Kaohsiung Journal of Medical Sciences (2018) xx, 1–5

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.kjms-online.com

Original Article

Pre-treatment with proton pump inhibitors decreases the success of primary *Helicobacter pylori* eradication using a vonoprazan-based regimen

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Received 19 December 2017; accepted 26 March 2018

KEYWORDS
Helicobacter pylori;
Potassium-competitive acid blocker;
Outcome measure;
Proton pump inhibitors

Abstract Vonoprazan-based regimens have improved the rate of successful *Helicobacter pylori* (*H. pylori*) eradication, but it has not reached 100%. The aim of this study is to clarify significant predictors of successful *H. pylori* eradication using a vonoprazan-based regimen. In this retrospective cohort study, 174 patients who underwent primary *H. pylori* eradication therapy were included. All patients underwent esophagogastroduodenoscopy before treatment. The vonoprazan-based regimen includes amoxicillin 750 mg, clarithromycin 200 mg and vonoprazan 20 mg twice daily for one week. Pre-treatment with a proton pump inhibitor (PPI) was defined as continued PPI use for more than four weeks prior to eradication therapy. The rates of successful eradication were 83% (145/174) in intention-to-treat analysis and 85% (145/171) in per-protocol analysis. Predictors of successful eradication among 171 patients were evaluated in per-protocol analysis. In univariate analysis, male gender was a significant positive predictor of successful eradication (odds ratio [OR] 3.813, 95% confidence interval [CI]

Conflicts of interest: Author S.S. received honoraria from Takeda, Eisai and Daiichi Sankyo Pharmaceuticals. Author H.O. received research grants and honoraria from Takeda, Otsuka, AstraZeneca and Daiichi Sankyo Pharmaceuticals. Author H.S. received a research grant from Takeda Pharmaceuticals. Author Y.H. has received honoraria from AstraZeneca, Eisai and Daiichi Sankyo Pharmaceuticals. Author Y. M. received honoraria from Takeda, Otsuka, AstraZeneca and Daiichi Sankyo Pharmaceuticals. Author H.Y. has received research grants and honoraria from Takeda, Otsuka, AstraZeneca, Eisai and Daiichi Sankyo Pharmaceuticals. Other authors declare no conflicts of interest regarding this study. The funding source had no role in the design, practice or analysis of this study.

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https://doi.org/10.1016/j.kjms.2018.03.009

1.363–10.663, p = 0.010) and pre-treatment with PPIs was a negative predictor (OR 0.193, 95%CI 0.076–0.485, p < 0.001). In multivariate analysis, male gender remained a positive predictor (OR 3.826, 95%CI 1.317–11.116, p = 0.013), and pre-treatment with PPIs (OR 0.232, 95% CI 0.087–0.615, p = 0.003) remained a negative predictor. In conclusion, pre-treatment with PPIs before eradication therapy decreases the rate of successful eradication. Therefore, it may be desirable to discontinue pre-treatment with PPIs prior to eradication therapy, because of the potential to improve the rate of successful eradication.

Introduction

Successful eradication of *Helicobacter pylori* (*H. pylori*) attracts the interest of not only primary care physicians but also gastroenterologists, because it decreases the incidence of peptic ulcer disease as well as the mortality and morbidity associated with gastric cancer [1–3]. However, the eradication rate has decreased to unacceptable levels since 2001 [4,5]. In 2013, the Japanese National Health Insurance System began reimbursement for the treatment of *H. pylori*-positive gastritis, and the number of patients successfully eradicated has exponentially increased to approximately 1,380,000 per year in 2013 [6].

In 2015, vonoprazan, a novel potassium-competitive acid blocker, was made available in Japan for *H. pylori* eradication therapy. First, a phase III trial revealed significant superiority of a vonoprazan-based regimen compared to a lansoprazole-based regimen [7]. Second, we first reported the superiority of a vonoprazan regimen over a rabeprazole-based regimen [8]. Third, a recent large Japanese study reported the superiority of a vonoprazan-based regimen over an esomeprazole-based regimen [9]. A recent meta-analysis has confirmed the superiority of a vonoprazan-based regimen over a proton pump inhibitor (PPI)-based regimen [10]. Despite the confirmed superiority of successful *H. pylori* eradication rate using vonoprazan-based regimens, the success rate ranged from 85% to 96% and did not reach 100% [11]. The aim of this study is to clarify significant predictors of successful *H. pylori* eradication therapy using a vonoprazan-based regimen.

Patients and methods

Study population

This is a retrospective cohort study. From February 2015 to September 2017, 174 consecutive patients who underwent primary *H. pylori* eradication therapy using a vonoprazan-based regimen at Shinozaki Medical Clinic were included in this study. Data abstracted from the medical record include gender, age, body mass index, current smoker, pre-treatment with a histamine-2 receptor antagonist (H2RA), PPI or vonoprazan, endoscopic findings, adverse events, method of confirming successful eradication and use of an eradication kit as part of a vonoprazan-based regimen. The eradication kit was designed to improve medication adherence for a seven day eradication period, and includes a triple-drug blister pack and explanations of the timing of oral administration (VONOSAP pack 400. Takeda Pharmaceutical Company Limited. Tokyo. Japan). All patients underwent esophagogastroduodenoscopy prior to eradication therapy. The presence of *H. pylori* was evaluated by positive *H. pylori* IgG serology (LZ test®, Eiken Chemical, Tokyo, Japan), ^{13}C-urea breath test (UBit-100®, Otsuka Pharmaceutical, Tokyo, Japan), histology or a stool antigen test (Meridian HpSA ELISA II®, Fujirebio, Tokyo, Japan). We specifically asked all patients about a history of prior *H. pylori* eradication therapy. The Institutional Review Board of Shinozaki Medical Clinic approved this retrospective review.

Primary *H. pylori* eradication therapy with vonoprazan-based regimen

The standard triple therapy vonoprazan-based regimen includes amoxicillin 750 mg, clarithromycin 200 mg and vonoprazan 20 mg twice daily for one week. The eradication kit was used after being made available in July 2016 to improve compliance with the therapeutic regimen. Pre-treatment with H2RA or PPI was defined as continued H2RA or PPI use for more than four weeks before eradication therapy. Successful eradication was determined by a negative ^{13}C-urea breath test (<2.5‰) or stool antigen test. The test for assessing the successful eradication was performed at least eight weeks after the completion of eradication therapy. Before the ^{13}C-urea breath test, PPI or vonoprazan was discontinued at least for two weeks. The stool antigen test was used for patients who could not discontinue PPI or vonoprazan use, even for two weeks before the ^{13}C-urea breath test. Successful eradication was assessed by intention-to-treat (ITT) and per-protocol (PP) analyses. Exclusion criteria for PP analysis included patients who did not visit the clinic to have a ^{13}C-urea breath test or stool antigen test for assessing the successful eradication. Patients in ITT analysis except PP analysis were considered to have failed eradication in this study.

Statistical analysis

Statistical analysis was done using StatFlex ver. 6.0 software (Artech Co. Ltd. Osaka, Japan), and differences with p < 0.05 were considered significant. Multiple logistic regression analysis was used for univariate and multivariate analyses. Factors with p-value <0.1 in the univariate analysis were selected for multivariate analysis.

Please cite this article in press as: Shinozaki S, et al., Pre-treatment with proton pump inhibitors decreases the success of primary *Helicobacter pylori* eradication using a vonoprazan-based regimen, Kaohsiung Journal of Medical Sciences (2018), https://doi.org/10.1016/j.kjms.2018.03.009