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EDITORIAL

Vonoprazan-amoxicillin dual regimen with *Saccharomyces boulardii* as a rescue therapy for *Helicobacter pylori*: Current perspectives and implications

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Abstract

Yu *et al*'s study in the *World Journal of Gastroenterology* (2023) introduced a novel regimen of Vonoprazan-amoxicillin dual therapy combined with *Saccharomyces boulardii* (*S. boulardii*) for the rescue therapy against *Helicobacter pylori* (*H. pylori*), a pathogen responsible for peptic ulcers and gastric cancer. Vonoprazan is a potassium-competitive acid blocker renowned for its rapid and long-lasting acid suppression, which is minimally affected by mealtime. Compared to proton pump inhibitors, which bind irreversibly to cysteine residues in the H^+/K^+-ATPase pump, Vonoprazan competes with the K^+ ions, prevents the ions from binding to the pump and blocks acid secretion. Concerns with increasing antibiotic resistance, effects on the gut microbiota, patient compliance, and side effects have led to the advent of a dual regimen for *H. pylori*. Previous studies suggested that *S. boulardii* plays a role in stabilizing the gut barrier which improves *H. pylori* eradication rate. With an acceptable safety profile, the dual-adjunct regimen was effective regardless of prior treatment failure and antibiotic resistance profile, thereby strengthening the applicability in clinical settings. Nonetheless, *S. boulardii* comes in various formulations and dosages, warranting further exploration into the optimal dosage for supplementation in rescue therapy. Additionally, larger, randomized, double-blinded controlled trials are warranted to confirm these promising results.

Key Words: Vonoprazan; *Saccharomyces boulardii*; *Helicobacter pylori*; Rescue therapy; Eradication rate

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Core Tip: Vonoprazan-amoxicillin dual therapy with *Saccharomyces boulardii* (*S. boulardii*, VAS regimen) emerges as a novel rescue therapy for eradicating *Helicobacter pylori* (*H. pylori*). Vonoprazan, a potassium-competitive acid blocker, exhibits superior acid suppression compared to proton pump inhibitors. Notably, dual therapy minimizes the use of an additional antibiotic while maintaining efficacy comparable to traditional triple therapy. This paper highlights the role of *S. boulardii*, a probiotic, in enhancing the efficacy of Vonoprazan dual therapy by restoring gut microbiota balance, directly affecting *H. pylori*, and regulating immunomodulation. The VAS regimen emerges as a promising treatment alternative, demonstrating remarkable eradication of *H. pylori*, even in triple-resistant strains.

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INTRODUCTION

Yu *et al*'s study introduced a novel regimen involving vonoprazan-amoxicillin dual therapy with *Saccharomyces boulardii* (*S. boulardii*) for the rescue therapy against *Helicobacter pylori* (*H. pylori*), a critical pathogen responsible for gastroduodenal diseases including peptic ulcers and gastric cancer[1]. First approved in Japan in 2014, vonoprazan is a potassium-competitive acid blocker renowned for its profound acid suppression, which is minimally affected by mealtime[2]. The target of action for vonoprazan is the H^+/K^+-ATPase, a proton pump that becomes activated when it gets inserted into the canalicular membrane to secrete acid (H^+) from the gastric parietal cells into the lumen[3]. The current first-line treatment regimen for *H. pylori* eradication includes a standard triple therapy with proton pump inhibitors (PPIs) and two antibiotics. PPIs are prodrugs that are activated in an acidic (low pH) environment and work by irreversibly binding to the cysteine residue on the H^+/K^+-ATPase pump. On the other hand, vonoprazan works independently of the pH level and competes with the K^+ ions, preventing the ions from binding to the pump and, therefore, blocking acid (H^+) secretion [4]. Due to the high negative logarithm of the acid dissociation constant (pKa), vonoprazan quickly accumulates in gastric tissue and has delayed clearance once bound to H^+/K^+-ATPase. This property allows vonoprazan to offer a more rapid and longer-lasting gastric acid suppression than the PPIs. In fact, compared to lansoprazole, vonoprazan resulted in a significantly greater 24-hour holding-time ratio for intragastric pH > 4 on days 1 and 7[3]. Therefore, the superior acid suppression properties of vonoprazan, compared to PPIs, highly attract its potential use for treating gastric acid-related disease[5].

