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Vonoprazan-based therapy for *Helicobacter pylori* eradication: experience and clinical evidence

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***Abstract*:** Stable suppression of gastric acid secretion is a crucial factor in *Helicobacter pylori* eradication. Vonoprazan is a potassium-competitive acid blocker recently approved for use in Japan. As vonoprazan has a long duration of action and causes rapid and strong inhibition of gastric acid secretion, it has gained clinical attention for treating erosive oesophagitis, peptic ulcers, and *H. pylori* infection. In this review, we discuss the recent knowledge regarding the safety and efficacy of vonoprazan, focusing on its use in *H. pylori* eradication. The latest literature and our clinical experience have shown that vonoprazan-based therapies have satisfactory eradication rates. Additionally, vonoprazan-based therapies are associated with similar rates of adverse events as standard triple therapies with conventional proton-pump inhibitors.

Keywords: Vonoprazan, *H. pylori*, PPI, Takecab, potassium-competitive acid blocker, P-CAB, TAK-438

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Helicobacter pylori eradication: current status and problems

Helicobacter pylori infection is the most common infectious disease, affecting half of the world population and causing peptic ulcers. In addition, the World Health Organization classified *H. pylori* as a group 1 carcinogen [Park *et al*. 2014]. In 2012, *H. pylori* infection was estimated as the cause of approximately 774,000 new cases of gastric cancer worldwide [Arikawa *et al*. 2012; Ferlay *et al*. 2014; Forman *et al*. 2014]. Eradication of *H. pylori* reduced the incidence of gastric cancer by over 30% in China since 2000 [Ma *et al*. 2012]. In Japan, *H. pylori* eradication was found to significantly decrease the incidence of secondary cancers after endoscopic resection of early gastric cancer [Fukase *et al*. 2008]. *H. pylori* eradication also leads to a favourable long-term outcome of gastric mucosa-associated lymphoid tissue lymphoma [Nakamura *et al*. 2014] and idiopathic thrombocytopenic purpura [Satake *et al*. 2007]. Using economic models and based on a threshold of US$50,000 per life year saved, *H. pylori* screening and treatment strategies were found to be cost effective [Park *et al*. 2014]. The Japanese government approved *H. pylori* eradication for the treatment of peptic ulcers and for patients with endoscopically proven gastritis in 2013, a measure expected to save lives and reduce medical costs due to gastric cancers [Asaka, 2014].

For over 20 years, the first-line therapy for *H. pylori* infection has comprised a combination of a proton-pump inhibitor (PPI) and two antibiotics, usually amoxicillin and clarithromycin. The commonly used PPIs include lansoprazole, omeprazole, rabeprazole, and esomeprazole (S-isomer of omeprazole), which are called 'conventional PPIs' in this review [Asaka *et al*. 2010; Megraud, 2012]. Recently, the eradication rates of *H. pylori* infection with first-line treatment have fallen below 80% in many countries, reaching less than 70% in some regions [Figura *et al*. 2016; Shinozaki *et al*. 2016]. One cause of the eradication failure is the growing resistance of *H. pylori* to the antibiotics used in the treatment regimens [Broutet *et al*. 2003; Graham *et al*. 2010; Megraud, 2012]. A clarithromycin-resistant strain of *H. pylori* has been reported in Japan and southern Europe, accounting for 30% and 20%, respectively, of the *H. pylori* eradication failures in those areas [Megraud, 2007]. In some regions, *H. pylori* strains resistant to other antibiotics have increased significantly. For example, in Singapore, *H. pylori*

resistance to metronidazole has increased from 24.8% to 48.2% in the last 15 years [Ang *et al.* 2016]. Efforts to overcome *H. pylori* eradication failure include treatment with various antibiotics. For instance, a 14-day quadruple therapy with bismuth, rabeprazole, minocycline, and amoxicillin as first-line therapy has resulted in an *H. pylori* eradication rate of over 90% [Song *et al.* 2016]. In addition, sequential treatment has been proposed, involving a two-step therapy, starting with a PPI and amoxicillin or clarithromycin for 5 days, followed by triple therapy with a PPI, clarithromycin, and a nitroimidazole, for an additional 5 days [Graham *et al.* 2010].

