Update on the Use of Vonoprazan: A Competitive Acid Blocker

Comparison of Vonoprazan and Traditional PPIs

Vonoprazan (TAK-438), a potassium-competitive acid blocker, inhibits acid secretion by competitively blocking availability of potassium to hydrogen-potassium ATPase. Chemically it is a pyrrole derivative (1-[5-(2- fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-*N*-methylmethanamine fumarate) currently being developed by the Takeda Pharmaceutical Company.[1,2] Vonoprazan is acid stable and rapidly absorbed fasting or fed, reaching C_{max} by 1.5–2.0 hours. It dissociates slowly from its target (half-life of approximately 7.7 hours).[3] Its high pKa (>9) promotes accumulation in the canalicular space of parietal cells, where it competitively inhibits active and resting proton pumps.[2] Interindividual variability in effect exists related to dose, sex, age, and CYP2C19.[2] No dosage adjustments are recommended for renal or liver disease. Vonoprazan inhibits CYP2B6 and CYP3A4/5, which extends the metabolism of coadministered drugs such as clarithromycin.[1]

Vonoprazan overcomes many of the perceived weakness of traditional proton pump inhibitor (PPI) therapy (short half-life, destruction in an acid environment requiring acid protection, inhibition of only activated proton pumps, requiring 3–5 cycles of administration before achieving full effect, and clinical variability related to CYP2C19 polymorphisms).[1,4] Vonoprazan has been approved in Japan for the treatment of gastric and duodenal ulcers, healing of reflux esophagitis and prevention from relapse, secondary prevention of low-dose aspirin or nonsteroidal anti-inflammatory drug–induced gastric mucosal damage, and for first and second-line *Helicobacter pylori* eradication therapy.[1,5,6]

Vonoprazan is more potent and longer acting than traditional PPIs. The relative potency of other antisecretory drugs has clinically been based on their ability to maintain intragastric pH above a desired value. For example, a pH of ≥3 for ulcer healing, a pH of ≥4 for reflux esophagitis, and a pH of ≥6 for cure of *H pylori* infections and prevention of rebleeding after endoscopic hemostasis.[7,8] Relative PPI potency is mostly based on pH4time, defined as the time the intragastric pH remains ≥4 over 24 hours after ≥5 days of therapy.[7,9] Relative PPI potency, defined in omeprazole equivalents (OE), has been determined for Western populations based on pH4time for once a day and twice a day administrations.[7,9] Owing to its longer half-life, vonoprazan comparison can best be considered a quasi-bid PPI.

Vonoprazan 20 mg given once daily achieves approximately 63% pH4time after 1 day, increasing to approximately 84% after 7 days.[3,7,10] In Western populations, studies of the weighted median pH4time for vonoprazan after 7 days reported pH4times for 10, 20, 30, and 40 mg of vonoprazan of 60.2%, 85.2%, 90.1%, and 93.2%, respectively.[7,10] Extrapolating those results to pH4time for PPIs suggests that 10 mg of vonoprazan once daily is approximately equivalent to 60 mg of omeprazole and 20 mg is approximately equivalent to omeprazole 60 mg bid, which is also approximately equal to esomeprazole 40 mg bid.[7,10] These relative potencies allow assessment of comparative trials of vonoprazan and PPIs in relation to whether they used comparable antisecretory doses. One caveat: Most vonoprazan studies have been reported in Japanese populations and current relative potency PPI data have only been established in Western populations.[7] Here, we use Western data for both, realizing that in Asian populations PPIs are often more potent but more variable owing to the marked differences in the prevalence of CYP2C19 polymorphisms and lower parietal cell mass of Asians. Overall, the majority of PPI–vonoprazan comparative studies have used markedly higher antisecretory doses of vonoprazan (60 mg omeprazole once or twice daily) than of PPIs (10 mg rabeprazole, OE of 18 mg; 20 mg esomeprazole, OE of 32 mg; 30 mg lansoprazole, OE of 27 mg; or 15 mg lansoprazole, OE of 13.5 mg). We note when this bias must be taken into consideration.

