Current Status of *Helicobacter pylori* Diagnosis and Eradication Therapy in Japan Using a Nationwide Database

Hisato Deguchi^a Akihito Uda^b Kazunari Murakami^c

^aJapan Medical Affairs, Takeda Pharmaceutical Company Limited, Osaka, Japan; ^bJapan Medical Affairs, Takeda Pharmaceutical Company Limited, Tokyo, Japan; ^cDepartment of Gastroenterology, Oita University Faculty of Medicine, Yufu, Japan

Keywords

Helicobacter pylori · Claims data · Diagnostic test · Eradication therapy · Drug resistance

Abstract

Background: *Helicobacter pylori* infection increases the risk of stomach cancer; therefore, eradication therapy is recommended for infected individuals. Although several methods are recommended for the diagnosis and therapy of *H. pylori* infection, their frequency and effectiveness have not been fully investigated in Japan. **Methods:** A nationwide claims database including >1.6 million patients (April 2008 – October 2016) in Japan was utilized. We analyzed the distribution of methods for *H. pylori* diagnosis and therapy, waiting period between eradication and diagnostic test, and success rate of primary therapy. **Results:** Data for 481,041 patients were extracted. After primary eradication therapy, urea breath test was used for >80% of diagnoses, and antibody measurement for 0.7%. The success rate of primary eradication was >80% for most diagnostic methods and 69.0% for antibody measurement; inappropriately-timed antibody measurement may have contributed to this disparity. The overall success rate of eradication therapy decreased from 2011 to 2014, but increased from 2015, coinciding with launch of the potassium-competitive acid blocker vonopra-

zan, which showed a higher success rate of eradication than proton-pump inhibitors. **Conclusions:** Diagnostic tests of *H. pylori* infection mostly followed Japanese Society for *Helicobacter* Research guidance, although some antibody measurements were timed inappropriately. Vonoprazan appears to increase the success rate of primary therapy.

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Published by S. Karger AG, Basel

Introduction

Gastric cancer is the third most common cause of death of all cancers [1]. Its prevalence is especially high in East Asia. In 2012, the incidences of gastric cancer in Korea, Japan, and China were ranked as first, third, and fifth in the world, respectively [1].

Helicobacter pylori-gastritis induces chronic inflammation in the gastric mucosa and is the cause of various disorders [2–6], including atrophic gastritis, which potentially leads to stomach cancer [7]. The International Agency for Research on Cancer of the World Health Organization classified *H. pylori* as a Group 1 carcinogen in 1994 [8] and verified this in 2009 [9]. Recent randomized controlled trials [10, 11] and meta-analyses [12–17] have indicated that the eradication of *H. pylori* reduces the risk of gastric cancer.

Several attempts have been made to facilitate the prevention of gastric cancer in Japan. For example, health insurance coverage was approved for *H. pylori* eradication therapy for gastric and duodenal ulcers in 2000. The target diseases covered by insurance have subsequently been expanded, and in 2013, *H. pylori* gastritis was included. Furthermore, the Japanese Society for *Helicobacter* Research (JSHR) revised their guidelines for diagnosis and treatment of *H. pylori* infection in 2016 and incorporated gastric cancer prevention by eradication and extermination of *H. pylori* [18]. The JSHR guidelines describe the methods of diagnosing *H. pylori* infection and of conducting standard eradication therapy.

According to the JSHR guidelines, one of the following 6 methods is appropriate for diagnosing *H. pylori* infection: a rapid urease test, direct microscopic count, microbial culture, urea breath test, antibody measurement, or stool antigen test [18]. The urea breath test and stool antigen test using monoclonal antibodies are also described as useful diagnostic methods after eradication therapy. To make a diagnosis of *H. pylori* infection after eradication therapy, it is recommended to wait at least 4 weeks after the termination of medication before conducting the test.