Another critical problem in *H. pylori* eradication is maintaining the pH of the gastric mucosa to preserve antibiotic function [Sugimoto *et al.* 2007]. The 24 h gastric pH ranges of 5.0–7.6 and 2.2–6.2 have been reported in patients with successful and failed *H. pylori* eradication, respectively, indicating that a relatively high gastric pH is optimal for successful *H. pylori* eradication [Sugimoto *et al.* 2007]. The membrane-bound H^+/K^+-ATPase (proton pump) maintains the acidity in the stomach. H^+/K^+-ATPase belongs to a P-type ATPase family and surfaces from the cytosol to the secretory membrane of the parietal cells when food is present in the stomach, pumping H^+ ions out of the cells and into the canaliculi in exchange for K^+ ions [Scott *et al.* 2015] [Figure 1(a)]. Conventional PPIs have been used to suppress intragastric acid secretion during *H. pylori* eradication for decades. Conventional PPIs are prodrugs, which are activated by acid and covalently bind to the H^+/K^+-ATPase [Abelo *et al.* 2000; Hunt *et al.* 2015] [Figure 1(a)]. Activated PPIs are not stable in acidic condition, whereas H^+/K^+-ATPase surfacing is stimulated by every food intake. Thus repeated PPI administration for several days is required to attain the maximum effect [Figure 1(a)] [Hunt *et al.* 2015]. Furthermore, conventional PPIs, especially lansoprazole and omeprazole, are extensively metabolized in the liver by cytochrome P450 2C19 (CYP2C19) genotype [Miki *et al.* 2003; Furuta *et al.* 2010]. It has been reported that *H. pylori* eradication rates of different PPIs vary significantly owing to CYP2C19 polymorphism: the rate of eradication tends to decrease in 'rapid metabolizers' because such individuals cannot achieve sufficiently high plasma concentration of PPIs to maintain high gastric pH during the therapy [Sugimoto *et al.* 2007].

Vonoprazan, a new H^+/K^+-ATPase inhibitor

Potassium-competitive acid blockers (PCABs) inhibit acid secretion in gastric parietal cells by competitively inhibiting the binding of potassium ion to H^+/K^+-ATPase [Parsons *et al.* 2005]. PCABs, including SCH28080l, have been developed since the 1990s and have been clinically tested [Mendlein *et al.* 1990; Dent *et al.* 2008]. However, in clinical trials, PCABs were shown to be hepatotoxic and did not exhibit significant superiority in acid suppression compared with PPIs [Berg *et al.* 2008; Dent *et al.* 2008].

Vonoprazan (1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamin monofumarate, initially called TAK-438) is a new PCAB that has been clinically available since 2015 in Japan [Arikawa *et al.* 2012; Garnock-Jones, 2015; Sakurai *et al.* 2016a]. Vonoprazan is a basic compound with pKa 9.06–9.3, which is significantly higher than the pKas of conventional PPIs (lansoprazole, pKa 3.8) and previously developed PCABs (SCH28080l, pKa 5.6) [Roche, 2006; Shin *et al.* 2011; Scott *et al.* 2015; Takeda Ltd, 2016]. The higher basicity of vonoprazan compared with that of conventional PPIs enables its concentration in low pH-secretory canaliculi. In addition, vonoprazan dissociates slowly from the H^+/K^+-ATPase [Hori *et al.* 2010; Scott *et al.* 2015]. Other advantages of vonoprazan are that it does not require acid activation [Hori *et al.* 2010], is rapidly absorbed in the intestine, and leads to fast inhibition of acid secretion [Scott *et al.* 2015] [Figure 1(b)]. In addition, vonoprazan is more stable at neutral pH compared with conventional PPIs: the half maximal inhibitory concentration (IC50) values at pH 7.5 were 66 and 0.028 μM for a conventional PPI and vonoprazan, respectively, in a study employing porcine H^+/K^+-ATPase [Hori *et al.* 2010]. Plasma half life of 5.7 and 7 h was reported for vonoprazan (20 mg) after a single dose and on the seventh day of administration in humans, respectively [Jenkins *et al.* 2015; Takeda Ltd, 2016], longer than the half life of conventional PPIs (<2 h). Importantly, as vonoprazan is mainly metabolized by CYP3A4, its acid inhibitory effect is least influenced by CYP2C19 haplotypes [Sakurai *et al.* 2015]. These features allow vonoprazan to exert rapid, strong, and stable inhibition of H^+/K^+-ATPase. Vonoprazan increased intragastric pH to over 4.0 within 4 h after the first administration in humans [Jenkins *et al.* 2015], creating conditions in which amoxicillin and clarithromycin are stable [Erah *et al.* 1997]. In