Clinical Comparisons

Overall, for conditions where PPIs with shorter pH4times are effective (eg, healing of peptic ulcer disease, nonerosive or mild erosive esophagitis), outcome with vonoprazan and PPIs typically proved noninferior (Table 1).[1,5,11–13] In contrast, for conditions where prolonged pH4times provide superior outcomes (eg, severe erosive esophagitis), vonoprazan seemed to be superior with the caveat that this superiority occurred with PPIs with lower pH4times. In nonerosive esophagitis or LA grades A/B esophagitis results with PPIs and vonoprazan have proved similar. For example, a dose-ranging study of lansoprazole 30 mg (27 mg OE) with vonoprazan (5, 10, 20, or 40 mg once daily) reported similar (noninferior) results in patients with LA grade A/B esophagitis.[14] Healing at 4 weeks in LA grade C/D with 30 mg of lansoprazole (pH4time of approximately 45%) was similar to therapy with 5 or 10 mg of vonoprazan (pH4 time of approximately 60%; eg, 87% vs 87.3% and 86.4%, respectively).[14] However, healing increased to >95% with vonoprazan doses producing a >80% pH4time (ie, 100% with 20 mg vonoprazan [pH4time of 84%] and 96% with 40 mg vonoprazan and [pH4time of 90%]).[7,14] Although not studied, one would expect similar healing if 20 mg of vonoprazan had been compared with esomeprazole or rabeprazole 40 mg bid (pH4time of approximately 85% with both).[7] These results clearly

Table 1. Examples of Comparative Studies With Vonoprazan and PPIs

Parameter	Lansoprazole 30 mg (%)	Vonoprazan 20 mg (%)
Healing esophagitis 8 wk[1,2]	99.0	95.5
LA grade A/B[14]	100.0	99.2
LA grade C/D[14]	87.5	98.7
Recurrence at 24 wk LA C/D*[,5]	39.0	13.2 and 4.7
Duodenal ulcer healing 6 wk[13]	98.3	95.5
Gastric ulcer healing 8 wk[13]	93.8	93.5
NSAID ulcer recurrence 24 wk*[1,2]	5.5	3.4
Bleeding after ESD†[,12]	10.0	1.3

ESD, endoscopic submucosal dissection; NSAD, nonsteroidal antiinflammatory drug.
*Lansoprazole 15 mg (13.5 mg vs vonoprazan 10 mg [60 mg omeprazole equivalent] or 20 mg [60 mg omeprazole equivalent bid]).
†Intravenous omeprazole days 1 and 2, rabeprazole 20 mg/d (36 mg omeprazole equivalent) with polaprezinc versus vonoprazan 20 mg plus polaprezinc.

show the importance of judging outcomes in relation to relative potency.[7]

Experience has shown that the majority of patients with gastroesophageal reflux disease have nonerosive disease and can be managed with once daily low-dose PPI. However, those with the more severe erosive disease (LA grades C or D) are likely to do better with higher levels of acid suppression (eg, longer pH4times).[7,15] Large randomized studies have shown that with once daily dosing with a high dose of once daily PPI (eg, OE of 60 mg or more once daily) is superior to lower dose PPI in only about 5% of cases.[7,16] Clinically PPIs may have an advantage over vonoprazan when low antisecretory is desired, because clinical PPI doses are available that range from 2.4 to 72 mg OE.[7] The advantage would shift to vonoprazan when one desires near 100% pH4time, as may be the case with a subset of those with severe erosive esophagitis, gastrointestinal bleeding, or for some *H pylori* eradication therapies (see below).

