Successful Eradication Therapy for *Helicobacter pylori*-positive Atrophic Gastritis at the Sixth Attempt: A Case Report

Ryuzo DEGUCHI[*1], Koichi SHIRAISHI[*1], Yoshitaka ARASE[*1], Makiko DEKIDEN[*1], Hideo SHIMADA[*2], Hiroshi MIYAKITA[*2], Takashi OGIMI[*2], Kazunori MYOJIN[*3] and Tetsuya MINE[*1]

*Departments of [*1]Gastroenterology, [*2]Surgery, and, [*3]Radiology , Tokai University School of Medicine*

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A 74-year-old woman undergoing outpatient follow-up for reflux esophagitis and atrophic gastritis tested positive for *Helicobacter pylori* and underwent primary eradication therapy with lansoprazole (LPZ) 30 mg, amoxicillin (AMPC) 750 mg, and clarithromycin (CAM) 200 mg twice daily for 1 week in August 2012. A urea breath test (UBT) after this treatment revealed that eradication had failed. Secondary eradication therapy was carried out with esomeprazole (EPZ) 20 mg, AMPC 750 mg, and metronidazole (MNZ) 250 mg twice daily for 1 week, but this also failed. The third attempt at eradication consisted of EPZ 20 mg, AMPC 750 mg, and sitafloxacin (STFX) 100 mg twice daily for 1 week, but this also ended in failure. A fourth attempt using rabeprazole (RPZ) 20 mg (4 times daily) with MNZ 250 mg and STFX 100 mg twice daily for 2 weeks also failed, as did a fifth attempt in April 2015 using vonoprazan (VPZ) 20 mg, AMPC 750 mg, and MNZ 250 mg twice daily for 1 week. Eradication was finally successful after the sixth attempt, in which the patient was treated with vonoprazan 20 mg, MNZ 250 mg, and STFX 100 mg twice daily for 2 weeks.

Key words: *H. pylori* eradication, *H. pylori*-positive gastritis, Vonoprazan, acid suppression

INTRODUCTION

Helicobacter pylori (*H. pylori*) eradication therapy for atrophic gastritis, which is believed to lead to the development of gastric cancer, was approved for coverage by Japanese health insurance in February 2013, and eradication therapy is now being proactively used in Japan with the aim of accelerating the decrease in the incidence of gastric cancer. However, the success rates for eradication are decreasing due to clarithromycin resistance [1] and the metabolism of proton pump inhibitors (PPIs) by CYP2C19 [2]. A patient in whom eradication therapy was successful at the sixth attempt thanks to the use of a new PPI in combination therapy, after previous attempts using existing PPIs had failed, is presented.

CASE REPORT

A 74-year-old woman (height 155 cm, weight 49 kg) who was undergoing outpatient follow-up for reflux esophagitis and atrophic gastritis (Figure) tested positive for *Helicobacter pylori* and underwent primary eradication therapy with lansoprazole (LPZ) 30 mg, amoxicillin (AMPC) 750 mg, and clarithromycin (CAM) 200 mg twice daily for 1 week in August 2012. The result of a urea breath test (UBT) after this treatment was 52.2‰ (negative reference value < 2.5‰), indicating that eradication had failed. Secondary eradication therapy was carried out with esomeprazole (EPZ) 20 mg, amoxicillin (AMPC) 750 mg, and metronidazole (MNZ) 250 mg twice daily for 1 week, but the subsequent UBT result was 34.3‰, indicating that this treatment had also failed. The third attempt at eradication consisted of EPZ 20 mg, AMPC 750 mg, and sitafloxacin (STFX) 100 mg twice daily for 1 week, but this also ended in failure, with a UBT result of 27.8‰. The result of another UBT performed before the next attempt was 20.0‰, and this fourth attempt was made using rabeprazole (RPZ) 20 mg (4 times daily) with MNZ 250 mg and STFX 100 mg twice daily for 2 weeks, but the result of a UBT after this treatment was 11.8‰, indicating another failure. By the time of the next attempt, the patient had been referred to another hospital, but she remained under our observation at her own request. Vonoprazan (VPZ) was approved for use in Japan in 2015, and in April that year, a fifth attempt at eradication was made using VPZ 20 mg, AMPC 750 mg, and MZN 250 mg twice daily for 1 week, but the result of the subsequent UBT test was 42.7‰, again indicating failure. For the sixth attempt, the patient was treated with VPZ 20 mg, MNZ 250 mg, and STFX 100 mg twice daily for 2 weeks. The result of a UBT after this treatment was 16.9‰. The patient continued to request further treatment, but an *H. pylori* stool antigen test for confirmation was negative. When the UBT was subsequently repeated, the result was 2.2‰, demonstrating that eradication had been successful (Table).