VONOPRAZAN DUAL THERAPY REGIMEN: BREAKTHROUGH AND EVIDENCE

Dual therapy against *H. pylori* is a relatively new treatment regimen approach. Previously, the standard triple therapy containing PPIs, Clarithromycin, and Amoxicillin or Metronidazole was the mainstay treatment for *H. pylori* eradication. However, antibiotic resistance has caused the eradication rate to diminish (< 80%)[6]. In fact, resistance to clarithromycin has continuously increased, with reports in Japan describing an increase from 7% to 28.5% over the course of 14 years[7] and in Australia suggesting an increase of 3.7% annually over the past 20 years[8]. In the United States, eradication rates of triple therapy with PPI have declined to less than 80%, attributable to both antibiotic resistance and failure to maintain the intragastric pH required for effective antimicrobial activity[9].

Yu *et al*'s prospective single-arm trial in the *World Journal of Gastroenterology* introduced a novel regimen involving vonoprazan-amoxicillin dual therapy with the addition of *S. boulardii* (VAS regimen) for the rescue therapy against *H. pylori* in patients with a history of treatment failure[1]. In this study, the resistance of *H. pylori* to clarithromycin, metronidazole, and levofloxacin was 91.3%, 100%, and 60.9%, respectively. Overall, the eradication rate of *H. pylori* was 92.6% (63/68). Interestingly, out of the patients with triple-resistant *H. pylori* (60.9%; n = 14/23), a 92.9% eradication rate was achieved with the vonoprazan-based rescue therapy. This suggested that such a regimen was effective and safe regardless of antibiotic resistance.

Previous studies investigating treatment-naïve patients showed promising findings for Vonoprazan dual therapy. In Chey *et al*'s phase 3 randomized controlled trial (RCT), the reported eradication rate for clarithromycin-resistant *H. pylori* with Vonoprazan-Amoxicillin dual therapy was 69.6%, while eradication rates were 65.8% with vonoprazan-amoxicillin-clarithromycin triple therapy and 31.9% with Lansoprazole triple therapy[9]. Despite not reaching values above 90%, the eradication rate was numerically higher in the dual therapy, suggesting that adding Clarithromycin may be unnecessary in treating clarithromycin-resistant strains. Zuberi *et al*'s study reported that the vonoprazan-based regimen was superior to the PPI triple therapy regimen in eradicating *H. pylori* (93.5% *vs* 83.9%)[10]. Similarly, Liu *et al*'s network meta-analysis suggested that vonoprazan-based therapies were significantly more effective in eradicating *H. pylori* than PPI triple therapy, with the best safety profile shown by the vonoprazan dual therapy[11]. Therefore, vonoprazan dual therapy

presents as a lower-cost, simple, yet effective treatment option for *H. pylori* eradication.

As for patients with a history of two treatment failures, vonoprazan-based triple therapy yielded a significantly higher success rate in comparison to esomeprazole-based therapy[12]. Similarly, for third-line therapy, the eradication rate with the vonoprazan-amoxicillin-sitafloxacin regimen was higher than the PPI-based regimen (75.8% *vs* 53.3%), despite no significant difference in the intention-to-treat analyses (P = 0.071)[13]. The duration of therapy might explain the insignificant difference in eradication rates since Sue *et al*[13] had prescribed the treatment regimens for only seven days, whereas Yu *et al*[1] provided the regimen for 14 d. Therefore, although no study has investigated the effect of therapy duration on eradication rates, available data suggest that long-term regimens may be more effective.

