM) is often used to assess esophageal motor function and provides clinically important information about esophageal function abnormalities in GERD and NERD patients.[15]

This pilot study aimed to investigate the characteristics of esophageal motility in patients with PPI-refractory NERD using MII-EM and to clarify the mode of action of RKT in PPI-refractory NERD.

Patients and Methods

Subjects and study procedure

Patients aged $\geq$20 years who were enrolled in the outpatient clinic of Chiba University Hospital from April 2008 to March 2010 for reflux symptoms based on the Japanese version of the Carisson-Dent self-administered questionnaire (QUEST) were eligible for this study. After undergoing mandatory upper GI endoscopy within 1 year before enrolment, patients without esophageal mucosal breaks (ie, NERD; n = 30) were enrolled. Therefore, the enrolled patients with NERD met the following selection criteria: diagnosed with GERD according to endoscopy findings and having a score $\geq$ 6 on the QUEST; presence of upper-GI symptoms, such as abdominal pain or dyspepsia; and provided written informed consent for participation in the study. Exclusion criteria were presence of severe cardiac failure, acute inflammatory disease, or other severe complications; pregnancy or considering pregnancy or lactation; serious disorder of the liver, gallbladder, or pancreas; gastrectomy; cannot tolerate oral administration; received drugs prohibited for concomitant use during the observation study period; ongoing intake of Kampo medicines; and any other factors considered inappropriate by the investigators during the study.

The study protocol was approved by the Ethics Committee of Chiba University Hospital (No. UMIN000003092). Patients with PPI-refractory NERD were defined as those with persistent GERD symptoms (QUEST score $\geq$ 6) despite a prior therapy with a standard PPI dose (RPZ 10 mg/d, omeprazole 20 mg/d, or lansoprazole 30 mg/d) for $\geq$4 weeks. MII-EM (Sandhill Scientific, Inc, Highlands Ranch, Colorado) was performed on all enrolled patients after washout of GI-related drugs and was repeated in patients with PPI-refractory NERD after 8 weeks of RKT treatment. Symptoms were assessed using the Gastrointestinal Symptom Rating Scale (GSRS) before and 4 or 8 weeks after starting following RKT treatment.

Questionnaire

The QUEST questionnaire was developed as a self-administered questionnaire for the diagnosis of GERD. The 7 questions in QUEST were devised to evaluate the nature of the symptoms experienced by patients and the temporal relationship between onset of symptoms and factors that were known to provoke (eg, meals, bending, stooping, and lifting); exacerbate (eg, fatty or spicy food); or relieve (eg, antacids) gastroesophageal reflux. Each response was assigned a score of positive, neutral, or negative; the score for each item was weighed.

The GSRS questionnaire is an inquiry table consisting of 15 items for the evaluation of general GI symptoms. Each GSRS item was rated on a 7-point Likert scale from no discomfort to very severe discomfort. Based on factor analysis, the 15 GSRS items broke down into the following 5 scales: abdominal pain (abdominal pain, hunger pain, and nausea), reflux syndrome (heartburn and acid regurgitation), diarrhea syndrome (diarrhea, loose stools, and urgent need for defecation), indigestion syndrome (borborygmus, abdominal distension, eructation, and increased flatus), and constipation syndrome (constipation, hard stools, and a feeling of incomplete evacuation).

Evaluation of esophageal and lower esophageal sphincter functions

Following a standardized methodology, esophageal and lower esophageal sphincter (LES) functions during swallowing were evaluated using a combined solid-state manometry and impedance assembly with 32 pressure channels and 5 impedance channels (MII-EM) before and after administration of RKT. The MII-EM assembly probe was inserted transnasally with the patient in a supine position. Using at least 3 intragastric sensors, the assembly was placed to record manometric data from the hypopharynx to the stomach. The sensors were positioned to record at least 1 intragastric impedance measurement from the beginning of the proximal esophageal segment through the distal esophagus and into the proximal stomach. The manometric protocol included 30 seconds without swallows, followed by 10 swallows of 5 mL distilled water with the patient in the supine position.