Vonoprazan in *H pylori* Therapy

Recently, the World Health Organization listed *H pylori* among the 16 antibiotic-resistant bacteria that pose the greatest threat to human health.[17] This announcement is part of a World Health Organization campaign to improve antibiotic stewardship and reduce antibiotic misuse. Their announcement coincided with publication of *H pylori* consensus guidelines attempting overcome increasingly treatment failures owing to antimicrobial resistance.[18,19] Vonoprazan was approved in Japan for first- and second-line *H pylori* eradication therapy in 2014. The initial Japanese treatment study compared vonoprazan 20 mg bid and lansoprazole 30 mg bid as a 7-day amoxicillin and clarithromycin first-line triple therapy.[6] PPI- and vonoprazan-containing therapies produced high and equivalent results for those with clarithromycin-susceptible infections.[20] Cure rates differed in those with clarithromycin resistance (cure rates were 80% vs 40% for vonoprazan and lansoprazole, respectively). Because clarithromycin resistance functionally removes clarithromycin from triple therapy the study actually consisted of 2 different regimens (triple therapy and dual therapy consisting of the potassium-competitive acid blocker or PPI plus amoxicillin) given simultaneously. The overall result is thus critically dependent on the proportion with resistant strains. This initial study also involved patients with prior peptic ulcers. Subsequent studies in Japan have treated "all comers" and the overall cure rates have generally been <90% and have been decreasing.[21] Cure rates with susceptible strains with both vonoprazan and PPI have also been lower than in the original trial.[21] The currently recommend vonoprazan-containing *H pylori* therapies have also not yet been optimized in terms of drugs, doses, or duration. All recent consensus statements have recommended 14-day regimens with PPI-containing therapies for best outcomes to overcome the persister state of *H pylori* and with PPIs to achieve full antisecretory activity (eg, with 7-day therapy full activity is present for only 3–4 days).[18,19] For example, one expects a cure rate of only approximately 90% with 7-day clarithromycin PPI triple therapy, even with susceptible infections.[7,22]

Vonoprazan–amoxicillin dual therapy cures approximately 80% of infections, irrespective of resistance to other drugs. This is consistent with previous studies with PPI–amoxicillin dual therapy, showing that outcome depended on the degree of antisecretory effect and the duration of therapy (reviewed in[23]). The current cure rates in Japan with vonoprazan clarithromycin triple therapy are now approaching the cure rates achieved with vonoprazan–amoxicillin dual therapy alone and the incremental gain with clarithromycin is only a few percent (Figure 1).[21,24] Because approximately 80% of patients would be cured without including the clarithromycin, vonoprazan, clarithromycin, and amoxicillin triple therapy represents misuse of antibiotics in that, for the majority of patients, clarithromycin can produce side effects and promote antimicrobial resistance within the population. Because metronidazole resistance is rare in Japan, the Japanese *H pylori* Study Group has petitioned the government to allow vonoprazan–metronidazole–amoxicillin as first-line therapy. However, this step will not eliminate antibiotic misuse, because 80% of patients would receive metronidazole unnecessarily.

There are a number of not mutually exclusive options to address this dilemma. The best approach is probably to optimize vonoprazan plus amoxicillin dual therapy. A high-dose PPI plus amoxicillin has proved effective in highly select populations, but overall has not been able to reliably achieve cure rates higher than 60%–80%.[23,25] Asian populations with a high prevalence of slow PPI metabolizers and corpus

