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Data collection were performed by Takuya Kuzumoto. Data analysis and manuscript writing were performed by Takuya Kuzumoto and Fumio Tanaka. This study was designed by Yasuhiro Fujiwara. Yasuhiro Fujiwara, Akinari Sawada, Yuji Nadatani, Koji Otani, Shuhei Hosomi, Noriko Kamata, Koichi Taira, Yasuaki Nagami, Tetsuya Tanigawa, and Toshio Watanabe revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Abstract

Background

Eosinophilic esophagitis (EoE) is a chronic allergic disease with esophageal symptoms and intraepithelial eosinophil infiltration. Effects of potassium-competitive acid blockers (P-CABs) on EoE have not been elucidated. We aimed to examine and compare effects of P-CABs and PPIs on symptomatic, endoscopic, and histological responses of patients with EoE.

Methods

We analyzed 118 EoE patients who received PPI or P-CAB therapy with rabeprazole 10 mg (RPZ10, N = 22), rabeprazole 20 mg (RPZ20, N = 34), esomeprazole 20 mg (EPZ20, N = 25), or vonoprazan 20 mg (VPZ20, N = 33). We evaluated symptomatic responses by classifying the patients into three groups: complete relief, partial relief, and no change. Endoscopic responses were evaluated using the endoscopic reference score (EREFS) following PPI or P-CAB therapy. Histological responses were evaluated by determining eosinophil counts in esophageal biopsy samples and classifying the patients into two groups: complete remission [0/1 eosinophil/high-power field (eos/HPF)] and remission (<15 eos/HPF).

Results

There were no difference among the therapy groups in terms of clinical characteristics, endoscopic findings, and histological findings of the patients before treatment. The rate of complete relief in clinical symptoms was 54.5% in the RPZ10 group, 64.7% in the RPZ20 group, 72.0% in the EPZ20 group, and 75.7% in the VPZ20 group. There were no significant differences in the therapeutic effect among the therapy groups. Similarly, endoscopic and histological complete remission rates were not significantly different among the therapy groups.

Conclusions

Vonoprazan showed similar efficacy to PPIs in EoE.

Keywords

Eosinophilic esophagitis, Proton pump inhibitors, Potassium-competitive acid blockers, Gastric acid, Esophagus

Introduction

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disorder characterized by clinical symptoms due to esophageal dysfunction and intraepithelial eosinophilic infiltration. It is diagnosed via biopsy, although care should be taken to follow an optimal protocol [1, 2]. The incidence and prevalence of EoE has been increasing worldwide, and the recognition of this disease is also increasing in clinicians [3]. EoE pathogenesis is according to response to food allergens and aeroallergen involving T helper type 2 cells, that is, (Th2)-mediated immune reaction [4, 5]. Initial therapy with PPIs can induce clinical, endoscopic, and histological remission in a subset of patients with EoE [6, 7].

In Japan, in 2015, potassium-competitive acid blockers (P-CABs) such as vonoprazan (VPZ) were introduced for use in inhibiting gastric acid secretion. P-CABs do not need to be activated by gastric acid, and they are generally stable in the acidic environment, providing prolonged activity in the canaliculus of parietal cells in the stomach even when the serum P-CAB concentration has already decreased. Meanwhile, PPIs need to be activated by gastric acid, and they are easily deactivated in acidic conditions. Consequently, P-CABs are characterized as rapid and long-acting acid secretion inhibitors. Furthermore, P-CABs have a stronger acid inhibitory effect than PPIs. P-CABs increase gastric pH above 4 in 3–24 hours after oral administration to healthy volunteers, although PPIs may not achieve this on the first day [8]. On day 7 after the administration of VPZ 20 mg once daily, the holding time ratio (HTR) of gastric pH > 4 was significantly higher than that after the administration of esomeprazole 20 mg once daily (95% vs. 68%) [9].

Although a case series of VPZ administered to PPI-resistant EoE has been reported, its effect as an initial treatment for EoE has not been elucidated [9]. Therefore, the aim of this study was to investigate the therapeutic effects of VPZ on symptomatic, endoscopic, and histological responses in patients with EoE compared with those of PPIs.