MII-EM data were analyzed using BioView software version 5.3.4 (Sandhill Scientific, Inc). High-resolution manometry system developed by Sandhill Scientific Inc has been validated.[16] Singh et al[17] evaluated the interobserver variability in esophageal body measurements among 4 novice physician users using a Sandhill Scientific Inc high-resolution manometry probe with 32 circumferential pressure sensors and 16 impedance channels. Complete bolus transit (CBT) was recorded as the passage of bolus from the most proximal site to all 4 distal impedance-measuring sites. Distal esophageal amplitude was the average contraction amplitude at 5 to 10 cm above the LES. Residual pressure was defined as the difference between the lowest pressure achieved during relaxation and the gastric baseline pressure. The percentages of people who deviated from normal range were

Table I
Demographic characteristics of patients with proton pump inhibitor (PPI)-refractory nonerosive reflux disease (NERD) and characteristics of patients with PPI-refractory or other NERD for esophageal motility using multichannel intraluminal impedance and esophageal manometry*

	The standard values	NERD		PPI-refractory NERD	
n		12		18	
Age, y		62.1 (42-75)		59.8 (38-80)	
Gender, M/F		6/6		8/10	
Current alcohol use, Y/N		4/8		4/14	
Current smoking, Y/N		2/10		2/16	
Overall GSRS score		2.0 (0.6)		2.2 (0.6)	
Lower esophageal sphincter functions			% of deviant		% of deviant
MRR pressure, mm Hg	10.0-45.0	19.5 (8.6)	16.7 (2/12)	18.6 (6.4)	11.1 (2/18)
Residual pressure, mm Hg	< 8.0	6.0 (4.3)	33.3 (4/12)	7.2 (4.7)	38.9 (7/18)
Esophageal motility					
CBT, %	> 75.0	67.5 (22.6)	41.7 (5/12)	54.4 (26.6)	83.3 (15/18)†
DEA, mm Hg	> 30.0	47.3 (22.6)	16.7 (2/12)	56.9 (4 5.1)	22.2 (4/18)
PC, %	> 80.0	79.2 (27.8)	25 (3/12)	56.1 (32.7)‡	66.7 (12/18)

CBT = complete bolus transit; DEA = distal esophageal amplitude; GSRS = Gastrointestinal Symptom Rating Scale; MRR = midrespiratory resting pressure; PC = peristaltic contractions.

* The bolus entry at each specific level obtained at the 50% point between 3-sec preswallow impedance baseline and impedance nadir during bolus presence and bolus exit determined as return to this 50% point on the impedance-recovery curve. CBT occurred if bolus entry occurred at the most proximal site and bolus exit points were recorded in all 4 distal impedance-measuring sites. The DEA was an average of contraction amplitude from 5 to 10 cm above the lower esophageal sphincter. The residual pressure is defined as the difference between the lowest pressure achieved during relaxation and the gastric baseline pressure.

† Significantly different (Wilcoxon's rank sum test) compared with patients with NERD at $P < 0.05$.

‡ Significantly different (Fisher exact test) compared with patients with NERD at $P < 0.05$.

calculated using the standard values of the MII-EM parameters[18,19] (Table I).

Statistical analysis

Statistical analyses were performed using the statistical program SAS version 9.4 (SAS Institute, Cary, North Carolina). Age and demographic factors were compared between groups using the Wilcoxon rank-sum test; the distribution of sex was compared using the Fisher exact test. Rates of the CBT and peristaltic contractions (PC) between PPI-refractory NERD and other NERD patients were compared by the Wilcoxon rank-sum test. Midrespiratory resting pressure, residual pressure, and distal esophageal amplitude were compared by paired *t* test. Treatment response within the groups was evaluated according to pre- and posttreatment GSRS scores using the Wilcoxon signed-rank test. *P* values < 0.05 were considered significant. All data are expressed as mean (SD).

