学 位 論 文 の 要 旨

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学 位 論 文 名　Effect of Age on Effectiveness of Vonoprazan in Triple Therapy for *Helicobacter pylori* Eradication

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論 文 内 容 の 要 旨

INTRODUCTION

In 2015, vonoprazan, a novel potassium-competitive acid blocker, was released and approved for eradication of *Helicobacter pylori* (*H. pylori)* infection. A higher rate of eradication of *H. pylori* was reported with vonoprazan-based in comparison with proton pump inhibitor-based therapy when either was used in combination with amoxicillin and clarithromycin for first-line therapy. On the other hand, the effectiveness of vonoprazan when used in second-line eradication therapy over proton pump inhibitor (PPI) administration has not been demonstrated. In addition, it remains unclear whether elderly patients require strong acid suppression drugs such as vonoprazan for eradication of *H. pylori*, because gastric acid secretion decreases with age, which is a major issue throughout the world because of aging populations.

In the present study, we evaluated eradication success in first- and second-line therapy cases in order to compare the efficacy of vonoprazan to PPI administration, and also examined the effects of age.

MATERIAL AND METHOD

In this retrospective single-center study we reviewed findings from patients who underwent a standard 7-day *H. pylori* eradication therapy protocol at Izumo-City General Medical Center from January 2013 to April 2017. Eradication rates according to age, gender, grade of gastric mucosal atrophy, and acid suppression drugs were determined. Gastric mucosal atrophy grade was included

in the analysis, as it is an indicator of acid secretion, which decreases with atrophic gastritis progression. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Izumo-City General Medical Center (approval number 26-17). PPI-based first-line therapy contained amoxicillin and clarithromycin with a PPI (PAC) twice daily for 1 week. Vonoprazan-based first-line therapy, which we began to prescribe in March 2015, contained amoxicillin and clarithromycin, with vonoprazan (VAC). PPI-based second-line therapy contained a PPI, amoxicillin, and metronidazole (PAM), and vonoprazan-based second-line therapy contained vonoprazan, amoxicillin and metronidazole (VAM). PPIs given to the present patients were esomeprazole, lansoprazole, or rabeprazole. A p value <0.05 was considered to indicate statistical significance.

RESULTS AND DISCUSSION

A total of 1201 patients completed *H. pylori* eradication treatments, with first-line therapy administrated to 1172 and second-line therapy to 157. The eradication rate for all patients was 96.8% (1162/1201), while that for first-line therapy cases was 86.9% (1019/1172) and for second-line cases was 91.1% (143/157). When the patients were divided according to use of acid suppression drugs, the success rate of first-line eradication therapy with vonoprazan was 92.5%, which was significantly higher than that with lansoprazole ($p=0.001$) or rabeprazole ($p<0.001$). In multivariate logistic regression analysis, with age, gender, gastric mucosal atrophy grade, and acid suppression drugs employed as variables, only vonoprazan had a significant impact on first-line eradication success (OR, 2.36; 95% CI 1.55 to 3.56), while none of those variables had a significant effect on the success of second-line therapy.

In comparison between vonoprazan and PPI, regardless of gender and grade of atrophy, the VAC regimen was superior to the PAC regimen when used as first-line therapy. On the other hand, neither regimen was superior in the older age groups (60-69 years: 91.9% versus 86.3%, $p=0.108$; $\geq$70 years: 86.2% versus 83.4%, $p=0.558$), while the VAC regimen was superior in the non-elderly patients ($\leq$39 years: 94.9% versus 66.2%, $p=0.001$; 40-49 years: 96.7% versus 86.4%, $p=0.038$; 50-59 years: 95.7% versus 87.1%, $p=0.024$). As for second-line eradication therapy, there were no significant differences found using the same analysis methods noted above.

Seven-day PPI-based amoxycillin clarithromycin triple therapy was the standard first-line therapy given for *H. pylori* eradication in Japan prior to the approval of vonoprazan. Both amoxicillin and clarithromycin require organism growth for their effectiveness. *H. pylori* organisms can grow in periplasm at a pH level ranging from 6.0 to 8.0. PPI administration increases the population of dividing organisms by elevating gastric pH, thus synergizes with antibiotics. Insufficient acid suppression can cause eradication failure. Vonoprazan, a novel potassium-competitive acid blocker, inhibits gastric H^+ and K^+-ATPase in a manner similar to that with PPIs, though in a K^+-competitive and reversible manner, unlike PPIs. Acid activation is not

required for vonoprazan to exert its acid secretion inhibiting effect. Vonoprazan has stronger, more rapid, and longer lasting acid-inhibitory effects than PPIs. Therefore, a VAC regimen has a higher eradication rate than a PAC regimen. Moreover, the rate of eradication by a VAC regimen is significantly higher in patients infected with clarithromycin-resistant strains, which is known to be major causes of eradication failure, as compared to a PAC regimen. Additionally, the superiority of a VAC regimen for the extensive metabolizer genotype CYP2C19, an enzyme known to metabolize PPIs, is shown.

However, in the present investigation, the superiority of vonoprazan-based as compared to PPI-based treatment was limited to younger or middle aged patients who underwent first-line therapy. Our results confirmed that the efficacy of a VAC regimen over a PAC regimen is conspicuous in patients ≤39 years old, then is reduced with aging and eventually becomes unclear in patients aged 60 years and older, which seems to be related to the fact that gastric acid secretion is abundant in younger individuals and decreases with aging. On the other hand, our result didn't clarify the association between gastric mucosal atrophy grade and eradication success. Gastric mucosal atrophy extends with aging, resulting in decreased gastric acid secretion in *H. pylori*-positive patients. However, gastric acid secretion in elderly patients is often reduced by factors other than atrophic gastritis caused by *H. pylori*. Aging, which can be directly evaluated, seems to be an important factor in relation to gastric acid secretion. Our results suggest that patient age may be more useful for choosing an acid suppression drug for *H. pylori* eradiation than endoscopic atrophy. Elderly patients, who have decreased acid secretion, might not require strong acid suppression drugs like vonoprazan for *H. pylori* eradication and a PPI may be adequate.

In the present study, the VAM regimen was not superior to the PAM regimen for second-line eradication therapy regardless of age. The main reason seems to be that metronidazole, targeting DNA, is independent of the stationary or growth phase distribution, as it is effective without requiring acid suppression. In addition, it may have had effects on equality, as metronidazole has a lower rate of resistance as compared to clarithromycin because of its limited use for anaerobic and protozoan infections in Japan, though increasing rates of metronidazole resistance have been reported in various regions of the world. It seems that the role of acid suppression is reduced in second-line therapy in comparison with first-line therapy.

CONCLUSION

The present findings demonstrate that the efficacy of vonoprazan is superior to that of PPI treatment for first-line therapy, while there were no significant differences seen between them when used for second-line therapy. Furthermore, the superiority of vonoprazan for first-line therapy in elderly patients was not clear.