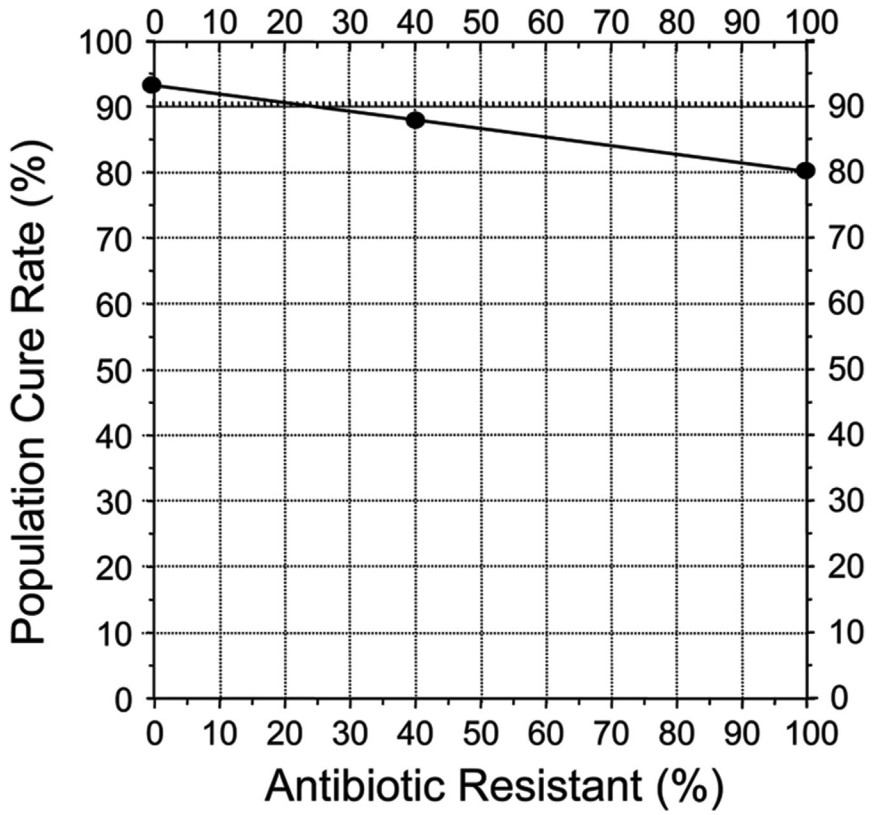

Figure 1. Example of the effects of clarithromycin resistance on the overall cure rate with 7-day vonoprazan clarithromycin triple therapy In this example, the cure rate with clarithromycin-susceptible and -resistant infections is 93% and 80%, respectively. A prevalence of clarithromycin resistance of 40% results in an 87% overall cure rate. The treatment-specific cure rates would be 80%, irrespective or the presence or absence of clarithromycin; the incremental increase with clarithromycin would be 7% and 13% would fail despite amoxicillin and clarithromycin.

gastritis have been able to achieve cure rates of >90%, but this type of population has been difficult to duplicate.[23,25] Although the variables critical for high cure rates with dual therapy are as yet unclear, maintaining the intragastric pH at >6 to stimulate *H pylori* replication and an adequate duration of therapy seem to be most important.[8,23,25] It has been suggested that maintaining a high minimum inhibitory concentration of amoxicillin is also important (eg, with every 6-hour administration),[26] but that hypothesis has not been systematically evaluated and many exceptions occur.[23,25] The goal of *H pylori* therapy is to reliably cure ≥95% of adherent patients and avoid antibiotic misuse. The prior extensive experience with PPI–amoxicillin should be used and along with a simple factorial design should rapidly provide answers. Reliably successful therapy could then be simplified (eg, 14 day, high and lower dose vonoprazan, and bid, tid, and qid amoxicillin with a total dose of approximately 2–3 g). It is important to focus on identifying what works best in terms of drugs, formulations, doses, and durations of therapy rather than to develop regimens based on perceived marketing advantages.

A second approach would be to treat patients with the vonoprazan and amoxicillin dual for 7–14 days (depending on the incremental gain with duration extension) with the remaining 10%–20% then receiving the best combination for that population (eg, vonoprazan, amoxicillin, metronidazole). This strategy would eliminate a high proportion from receiving an unnecessary antibiotic, but is less elegant. A third option is to add a nonantibiotic component to vonoprazan amoxicillin dual therapy, such as bismuth or a probiotic. There are theoretical reasons why bismuth might be ineffective, but this limitation could possibly be overcome by giving it as the oxychloride or with citric acid.[23]

Prevention of Rebleeding After Successful Endoscopic Hemostasis

It has proven to be impossible to reliably achieve an intragastric pH of >6 in fed patients using orally administered PPIs given 1, 2, or 3 times daily.[7] The options are to add an antacid, use vonoprazan, or both. The advantages of vonoprazan include rapid onset of action and suppression of both active and inactive proton pumps. Single dose studies have shown that may be able to be achieved even on day 1 with an 80-mg dose orally. The availability of vonoprazan will allow direct testing of the theory that protecting the clot will further reduce or eliminate rebleeding after successful hemostasis.