Results

Comparison of esophageal motility among NERD patients according to PPI response

Comparisons between PPI-refractory NERD patients and other NERD patients in terms of LES function and esophageal motility on MII-EM are shown in Table I. In the PPI-refractory NERD patients (n = 18), deviation from the standard values was seen in 66.7% (12 out of 18) of patients who had a mean PC rate of 56.1% (32.7%) (standard value, ≥ 80%) and in 83.3% (15 out of 18) of patients who had a mean CBT rate of 54.4% (26.6%) (standard value, ≥ 75%). On the other hand, in the 12 patients without refractory NERD, the proportion of patients with such deviations was 25.0% (3 out of 12) for PC rate and 41.7% (5 out of 12) for CBT rate. The PC rate in patients with PPI-refractory NERD was significantly lower than that in other patients with NERD (56.1% [32.7%] vs 79.2% [27.8%]; $P < 0.05$).

The proportions of patients with nonstandard values of midrespiratory resting LES pressure (NERD, 16.7% [2 out of 12] vs PPI-refractory NERD, 11.1% [2 out of 18]) and residual LES pressure during swallows (NERD, 33.3% [4 out of 12] vs PPI-refractory NERD, 38.9% [7 out of 18]) were comparable between the 2 patient groups.

Effects of RKT on CBT, PC, and residual pressure of LES in patients with PPI-refractory NERD

Eight weeks of RKT treatment did not significantly change the midrespiratory resting pressure and distal esophageal amplitude of patients with PPI-refractory NERD (data not shown), but it significantly increased the mean PC rate from 54.44% (26.62%) to 81.54% (14.63%) and the mean CBT rate from 54.44% (26.62%) to 81.54% (14.63%) (Figure 1A and 1B). It significantly decreased the mean residual LES pressure from 7.19 (4.68) mm Hg to 4.98 (3.82) mm Hg (Figure 1C). After 8 weeks of RKT treatment, the CBT rate, PC rate, and residual pressure of the LES deviated from the normal values in 46.15% (6 out of 13), 23.08% (3 out of 13), and 15.38% (2 out of 13) of patients, respectively.

Effects of RKT on GI symptoms in PPI-refractory NERD

Changes in GSRS scores after RKT treatment in PPI-refractory NERD patients are shown in Table II. Eight weeks of RKT treatment significantly improved overall score ($P < 0.05$) and the subscale scores of acid reflux syndrome ($P < 0.05$), abdominal pain ($P < 0.05$), and indigestion syndrome ($P < 0.01$) in GSRS, but it did not improve the subscale GSRS scores of diarrhea and constipation syndromes.

Discussion

In the present study, majority of patients with NERD had midrespiratory resting pressure within the standard values. In contrast, percentages of people who deviated from normal range in residual pressure during swallowing were 38.9% (7 out of 18) and 33.3% (4 out of 12) in patients with PPI-refractory NERD and other NERD, respectively. These results suggest that relaxant effect of LES during swallowing may be attenuated in patients with NERD. In addition, percentages of people who deviated from normal range in CBT rate and PC rate were higher ($P < 0.05$) in

