Strategy for treatment of nonerosive reflux disease in Asia

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Abstract

The paper is to review the clinical and pathophysiologic differences between of nonerosive reflux disease (NERD) and reflux esophagitis (RE), and to propose a treatment strategy for NERD, especially for patients in Asia. A Medline search was performed regarding the clinical and pathophysiologic differences between NERD and RE, and treatment of NERD and RE. The characteristics of NERD patients in Asia are as follows: (1) high proportion of female patients, (2) low frequency of hiatal hernia, (3) high frequency of H pylori infection, (4) severe glandular atrophy of the gastric mucosa, and (5) frequent resistance to proton pump inhibitor (PPI) therapy. In Asian NERD patients, exposure of the esophagus to acid is not increased, and esophageal motility is normal. These characteristics are similar to those of patients in Western countries. Our recommended first-choice treatment is administration of PPI in combination with a prokinetic agent. However, at present, because there is limited evidence regarding effective treatments for NERD, it is best to try several different treatment strategies to find the best treatment for each patient.

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Key words: Nonerosive reflux disease; Asia; Treatment

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition that develops when reflux of stomach contents causes troublesome symptoms and/or complications[1]. GERD is more common in Western countries than in Asian countries, such as China, Korea, and Japan. Epidemiologic studies show a prevalence of GERD symptoms in Western countries ranging from 20% to 40%[2,3] and in Asian countries ranging from 5% to 17%[4]. The prevalence in Asian countries has increased gradually[4]. Esophagogastroduodenoscopy (EGD) is the gold standard for the diagnosis of erosive GERD (reflux esophagitis (RE)), and the Los Angeles (LA) classification of esophagitis is generally accepted as the best means for endoscopic assessment of GERD[5]. In Japan, the prevalence of RE (LA classification grades A, B, C, and D) is approximately 15%, and most of these cases are grade A or B[6]. The majority of GERD cases are cases of nonerosive reflux disease (NERD).

NERD was previously considered a mild/early type of RE that would progress to severe RE. However, it was reported that, regardless of therapy, only 2.7% of NERD patients develop RE after 3 years and only 3% of patients develop RE after 6 years[7]. A recent retrospective study of 2306 GERD patients found that these patients at least two separate upper endoscopic examinations during the 7-year (mean) follow-up period. Examinations revealed that 69% of the patients were unchanged, 21% were improved, and 11% became worse[8]. Another study[9] reported similar results. These studies suggest that NERD rarely progresses to RE over time. In addition, NERD is significantly more refractory to treatment than RE[10]. Therefore, it was recently suggested that the underlying mechanism of development of NERD is different from that of RE. Here we review the clinical and pathophysiologic differences between NERD and RE and propose a treatment strategy for NERD, especially for patients in Asia.
It seems that there are differences in pathophysiology between Asian RE patients and Western RE patients, because the grades of motility index abnormalities are different between them. However, there seems no significant difference in pathophysiology between Asian NERD and Western NERD patients, because clinical and esophageal motility characteristics are considerably similar between them.

PATHOPHYSIOLOGY OF NERD

The main pathophysiology of RE is excessive exposure of the esophagus to gastric acid. Approximately 90% of patients with RE can be cured with a PPI, which is the strongest type of gastric acid suppressor. In contrast, only one-third of NERD patients can be cured with a PPI. Although the cause of NERD that is responsive to PPI may be excessive exposure of the esophagus to acid, PPI-resistant NERD may be associated with the factors described below.

Incomplete acid suppression

In some patients, even the highest approved dose of PPI cannot sufficiently suppress gastric acid secretion. In patients with insufficient gastric acid suppression, gastric juice may reflux, exposing the esophagus to acid. The time required for metabolism of PPI differs between patients possibly due to polymorphisms in the genes encoding metabolic enzymes, such as CYP2C19. In patients with the rapid metabolic phenotype, administration of twice the approved dose of PPI and concomitant administration of PPI and H$_2$-receptor antagonist (H$_2$RA) may be more effective. It has also been reported that administration of an aluminum- and magnesium-containing antacid may be effective for some NERD patients.