Materials and methods

Patients and study design

We retrospectively reviewed 197 adult patients who were diagnosed with esophageal eosinophilia in Osaka City University Hospital or Osaka City University Hospital Advanced Medical Center for Preventive Medicine (MedCity21) from January 2010 to June 2019. Esophageal eosinophilia was defined as a condition of ≥15 eosinophils per high-power field (eos/HPF) in at least one esophageal biopsy sample.

Inclusion criteria were EoE patients who received initial PPI or P-CAB therapy including rabeprazole, esomeprazole, and vonoprazan for at least 8 weeks. EoE was diagnosed as patients who with esophageal eosinophilia presenting with clinical symptoms due to esophageal dysfunction such as dysphagia, heartburn, and chest pain according to the United European Gastrointestinal guideline in 2017 and updated international consensus of the AGREE conference in 2018 [1, 11]. Exclusion criteria were as follows: patients with eosinophilic gastroenteritis (EGE), patients with esophageal eosinophilia from other causes including pemphigoid, systemic lupus erythematosus (SLE), and drug-induced eosinophilia; patients with no symptoms; patients treated with steroids or non-PPI or P-CAB medication such as histamine H_2 receptor antagonists (H_2RA) and antiallergic agents; patients lost to follow-up; and patients who underwent less than 5 biopsies to evaluate histological responses after PPI/P-CAB therapy. We determined the clinical characteristics from the medical records including age, sex, body mass index (BMI), current cigarette smoking and alcohol drinking habits, blood test results, and clinical symptoms.

Endoscopic and histological findings

Endoscopic findings of EoE were assessed by the Endoscopic Reference Score (EREFS), which consist of five parameters (exudates: 0–2, rings: 0–3, edema: 0/1, furrows: 0/1, and strictures: 0/1) according to the modified classification and grading system for endoscopic assessment of the esophageal features of EoE [12]. Inflammatory EREFS score was defined as the sum of exudates, edema, and furrows scores. Fibrostenotic EREFS score was defined as the sum of rings and strictures scores. EREFS score was calculated from esophagogastroduodenoscopy (EGD) findings performed before and after PPI or P-CAB therapy. The biopsy samples were collected at two locations from the lower esophagus, two from the middle esophagus, and one or two from the upper esophagus. The number of eosinophils in the esophageal epithelial layers was counted. Reflux esophagitis was evaluated endoscopically and classified according to the Los Angeles classification [13]. Grades A through D were defined as reflux esophagitis, and grade M was excluded. Classification of atrophic gastritis was based on the extent of atrophic area of the gastric mucosa, according to the Kimura–Takemoto classification [14].

Treatment efficacy

To evaluate symptomatic responses, we counted the number of patients with dysphagia, heartburn, and

chest pain before and after PPI or P-CAB therapy and classified them into three groups: complete relief, partial relief, and no change. Symptom evaluation after PPI or P-CAB therapy was performed by detailed interview when the patients were administered each acid suppressive agent for 8 complete weeks. Definition of complete relief was patients reporting absolutely no clinical symptoms. Partial relief was defined as when symptoms had partially disappeared. Endoscopically, therapeutic responses were evaluated by the number of patients who achieved complete remission defined as the total EREFS score of 0 points. Histologically, we evaluated the therapeutic responses by the number of eosinophils in the biopsy samples after treatment and classified patients into two groups: complete remission (0/1 eos/HPF) and remission (<15 eos/HPF) [15].

Statistical analysis

Data are expressed as median and interquartile range or mean and standard deviation for continuous variables and as numbers and percentage for categorical variables. Statistical comparisons were performed using the Kruskal–Wallis test and Pearson's $\chi 2$ test for continuous and categorical variables, respectively. Differences with $p < 0.05$ were considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). It is a modified version of R commander designed to add statistical functions frequently used in biostatistics [16].