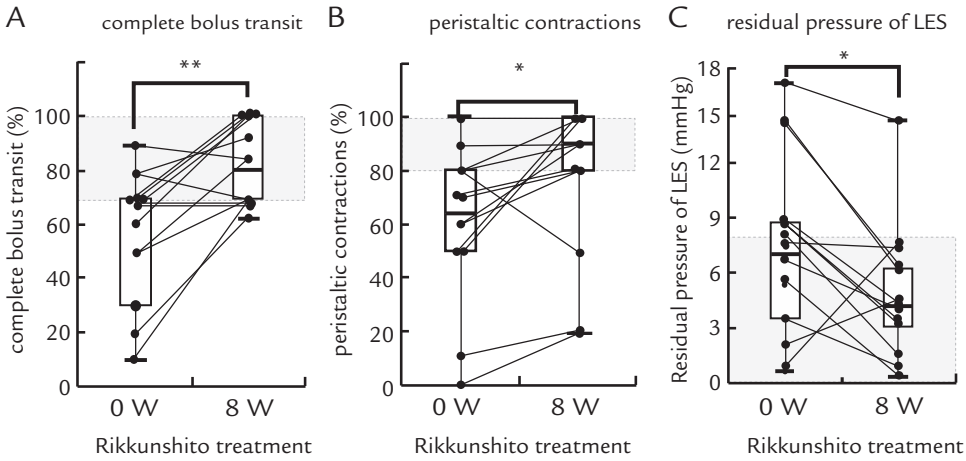

Figure 1. Effects of rikkunshito on the complete bolus transit rate, peristaltic contractions rate, and residual lower esophageal sphincter (LES) pressure during swallows in patients with proton pump inhibitor-refractory nonerosive reflux disease. (A) Complete bolus transit rate rate. (B) Peristaltic contractions rate. (C) Residual LES pressure during swallows before and after rikkunshito treatment. $^{*}P < 0.05$ and $^{**}P < 0.01$ indicate a significant difference between before and after treatment (Wilcoxon's signed rank test or paired *t* test). The gray area represents the standard values of complete bolus transit rate (> 75%), peristaltic contractions rate (80%), and residual LES pressure during swallows (< 8.0 mm Hg).

patients with PPI-refractory NERD than in other patients with NERD. That is to say, results of the evaluation of the esophageal peristaltic motor function of patients with NERD implied that swallowed food may easily stagnate in the esophagus of patients with PPI-refractory NERD. Likewise, Izawa et al[20] reported that esophageal motility disorders, such as ineffective esophagus motility, nonspecific esophageal motility disorders, and hypertensive LES, were found in 25% of patients with PPI-refractory NERD.

Several reports have described that symptom onset in patients with PPI-refractory NERD was primarily associated with non-acid reflux.[6,8] Therefore, administration of PPI alone to inhibit gastric acid secretion and ameliorate symptoms might be challenging in these patients. Several studies have attempted to combine PPI and prokinetic drugs (eg, mosapride citrate and RKT) for the treatment of PPI-refractory NERD.[14,21] RKT, a Japanese herbal medicine, is a prokinetic agent that enhances gastric emptying[11] and improves gastric accommodation.[12] A randomized, placebo-controlled, double-blind clinical trial on RKT showed that RKT improved mental QOL and dyspeptic symptoms in patients with PPI-refractory NERD.[14] In the present study, improvement of the subscale GSRS scores of acid reflux syndrome, abdominal pain, and indigestion implied that RKT may be useful for treatment of PPI-refractory NERD.

The present study demonstrated that the residual LES pressure during swallows, CBT rate, and PC rate of patients with PPI-refractory NERD were improved after 8 weeks of RKT treatment. On the other hand, Morita et al[22] reported that RKT at a standard dose did not have a significant effect on esophageal motor activity in healthy adults. This difference might be due to varying esophageal motor function between healthy adults and patients with PPI-refractory NERD. We speculate that RKT did not affect esophageal motor activity because healthy people have normal esophageal motor function. Our results suggested that RKT alleviated upper-GI symptoms by improving esophageal clearance.

Functional dyspepsia often overlaps with NERD in terms of pathology.[23] Kusunoki et al[12] demonstrated on extracorporeal ultrasonography that RKT enhanced meal-induced gastric accommodation reflex, gastric emptying rate, and motility index in patients with functional dyspepsia. In addition, a basic study on a GERD rat model revealed that GI dysmotility was associated with impaired ghrelin signaling and that RKT restored GI motility by improving the ghrelin response.[24] Considering these reports and our results, RKT might work by returning the gastric contents from the esophagus into the stomach through coordinated movement of the upper-GI tract (esophagus-stomach-duodenum) leading to improvement of GERD symptoms.