Esophageal hypersensitivity to acid

Some patients with severe RE do not have symptoms of acid regurgitation, even if severe esophageal acid exposure is confirmed. However, many NERD patients have a normal level of esophageal acid exposure. Therefore, there appears to be significant esophageal hypersensitivity to acid exposure in PPI-resistant NERD patients, and symptoms may occur when gastric acid is refluxed. Hyperosmotic foods, such as cake and chocolate, and alcoholic beverages may be the cause of this esophageal hypersensitivity. Ingestion of such foods may induce acid reflux and subsequent symptoms in PPI-resistant NERD patients.
foods and drinks may cause heartburn. It has been suggested that ingestion of hyperosmotic foods/drinks loosens the tight junctions between esophageal epithelial cells, and when gastric acid is refluxed, it easily intrudes between epithelial cells and stimulates the terminals of sensory nerves[26].

Esophageal hypersensitivity to esophageal wall distension
In NERD patients, heartburn symptoms are induced by distension of the esophageal wall by balloon dilatation or by pumping saline into the esophageal lumen[29]. These findings suggest the possibility that foods, air, and fluids that contain no acid may cause heartburn symptoms simply by distending of the esophageal wall.

Reflex of duodenal juice (bile and pancreatic juice)
PPI suppresses gastric acid excretion but has no effect on reflux itself. Therefore, in patients with duodenogastric reflux, duodenal juice (bile and pancreatic juice) may be refluxed into the esophagus. It is possible that the refluxed duodenal juice may affect the esophageal mucosa[30]. NERD patients frequently have functional dyspepsia[4], and significant duodenogastric reflux and delayed gastric emptying time in patients with functional dyspepsia have been reported[31,32]. These findings support the idea that reflux of duodenal juice into the esophagus causes NERD.

Esophageal motility abnormalities
It has been reported that NERD patients show normal resting LES pressure and primary contraction waves but significantly reduced frequency of secondary contraction waves[19,33]. This may be due to a reduced response to distension of the esophageal wall. Secondary contraction waves are stimulated by distension of the esophageal wall and act to discharge refluxed gastric acid and air into the stomach. Heartburn symptoms may be associated with reduced motility function in the esophageal wall.

Sustained esophageal contraction
Sustained contraction of the longitudinal muscles of the esophagus causes heartburn, and prolonged contraction may lead to chest pain. This phenomenon is called sustained esophageal contraction (SEC) and is identified by intraluminal ultrasonography[34,35]. SEC occurs just before the onset of heartburn symptoms. There are two types of SEC: SEC with or without subsequent acid reflux. Because patients with the latter type also have heartburn symptoms, the association of SEC with NERD is of great interest.

Psychological factors
NERD patients frequently have mental disorders[33]. Psychological factors are associated with response to treatment as well as symptoms[36]. A high level of anxiety is predictive for the nonresponse to acid suppression therapy.

Eosinophilic esophagitis
Eosinophilic esophagitis affects both children and adults and is characterized by symptoms of GERD and dense esophageal eosinophilia, both of which are unresponsive to PPI[37,38]. This disease is caused by food allergies or by aeroallergens. Effective treatment include systemic/topical corticosteroids, or specific food elimination. Esophageal stricture is a potential complication, and the natural history of the disease is still unknown. Eosinophilic esophagitis may be diagnosed as PPI-resistant NERD, but should be excluded from the diagnosis of NERD.

TREATMENT STRATEGY FOR NERD IN ASIA
At present, PPI-based step-down treatment is recommended for GERD patients[39,40]. In a meta-analysis, the relative risks of PPI and H2RA treatment for NERD compared with placebo were 0.69 (95% confidence interval, 0.62-0.78) and 0.84 (0.74-0.95), respectively, indicating that PPI is a more effective treatment than H2RA[41]. PPI treatment can eliminate NERD symptoms faster than H2RA treatment. In addition, PPI treatment has been reported to be more cost-effective than other treatment[42].

Prokinetics such as mosapride, itopride, metoclopramide, and domperidone are also effective for treatment of NERD[43-45]. Prokinetics are thought to work by reducing reflux of duodenal juice into the esophagus[35] and speeding absorption of PPI. In addition, mosapride improves esophageal motility, whereas metoclopramide and domperidone do not have this ability[46]. Mosapride shortens bolus transit time in the esophagus, reduces the duration of the longest reflux episode and reflux fraction time, and enhances the contraction strength in the lower esophagus.