DISCUSSION

In February 2013, atrophic gastritis, which is believed to lead to the development of gastric cancer, was added to the other disorders for which the use of *H. pylori* eradication therapy is covered by Japanese health insurance: peptic ulcer (gastric/duodenal ulcer), gastric mucosa-associated lymphoid tissue (MALT) lympho-

Ryuzo DEGUCHI, Department of Gastroenterology, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan
Tel: +81-463-72-3211 Fax: +81-463-72-2256 E-mail: deguchi@is.icc.u-tokai.ac.jp

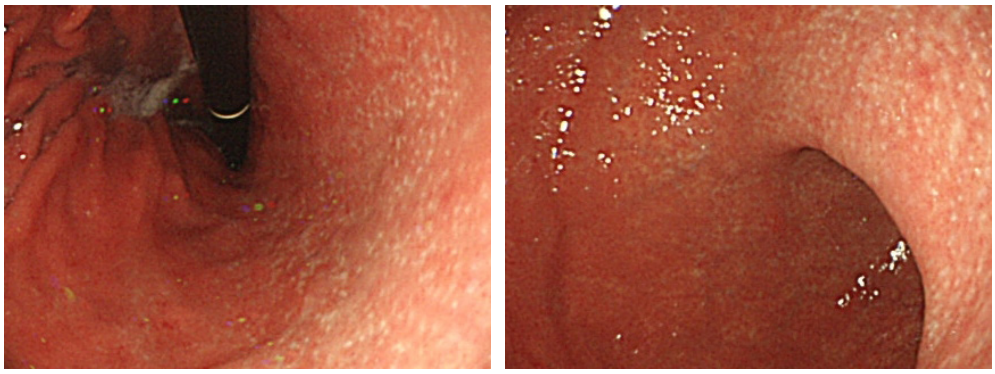

Figure Other than atrophic changes of the gastric mucosa from the lesser curvature in the cardiac region to the antrum, no obvious abnormalities are evident.

Table Results of eradication tests over time during eradication attempts 1–6

	Eradication attempt								
	1. After LAC	2. After EAM	3. After EAS	Before 4th attempt	4. After RMS	5. After VAM	6. After VMS		Repeated test after 6th attempt
UBT	52.2	34.3	27.8	20	11.8	42.7	16.9	Stool antigen test negative	2.2
date	2012.11.2	2013.2.26	2013.4.16	2013.5.17	2013.7.12	2015.5.30	2015.7.18	2015.7.21	2015.8.15

UBT (Urea Breath Test)
LAC (lansoprazole + amoxicillin + clarithromycin)
EAM (esomeprazole + amoxicillin + metronidazole)
EAS (esomeprazole + amoxicillin + sitafloxacin)
RMS (rabeprazole + metronidazole + sitafloxacin)
VAM (vonoprazan + amoxicillin + metronidazole)
VMS (vonoprazan + metronidazole + sitafloxacin)

ma, idiopathic thrombocytopenic purpura (ITP), and remnant stomach following endoscopic resection of early gastric cancer. This is expected to accelerate the decrease in the incidence of gastric cancer.

Primary *H. pylori* eradication therapy comprising an existing PPI (lansoprazole 30 mg, omeprazole 20 mg, or rabeprazole 10 mg) twice daily together with AMPC 750 mg twice daily and clarithromycin 200 mg or 400 mg twice daily (for 1 week) has a reported eradication rate of 77.8%–91.1% [3–5]. Factors that may reduce this eradication rate include clarithromycin resistance, metabolism of PPIs by CYP2C19, smoking, and drug compliance, of which clarithromycin resistance is regarded as the most important in Japan [6]. In the present case, resistance to clarithromycin, which was used in primary eradication, was not tested. A later investigation revealed that the patient had been undergoing treatment in the Department of Respiratory Disease for bronchiectasis since December 2008, and this was still ongoing at the time of publication, and as her treatment records showed that she had been prescribed clarithromycin for a total of 10 weeks prior to eradication therapy, it may be conjectured that bacterial resistance was present. Endoscopic findings prior to eradication also showed that gastric mucosal atrophy was not severe, and it is also possible that large amounts of gastric juice may have prevented the adequate inhibition of acid secretion during eradication.

