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Efficacy and Tolerability of Second-Line Metronidazole Triple Therapy Using Vonoprazan for *Helicobacter pylori* Eradication in Japan—Comparative Study: Vonoprazan vs. Proton Pump Inhibitors

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Abstract

Aim: To investigate the efficacy and tolerability of second-line metronidazole triple therapy with vonoprazan (VPZ) for *Helicobacter pylori* (*H. pylori*). Methods: We retrospectively reviewed medical records of patients who experienced clarithromycin triple therapy failure and were treated with second-line (20 mg VPZ (n = 274)/30 mg lansoprazole (n = 323) or 10 mg rabeprazole (n = 141) twice daily, 750 mg amoxicillin twice daily, 250 mg metronidazole twice daily for 7 days) eradication therapies. Successful eradication rates were compared between two groups: those receiving VPZ and those receiving a proton pump inhibitor (PPI). Adverse events were also investigated. Results: Successful second-line eradication rates according to ITT analysis and PP analysis, respectively, were 79.9% and 92.4% for VPZ therapy and 83.6% and 93.3% for PPI therapy. There were no significant differences between treatment groups. The eradication rates in those who had received first-line VPZ therapy previously according to ITT and PP analysis were 75.2% and 88.1%, respectively; in contrast, values were 82.5% and 95.4%, respectively, for those who had received first-line PPI therapy previously. In second-line therapy, the overall adverse event rate for VPZ therapy was the same as for PPI therapy. Conclusions: The efficacy and tolerability of metronidazole-containing second-line triple therapy with VPZ or a PPI were equivalent.

Keywords

Vonoprazan, Metronidazole, Proton Pump Inhibitor, Second-Line Eradication, *Helicobacter pylori*

1. Introduction

Helicobacter pylori (*H. pylori*) in humans is commonly associated with gastroduodenal diseases, such as chronic gastritis, peptic ulcer diseases, mucosal-associated lymphoid tissue lymphoma (MALT lymphoma), and gastric neoplasms [1] [2]. Curative treatment of *H. pylori* infection was proved to markedly reduce the rate of recurrence of a variety of gastroduodenal diseases [2] [3]. In 2014, The International Agency for Research on Cancer (IARC) Working Group recommended *H. pylori* eradication as a strategy for preventing gastric cancer [4]. It encouraged all countries to explore the possibility of introducing population-based *H. pylori* screening and treatment programs adjusted to local healthcare environments and needs [5].

The standard triple therapy for *H. pylori* eradication is amoxicillin (AMPC), clarithromycin (CAM) and a proton pump inhibitor (PPI) twice a day for 1 week [6]. However, the *H. pylori* eradication rate for standard triple therapy is currently less than 80% in most parts of the world [7] [8]. The main cause of this ineffectiveness may be explained by bacterial resistance to CAM [7] [8]. Several approaches were proposed to overcome these low eradication rates; either sequential therapy or concomitant therapy achieved better results than standard triple therapy [9] [10]. The latest guidelines recommended quadruple therapies comprised of PPI + AMPC + CAM + metronidazole (MNZ) or PPI + bismuth + MNZ + tetracycline, with all treatments given for 14 days [2] [3].

Potassium-competitive acid blockers (P-CABs) are a new class of gastric acid suppressive agents. Similar to PPIs, P-CABs inhibit gastric hydrogen/potassium-ATPase but, unlike PPIs, P-CABs inhibit the enzyme in a potassium-competitive and reversible manner [11]. Vonoprazan (VPZ) is a novel orally administered member of this class. VPZ has a potent and long-lasting anti-secretory effect on hydrogen/potassium-ATPase because of its high level of accumulation and slow clearance from gastric tissue [11] [12]. The acid-inhibitory effects of VPZ are much more potent than those of PPIs; therefore, it can be expected to be more effective when used for *H. pylori* eradication. A double-blind phase 3 study of triple therapy with VPZ (VAC) for first-line *H. pylori* eradication showed a high success rate of 92.6% [13]. Recently, a retrospective study with a large sample size [14], a meta-analysis [15] and prospective studies [16] [17] showed that the eradication rate of first-line VPZ (VAC) therapy was higher than that with PPI (PAC) therapy. In Japan, MNZ triple therapy is decided as second-line therapy under the National Health Insurance System. There were several reports on the results of MNZ triple therapy with VPZ (VAM) [13] [17]-[23]. The aim of this

study was to evaluate the efficacy and tolerability of 7-day MNZ triple therapy with VPZ in comparison to PPI-based triple therapy for second-line therapy.