Reflex of stomach contents is related to transient LES relaxation (TLESR) in NERD patients[47]. Therefore, control of TLESR is another important point for NERD treatment. 5-HT, cholecystokinin (CCK)-A, and gamma-aminobutyric acid (GABA) receptors influence TLESR[48,50]. 5-HT3 receptor antagonist, CCK-A receptor antagonist, and GABA receptor agonist reduce the frequency of TLESR. Mosapride is a selective 5-HT3 receptor antagonist, and the metabolite acts as a 5-HT3 receptor antagonist[51,52]. Therefore, mosapride reduces the frequency of TLESR, leading to reduced gastric acid reflux in NERD patients.

Some NERD cases are refractory to PPI and/or prokinetics. In these patients, psychological factors may be associated with symptoms. In these patients, administration of an antidepressant and/or minor tranquilizer should be considered. However, evidence for the benefits of these agents in treatment of NERD is weak[53], and further studies are needed to clarify the effects of such medications on NERD.

For NERD patients with infrequent symptoms of heartburn, on-demand therapy with PPI (and/or prokinetics) is proposed as the best treatment option[44,54]. Additional studies of the effectiveness of this treatment regimen are needed.

Here we propose a new strategy for treatment of NERD in Asia based on the basic idea of step-down
therapy (Figure 1). The recommended first-choice treatment is administration of PPI in combination with a prokinetic agent such as mosapride. PPI can cure only one-third of NERD patients, a prokinetic agent in conjunction with the PPI can increase the efficacy. NERD is frequently associated with functional dyspepsia that can be treated with prokinetic agents. In addition, because the quality of life of NERD patients is quite low, NERD patients need quicker and more effective treatment options. If this treatment is not effective, twice the recommended dose of PPI or combined treatment with PPI and an H2 RA is recommended. PPI together with on-demand aluminum- and magnesium-containing antacid might be effective. If these treatments are not effective, administration of an antidepressant or minor tranquilizer should be considered. Herbal medicines such as rikkunshito may provide relief for some patients, and are often administered especially in Asian countries.

For patients with infrequent symptoms, on-demand treatment with PPI and/or a prokinetic agent is recommended. However, there is not sufficient evidence for a best treatment for NERD. Further studies are needed to clarify the efficacy of treatment. Large-scale, double-blind, randomized controlled trials of PPI vs PPI with a prokinetic agent are also needed to clarify the benefit of the prokinetic agent.

Further trials are needed to establish the strategy for treatment of NERD. At present, because there is limited evidence regarding effective treatments for the disease, it is best to try several different treatment strategies to find the best treatment for each patient.

REFERENCES

1. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006; 101: 1900-1920; quiz 1943
2. Moayyedi P, Talley NJ. Gastro-oesophageal reflux disease. Lancet 2006; 367: 2086-2100
3. Fass R. Erosive esophagitis and nonerosive reflux disease (NERD): comparison of epidemiologic, physiologic, and therapeutic characteristics. J Clin Gastroenterol 2007; 41: 131-137
4. Wong BC, Kinoshita Y. Systematic review on epidemiology of gastroesophageal reflux disease in Asia. Clin Gastroenterol Hepatol 2006; 4: 398-407
5. Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, Johnson F, Hongo M, Richter JE, Spechler SJ, Tytgat GN, Wallin L. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999; 45: 172-180
6. Manabe N, Yoshihara M, Sasaki A, Tanaka S, Haruma K, Chayama K. Clinical characteristics and natural history of patients with low-grade reflux esophagitis. J Gastroenterol Hepatol 2002; 17: 949-954
7. Kuster E, Ros E, Toledo-Pimentel V, Pujol A, Bordas JM, Grande L, Pera C. Predictive factors of the long term outcome in gastro-oesophageal reflux disease: six year follow up of 107 patients. Gut 1994, 35: 8-14
8. Sontag SJ, Sonnenberg A, Schnell TG, Leya J, Metz A. The long-term natural history of gastroesophageal reflux disease. J Clin Gastroenterol 2006; 40: 398-404
9. Fullard M, Kang JY, Neild P, Poullis A, Maxwell JD. Systematic review: does gastro-oesophageal reflux disease progress? Aliment Pharmacol Ther 2008; 24: 33-45
10. Fujiwara Y, Higuchi K, Shibata M, Yamamori K, Watanabe Y, Sasaki E, Tominaga K, Watanabe T, Oshitani N, Arakawa T. Differences in clinical characteristics between patients with endoscopy-negative reflux disease and erosive esophagitis in Japan. Am J Gastroenterol 2005; 100: 754-758
11. Nakamura T, Shikakawa K, Masuyama H, Sugaya H, Hiraishi H, Terano A. Minimal change esophagitis: a disease with characteristic differences to erosive esophagitis. Aliment Pharmacol Ther 2005; 21 Suppl 2: 19-26
12. Mishima I, Adachi K, Arima N, Amano K, Takashima T, Moritani M, Furuta K, Kinoshita Y. Prevalence of endoscopically negative and positive gastroesophageal reflux disease in the Japanese. Scand J Gastroenterol 2005; 40: 1005-1009
13. Wu JC, Cheung CM, Wong VW, Sung JJ. Distinct clinical characteristics between patients with nonerosive reflux disease and those with reflux esophagitis. Clin Gastroenterol Hepatol 2007; 5: 690-695
14. Miwa H, Sasaki M, Furuta T, Koike T, Habu Y, Ito M, Fujiwara Y, Wada T, Nagahara A, Hongo M, Chiba T, Kinoshita Y. Efficacy of rabeprazole on heartburn symptom resolution in patients with non-erosive and erosive gastro-oesophageal