SACCHAROMYCES BOULARDII AS AN ADJUNCT THERAPY IN *H. PYLORI* ERADICATION

The use of antibiotics in treatment regimens for eradicating *H. pylori* has been shown to disrupt the balance of gut microbiota and may elicit adverse events. Recent studies have shown that probiotics, including *S. boulardii*, may contribute to mitigating these effects by: (1) Maintaining the balance and integrity of the normal gut microbiota; (2) direct activity against the pathogenesis of *H. pylori*; and (3) immunomodulation (Figure 1)[14]. In the context of therapy, Keikha and Kamali[14] investigated the addition of *S. boulardii* to the standard triple regimen, and the addition of *S. boulardii* was shown to be associated with a lower proportion of anaerobic bacteria, including *Bacteroides* and *Clostridium*, as well as higher proportion of commensal bacteria including *Bifidobacterium* and *Lactobacillus*[14]. Sakarya and Gunay[15] *in vivo* study proved that *S. boulardii* may also directly contribute to the eradication of *H. pylori via* the α2,3-linked sialic acid–selective neuraminidase activity, leading to reduced adhesion to host cells. Additionally, *S. boulardii* may produce proteins that modulate cytokines, contribute to the activation of peroxisome proliferator-activated receptor-gamma, and trigger antibody production, leading to an anti-inflammatory effect that sustains the gastrointestinal system[16].

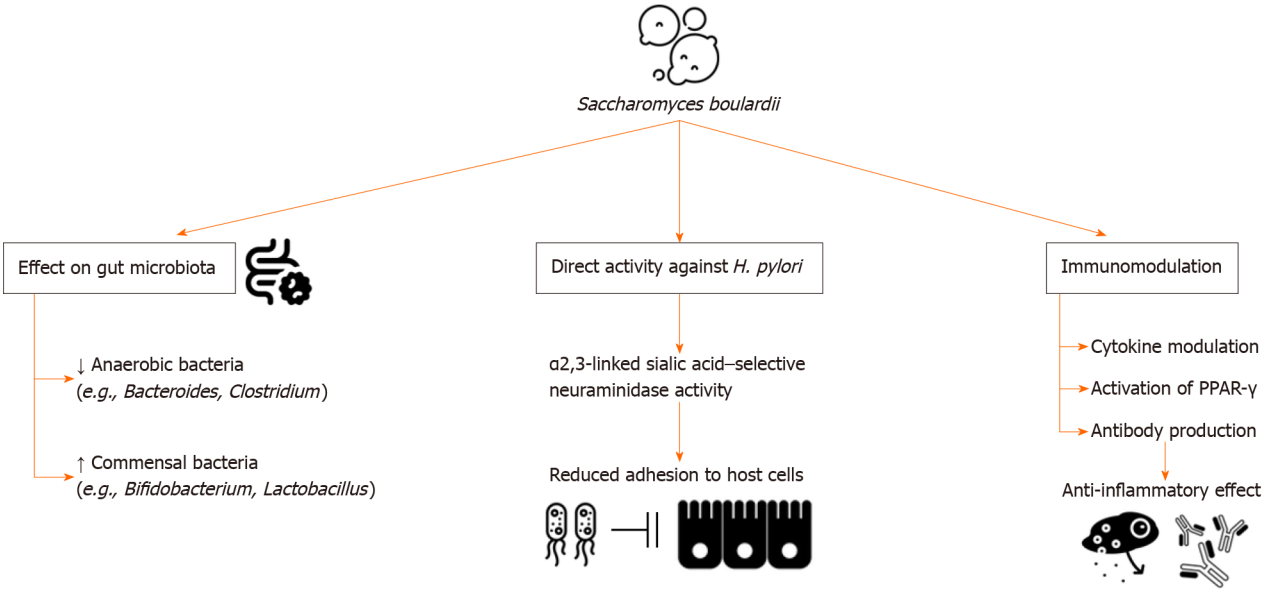

Figure 1 Mechanism of action of *Saccharomyces boulardii* in *Helicobacter pylori* eradication. *H. pylori*: *Helicobacter pylori*.