Secondary *H. pylori* eradication therapy comprises a PPI twice daily together with AMPC 750 mg twice daily and MNZ 250 mg twice daily (for 1 week), and the eradication rate for this treatment is maintained at around 90% [7]. In Japan, the use of MNZ is restricted to only some patients, and bacterial resistance is therefore believed to be uncommon.

Third and subsequent attempts at *H. pylori* eradication therapy are not covered by Japanese health insurance, and a wide range of different regimens has been reported. Examples include: (a) a PPI with AMPC 500 mg 4 times daily for 2 weeks; (b) a PPI with STFX 100 mg and MNZ 250 mg twice daily (for 1 week); (c) a PPI twice daily together with MNZ 250 mg twice daily and minomycin 100 mg twice daily (for 1 week); and (d) a PPI twice daily together with AMPC 750 mg twice daily and SFTX 100 mg twice daily (for 1 week). Their reported eradication rates in Japan have been reported to be (a) 54.3%, (b) 90.9%, (c) 85.1%, and (d) 80%, respectively [8–11]. In the present case, regimen (d) was used, including an existing PPI, but eradication was unsuccessful. At the patient's request, for the fourth attempt, an existing PPI was administered 4 times daily for 2 weeks to achieve intensive suppression of gastric acid secretion, as a modified procedure for (b), but this also failed, and the patient took a break from treatment.

In March 2015, the powerful gastric acid secretion inhibitor vonoprazan (VPZ) was approved for prescription use in Japan, and a fifth attempt at eradication was made using VPZ 20 mg together with AMPC 750 mg and MNZ 250 mg twice daily (for 1 week), but this

also ended in failure. After the effect of suppressing acid secretion in eradication therapy had been explained to and fully understood by the patient, a sixth attempt was made using VPZ 20 mg twice daily together with STFX 100 mg twice daily and MNZ 250 mg twice daily (for 2 weeks), and this was finally successful. The reported outcomes of eradication therapy using VPZ in Japan are 92.6% for primary therapy with VPZ 20 mg twice daily, AMPC 750 mg twice daily, and CAM 200 mg twice daily for 1 week, and 98.0% for secondary therapy with VPZ 20 mg twice daily, AMPC 750 mg twice daily, and MNZ 250 mg twice daily for 1 week [12]. The distinguishing characteristic of the pharmacological action of VPZ is that it does not require activation by acid in the secretory canaliculi of gastric parietal cells, but it reversibly blocks H^+ and K^+-ATPase as a result of ionic and hydrogen bonds [13]. It has a higher acid dissociation constant compared with older PPIs, and as it is almost completely ionized in the secretory canaliculi, it is believed to be localized there in high concentrations [14], meaning that its powerful inhibition of acid secretion holds potential for eradication therapy in future.

Studies have found that it is important for eradication that *H. pylori* be in the proliferative phase in the stomach [8], that the pH in the stomach be maintained at 5 or above, and a pH of 6 or over is required to achieve sensitivity to the various antibiotics [9]. The use of a PPI in combination with AMPC and CAM has also been reported to increase the concentration of antibiotic in the gastric mucosa [10]. Conventional PPIs require acid for their activation, and administering a PPI to suppress gastric acid secretion decreases the activity of that PPI, making it difficult to maintain a neutral pH in the stomach [11]. In the present case, even the administration of a PPI 4 times daily during the fourth attempt did not lead to successful eradication, and the patient took a break from treatment for several years.

Vonoprazan is a PPI that does not require acid for its activation, and it is anticipated that the acid secretion inhibitory effect will be intensified by increasing the dose rather than the number of times it is taken per day. Nevertheless, a fifth attempt using this agent was still unsuccessful. Vonoprazan has a long half-life in the blood after administration and is stable in an acid environment, meaning that it persists at high concentrations within the secretory canaliculi of the gastric parietal cells for a long time. When this had been fully explained to the patient, a sixth attempt was made with the PPI administered twice daily, and this was finally successful in achieving eradication.

Third and subsequent eradication attempts are currently under consideration in Japan, and studies of new gastric acid secretion inhibitors and the use of antibiotics in *H. pylori* eradication therapy may increase the reliability of eradication methods in the future.

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