Figure 1 Proposed treatment strategy for NERD patients in Asia. A: Patients with moderate or severe symptoms; B: Patients with infrequent symptoms.
reflux disease: a multicenter study from Japan. *Aliment Pharmacol Ther* 2007; 26: 69-77

15 Kinosita Y, Kobayashi T, Kato M, Ashahina K, Haruma K, Shimatani T, Inoue S, Kurematsu S, Kurosawa S, Kuwayama H, Aoki T, Hayakawa M, Kiyama S, Yamamoto M, Suzuki J, Suzuki H, Matsumoto K, Aoshima M. The pharmacodynamic effect of omeprazole 10 mg and 20 mg once daily in patients with nonerosive reflux disease in Japan. *J Gastroenterol* 2006; 41: 554-561

16 Cheung TK, Wong WM, Wong NY, Chan CK, Fung J, Yuen MF, Chan AO, Tong TS, Wong BC. Symptom resolution does not predict healing of erosive oesophagitis in Chinese. *Digestion* 2007; 75: 128-134

17 Dinakaran NH, Rajkumar JS, Potdar NP, Desai A. An open non-comparative clinical study for the evaluation of safety and efficacy of esomeprazole in patients of reflux oesophagitis in Indian population. *J Indian Med Assoc* 2002; 100: 624-626

18 Lee YC, Lin JT, Wang HP, Chiu HM, Wu MS. Influence of cytochrome P450 2C19 genetic polymorphism and dosage of rabeprazole on accuracy of proton-pump inhibitor testing in Chinese patients with gastrooesophageal reflux disease. *J Gastroenterol Hepatol* 2002; 17: 1286-1292

19 Wong WM, Lai KC, Hui WM, Hu WH, Huang JQ, Wong NY, Xia HH, Chan OO, Lam SK, Wong BC. Pathophysiology of gastroesophageal reflux diseases in Chinese–role of transient lower esophageal sphincter relaxation and esophageal motor dysfunction. *Am J Gastroenterol* 2004; 99: 2088-2093

20 Sifrim D, Zhang X. Pathophysiology of GERD in China: the same factors at a lower scale. *Am J Gastroenterol* 2004; 99: 2094-2097

21 Horai Y, Kimura M, Furui H, Matsuguma I, Irie S, Koga Y, Nagahama T, Murakami M, Matsu T, Yao T, Urae A, Ishizaki T. Pharmacodynamic effects and kinetic disposition of rabeprazole in relation to CYP2C19 genotypes. *Aliment Pharmacol Ther* 2001; 15: 793-803

22 Sakurai Y, Hayama M, Hashimoto M, Tanaka T, Hasegawa I, Irie S, Ashida K, Kayano Y, Taguchi M, Hashimoto Y. Population pharmacokinetics and proton pump inhibitory effects of intravenous lansoprazole in healthy Japanese males. *Biopharm Drug Dispos* 2007; 30: 2228-2243