2. Materials and Methods

2.1. Ethics

This study was conducted in accordance with the Declaration of Helsinki. The institutional review board of Yamanashi Koseiren Health Care Center approved the study protocol (27-014).

2.2. Study Participants

This was a retrospective, single institution study. We reviewed the medical records of patients who underwent esophago-gastro-duodenoscopy screening as part of a general medical checkup program, who were infected with *H. pylori*, and who received *H. pylori* eradication therapy from January 2013 to July 2017 at Yamanashi Koseiren Health Care Center. All patients were ≥20 years of age. In addition to age, exclusion criteria were: 1) consumption of antibiotics, non-steroidal anti-inflammatory drugs, antithrombotic agents, PPIs, or probiotics supplementation during the treatment; 2) allergy to antibiotics or PPIs; 3) previous gastric surgery; 4) severe concomitant cardiopulmonary disease or serious hepatic/renal dysfunction or malignancy; and 5) pregnancy or lactation. Patients who had previously received first-line CAM triple *H. pylori* eradication therapy were given second-line *H. pylori* eradication therapy. However, patients who had received treatment with both CAM and MTZ triple therapy for *H. pylori* eradication in the past were excluded.

Of the 790 consecutive patients who received second-line *H. pylori* eradication therapy, 7 who received the eradication therapies after stomach surgery, 38 who had received supplementation with probiotics, and 7 who were prescribed antibiotics or a PPI were excluded. As a result, 738 patients were enrolled in this study; the 274 patients who received VPZ therapy were compared to 464 patients who received PPI therapy (**Figure 1**).

2.3. *H. pylori* Eradication

The presence of *H. pylori* was confirmed before treatment by one or more of the following methods: the rapid urease test (PyloriTek; Serim Research Corp., Elkhart, IN, USA) or ^{13}C-urea breath test (UBIT 100 mg tablet/POCone; Otsuka Pharmaceutical Co., Tokyo, Japan) ≥2.5‰.

Patients who experienced first-line eradication failure were treated with rescue (second-line eradication) therapy. VPZ therapy (VAM) was comprised of 20 mg of VPZ + 750 mg of AMPC + 250 mg of MNZ, all administered twice a day for 7 days; the entire dosage regimen was contained in one package (or VONOPION Pack; Takeda Pharmaceutical Co., Tokyo, Japan). The PPI therapy (PAM) was comprised of 30 mg of LPZ (LAMPION Pack; Takeda Pharmaceutical Co., Tokyo, Japan) or 10 mg of RPZ (Rabefine Pack; Eisai, Tokyo, Japan) + 750 mg of