For eradication therapy, the following treatments are described in the JSHR guidelines. As the standard primary eradication therapy, 3 drugs (amoxicillin, clarithromycin [CAM], and either a proton-pump inhibitor [PPI] or potassium-competitive acid blocker [P-CAB]) are administered for 7 days [18]. In second-line regimens, metronidazole is used instead of CAM; the other drugs used and administration period are the same as those for primary therapy. Four PPIs (omeprazole, rabeprazole, lansoprazole, and esomeprazole) and one P-CAB (vonoprazan) are currently approved for eradication therapy in Japan. Of these, vonoprazan is the newest drug, being launched in February 2015. Although a direct comparison of the eradication effect between drugs using data from clinical trials is inappropriate because of the different timing and conditions in each trial, the eradication rate appears to differ among the prescribed PPIs and P-CABs, ranging from 78.8% [19] for omeprazole to 92.6% for vonoprazan [20]. A direct comparison study of the 3 different PPIs (rabeprazole, omeprazole, and lansoprazole) has not shown a difference in eradication rate [18].

H. pylori has been reported to acquire resistance to various antimicrobial drugs, and the proportion of patients with drug-resistant *H. pylori* has been increasing [21–23]. Between 2013 and 2014, the percentage of CAM-resistant *H. pylori* cases was reported to be 38.5%

[21]. In parallel with this increase, the eradication success rate of *H. pylori* has been declining [22].

To facilitate the prevention of gastric cancer by the eradication of *H. pylori* infection, it is important to make an appropriate diagnosis of the infection status and provide proper eradication therapy. Although there are several methods available for diagnosis and therapy, a nationwide study has not been performed to investigate the status of diagnosis and therapy, and the extent to which the guidelines are followed at a practical level. Such information is essential for promoting the appropriate method of diagnosis and therapy. Furthermore, monitoring the success rate of *H. pylori* eradication using real-time data *per se* can be useful to detect the emergence of drug-resistant strains.

The objective of our study, therefore, was to conduct a nationwide investigation into the diagnosis and treatment of *H. pylori* infection. We analyzed the distribution of methods of primary eradication therapy and diagnostic testing used before and after therapy, the waiting period from the termination of medication until the diagnostic test, and the success rate of *H. pylori* eradication following various methods of diagnosis and therapy.

Materials and Methods

Study Design

This study was a claims-based analysis of the patients who received a diagnosis of and/or therapy for *H. pylori* infection from a database of hospitals that have adopted the Diagnosis Procedure Combination system (DPC hospitals) – a claims payment system which operates on a per-day payment model rather than a per-case payment model.

Data Source

A claims database from the DPC hospitals provided by Medical Data Vision Co., Ltd. (Tokyo, Japan) was used. Three investigators had access to this database. This database contains patient medical data from over 13.6 million individuals (>10% of the Japanese population) from over 200 DPC hospitals across Japan, including hospitals that treat acute or seriously ill patients on a 24-h basis. Data were cleaned by the database provider. The database covers claims from April 2008 until October 2016. This database has been widely used for similar investigations, including those that describe the actual treatment status for a particular disease in Japan [24–27].

Definition of Patients, Diagnostic Tests, and Therapeutic Methods

For our analyses, we selected patients who had a record of diagnostic testing for *H. pylori* infection and/or a record of prescription for the 3 medications (either a combination of single drugs or a combination pack) that were used in the standard eradication therapy for *H. pylori* infection. Codes were used to identify patients.

Methods of diagnosis were defined by the procedure codes in the claims data (online suppl. Table S1; for all online suppl. mate-

rial, see www.karger.com/doi/10.1159/000500819). Prescribed medications were defined from the anatomical therapeutic chemical codes, procedure codes, or general names in the claims data. Primary and secondary eradication therapies were defined according to the constituents of each regimen (the 3 prescribed medications) used in the standard treatment (online supp. Table S2).

Diagnostic tests for *H. pylori* infection were subdivided into the following 2 types. One was the diagnostic test before eradication therapy, which is the latest test within 150 days before the starting day of the treatment, and the other was the diagnostic test after eradication therapy, which is the earliest test from 7 days until 150 + 7 days after the starting date of the therapy.