Results

Clinical characteristics in each therapy group

The study flow is shown in Fig. 1. Of 197 patients with esophageal eosinophilia, we excluded patients with EGE (N = 6), eosinophilia due to other causes (N = 8), and no symptoms (N = 31). A total of 152 patients were diagnosed as having EoE. We also excluded patients receiving steroid therapy (N = 10) and other therapies such as H_2RA and antiallergic agent (N = 6). A total of 136 patients received PPI or P-CAB therapy. Of these, we excluded patients lost to follow-up (N = 13) and those who underwent <5 biopsies (N = 9). Finally, we analyzed 114 EoE patients who received initial PPI/P-CAB therapy. Patients were divided into four groups according to the type of medication administered: rabeprazole 10 mg (RPZ10, N

= 22), rabeprazole 20 mg (RPZ20, N = 34), esomeprazole 20 mg (EPZ20, N = 25), and vonoprazan 20 mg (VPZ20, N = 33). Dysphagia was more frequently observed (80.7%) than heartburn (23.7%) and chest pain (14.0%). There were no significant differences in age, sex, BMI, current cigarette smoking, alcohol drinking habits, allergic diseases, and blood test results including white blood cell count, eosinophil count, proportion of eosinophils, and immunoglobulin (Ig) E level among the therapy groups. In addition, the proportion of patients complaining of heartburn, dysphagia, and chest pain was not significantly different among the therapy groups (Table 1).

Endoscopic findings before treatment in each therapy group

Endoscopic examination before treatment revealed rings in 44 patients (38.6%) and strictures in 3 patients (2.6%). The proportion of patients with rings or strictures was less than that of patients with exudates (75.4%), edema (90.3%), and furrows (96.5%). Endoscopic findings in each therapy group are shown in Table 2. There were no significant differences in the scores for exudates, rings, edema, furrows, strictures, the total EREFS score, the fibrostenotic EREFS score, the inflammatory EREFS score, and the proportion of patients with reflux esophagitis and atrophic gastritis among the therapy groups. Histologically as well as endoscopically, there were no differences in the number of eosinophils in the esophageal biopsy samples before treatment among the therapy groups.

Efficacy of PPIs and P-CAB in symptomatic, endoscopic and histological response

Symptomatic, endoscopic, and histological responses of each therapy group are summarized in Fig. 2. There was no statistically significant difference in the symptomatic response among the therapy groups. The rate of complete relief was 54.5% (N = 12) in the RPZ10 group, 64.7% (N = 22) in the RPZ20 group, 72.0% (N = 18) in the EPZ20 group, and 72.7% (N = 24) in the VPZ20 group. The rate of partial relief was 27.3% (N = 6), 29.4% (N = 10), 16.0% (N = 4), and 24.2% (N = 8), respectively.

There was no significant difference in endoscopic response among the therapy groups. The rate of endoscopic complete remission was 31.8% (N = 7) in the RPZ10 group, 38.2% (N = 13) in the RPZ20 group, 48.0% (N = 12) in the EPZ20 group, and 48.5% (N = 16) in the VPZ20 group. Endoscopic responses were also evaluated by comparing changes in EREFS score, which were not significantly different among the therapy groups (Table 3).

Regarding histological response, there were no significant differences among the groups. The rate of histological complete remission (0/1 eos/hpf) was 18.2% (N = 4) in RPZ10 group, 26.5% (N = 9) in RPZ20 group, 32.0% (N = 8) in EPZ20 group, and 39.4% (N = 13) in VPZ20 group. The rate of remission (<15 eos/hpf) was 59.1% (N = 13), 35.3% (N = 12), 32.0% (N = 8), and 39.4% (N = 13), respectively.

Comparison between the P-CAB group and all other PPIs

There were no significant differences in symptomatic, endoscopic, and histological responses between the P-CAB group and all other PPIs (complete relief in clinical symptoms, 72.7% vs. 64.2%, p = 0.367; endoscopic complete remission, 48.5% vs. 39.5%, p = 0.502; and histological complete remission, 39.4% vs. 25.9%, p = 0.274).

Discussion

To the best of our knowledge, this is the first study to demonstrate that the efficacy of VPZ is similar to that of PPIs for the initial treatment of patients with EoE. These results show that acid suppression therapy using P-CABs could be a candidate for the initial therapy as same as PPIs.