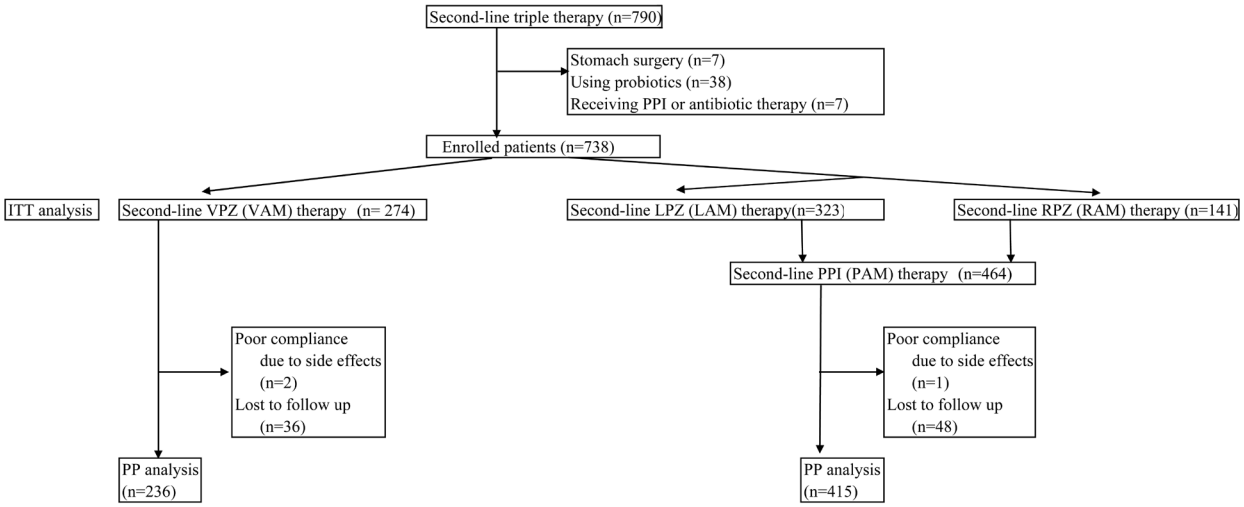

Figure 1. Study flow chart. ITT, intention-to-treat; PP, per-protocol; VPZ, vonoprazan; LPZ, lansoprazole; RPZ, rabeprazole; PPI, a proton pump inhibitor; AMPC, amoxicillin; MNZ, metronidazole; VAM, VPZ + AMPC + MNZ triple therapy; LAM, LPZ + AMPC + MNZ triple therapy; RAM, RPZ + AMPC + MNZ triple therapy; PAM, a PPI + AMPC + MNZ triple therapy.

AMPC + 250 mg of MNZ, all given twice a day for 7 days. The type of eradication therapy depended on the date of therapy; all patients treated before November 2013 received PPI therapy with LPZ (LAM) and those treated from November 2013 to February 2015 received eradication therapy using LPZ or rabeprazole (RPZ). Then from March 2015, all patients were treated with VAM.

Treatment duration and antibiotic dosages were determined according to the approved indication in Japan for *H. pylori* eradication. We instructed all patients not to smoke or drink alcohol during the eradication treatment.

Patients were requested to come to the Center again at least 8 weeks after the treatment period to evaluate their *H. pylori* status, to confirm compliance during therapy, and to identify possible side effects. *H. pylori* eradication was assessed by the ^{13}C-urea breath test with success defined as a result of <2.5‰.

2.4. Endoscopic Findings

All patients had undergone esophago-gastro-duodenoscopy before the first-line *H. pylori* eradication therapy. Diseases associated with *H. pylori* infection were diagnosed by endoscopic findings. The definition of atrophic gastritis was diagnosed as Closed type-2 (C-2) or higher by the classification of Kimura and Takemoto [24].

2.5. Procedures

The primary outcome in this study was second-line *H. pylori* eradication rates for VAM and PAM. We used intention-to-treat (ITT) and per-protocol (PP) analysis in the assessment of eradication efficacy. All enrolled patients who started medication were included in the ITT analysis regardless of compliance with medications. In the PP analysis, patients were excluded due to poor compliance or being lost to follow up. The secondary outcome in this study was the

adverse-event rates related to the second-line eradication therapy.

2.6. Statistical Analysis

We compared continuous variables in the univariate analysis with the t test and presented arithmetic means and standard deviations. Categorical variables were analyzed with the chi-square test. For the primary and secondary outcomes, the frequency and two-sided 95% confidence intervals (CIs) were calculated for each treatment group. P values less than 0.05 were considered statistically significant. All analyses were performed using JMP 12.1 software (SAS Institute, Cary, NC).

3. Results

3.1. Baseline Characteristics of Patients Undergoing Second-Line Treatment

Table 1 shows the baseline characteristics of patients who received second-line therapy. Patients in the VAM group were aged 58.2 ± 11.6 years (50.7% males) and those in the PAM group were aged 60.7 ± 11.1 years ($p = 0.0048$) (48.9% males). The average BMI values were 22.7 ± 3.4 and 22.5 ± 2.9 for those receiving VPZ and PPI therapies, respectively, and there was no significant difference between these groups. Of those patients who received second-line VAM, all had previously received first-line VAC; therefore, 47.1% (129/274) of the patients receiving second-line VAM had been treated with first-line VAC ($p < 0.0001$). Endoscopic findings showed significantly more atrophic changes in the PAM group than in the VAM group ($p = 0.0028$). Successful second-line eradication rates according to ITT analysis and PP analysis, respectively, were 79.9% (95% CI, 74.8% - 84.2%; 219/274) and 92.4% (95% CI, 88.3% - 95.1%; 218/236) for VAM and 83.6% (95% CI, 78.0% - 86.7%; 388/464) and 93.3% (95% CI, 90.4% - 95.3%; 387/415) for PAM. There was no significant difference between treatment groups.