The success rate of the primary eradication of *H. pylori* was determined in those patients who received primary eradication therapy who also had a subsequent diagnostic test after eradication therapy. Of these, patients who did not receive secondary eradication therapy were defined as being successful cases of eradication therapy.

Data and Statistical Analysis

Study size was determined by the number of eligible patients in the DPC database. Counts of patients for each diagnostic method used before and after eradication therapy and that for the interval (in days) between the therapy and diagnosis for each and all diagnostic methods were calculated for the entire time period. Monthly counts of patients who received primary eradication therapy for each medication were also calculated over the entire period of the database. Patients who were lost to follow-up were excluded.

The following success rates of primary *H. pylori* eradication were estimated with a 95% CIs: the success rates measured by each diagnostic method over the entire period, success rates by time interval from the eradication therapy to the subsequent diagnostic test for *H. pylori* infection over the entire period, monthly success rates for all types of therapy over the entire period, and success rate for therapy including each type of PPI and P-CAB between January 2015 and March 2016.

Descriptive statistics were used to analyze the data, and confidence intervals were calculated for differences. Statistical analysis was performed using Excel 2010 (Microsoft Corp., Redmond, WA, USA) and SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patients

At the beginning of the analysis, records for 481,041 patients were extracted from the database. Among those patients, 473,011 had a history of receiving a test of *H. pylori* infection, and 250,197 had a history of receiving eradication therapy. Among those patients who received primary eradication therapy, 196,509 had a history of receiving a diagnostic test after eradication therapy. The estimated number of patients receiving eradication therapy for *H. pylori* infection in Japan was approximately 60,000 per year in 2011 and 2012 and 140,000 per year in 2013 through 2016 [28], thus, roughly 30% of all patients receiving eradication therapy in Japan from 2011 to 2016 were covered in this study.

Diagnostic Test Methods of H. pylori Infection and the Success Rate of Eradication Therapy

Various test methods were used for diagnosis before eradication therapy. The urea breath test was the most frequently used (27.5%), followed by the antibody measurement (25.9%) and rapid urease (21.8%) tests (Table 1). Meanwhile, the diagnostic method employed after eradication therapy was predominantly the urea breath test (89.6%), and in a few cases (0.7%), antibody measurement (Table 1). The most frequent time interval between eradication therapy and the subsequent diagnostic test was 8–9 weeks (average 9.2 weeks, median 8.9 weeks), and the frequency for a period of <4 weeks was 0.3%. The average success rates of eradication of *H. pylori* were >80% regardless of the period between the therapy and subsequent diagnostic test. Success rates differed as measured by various diagnostic tests after primary eradication therapy. The success rate as measured by the antibody measurement alone was the lowest (69.0%) compared with that by other methods (>80%; Table 2). As shown in Figure 1, the success rate as measured by the urea breath test was >80% for eradication of *H. pylori* regardless of the interval between the therapy and diagnostic test, while the success rate as measured by the antibody measurement was lower (Fig. 1); notably, the success rate was lower when there was a shorter interval between the therapy and the subsequent diagnostic test.

Therapeutic Methods of H. pylori Eradication and the Success Rate

The success rate of *H. pylori* eradication for all types of therapy decreased from 83% to <80% between 2011 and 2014, and then increased to ≥85% in 2015 (Fig. 2). Among the medications used for eradication therapy, the proportion of regimens including a P-CAB has increased rapidly since its launch in February 2015 (Fig. 3). A positive correlation was observed between the success rate of eradication therapy and the percentage of patients treated with vonoprazan (Fig. 4).

The mean success rate of eradication therapy from January 2015 to March 2016 was >90% for primary therapy including vonoprazan, which was higher than that for other therapies including PPIs (77.6–82.0%; Table 3).