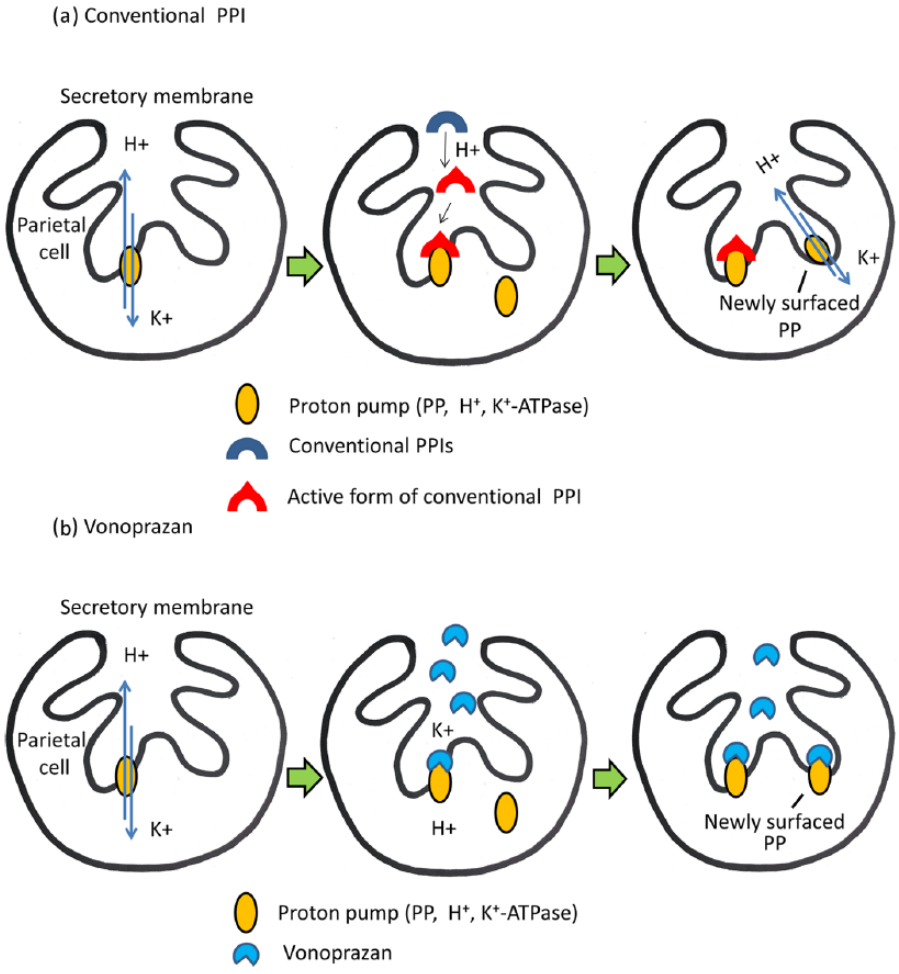

Figure 1. Simplified schematic description: differences between 'conventional' proton-pump inhibitors (PPIs) (a) and vonoprazan (b). (a) The H^+/K^+-ATPase is located on the secretary membrane of parietal cells and maintains the acidity in the stomach. The enzyme is responsible for pumping H^+ ions out of the cells into the canaliculi, in exchange for K^+ ions. Conventional PPIs are absorbed in the small intestine and subsequently reach the gastric parietal cells where they are converted to their active forms upon acid exposure, and covalently bind to the H^+/K^+-ATPase. Since conventional PPIs are unstable in canaliculi and are rapidly degraded, they are not able to inhibit new proton pumps (PPs) that surface after administration of the drug. Thus they require a few days to reach their maximum effect. (b) Vonoprazan, a potassium-competitive acid blocker, does not require acid activation. Vonoprazan is rapidly absorbed in the small intestine and accumulates in the canalicular membranes of parietal cells, binding to H^+/K^+-ATPase in a K^+-competitive manner. Vonoprazan is more stable than conventional PPIs in the canaliculi, allowing fast and stable inhibition of gastric acid secretion.