3.2. Analysis of Subgroups Administered Second-Line VAM and PAM (Table 2)

The second-line VAM group was divided into a VPZ usage (VAC) subgroup and a PPI usage (PAC) subgroup according to the first-line therapy administered. The eradication rates in the VAC subgroup according to ITT and PP analyses were 75.2% (95%CI, 67.1% - 81.8%; 97/129) and 88.1% (95%CI, 80.7% - 92.9%; 96/109), respectively; in contrast, values were 82.5% (95% CI, 75.0% - 88.2%; 104/126) and 95.4% (95% CI, 89.8% - 98.0%; 104/109), respectively, for PAC subgroup. There were no significant differences in the eradication rates between the two first-line therapies.

The second-line PAM group was divided into the LPZ usage (LAM) subgroup and the RPZ usage (RAM) subgroup. There were no significant differences in the baseline characteristics of patients undergoing second-line LAM or second-line RAM. The eradication rates in the RAM subgroup according to ITT and PP

Table 1. Characteristics of the patients who received the second-line eradication therapy for *Helicobacter pylori.*

	VPZ (VAM) therapy	PPI (PAM) therapy	*p* value
No. of patients enrolled	274	464	
Age (Years)	58.2 ± 11.6	60.7 ± 11.1	0.0048
Gender			0.6351
Male	139	227	
Female	135	237	
BMI (kg/m^2)	22.7 ± 3.4	22.5 ± 2.9	0.2901
First-line treatment			<0.0001
with VPZ (VAC)	129	0	
with PPI (PAC)	126	464	
unknown	19		
Endoscopic findings			0.0028
No abnormality	16	3	
Duodenal ulcer	5	9	
Atrophic gastritis	242	427	
Gastric ulcer	10	25	
After ER for GC	1	0	
Smoking (yes)	38	65	0.9577
Drinking (yes)	143	213	0.0988
Successful eradication	219	388	
ITT analysis % (95% CI)	79.9 (74.8 - 84.2)	83.6 (78.0 - 86.7)	0.2045
PP analysis % (95% CI)	92.4 (88.3 - 95.1)	93.3 (90.4 - 95.3)	0.6736
Adverse events (%, 95% CI)	14 (5.1%, 3.1 - 8.4)	12 (2.6%, 1.5 - 4.5)	0.0724

VPZ, vonoprazan; PPI, a proton pump inhibitor (lansoprazole or rabeprazole); AMPC, amoxicillin; CAM, clarithromycin; MNZ, metronidazole; VAM, VPZ + AMPC + MNZ triple therapy; PAM, a PPI + AMPC + MNZ triple therapy; BMI, body mass index; VAC, VPZ + AMPC + CAM triple therapy; PAC, a PPI + AMPC + CAM triple therapy; ER, endoscopic mucosal resection; GC, gastric cancer; ITT, intention-to-treat; PP, per-protocol; CI, confidence interval.

analysis were 90.1% (95%CI, 84.0% - 94.0%; 127/141) and 94.1% (95%CI, 88.7% - 97.0%; 127/135), respectively; in contrast, values were 80.8% (95% CI, 76.2% - 84.7%; 261/323) and 92.9% (95% CI, 89.2% - 95.3%; 260/280), respectively, for the LAM subgroup. There was a significant difference in eradication rates between the two second-line PPI therapies by ITT analysis (p = 0.0131).

Of the 3 patients who had discontinued the treatment regimen, 1 VAM case and 1 LAM case experienced successful eradication of *H. pylori.*

3.3. Adverse Events and Compliance

In second-line therapy, the overall adverse event rate for VAM (5.1%, 95%CI, 3.1 - 8.4; 14/274) was the same as for PAM (2.6%, 95%CI, 1.5 - 4.5; 12/464) (**Table 1**).

Table 3 shows adverse events and their incidence in each group. The adverse event with the highest incidence was diarrhea in all groups (0.9% - 2.9%) and the second most common was skin rash in all groups (0.6% - 1.1%). All adverse events were less than grade 3 (Common Terminology Criteria for Adverse Event Version 4.0), and all events resolved spontaneously without treatment. *H. pylori* eradication therapy using VAM was interrupted in 1 patient who had a skin rash and 1 with abdominal pain.