Discussion/Conclusion

We showed the current status of diagnostic testing and eradication therapy of *H. pylori* based on analyses of a nationwide claims database. The diagnostic testing of *H.*

Table 1. Diagnostic methods of *Helicobacter pylori* infection and their implementation rate between April 2008 and October 2016

Methods of diagnosis	Number of patients who received eradication therapy	Combined proportion, %
Before both primary and secondary eradication therapy		
Urea breath test	60,750	27.5
Antibody measurement ¹	57,299	25.9
Rapid urease test	48,250	21.8
Antibody measurement (qualitative) ²	22,432	10.1
Stool antigen test	8,585	3.9
Microbial culture	7,908	3.6
Rapid urease test and direct microscopic count	4,991	2.3
Direct microscopic count	4,971	2.2
Direct microscopic count and microbial culture	1,081	0.5
Direct microscopic count and antibody measurement	970	0.4
Rapid urease test and antibody measurement	564	0.3
Direct microscopic count and urea breath test	494	0.2
Antibody measurement and urea breath test	481	0.2
Direct microscopic count and antibody measurement (qualitative)	476	0.2
Antibody measurement (qualitative) and urea breath test	441	0.2
Urea breath test and stool antigen test	331	0.1
Rapid urease test and microbial culture	249	0.1
Antibody measurement and stool antigen test	141	0.1
Microbial culture and antibody measurement	132	0.1
Rapid urease test and antibody measurement (qualitative)	119	0.1
Other tests	507	0.2
Total	221,172	100.0
After both primary and secondary eradication therapy		
Urea breath test	212,759	89.6
Stool antigen test	18,146	7.6
Antibody measurement ¹	1,571	0.7
Urea breath test and stool antigen test	1,551	0.7
Rapid urease test	924	0.4
Direct microscopic count	755	0.3
Antibody measurement (qualitative) ²	479	0.2
Microbial culture	279	0.1
Antibody measurement and urea breath test	262	0.1
Direct microscopic count and urea breath test	234	0.1
Rapid urease test and direct microscopic count	181	0.1
Other tests	206	0.1
Total	237,347	100.0

¹ Antibody measurement: it was measured with an apparatus (the latex agglutination method and enzyme immunoassay method).

² Antibody measurement (qualitative): it is possible to measure by visual observation (the immunochromatography method and gold colloidal method).

pylori infection before eradication therapy was performed using various methods. However, after eradication therapy, the urea breath test was used for the vast majority of diagnostic tests. The success rate of *H. pylori* eradication as measured by most diagnostic methods after primary eradication therapy was >80%. In contrast, the success rate measured by the antibody measurement test alone

was noticeably lower (69.0%). The success rate of eradication of *H. pylori* after therapy decreased from 2011 until 2014, but increased from 2015. Following the launch of vonoprazan in 2015, its use has increased markedly compared with that of PPIs. The success rate of vonoprazan for the eradication of *H. pylori* (January 2015 to March 2016) was higher than PPIs at >90%.

Table 2. Methods of diagnosis after primary eradication therapy and their measured success rate of eradication of *Helicobacter pylori* between April 2008 and October 2016

Methods of diagnosis	Number of patients who received primary eradication therapy	Number of patients who received both primary and secondary eradication therapy	Success rate of primary eradication therapy, %	95% CI, %
Urea breath test	175,781	31,009	82.4	82–83
Stool antigen test	15,272	2,563	83.2	83–84
Urea breath test and stool antigen test	1,314	236	82.0	80–84
Antibody measurement ¹	1,260	390	69.0	66–72
Rapid urease test	829	146	82.4	80–85
Direct microscopic count	678	85	87.5	85–90
Antibody measurement (qualitative) ²	385	124	67.8	63–72
Microbial culture	225	31	86.2	82–91
Antibody measurement and urea breath test	213	41	80.8	75–86
Direct microscopic count and urea breath test	213	29	86.4	82–91
Rapid urease test and direct microscopic count	161	33	79.5	73–86
Other tests	178	33	81.5	76–87
Total	196,509	34,720	82.3	82–83

¹ Antibody measurement: it was measured with an apparatus (the latex agglutination method and enzyme immunoassay method).

² Antibody measurement (qualitative): it is possible to measure by visual observation (the immunochromatography method and gold colloidal method).

Fig. 1. Success rate of primary *H. pylori* eradication at different time intervals between primary eradication and the subsequent test for diagnosis.