addition, amoxicillin and clarithromycin are growth-dependent antibiotics, exerting optimal effects against *H. pylori* at pH 6–7. However, lower pH values suppresses growth of *H. pylori*, leading to antibiotic resistance [Hassan *et al.* 1999; Scott *et al.* 2015]. A recent study in humans showed that intragastric pH greater than 5 holding time ratio was 99% with vonoprazan at 20 mg twice daily and 84% with esomeprazole at 20 mg twice daily when administered for 7 days [Kagami *et al.* 2016]. In the same study, the acid inhibitory effect of vonoprazan was superior to that of esomeprazole. As expected, the effect of vonoprazan was not influenced by the CP2C19 genotype. Further, a single administration of vonoprazan raised the gastric pH to over 6 for several hours [Jenkins *et al.* 2015]. Similar pharmacodynamics of vonoprazan were reported in studies from Japan and the UK [Jenkins *et al.* 2015]. Taken together, these observations imply the improved potential

of vonoprazan for eradicating *H. pylori* compared with that of conventional PPIs, as discussed in the next section.

Helicobacter pylori treatment with vonoprazan

Published data on the efficacy and safety of vonoprazan in treating *H. pylori* infection are still limited. An eradication regimen of 20 mg vonoprazan + 750 mg amoxicillin + 200 or 400 mg clarithromycin, twice daily for 7 days, has been approved and has been covered under health insurance for first-line therapy in Japan since 2015. In a phase III clinical study, Murakami and colleagues observed an *H. pylori* eradication rate of 92.6% with vonoprazan against a 75.9% rate with lansoprazole, as part of first-line therapy [Murakami *et al.* 2016]. In addition, a retrospective study showed that the eradication rate with vonoprazan-based therapy was significantly higher than the rate obtained with a lansoprazole-based therapy in both an intention-to-treat analysis (89.1% *versus* 70.9%) and a per protocol analysis (92.1% *versus* 71.7%) [Suzuki *et al.* 2016]. Another study that retrospectively reviewed the medical records of 573 patients with triple therapy employing either rabeprazole (10 mg), lansoprazole (30 mg), esomeprazole (20 mg), or vonoprazan (20 mg) showed a superior eradication rate of vonoprazan compared with lansoprazole and rabeprazole (vonoprazan 83%, lansoprazol 66%, and rabeprazole 67%; $p < 0.01$) [Shinozaki *et al.* 2016]. However, in this study, the eradication rates using esomeprazole and vonoprazan did not differ significantly. Nevertheless, vonoprazan showed better eradication rates in patients with gastric atrophy, a condition with high risk for gastric cancer. As severe gastric atrophy leads to decreased acid secretion, the stability of vonoprazan at high pH might have contributed to higher eradication rates in these patients. Further clinical studies are required to elucidate this point. In our single-centre study involving 669 patients, *H. pylori* eradication was achieved in 614 patients (91.4%) [Fukuda *et al.* 2016] using the vonoprazan-based triple regimen, a result comparable to previously reported rates [Murakami *et al.* 2016]. Other recent reports from Japan have also indicated *H. pylori* eradication rates ranging from 88% to 94% with the government approved vonoprazan-based first-line triple therapy [Matsumoto *et al.* 2016; Murayama *et al.* 2016; Sue *et al.* 2016].

The efficacy of vonoprazan after *H. pylori* eradication failure with first-line treatment is largely unknown. However, in the study by Murakami and colleagues second-line triple therapy with 250 mg metronidazole + 750 mg amoxicillin + 20 mg vonoprazan, twice daily for 7 days (approved and covered under health insurance in Japan as second-line therapy), resulted in an eradication rate of 98% ($n = 50$). Similarly, in our latest study, a 100% eradication rate was achieved using this second-line therapy ($n = 95$, 100%) [Akazawa *et al.* in press]. Inaba and colleagues investigated the effects of a 1-week treatment with amoxicillin, clarithromycin, and vonoprazan, following the failure of a first-line 1-week treatment with amoxicillin, clarithromycin, and rabeprazole. The results of the study showed that, for 70.2% of the cases in which the rabeprazole-based therapy had failed, eradication was achieved with the vonoprazan-based therapy [Inaba *et al.* 2016]. Interestingly, Murakami and colleagues reported that, in Japanese patients carrying clarithromycin-resistant *H. pylori* strains, an 82% eradication rate was achieved with first-line treatment using clarithromycin, amoxicillin, and vonoprazan compared with a 42% eradication rate with clarithromycin, amoxicillin, and lansoprazole [Murakami *et al.* 2016]. Why did the vonoprazan-based treatment show a relatively high eradication rate against clarithromycin-resistant *H. pylori*? A plausible explanation is that, since vonoprazan, amoxicillin, and clarithromycin are metabolized by CYP3A4, a combined treatment with these three drugs can delay their clearance. In addition, the strong and fast-acting acid inhibitory effect of vonoprazan allowed the antibiotics, especially amoxicillin, to eradicate the *H. pylori*. These possibilities raise a question: is dual therapy with amoxicillin and vonoprazan sufficient for *H. pylori* eradication? A very recent 1-week study with a small number of patients implied this possibility. In the study, eradication rates of 95% ($n = 19/20$) and 90% ($n = 18/20$) were achieved with the dual therapy as first- and second-line treatment, respectively. The regimen used was 20 mg vonoprazan twice daily + 500 mg amoxicillin three times a day [Furuta *et al.* 2016]. Although this regimen required a higher dosing frequency for amoxicillin, the three doses per day exerted a sufficient effect. Further, administering the dual treatment for longer periods (10 or 14 days) might result in even better *H. pylori* eradication outcomes [Graham, 2016]. Low *H. pylori* resistance to amoxicillin makes the suggested