4. Discussion

The second-line eradication rate of *H. pylori* with VAM was found to be 79.9% by ITT analysis and 92.4% by PP analysis, which was not significantly different

Table 2. Analysis of subgroups administered second-line VPZ (VAM) and PPI (PAM) therapies for *Helicobacter pylori.*

	VPZ (VAM) therapy			PPI (PAM) therapy		
First-line treatment	VAC	PAC	*p* value			
Second-line treatment				LAM	RAM	*p* value
No. of patients enrolled	129	126		323	141	
Age (Years)	57.8 ± 12.1	58.7 ± 11.1	0.5205	60.8 ± 11.2	60.4 ± 11.1	0.8522
Gender			0.9483			0.2053
Male	64	62		151	76	
Female	65	64		172	65	
BMI (kg/m^2)	22.8 ± 3.7	22.5 ± 3.0	0.4157	22.6 ± 2.9	22.1 ± 3.2	0.1244
Endoscopic findings			0.0835			0.1710
No abnormality	13	2		2	1	
Duodenal ulcer	1	3		5	4	
Atrophic gastritis	110	116		297	130	
Gastric ulcer	4	5		19	6	
After ER for GC	1	0		0	0	
Smoking (yes)	15	19	0.4176	44	21	0.9101
Drinking (yes)	68	68	0.8408	152	61	0.4152
Successful eradication	97	104		261	127	
ITT analysis % (95% CI)	75.2 (67.1 - 81.8)	82.5 (75.0 - 88.2)	0.1511	80.8 (76.2 - 84.7)	90.1 (84.0 - 94.0)	0.0131
PP analysis % (95% CI)	88.1 (80.7 - 92.9)	95.4 (89.8 - 98.0)	0.0826	92.9 (89.2 - 95.3)	94.1 (88.7 - 97.0)	0.6433
Adverse events	5	7	0.5266	8	4	0.7489

VPZ, vonoprazan; PPI, a proton pump inhibitor (lansoprazole or rabeprazole); AMPC, amoxicillin; CAM, clarithromycin; MNZ, metronidazole; VAM, VPZ + AMPC + MNZ triple therapy; PAM, a PPI + AMPC + MNZ triple therapy; VAC, VPZ + AMPC + CAM triple therapy; PAC, a PPI + AMPC + CAM triple therapy; LAM, Lansoprazole + AMPC + MNZ triple therapy; RAM, rabeprazole + amoxicillin + MNZ triple therapy; BMI, body mass index; ER, endoscopic mucosal resection; GC, gastric cancer; ITT, intention-to-treat; PP, per-protocol; CI, confidence interval.

Table 3. Adverse events in second-line MNZ triple therapy.

	VPZ (VAM) therapy	LPZ (LAM) therapy	RPZ (RAM) therapy
n	274	323	141
Diarrhea (%)	8 (2.9)	3 (0.9)	4 (2.8)
Skin rash (%)	3 (1.1)	2 (0.6)	0
Nausea, Vomiting (%)	1 (0.4)	1 (0.3)	0
Abdominal pain (%)	1	0	0
Constipation (%)	0	1 (0.3)	0
Stomatitis (%)	0	1 (0.3)	0
Abdominal fullness (%)	1 (0.4)	1 (0.3)	0
Total (%)	14 (5.1)	8 (2.5)	4 (2.8)

VPZ, vonoprazan; LPZ, lansoprazole; RPZ, rabeprazole; AMPC, amoxicillin; MNZ, metronidazole; VAM, VPZ + AMPC + MNZ triple therapy; LAM, LPZ + AMPC + MNZ triple therapy; RAM, RPZ + amoxicillin + MNZ triple therapy.

from findings for PAM. Adverse events did not differ between the VAM and PPI groups.