The present study has some limitations. First, the number of cases per group was limited, and the primary end points, sample size, and multiple comparisons were not set. This is because we position this study as a pilot study. Second, the evaluations were not done by blinded personnel. Validation of this study will be necessary in the future.

Table II
Effects of rikkunshito on gastrointestinal symptoms in patients with proton pump inhibitor-refractory nonerosive reflux disease

Gastrointestinal Symptom Rating Scale subscale	Week	Mean (SD)	*P* value
Overall	0	2.19 (0.60)	
	4	2.32 (0.60)	0.677
	8	1.56 (0.40)**	0.013
Reflex syndrome	0	3.64 (1.90)	
	4	3.42 (1.50)	0.662
	8	2.12 (1.00)*	0.028
Abdominal pain	0	1.87 (0.90)	
	4	2.14 (0.90)	0.949
	8	1.41 (0.40)*	0.027
Indigestion syndrome	0	2.36 (1.00)	
	4	2.68 (1.20)	0.195
	8	1.58 (0.60)**	0.006
Diarrhea syndrome	0	1.39 (1.00)	
	4	1.67 (0.50)*	0.020
	8	1.58 (0.50)	0.805
Constipation syndrome	0	1.69 (0.80)	
	4	1.78 (1.00)	1.000
	8	1.36 (0.60)	0.219

* Significantly different from score at 0 week (Wilcoxon's signed rank test) at $P < 0.05$.

** Significantly different from score at 0 week (Wilcoxon's signed rank test) at $P < 0.01$.

Conclusions

In this pilot study, disorders of esophageal motility and impaired esophageal clearance were observed in patients with PPI-refractory NERD. Although large-scale clinical research for

verification is required, RKT may be useful for the treatment of PPI-refractory NERD by improving esophageal clearance. Further studies examining esophageal motor activity of RKT in PPI-refractory NERD will be necessary and worth conducting.

Conflict of Interest Statement

Takeo Odaka has received grant support from Tsumura & Co. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

Acknowledgments

Takeo Odaka contributed to the study concept and design, interpretation of data, acquisition of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. Shigeru Yamato contributed to the study concept and design. Osamu Yokosuka contributed to the study concept and design and interpretation of data. The authors thank Dr. Teruo Kozu for providing advice on the study concept and design.