treatments promising. In addition, amoxicillin is available worldwide and has been proven to be relatively safe [Furuta *et al.* 2010]. Excluding clarithromycin from *H. pylori* treatment regimens would attenuate newly developing clarithromycin-resistant *H. pylori* strains. This paradigm should be examined carefully in a larger number of patients and the effects of ethnicity should be investigated.

According to literature and our experience with 1118 patients, adverse effects of vonoprazan include erythema and gastrointestinal symptoms, without any life-threatening events reported so far [Jenkins *et al.* 2015; Sakurai *et al.* 2016b; Kamiya *et al.* 2016]. During a randomized study on erosive oesophagitis by Ashida and colleagues treatment-emergent adverse events (TEAEs) associated with a dose of up to 20 mg vonoprazan which led to discontinuation of the drug were comparable to those associated with 30 mg lansoprazole [Ashida *et al.* 2016]. In addition, the report by Murakami and colleagues showed a comparable rate of overall TEAEs between lansoprazole and vonoprazan. The most frequent adverse event was diarrhoea [Murakami *et al.* 2016]. In our studies on H. pylori eradication in the Japanese population using vonoprazan-based therapies, the overall rate of grade 2 adverse events was 2.1%. The side effects included diarrhoea, nausea and vomiting, constipation, abdominal pain, skin rash, and heartburn [Akazawa *et al.* in press]. One case of erythema multiforme, which required oral steroid treatment, has been reported during first-line treatment with vonoprazan [Kamiya *et al.* 2016]. Another study reported a slightly higher rate of skin rash in vonoprazan-treated patients compared with patients treated with conventional PPIs [Suzuki *et al.* 2016]. Nonetheless, caution should be exercised when drugs metabolized by CYP3A4 are coadministered with vonoprazan in patients with liver diseases. Vonoprazan has been reported to induce higher serum gastrin concentrations compared with conventional PPIs, with a stronger feedback mechanism triggered by the hypoacidity it causes reported as a possible cause [Murakami *et al.* 2016]. This phenomenon may be more concerning in patients with endocrine tumours who require long-term treatment [Jianu *et al.* 2012]. In fact, serum gastrin levels after 8 weeks of therapy were not statistically different between patients treated with vonoprazan and conventional PPIs [Murayama *et al.* 2016]. Taken together, the data from our studies and other reports show that the adverse effects of vonoprazan-based therapies are comparable to conventional PPI-based therapies. However, long-term studies on the effects of vonoprazan are required.

Conclusion

Although various strategies for eradicating *H. pylori* focus on overcoming the increasing antibiotic resistance, studies have indicated that eradication failure can be largely overcome by maintaining high pH levels in the stomach, which can be achieved by the use of an efficient acid blocker such as vonoprazan. Thus far, the data available from various studies have shown vonoprazan-based therapies to be efficient and safe for the treatment of *H. pylori* infection.

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References

Abelo, A., Eriksson, U., Karlsson, M., Larsson, H. and Gabrielsson, J. (2000) A turnover model of irreversible inhibition of gastric acid secretion by omeprazole in the dog. *J Pharmacol Exp Ther* 295: 662–669.

Ang, T., Fock, K., Ang, D., Kwek, A., Teo, E. and Dhamodaran, S. (2016) The changing profile of *Helicobacter pylori* antibiotic resistance in Singapore: a 15-year study. *Helicobacter* 21: 261–265.