Our results also indicate that acid reflux is partly involved in EoE pathophysiology. Esophageal acid exposure can impair mucosal integrity, allowing allergen exposure into epithelium from the lumen side and subsequent eosinophilia. Because both PPIs and P-CABs inhibit gastric acid secretion, they can protect mucosal integrity, consequently decreasing immune responses within the esophageal mucosa. We have previously reported that the predictive factors for responsiveness to PPIs are the presence of concomitant reflux esophagitis and the absence of esophageal rings [17]. EoE and GERD are not mutually exclusive and share a complex relationship [1, 11]. EoE can lead to prolonged esophageal acid exposure due to esophageal dysfunction and low compliance. We previously reported that risk factors such as obesity and hiatal hernia are common in both esophageal eosinophilia and GERD, suggesting an overlap between EoE and GERD [18]. Therefore, acid suppression therapy using either P-CABs or PPIs can be useful for patients with EoE since the pathophysiology of EoE is partially similar to that of GERD.

Interestingly, the therapeutic efficacy of VPZ was not superior to that of PPIs. These results indicate a potentially limited therapeutic efficacy of inhibiting proton pumps in cases of EoE. VPZ exerts a stronger acid inhibitory effect than PPIs. One study reported that on day 7 after the administration of VPZ 20 mg

once daily, gastric pH > 4 HTR was 95%, which was significantly longer than after the administration of esomeprazole 20 mg once daily (68%) [10]. Surprisingly, almost always, gastric acid secretion was adequately inhibited by VPZ. Even if the secretion of gastric acid was strongly inhibited by P-CABs, there was no therapeutic gain compared with PPIs. The underlying reason may be the fact that the association of acid reflux is only part of the pathophysiology of EoE. Blocking proton pumps is not sufficient to get complete disease control in a subset of EoE. This is an important consideration when deciding how to control EoE in clinical settings.

PPIs have acid-independent anti-inflammatory effects, which may contribute to additional therapeutic gain. Some inflammatory cells also have H^+/K^+ adenosine triphosphatases (proton pumps), which pump protons into the extracellular space or into intracellular organelles such as lysosomes [19]. In neutrophils and monocytes, PPIs can inhibit the oxidative burst and cell migration by inhibiting proton pumps [20, 21]. In experiments using epithelial cells from patients with EoE and GERD, omeprazole has been shown to inhibit the secretion of eotaxin-3 induced by interleukin (IL)-4 and IL-13, which is involved in Th2-mediated immune reactions [22, 23]. To our knowledge, anti-inflammatory properties have not been reported in P-CABs so far. However, P-CABs may also have anti-inflammatory effects because they can inhibit proton pumps more strongly than PPIs. Even if that is true, however, our results showed that such an anti-inflammatory effect of P-CABs did not contribute to a greater therapeutic gain compared with PPIs in patients with EoE.

There were some limitations in this study. First, this was a single-center, retrospective observational study. The number of participants was relatively small. A prospective randomized controlled study may be warranted to evaluate the non-inferiority of P-CAB; however, it may be difficult to conduct in a single-center study because EoE is a rare disease in Japan. Therefore, we concluded that P-CAB and PPIs had similar effects on EoE, owing to the absence of significant differences between the therapeutic response to P-CAB and to PPIs. Second, the improvement of symptoms was not assessed using a validated questionnaire; instead, physicians asked patients their symptoms in detail before and after the treatment. In addition, symptomatic response was assessed on the basis of detailed interview, but the decision on partial relief or no change was dependent largely on the patient's subjectivity. Therefore, it is considered that these responses were difficult to distinguish clearly. Third, the interobserver variability in EREFS score has not been tested. However, this grading system has been reported to have good interobserver agreement among

academic gastroenterologists [12]. Finally, the methods used to evaluate pharmacological response have not been fully established. Previous systematic reviews have shown heterogeneity of outcome measures including the definition of clinical, endoscopic, and histological response [24]. Therefore, we set our outcome measurement using frequently reported methods.

In conclusion, P-CABs have similar therapeutic efficacy to PPIs as an initial therapy for patients with EoE. These results may have an impact on the clinical management of EoE.

Ethical statement

The study protocol was in accordance with the Declaration of Helsinki and was approved by the institutional review board of the Osaka City University Graduate School of Medicine (September 2018, Protocol number 4141). The need for informed consent has been waived by the institutional review board of the Osaka City University Graduate School of Medicine. We have disclosed the information about this study on our home page on the Internet and the patients had the opportunity to opt-out.

Conflict of interest

All authors have declared no conflict of interest with regards to this manuscript.