References

1. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence based consensus. *Am J Gastroenterol.* 2006;101:1900–20.
2. Fujiwara Y, Arakawa T. Epidemiology and clinical characteristics of GERD in the Japanese population. *J Gastroenterol.* 2009;44:518–34.
3. Suzuki H, Matsuzaki J, Masaoka T, Inadomi JM. Greater loss of productivity among Japanese workers with gastro-esophageal reflux disease (GERD) symptoms that persist vs resolve on medical therapy. *Neurogastroenterol Motil.* 2014;26:764–71.
4. Coté GA, Howden CW. Potential adverse effects of proton pump inhibitors. *Curr Gastroenterol Rep.* 2008;10:208–14.
5. Fass R. Proton-pump inhibitor therapy in patients with gastro-oesophageal reflux disease: putative mechanisms of failure. *Drugs.* 2007;67:1521–30.
6. Fass R, Shapiro M, Dekel R, Sewell J. Systematic review: proton pump inhibitor failure in gastro-oesophageal reflux disease. Where next? *Aliment Pharmacol Ther.* 2005;22:79–94.
7. Nojkov B, Rubenstein JH, Adlis SA, et al. The influence of comorbid IBS and psychological distress on outcomes and quality of life following PPI therapy in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther.* 2008;27:473–82.
8. Iwakiri K, Kawami N, Sano H, et al. Acid and non-acid reflux in Japanese patients with non-erosive reflux disease with persistent reflux symptoms, despite taking a double-dose of proton pump inhibitor: a study using combined pH-impedance monitoring. *J Gastroenterol.* 2009;44:708–12.
9. Fass R, Sifrim D. Management of heartburn not responding to proton pump inhibitors. *Gut.* 2009;58:295–309.
10. Tominaga K, Arakawa T. Kampo medicines for gastrointestinal tract disorders: a review of basic science and clinical evidence and their future application. *J Gastroenterol.* 2013;48:452–62.
11. Tatsuta M, Iishi H. Effect of treatment with liu-jun-zi-tang (TJ-43) on gastric emptying and gastrointestinal symptoms in dyspeptic patients. *Aliment Pharmacol Ther.* 1993;7:459–62.
12. Kusunoki H, Haruma K, Hata J, et al. Efficacy of Rikkunshito, a traditional Japanese medicine (Kampo), in treating functional dyspepsia. *Intern Med.* 2010;49:2195–202.
13. Tominaga K, Iwakiri R, Fujimoto K, et al. Rikkunshito improves symptoms in PPI-refractory GERD patients: a prospective, randomized, multicenter trial in Japan. *J Gastroenterol.* 2012;47:284–92.
14. Tominaga K, Kato M, Takeda H, et al. A randomized, placebo-controlled, double-blind clinical trial of rikkunshito for patients with non-erosive reflux disease refractory to proton-pump inhibitor: the G-PRIDE study. *J Gastroenterol.* 2014;49:1392–405.
15. Conchillo JM, Smout AJ. Review article: intra-oesophageal impedance monitoring for the assessment of bolus transit and gastro-oesophageal reflux. *Aliment Pharmacol Ther.* 2009;29:3–14.
16. Herregods TV, Roman S, Kahrilas PJ, Smout AJ, Bredenoord AJ. Normative values in esophageal high-resolution manometry. *Neurogastroenterol Motil.* 2015;27:175–87.
17. Singh ER, Rife C, Clayton S, Naas P, Nietert P, Castell DO. Interobserver variability in esophageal body measurements with high-resolution manometry among new physician users. *J Clin Gastroenterol.* 2013;47:e12–6.
18. Wilson JA, Mainie I, Tutuian R, Agrawal A, Castell DO. Multichannel intraluminal impedance and esophageal manometry data for unrestricted swallowing: establishing normal values. *Dis Esophagus.* 2008;21:51–6.
19. Castell DO, Diederich LL, Castell JA. Esophageal motility and pH testing technique and interpretation. 3rd ed. Sandhill Scientific, Inc. 2000.
20. Izawa S, Funaki Y, Iida A, et al. The role of gastroesophageal reflux in relation to symptom onset in patients with proton pump inhibitor-refractory nonerosive reflux disease accompanied by an underlying esophageal motor disorder. *Digestion.* 2014;89:61–7.
21. Miwa H, Inoue K, Ashida K, et al. Randomised clinical trial: efficacy of the addition of a prokinetic, mosapride citrate, to omeprazole in the treatment of patients with non-erosive reflux disease - a double-blind, placebo-controlled study. *Aliment Pharmacol Ther.* 2011;33:323–32.
22. Morita T, Furuta K, Adachi K, et al. Effects of Rikkunshito (TJ-43) on Esophageal Motor Function and Gastroesophageal Reflux. *Neurogastroenterol Motil.* 2012;18:181–6.
23. Noh YW, Jung HK, Kim SE, Jung SA. Overlap of Erosive and Non-erosive Reflux Diseases With Functional Gastrointestinal Disorders According to Rome III Criteria. *J Neurogastroenterol Motil.* 2010;16:148–56.
24. Nahata M, Muto S, Oridate N, et al. Impaired ghrelin signaling is associated with gastrointestinal dysmotility in rats with gastroesophageal reflux disease. *Am J Physiol Gastrointest Liver Physiol.* 2012;303:G42–53.