Through the Japanese National Health Insurance System, it was decided to use MNZ triple therapy as second-line therapy for *H. pylori* eradication. According to Japanese guidelines for clinical practice regarding *H. pylori* [25], first-line therapy is the standard triple therapy, which is PAC or VAC twice daily for 7 days, and second-line therapy is triple therapy, which is PAM or VAM twice daily for 7 days. Several studies have investigated the efficacy of second- line eradication of *H. pylori* with VAM, and successful eradication rates were 71.8% - 98.0% by ITT analysis and 82.4% - 98.0% by PP analysis [13] [17]-[23]. For second-line therapy, the effect of VAM was equivalent to that of PAM. Murakami *et al.* [13] showed high success rates for VAM in second-line *H. pylori* therapy, with an eradication rate of 98%. The eradication rate in patients for whom the first-line VAC had failed is more important. Katayama *et al.* [23] reported that the eradication rate for *H. pylori* was 87.0% when VPZ was used as a second-line therapy (VAM) in patients for whom first-line VAC failed. In our cases, the successful first-line eradication rates according to ITT analysis and PP analysis, respectively, were 79.8% (95% CI, 77.5% - 81.9%) and 91.4% (95% CI, 89.6% - 92.9%) for VAC and 66.3% (95% CI, 64.6% - 68.0%) and 78.9% (95% CI, 77.2% - 80.5%) for PAC [14]. Among the patients who had not achieved eradication with first-line VAC the eradication rate was low with second-line VAM (75.2% in the ITT analysis, 88.1% in the PP analysis); this rate tended to be lower than that among those who previously were given first-line PAC (82.5% in the ITT analysis, 95.4% in the PP analysis). Inaba *et al.* [26] reported that second-line VAC was administered after first-line RAC failure and its success rate was 70.2% (26/37). When VAC therapy is provided as second-line therapy after first-line PPI therapy (PAC) failure, success in eradication may be achieved in a few patients. In the case of first-line VPZ (VAC) therapy, such success cannot be

obtained with second-line VPZ (VAM) therapy.

The lack of superiority of second-line VPZ therapy shows that acid suppression is important for both AMPC and CAM in first-line therapy, but not for MNZ. That is, MTZ is very stable in gastric juice at pH 2 to 7, with a half-life of over 800 hours [27]. AMPC has poor stability, particularly at a low pH, but nevertheless has a half-life of over 15 hours at pH 2. CAM is the most acid labile, having a half-life of less than 1 hour at pH 2. AMPC and CAM are easily degraded in acidic conditions. In addition, *H. pylori* regains its replicative capability at pH > 6, so that it is more susceptible to antibiotics in this environment [27]. The sensitivity of *H. pylori* to MNZ is 4.2 times greater at pH 7.5 than at pH 5.5 [28]. Likewise, the sensitivity of *H. pylori* to AMPC and CAM is 8.3 to 20 and 160 times greater, respectively, at pH 7.5 than at pH 5.5.

According to the Toronto consensus [3], a meta-analysis of data from randomized controlled trials (RCTs) assessing bismuth quadruple therapy after failure of standard triple therapy reported an eradication success rate of 78% (95% CI, 75% - 81%). There was a trend toward higher eradication rates with longer durations of therapy. The Maastricht V/Florence consensus report recommended either a bismuth-containing quadruple therapy or a levofloxacin-containing triple therapy after failure of standard triple therapy [2]. Similar efficacy of PPI-levofloxacin-amoxicillin triple therapy and bismuth-containing quadruple therapy after first-line treatment failure with PPI-amoxicillin-clarithromycin was shown, providing cure rates of 76% and 78%, respectively. We consider that the eradication rates of the second-line therapies recommended by well-known guidelines and that of second-line MNZ triple therapy in Japan were similar, although there have been no comparative studies.

The prevalence of MNZ resistance to the treatment of *H. pylori* is 9% - 12% in Japan [29]. However, this resistance rate has been increasing in Japan recently (30% - 37.8%) [30]. According to antimicrobial susceptibility testing in Japan, the MNZ resistance rate after eradication therapy increased from 3% without an eradication history to 13.3% after first-line therapy failure and 52.4% for second-line therapy failure [30]. In the future, MNZ resistance rates will increase in Japan as in many countries [31].

A limitation of this study was its non-randomized and retrospective study design. In addition, this was a single-institution study and included only Japanese patients. We did not consider CAM and MNZ resistance, which have been reported to be major factors related to the success of *H. pylori* eradication therapy. In conclusion, efficacy and tolerability of 7-day VAM were equivalent to those for PAM for second-line therapy.

Supporting Foundations

None.

Disclosure

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