The JSHR guidelines for diagnosis and treatment of *H. pylori* infection describe 6 methods of diagnostic testing for *H. pylori* infection, but do not recommend any particular method [18]. The urea breath test is a noninvasive method; it is simple, easy, and sensitive and has

high specificity [29–34]. It is also described as a useful method for determining *H. pylori* eradication in the JSHR guidelines [18]. Our findings support the urea breath test as the preferred diagnostic test in clinical practice.

Fig. 2. Transition of primary *H. pylori* eradication success rate between April 2008 and March 2016. The red line and pink area indicate the point estimate of the success rate and 95% CI, respectively. The success rate of primary eradication of *H. pylori* was defined as the proportion of patients who did not receive second-

ary eradication therapy among the cumulative total patient population at each time point. The 95% CI was calculated as the lower and upper bounds of the success rate based on the population size at each time point.

Fig. 3. Transition of the proportion of patients taking the standard eradication therapy regimen for *H. pylori* infection between April 2008 and October 2016. PPI, proton-pump inhibitor; AMPC, amoxicillin; MNZ, metronidazole; CAM, clarithromycin; P-CAB, potassium-competitive acid blocker.

The antibody measurement method is used to determine *H. pylori* infection by measuring the amount of antibodies produced as an immune response against the infection in the gastric mucosal membrane [18]. This method is useful in patients with low gastric bacterial density, such as those with atrophic gastritis, and in

those where false-positive results are suspected with other methods [18]. Furthermore, this method has the advantage that drug withdrawal is not a factor as it is not affected by PPIs and defense function enhancers [18]. However, given that negative conversion of the serum antibody can take more than a year after successful *H.*

Fig. 4. Success rate and proportion of patients taking vonoprazan among all standard primary eradication therapies for *H. pylori* infection. The blue dots indicate actual data calculated for each month. The black line is a fitted regression line drawn by the regression equation described below the line. R^2 is the coefficient of determination.

Table 3. Success rate of primary eradication therapy for *Helicobacter pylori* infection with PPI and P-CAB between January 2015 and March 2016

	PPIs				P-CAB
	omeprazole	rabeprazole	lansoprazole	esomeprazole	vonoprazan
No. of total patients	269	19,236	18,339	4,984	31,171
Proportion of each treatment, %	0.4	26.0	24.8	6.7	42.1
No. of failed patients	52	04,308	3,740	899	2,889
Success rate, %	80.7	77.6	79.6	82.0	90.7
95% CI, %	76.0–85.4	77.0–78.2	79.0–80.2	80.9–83.0	90.4–91.1
Success rate in clinical trials ¹ , % (n)	78.8 (19)	85.7–89.0 (28)	83.7–91.1 (29)	–	92.6 (20)

¹ Data in clinical trials used for the development of information written in the package insert in Japan.
P-CAB, potassium-competitive acid blocker; PPIs, proton pump inhibitors.

pylori eradication [35], this method is not suitable when *H. pylori* eradication needs to be determined shortly after eradication therapy. Furthermore, to use this method to determine *H. pylori* eradication, a quantitative comparison is recommended between results before and 6 months after eradication therapy [36]. Our study revealed that even with such prerequisites, the antibody measurement is used alone in a small fraction of diagnoses (0.7%) of *H. pylori* infection after eradication therapy, and that the test was even conducted within 6 months of therapy. In such cases, if the test is performed before the negative conversion of the serum antibody, then patients could be misdiagnosed as having failed primary eradication therapy and receive an unnecessary second course of eradication therapy. This may account for the antibody measurement test having the lowest measured success rate of *H. pylori* eradication. Furthermore, receiving an unnecessary secondary eradication therapy is undesirable due to both the safety concerns of patients

and use of unnecessary medical resources. Our study indicates that such inappropriate use of this diagnostic method may be taking place in relatively large hospitals. Further research is required to determine the extent of the inappropriate use of diagnostic testing at other types of facilities in Japan.