Yu *et al*[1] were the first to investigate the combination of a vonoprazan dual regimen with *S. boulardii* as an adjunct therapy, providing new insights into its efficacy in rescue therapy. This data builds on previous studies investigating the addition of *S. boulardii* for standard triple or quadruple therapy. Qu *et al*[17] provided a two-stage intervention for rescue therapy, during which the patients were administered *S. boulardii* as monotherapy for two weeks, followed by bismuth quadruple therapy if required. The eradication rates in patients receiving *S. boulardii* were reported to be higher than those who did not receive *S. boulardii*, thus supporting its effectiveness. However, several other studies, including Zojaji *et al*[18], did not show any significant improvement in eradication with the addition of *S. boulardii; however*, it was noted that the side effects, including nausea, bloating, and diarrhea, were lower. In addition, a meta-analysis by Liu *et al*[11] investigating *S. boulardii* in addition to standard triple therapy suggested that it yielded beneficial outcomes in eradication, the occurrence of adverse effects, and symptom reduction. Another meta-analysis of 18 RCTs by Zhou *et al*[19] demonstrated a slight pooled improvement in the eradication rate by 9% while decreasing the adverse effects by half. Therefore, while the effectiveness of adding *S. boulardii* for eradicating *H. pylori* might be modest, the reduction of adverse effects makes it worthwhile for this probiotic to be added to the regimen.

FACTORS AFFECTING TREATMENT FAILURE OF THE VONOPRAZAN-AMOXICILLIN- *S. BOULARDII*

Demographic factors such as age, gender, smoking history, and alcohol consumption were not associated with the VAS treatment regimen failure in Yu *et al*[1] study. Several socio-demographic characteristics, such as gender and areas of residence, have been significantly associated with *H. pylori* eradication failure[20] despite inconsistent results observed across studies[21,22]. This suggests that the impact of socioeconomic and demographic factors on treatment outcomes may vary across different patient populations. Such variations may stem from differences in antibiotic usage patterns, antimicrobial resistance, and medication adherence[23-25].

It is interesting to note that anxiety was identified as a risk factor for treatment failure with the VAS treatment regimen. This finding aligns with previous research linking psychological factors to dyspeptic symptoms. For instance, patients with disorders of the gut-brain interaction were noted to have higher rates of anxiety and depression[26]. This relationship may be correlated to the intricate brain-gut axis, a circuit linking the central, peripheral, and autonomic nervous systems with gastrointestinal functions. Gut microorganisms, including *H. pylori* infection, were hypothesized to interact with this axis, as evident by the observation that stress and emotional disorders negatively impact intestinal flora and digestive function[27]. Further investigations suggest that this relationship may be bidirectional. *H. pylori* infection was associated with altered eating behavior, anxiety and depression-like behaviors, cognitive dysfunction, and lower pain thresholds[27-29]. On the other hand, a study in mice models by Guo *et al*[30] demonstrated that the induction of psychological stress significantly increased *H. pylori* colonization and was associated with more extensive gastric mucosal injury. The underlying mechanisms of altered brain-gut axis potentially involve direct neurotoxic effects, activation of proinflammatory responses, and micronutrient deficiencies, areas which are still highly subject to research[27]. The complex interplay between psychological disorders and *H. pylori* infection underscores the importance of psychological assessments and interventions, such as cognitive behavioral therapy or counseling sessions, to enhance treatment success in *H. pylori* infections[31,32].