Arikawa, Y., Nishida, H., Kurasawa, O., Hasuoka, A., Hirase, K., Inatomi, N. *et al.* (2012) Discovery of a novel pyrrole derivative 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1h-pyrrol-3-Yl]-N-methylmethanamin E fumarate (TAK-438) as a potassium-competitive acid blocker (P-Cab). *J Med Chem* 55: 4446–4456.

Asaka, M. (2014) Strategy to eliminate gastric cancer deaths in Japan. *International Agency for Research on Cancer (IARC Working Group Reports, No 8: 21–23)*. Available at http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk28/index.php (accessed 5 May 2016).

Asaka, M., Kato, M., Takahashi, S., Fukuda, Y., Sugiyama, T., Ota, H. *et al.* (2010) Guidelines for the management of *Helicobacter pylori* infection in Japan: 2009 revised edition. *Helicobacter* 15: 1–20.

Ashida, K., Sakurai, Y., Hori, T., Kudou, K., Nishimura, A., Hiramatsu, N. *et al.* (2016) Randomised clinical trial: vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the healing of erosive oesophagitis. *Aliment Pharmacol Ther* 43: 240–251.

Berg, A., Bottcher, G., Andersson, K., Carlsson, E., Lindstrom, A., Huby, R. *et al.* (2008) Early stellate cell activation and veno-occlusive-disease (VOD)-like hepatotoxicity in dogs treated with AR-H047108, an imidazopyridine proton pump inhibitor. *Toxicol Pathol* 36: 727–737.

Broutet, N., Tchamgoue, S., Pereira, E., Lamouliatte, H., Salamon, R. and Megraud, F. (2003) Risk factors for failure of *Helicobacter pylori* therapy – results of an individual data analysis of 2751 patients. *Aliment Pharmacol Ther* 17: 99–109.

Dent, J., Kahrilas, P., Hatlebakk, J., Vakil, N., Denison, H., Franzen, S. *et al.* (2008) A randomized, comparative trial of a potassium-competitive acid blocker (AZD0865) and esomeprazole for the treatment of patients with nonerosive reflux disease. *Am J Gastroenterol* 103: 20–26.

Erah, P., Goddard, A., Barrett, D., Shaw, P. and Spiller, R. (1997) The stability of amoxycillin, clarithromycin and metronidazole in gastric juice: relevance to the treatment of *Helicobacter pylori* infection. *J Antimicrob Chemother* 39: 5–12.

Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M. *et al.* (2014) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 136: E359–E386.

Figura, N., Moretti, E., Vaglio, L., Langone, F., Vernillo, R., Vindigni, C. *et al.* (2016) Factors modulating the outcome of treatment for the eradication of *Helicobacter pylori* infection. *New Microbiol* 35: 335–340.

Forman, D. and Sierra, M. (2014) The current and projected global burden of gastric cancer. *International Agency for Research on Cancer (IARC Working Group Reports, No 8):* 5–14. Available at http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk18/index.php (accessed 5 May 2016).

Fukase, K., Kato, M., Kikuchi, S., Inoue, K., Uemura, N., Okamoto, S. *et al.* (2008) Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 372: 392–397.

Fukuda, D., Akazawa, Y. and Fukuda, Y. (2016) Safety and efficacy of vonoprazan-based triple therapy against *Helicobacter pylori* infection: a single-center experience with 1118 patients. *Ther Adv Gastroenterol* 9: 747–748.

Furuta, T. and Graham, D. (2010) Pharmacologic aspects of eradication therapy for *Helicobacter pylori* infection. *Gastroenterol Clin N Am* 39: 465–480.

Furuta, T., Sahara, S., Ichikawa, H., Kagami, T., Uotani, T., Yamade, M. *et al.* (2016) Dual therapy with vonoprazan and amoxicillin is as effective as standard PPI-based triple therapy with amoxicillin and clarithromycin or metronidazole in Japan. *Gastroenterology* 150: S877.

Garnock-Jones, K. (2015) Vonoprazan: first global approval. *Drugs* 75: 439–443.

Graham, D. (2016) Vonoprazan *Helicobacter pylori* eradication therapy: ethical and interpretation issues. *Gut* 7 April 2016. [Epub ahead of print]

Graham, D. and Fischbach, L. (2010) *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. *Gut* 59: 1143–1153.

Hassan, I., Stark, R., Greenman, J. and Millar, M. (1999) Activities of β-lactams and macrolides against *Helicobacter pylori*. *Antimicrob Agents Chemother* 43: 1387–1392.