23 Watson RG, Tham TC, Johnston BT, McDougall NI. Double blind cross-over placebo controlled study of omeprazole in the treatment of patients with reflux symptoms and physiological levels of acid reflux—the “sensitive oesophagus”. *Gut* 1999; 41: 597-599

24 Tytgat GN. Review article: treatment of mild and severe cases of GERD. *Aliment Pharmacol Ther* 2002; 16 Suppl 4: 73-78

25 Graham DY, Patterson DJ. Double-blind comparison of liquid antacid and placebo in the treatment of symptomatic reflux esophagitis. *Dig Dis Sci* 1983; 28: 559-563

26 Barlow WJ, Orlando RC. The pathogenesis of heartburn in nonerosive reflux disease: a unifying hypothesis. *Gastroenterology* 2005; 128: 771-778

27 Nagahara A, Miwa H, Minoo T, Hojo M, Kawabe M, Osada T, Kurosawa A, Asaoka D, Terai T, Okhusa T, Sato N. Increased esophageal sensitivity to acid and saline in patients with nonerosive gastro-esophageal reflux disease. *J Clin Gastroenterol* 2006; 40: 891-895

28 Fox M, Barr C, Nolan S, Lomer M, Anggiansah A, Wong T. The effects of dietary fat and calorie density on esophageal acid exposure and reflux symptoms. *Clin Gastroenterol Hepatol* 2007; 5: 439-444

29 Rodriguez-Stanley S, Robinson M, Earnest DL, Greenwood-Van Meerveld B, Miner PB Jr. Esophageal hypersensitivity may be a major cause of heartburn. *Am J Gastroenterol* 1999; 94: 628-631

30 Tack J. Review article: the role of bile and pepsin in the pathophysiology and treatment of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2006; 24 Suppl 2: 10-16

31 Kusunoki H, Haruma K, Hata J, Tani H, Okamoto E, Sumii K, Kajiyama G. Real-time ultrasonographic assessment of antroduodenal motility after ingestion of solid and liquid meals by patients with functional dyspepsia. *J Gastroenterol Hepatol* 2000; 15: 1022-1027

32 Aoki S, Haruma K, Kusuda H, Hata J, Haru M, Yoshida S, Tanaka S, Chayama K. Evaluation of gastric emptying measured with the 13C-octanoic acid breath test in patients with functional dyspepsia: comparison with ultrasonography. *Scand J Gastroenterol* 2002; 37: 662-666

33 Fass R. Epidemiology and pathophysiology of symptomatic gastroesophageal reflux disease. *Am J Gastroenterol* 2003; 98: S2-S7

34 Baldan DH, Yamamoto Y, Liu J, Pehlivanov N, Wisniewski R, DeSilve D, Mittal RK. Sustained esophageal contraction: a marker of esophageal chest pain identified by intraluminal ultrasonography. *Gastroenterology* 1999; 116: 29-37

35 Pehlivanov N, Liu J, Mittal RK. Sustained esophageal contraction: a motor correlate of heartburn symptom. *Am J Physiol Gastrointest Liver Physiol* 2001; 281: G743-G751

36 Wiklund I, Carlsson R, Carlsson J, Glise H. Psychological factors as a predictor of treatment response in patients with heartburn: a pooled analysis of clinical trials. *Scand J Gastroenterol* 2006; 41: 288-293

37 Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007; 133: 1342-1363

38 Furuta GT, Straumann A. Review article: the pathogenesis and management of eosinophilic esophagitis. *Aliment Pharmacol Ther* 2006; 24: 173-182

39 Mine S, Iida T, Tabata T, Kishikawa H, Tanaka Y. Management of symptoms in step-down therapy of gastroesophageal reflux disease. *J Gastroenterol Hepatol* 2005; 20: 1365-1370

40 Ofman JJ. The economic and quality-of-life impact of symptomatic gastroesophageal reflux disease. *Am J Gastroenterol* 2003; 98: 58-514

41 van Pinxteren B, Numans ME, Bonis PA, Lau J. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database Syst Rev* 2006; 3: CD002095