Vonoprazan and Serum Gastrin and Other Potential Cautions

Vonoprazan potently reduces acid secretion and stimulates gastric release. Serum gastrin measurement provides a simple method of gauging the degree of acid suppression with achlorhydria being required for very high gastrin levels.[27,28] Gastrin increases have varied from slightly above normal to >1000 pg/mL, with standard vonoprazan dosing most likely reflecting the variability of the drug to influence acid secretion. In most studies of hypergastrinemia associated with antisecretory drug use, gastrin levels do not continue to increase and promptly return to normal after discontinuation of therapy.[27] The results of a 52-week esophageal healing maintenance study provided somewhat alarming and as yet unexplained results.[11] In that study, patients with gastroesophageal reflux disease with healed esophagitis received 52 weeks of maintenance vonoprazan of 10 or 20 mg/d and

experienced striking and progressive increases in serum gastrin (eg, from 317 ± 336 pg/mL after 8 weeks increasing to 777.6 ± 678.0 pg/mL at 52 weeks with 20 mg/d and 291 ± 219 to 514.5 ± 435.0 with 10 mg vonoprazan).[11] No significant effects on gastric neuroendocrine cells at 24 and 52 weeks or changes in pepsinogen levels were identified. It is difficult to understand why the gastrin levels were so high and continued to increase. Theoretically, these changes reflect increasing acid suppression. Detailed analyses of the histology of the antral and corpus mucosa were not reported. This observation remains to be explained.

It has been postulated that vonoprazan likely inhibits the renal HKα_1-ATPase located in the renal medullary collecting ducts whereas traditional PPIs do not. The significance, if any, of this inhibition has not yet been clarified.[29] Vonoprazan as a potent antisecretory PPI potentially can affect nutrient absorption (eg, iron and vitamin B_{12}) and reduce the acid barrier, leading to changes in risk of enteric infections particularly for those traveling in tropical regions and to changes in the intestinal microbiome. Like other potent PPIs the effect is likely related to the effectiveness of acid inhibition, but this has yet to studied systematically, because most data are class data and thus very heterogenous. Whether the risks differ from traditional PPIs with similar potency remains to be examined.

Summary

Vonoprazan can be considered as a potent and long-acting PPI with some potential advantages over traditional PPIs. Both PPIs and vonoprazan therapy can be tailored to achieve more or less acid inhibition allowing the degree of acid suppression to be tailored to the need. Current clarithromycin- and vonoprazan-containing *H pylori* eradication therapies likely result in misuse of clarithromycin or metronidazole.[30] Vonoprazan offers the promise of being able to reliably achieve an intragastric pH of >5 and possibly >6, which may make it useful as an adjuvant to preventing recurrent bleeding after endoscopic hemostasis or for *H pylori* eradication therapy and to reliably achieve high cure rates with amoxicillin plus an antisecretory agent therapy. Vonoprazan may also assist in the management of fat malabsorption in patients with pancreatic insufficiency. Currently available enteric-coated pancreatic enzyme microbeads tend to dissociate from the meal and dissolve slowly and unpredictably during passage through the small intestine, precluding coordinated emptying of enzymes and nutrients. Unprotected enzymes mix well and empty with nutrients, but are inactivated at a pH of ≤4. The ability to reliable maintain an intragastric pH of >4 for very long periods may allow routine use of non–enteric-coated enzymes.[31] The long duration of action, good bioavailability, stability in acid, and inhibition of both active and inactive proton pumps suggest that vonoprazan may also be useful for difficult to manage patient such as those with Roux-en-Y gastric bypass or other bariatric surgeries in which lack of antral release of gastrin, rapid gastric emptying, and the small absorptive area for dissolution and absorption of enteric-coated PPIs make traditional antisecretory therapy difficult.[32] Currently, vonoprazan plays an important and unique role when more acid suppression is needed than can be obtained with 60–70 mg of OE bid. However, situations are rare and, except for Zollinger–Ellison syndrome, would generally be of short duration. Whether vonoprazan is appropriate and safe for long-term, even life-long, use remains to be determined.

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Conflicts of interest
The authors disclose no conflicts.

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