Hori, Y., Imanishi, A., Matsukawa, J., Tsukimi, Y., Nishida, H., Arikawa, Y. *et al.* (2010) 1-[5-(2-Fluorophenyl)-1-(Pyridin-3-ylsulfonyl)-1h-pyrrol-3-Yl]-N-methylmethanamin E monofumarate (TAK-438), a novel and potent potassium-competitive acid blocker for the treatment of acid-related diseases. *J Pharmacol Exp Ther* 335: 231–238.

Hunt, R. and Scarpignato, C. (2015) Potassium-competitive acid blockers (P-CABs): are they finally ready for prime time in acid-related disease? *Clin Transl Gastroenterol* 6: e119.

Inaba, T., Iwamuro, M., Toyokawa, T. and Okada, H. (2016) Letter: promising results of *Helicobacter pylori* eradication with vonoprazan-based triple therapy after failure of proton pump inhibitor-based triple therapy. *Aliment Pharmacol Ther* 43: 179–180.

Jenkins, H., Sakurai, Y., Nishimura, A., Okamoto, H., Hibberd, M., Jenkins, R. *et al.* (2015) Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. *Aliment Pharmacol Ther* 41: 636–648.

Jianu, C., Fossmark, R., Viset, T., Qvigstad, G., Sordal, O., Marvik, R. *et al.* (2012) Gastric carcinoids after long-term use of a proton pump inhibitor. *Aliment Pharmacol Ther* 36: 644–649.

Kagami, T., Sahara, S., Ichikawa, H., Uotani, T., Yamade, M., Sugimoto, M. *et al.* (2016) Potent acid inhibition by vonoprazan in comparison with esomeprazole with reference to CYP2C19 genotype. *Aliment Pharmacol Ther* 43: 1048–1059.

Kamiya, K., Nishio, E., Horio, A. and Tokura, Y. (2016) Erythema multiforme caused by triple therapy with amoxicillin, clarithromycin and vonoprazan for *Helicobacter pylori*. *J Dermatol* 43: 340–341.

Ma, J., Zhang, L., Brown, L., Li, J., Shen, L., Pan, K. *et al.* (2012) Fifteen-year effects of *Helicobacter pylori*, garlic, and vitamin treatments on gastric cancer incidence and mortality. *J Natl Cancer Inst* 104: 488–492.

Matsumoto, H., Kamada, T., Oosawa, M., Katsumata, R. and Fujita, M. (2016) Potassium-competitive acid blocker antisecretory therapy improves *H. pylori* eradication. *Gastroenterolgy* 150: S878.

Megraud, F. (2007) *Helicobacter pylori* and antibiotic resistance. *Gut* 56: 1502.

Megraud, F. (2012) The challenge of *Helicobacter pylori* resistance to antibiotics: the comeback of bismuth-based quadruple therapy. *Ther Adv Gastroenterol* 5: 103–109.

Mendlein, J. and Sachs, G. (1990) Interaction of a K^+-competitive inhibitor, a substituted imidazo [1,2a] pyridine, with the phospho-and dephosphoenzyme forms of H^+, K^+-ATPase. *J Biol Chem* 265: 5030–5036.

Miki, I., Aoyama, N., Sakai, T., Shirasaka, D., Wambura, C., Maekawa, S. *et al.* (2003) Impact of clarithromycin resistance and CYP2C19 genetic polymorphism on treatment efficacy of *Helicobacter pylori* infection with lansoprazole-or rabeprazole-based triple therapy in Japan. *Eur J Gastroenterol Hepatol* 15: 27–33.

Murakami, K., Sakurai, Y., Shiino, M., Funao, N., Nishimura, A. and Asaka, M. (2016) Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for *Helicobacter pylori* eradication: a phase III, randomised, double-blind study. *Gut* 65: 1439–1446.

Murayama, M., Kubota, D., Miyajima, M., Kimura, T., Tokutake, K. and Imai, R. (2016) A randomized controlled trial comparing the first-line eradication rateusing vonoprazan or PPI for *Helicobacter pylori* infectious gastritis. *Gastroenterology* 150: S1269.

Nakamura, S., Sugiyama, T., Matsumoto, T., Iijima, K., Ono, S., Tajika, M. *et al.* (2014) Long-term clinical outcome of gastric MALT lymphoma after eradication of *Helicobacter pylori*: a multicentre cohort follow-up study of 420 patients in Japan. *Gut* 61: 507–513.