Since 2011, changes have been observed in the success rate of *H. pylori* eradication. Nationwide surveillance of drug-resistant strains performed by the JSHR has indicated that CAM-resistant strains increased from 18.9% in 2002 to 21.1% in 2003, 31% in 2010–2011, and 38.5% in 2013–2014 [21]. This increase may be reflected in the declining success rate of *H. pylori* eradication observed until 2014 in our study. Since 2015, the success rate of *H. pylori* eradication has been increasing. Vonoprazan was released in February 2015, and subsequently, its use among patients has been increasing. The success rate of *H. pylori* eradication showed a positive correlation with the percentage of patients treated with vonoprazan. The

success rate for the regimen that included vonoprazan was >90%, which was higher than that for PPIs in this study. The success rate was also reported to be >90% in a randomized controlled trial [18]. Therefore, this increase in the success rate of *H. pylori* eradication might be attributed to the use of vonoprazan.

This present study has several limitations. The claims data used were only from large hospitals; the proportion of the hospitals with a total number of beds of <199, 200–499, and >500 were approximately 20, 60, and 20%, respectively. All hospitals included in this study were acute hospitals, covering around 16% of all acute hospitals in Japan, and thus the study population may have different characteristics compared with the general Japanese population. Another analysis using data from middle- and small-sized hospitals is required to better describe the whole picture throughout the country. This study defined successful cases of primary eradication therapy as those patients who received primary eradication therapy followed by testing for *H. pylori* infection and did not receive secondary eradication therapy. However, there may be patients who tested positive for *H. pylori* infection after the primary therapy (i.e., failure of primary therapy) and yet did not receive secondary eradication therapy, or received a second-line treatment other than those defined in this study (i.e., combination pack, PPI, amoxicillin, and metronidazole), or were lost at follow-up. If such patients exist in the database, then they would be incorrectly considered as achieving successful primary eradication therapy in our analysis. Therefore, the actual success rate of primary eradication therapy may be lower than that calculated in this study. Of note, a recent retrospective study has reported rates of patients who were lost at follow-up to be 3.5 and 4.4% for vonoprazan and PPI, respectively [37, 38]; thus, the extent of overestimation of the success rate due to the lack of follow-up may not be large in general.

In conclusion, using data from 481,041 patients, we found that in large hospitals, the diagnostic testing of *H. pylori* infection is performed mostly in accordance with the JSHR guidelines. However, antibody measurement testing was conducted too soon after eradication therapy in some cases, which may lead to unnecessary secondary eradication therapy. The success rate of *H. pylori* eradication decreased from 2011 until 2014, which was probably due to the increase of drug-resistant strains. The success rate has been gradually increasing following the clinical application of vonoprazan and its expanded patient use. Use of medications with a high eradication capacity is expected to contribute to the increased success rate of pri-

mary eradication therapy, reducing the burden to patients and the health-care system associated with secondary eradication therapy.

Acknowledgments

The authors would like to thank Kosuke Iwasaki, MBA, and Tomomi Takeshima, PhD, employees of Milliman, for performing data analysis and providing the manuscript draft and editorial support, respectively. We would also like to acknowledge Editage (www.editage.jp) for English language editing.

Statement of Ethics

This study was performed using anonymized and personally unidentifiable data; therefore, no informed consent was required, based on Ethical Guidelines for Epidemiological Research issued by the Japanese Ministry of Health, Labor, and Welfare.

Disclosure Statement

H.D. and A.U. are employees of Takeda Pharmaceutical Company Limited. K.M. received lecture fees from Takeda Pharmaceutical Company Limited.

Funding Sources

This study was funded by Takeda Pharmaceutical Company Limited. The authors thank Shinzo Hiroi, PhD, at the time employed by Takeda and Kazuo Ueda, MD, employee of Takeda, for contributing to the study design and interpretation of data, respectively.

Author Contributions

H.D.: conception and design, data analysis and interpretation, drafting the manuscript, writing the manuscript, and final approval of the manuscript. A.U.: data analysis and interpretation, writing the manuscript, and final approval of the manuscript. K.M.: conception and design, data analysis and interpretation, writing the manuscript, and final approval of the manuscript.

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