42 Habu Y, Maeda K, Kusuda T, Yoshino T, Shio S, Yamazaki M, Hayakumo T, Hayashi K, Watanabe Y, Kawai K. “Proton-pump inhibitor-first” strategy versus “step-up” strategy for the acute treatment of reflux esophagitis: a cost-effectiveness analysis in Japan. *J Gastroenterol Hepatol* 2005; 20: 1029-1035

43 Miyamoto M, Haruma K, Takeuchi K, Kuwabara M. Frequency scale for symptoms of gastroesophageal reflux disease predicts the need for addition of prokinetics to proton pump inhibitor therapy. *J Gastroenterol Hepatol* 2008; 23: 746-751

44 Ruth M, Hamelin B, Rohss K, Ludell L. The effect of mosapride, a novel prokinetic, on acid reflux variables in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1998; 12: 35-40

45 Kim YS, Kim TH, Choi CS, Shon YW, Kim SW, Seo GS, Nah YH, Choi MG, Choi SC. Effect of itopride, a new prokinetic, for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Am J Gastroenterol* 2005; 100: 4210-4214

46 Ruth M, Finizia C, Cange L, Lundell L. The effect of mosapride on oesophageal motor function and acid reflux in patients with gastro-oesophageal reflux disease. *Eur J Gastroenterol Hepatol* 2003; 15: 1115-1121

47 Iwakiri K, Hayashi Y, Kotoyori M, Tanaka Y, Kawakami A, Sakamoto C, Holloway RH. Transient lower esophageal sphincter relaxations (TLESRs) are the major mechanism of gastroesophageal reflux but are not the cause of reflux disease. *Dig Dis Sci* 2005; 50: 1072-1077

48 Koutsoumba P, Epanomeritakis E, Tsiaoulos J, Athanasakis H, Chrysos E, Zoras O, Vassilakis JS, Xynos E. The effect of erythromycin on human esophageal motility is mediated by serotonin receptors. *Am J Gastroenterol* 2000; 95: 3388-3392
49 Adelson DW, Million M, Kanamoto K, Palanca T, Tache Y. Coordinated gastric and sphincter motility evoked by intravenous CCK-8 as monitored by ultrasonomicrometry in rats. Am J Physiol Gastrointest Liver Physiol 2004; 286: G321-G322

50 McDermott CM, Abrahams TP, Partosoadarso E, Hyland N, Ekstrand J, Monroe M, Hornby PJ. Site of action of GABA(B) receptor for vagal motor control of the lower esophageal sphincter in ferrets and rats. Gastroenterology 2001; 120: 1749-1762

51 Hiyama T, Yoshihara M, Matsuo K, Kusunoki H, Kamada T, Ito M, Tanaka S, Nishi N, Chayama K, Haruma K. Meta-analysis of the effects of prokinetic agents in patients with functional dyspepsia. J Gastroenterol Hepatol 2007; 22: 304-310

52 Hiyama T, Yoshihara M, Matsuo K, Kusunoki H, Kamada T, Ito M, Tanaka S, Chayama K, Haruma K. Treatment of functional dyspepsia with serotonin agonists: a meta-analysis of randomized controlled trials. J Gastroenterol Hepatol 2007; 22: 1566-1570

53 Tack J, Fass R. Review article: approaches to endoscopic-negative reflux disease: part of the GERD spectrum or a unique acid-related disorder? Aliment Pharmacol Ther 2004; 19 Suppl 1: 28-34

54 Metz DC, Inadomi JM, Howden CW, van Zanten SJ, Bytzer P. On-demand therapy for gastroesophageal reflux disease. Am J Gastroenterol 2007; 102: 642-653

55 Juul-Hansen P, Rydning A. On-demand PPI requirements in patients with endoscopy-negative GERD. J Clin Gastroenterol 2004; 38: 746-749

56 Prasad M, Rentz AM, Revicki DA. The impact of treatment for gastro-oesophageal reflux disease on health-related quality of life: a literature review. Pharmacoeconomics 2003; 21: 769-790

57 Kawahara H, Kubota A, Hasegawa T, Okuyama H, Ueno T, Ida S, Fukuzawa M. Effects of rikkunshito on the clinical symptoms and esophageal acid exposure in children with symptomatic gastroesophageal reflux. Pediatr Surg Int 2007; 23: 1001-1005

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