Park, J., Greenberg, E., Parsonnet, J., Wild, C., Forman, D. and Herrero, R. (2014) Summary of IARC Working Group Meeting on *Helicobacter pylori* eradication as a strategy for preventing gastric cancer: Lyon, France. *International Agency for Research on Cancer (IARC Working Group Reports, No 8):* 1–4. Available at http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk8/index.php (accessed 5 May 2016).

Parsons, M. and Keeling, D. (2005) Novel approaches to the pharmacological blockade of gastric acid secretion. *Expert Opin Invest Drugs* 14: 411–421.

Roche, V. (2006) The chemically elegant proton pump inhibitors. *Am J Pharm Educ* 70: 101.

Sakurai, Y., Mori, Y., Okamoto, H., Nishimura, A., Komura, E., Araki, T. *et al.* (2016a) Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 Mg in healthy adult male subjects: a randomised open-label cross-over study. *Aliment Pharmacol Ther* 42: 719–730.

Sakurai, Y., Nishimura, A., Kennedy, G., Hibberd, M., Jenkins, R., Okamoto, H. *et al.* (2015) Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising TAK-438 (vonoprazan) doses in healthy male Japanese/non-Japanese subjects. *Clin Transl Gastroenterol* 6: e94.

Sakurai, Y., Shiino, M., Okamoto, H., Nishimura, A., Nakamura, K. and Hasegawa, S. (2016b) Pharmacokinetics and safety of triple therapy with vonoprazan, amoxicillin, and clarithromycin or metronidazole: a phase 1, open-label, randomized, crossover study. *Adv Ther*: 1–17.

Satake, M., Nishikawa, J., Fukagawa, Y., Akashi, K., Okamoto, T., Yoshida, T. *et al.* (2007) The long-term efficacy of *Helicobacter pylori* eradication therapy in patients with idiopathic thrombocytopenic purpura. *J Gastroenterol Hepatol* 22: 2233–2237.

Scott, D., Munson, K., Marcus, E., Lambrecht, N. and Sachs, G. (2015) The binding selectivity of vonoprazan (TAK-438) to the gastric H^+, K^+-ATPase. *Aliment Pharmacol Ther* 42: 1315–1326.

Shin, J., Inatomi, N., Munson, K., Strugatsky, D., Tokhtaeva, E., Vagin, O. *et al.* (2011) Characterization of a novel potassium-competitive acid blocker of the gastric H,K-ATPase, 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1h-pyrrol-3-Yl]-N-methylmethanamin E monofumarate (TAK-438). *J Pharmacol Exp Ther* 339: 412–420.

Shinozaki, S., Nomoto, H., Kondo, Y., Sakamoto, H., Hayashi, Y., Yamamoto, H. *et al.* (2016) Comparison of vonoprazan and proton pump inhibitors for eradication of *Helicobacter pylori. Kaohsiung J Med Sci* 32: 255–260.

Song, Z., Suo, B., Zhang, L. and Zhou, L. (2016) Rabeprazole, minocycline, amoxicillin, and bismuth as first-line and second-line regimens for *Helicobacter pylori* eradication. *Helicobacter.* 6 April 2016. [Epub ahead of print].

Sue, S., Arima, I., Kuwashima, I., Sanga, K. and Oka, I. (2016) Efficacy and safety of novel class of acid suppressants: P-Cab-based amoxicillin and clarithromycin 1 week triple therapy as first line eradication of *H. pylori* in Japan. A multicenter study. *Gastroenterology* 150: S880.

Sugimoto, M., Furuta, T., Shirai, N., Kodaira, C., Nishino, M., Ikuma, M. *et al.* (2007) Evidence that the degree and duration of acid suppression are related to *Helicobacter pylori* eradication by triple therapy. *Helicobacter* 12: 317–323.

Suzuki, S., Gotoda, T., Kusano, C., Iwatsuka, K. and Moriyama, M. (2016) The efficacy and tolerability of a triple therapy containing a potassium-competitive acid blocker compared with a 7-day PPI-based low-dose clarithromycin triple therapy. *Am J Gastroenterol* 111: 949–956.

Takeda Ltd (2016) *The Interview Form for Vonoprazan Fumarate (Takecab Tablets 10 mg and 20 mg)*. Version 7 (in Japanese). Available at: http://www.takeda.co.jp/ (accessed 5 May 2016).