Notably, Yu *et al*[1] also showed that the number of previous treatment failures was not associated with treatment failure in this VAS regimen. Eradication rates were consistently high, irrespective of resistance to clarithromycin and levofloxacin. This is in contrast to a prior study that identified any prior exposure to antibiotics as a risk factor for treatment failure with a clarithromycin-containing triple therapy regimen[33]. Clarithromycin resistance was shown to be associated with Metronidazole resistance[34], leading to the prevalence of double-resistant strains, particularly in individuals who had previously failed two eradication treatments[35-38]. Furthermore, sufficient acid inhibition is required for successful *H. pylori* eradication, as it influences the stability and bioavailability of some antibiotics, including amoxicillin. Eradication failure was often observed in patients who are extensive CYP2C19 metabolizers of PPI, as they exhibit rapid PPI inactivation and insufficient acid suppression[39,40]. Vonoprazan exhibits stronger and longer acid suppression than PPI[41], which may explain the significant superiority of a vonoprazan-based regimen over PPI-based therapy regarding *H. pylori* eradication success[42]. This suggests the potential use of the VAS regimen as a rescue therapy for *H. pylori* infections resistant to other essential antibiotics, particularly in the context of increasing global antimicrobial resistance.

SAFETY PROFILE OF VONOPRAZAN-BASED THERAPIES

The impact of adverse events on therapy discontinuation and treatment adherence is a critical aspect of any treatment regimen. In Yu *et al*'s study[1], the VAS regimen exhibited a low rate of adverse events, all of which were reported as mild or moderate. The safety profile of vonoprazan, as reported in numerous clinical studies, consistently demonstrates its superiority or, at the very least, equivalence to that of PPIs. A meta-analysis of RCTs demonstrated a significantly lower rate of adverse events with vonoprazan-based triple therapy (32.7%) compared to PPI-based triple therapy (40.5%) while maintaining a higher efficacy in terms of *H. pylori* eradication rate[43].

Commonly reported adverse events include diarrhea, dysgeusia, loose stool, and skin eruption[44]. While Suzuki *et al*[45] noted a slightly higher incidence of skin rash in vonoprazan-based therapy, it is noteworthy that the vonoprazan-based regimen was generally well-tolerated, and no instances of therapy discontinuation occurred due to the adverse events.

CONCLUSION

The superiority of the vonoprazan-based regimen in terms of both efficacy and safety highlights its potential as an excellent alternative for *H. pylori* treatment and positions it as an effective option for rescue therapy. Notably, the vonoprazan-amoxicillin dual therapy has exhibited acceptable efficacy in *H. pylori* eradication, comparable to the outcomes of vonoprazan-based triple therapy. Given the increasing rates of clarithromycin resistance in various geographical regions, adding clarithromycin to vonoprazan and amoxicillin may only offer a marginal benefit. The dual regimen minimizes the use of an unnecessary additional antibiotic while maintaining efficacy similar to that of triple therapy, a crucial consideration amid the current surge in antibiotic resistance[46]. Additionally, the supplementation of *S. boulardii* as an adjunct therapy to vonoprazan-based regimens has shown positive effects on *H. pylori* eradication and reduced adverse events, possibly attributed to the maintenance of normal gut microbiota.

However, it is essential to acknowledge certain limitations in this study. While this study supported the efficacy of a dual vonoprazan-based regimen with the addition of *S. boulardii* for rescue therapy, it should be noted that the number of study participants is considered small. Additionally, the generalizability of the reduction of adverse events seen with the addition of *S. boulardii* might be limited since different populations possess different gut microbiota, which is affected by geography and dietary habits[47]. Given the various formulations and dosages available, further exploration is needed to determine the optimal dosing of *S. boulardii* supplementation in such rescue therapy. Lastly, as this study employed a single-arm design, direct comparisons of the VAS regimen to currently recommended regimens are lacking. Therefore, randomized double-blinded controlled trials with large sample sizes are required to validate these promising results.

FOOTNOTES

Author contributions: Dirjayanto VJ, Audrey J, and Simadibrata DM reviewed the literature, drafted the original manuscript, and critically revised the manuscript for important intellectual content; all authors have read and approved the final version of the manuscript.

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