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Table 1. Clinical characteristics in each therapy group

	RPZ10 (N=22)	RPZ20 (N=34)	EPZ20 (N=25)	VPZ20 (N=33)	p value
Age	41.2 ± 7.9	45.2 ± 11.2	46.7 ± 11.2	45.4 ± 8.6	0.266
Male	15 (68.2%)	22 (64.7%)	13 (52%)	24 (72.7%)	0.420
BMI (kg/m^2)	24.8 ± 5.6	23.6 ± 3.8	24.0 ± 5.8	23.4 ± 3.1	0.967
Current cigarette smoking	5 (22.7%)	1 (2.9%)	6 (24%)	5 (15.2%)	0.089
Current alcohol drinking	13 (61.9%)	25 (73.5%)	17 (70.8%)	22 (66.6%)	0.817
Clinical symptoms					
Heartburn	5 (22.7%)	7 (20.6%)	6 (24%)	9 (27.3%)	0.934
Dysphagia	19 (86.4%)	27 (79.4%)	22 (88%)	24 (72.7%)	0.442
Chest pain	2 (9.1%)	7 (20.6%)	4 (16%)	3 (9.1%)	0.493
Allergic diseases					
Atopic dermatitis	2 (9.1%)	1 (2.9%)	3 (12%)	5 (15.2%)	0.381
Asthma	6 (27.3%)	9 (26.5%)	6 (24%)	4 (12.1%)	0.441
Rhinitis	7 (31.8%)	16 (47.1%)	12 (48%)	12 (36.4%)	0.557
Food	4 (18.2%)	10 (29.4%)	5 (20%)	6 (18.2%)	0.655
Blood test					
WBC (/μL)	6000 ± 1400	5700 ± 1300	5400 ± 1200	5900 ± 1700	0.527
Number of eosinophils (/μL)	424 ± 290	349 ± 194	317 ± 236	298 ± 202	0.382
Proportion of eosinophils (%)	6.7 ± 3.6	6.3 ± 3.7	6.0 ± 4.4	5.1 ± 3.2	0.340
IgE (IU/mL)	343 ± 555	225 ± 280	1646 ± 4596	688 ± 1064	0.328

Data are expressed as mean ± SD for continuous variables and as numbers (percentage) for categorical variables.
BMI, body mass index; EPZ, esomeprazole; RPZ, rabeprazole; SD, standard deviation; VPZ, vonoprazan; WBC, white blood cell

Table 2. Endoscopic and histological findings before treatment in each therapy group

	RPZ10 (N=22)	RPZ20 (N=34)	EPZ20 (N=25)	VPZ20 (N=33)	p value
Endoscopic Reference Score					
Exudates					0.458
Grade 0	7 (31.8%)	9 (26.5%)	4 (16%)	8 (24.2%)	
Grade 1	15 (68.2%)	21 (61.8%)	20 (80%)	21 (63.6%)	
Grade 2	0 (0%)	4 (11.8%)	1 (4%)	4 (12.1%)	
Rings					0.988
Grade 0	13 (59.1%)	22 (64.7%)	14 (56%)	21 (63.6%)	
Grade 1	7 (31.8%)	9 (26.5%)	8 (32%)	8 (24.2%)	
Grade 2	2 (9.1%)	3 (8.8%)	3 (12%)	4 (12.1%)	
Grade 3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Edema					0.783
Grade 0	3 (13.6%)	3 (8.8%)	3 (12%)	2 (6.1%)	
Grade 1	19 (86.4%)	31 (91.2%)	22 (88%)	31 (94.6%)	
Furrows					0.189
Grade 0	0 (0%)	1 (2.9%)	0 (0%)	3 (9.1%)	
Grade 1	22 (100%)	33 (97.1%)	25 (100%)	30 (90.9%)	
Stricture					0.158
Grade 0	20 (90.9%)	34 (100%)	25 (100%)	32 (97.0%)	
Grade 1	2 (9.1%)	0 (0%)	0 (0%)	1 (3.0%)	
Fibrostenotic EREFS score	0.6 ± 0.8	0.4 ± 0.7	0.6 ± 0.7	0.5 ± 0.8	0.861
Inflammatory EREFS score	2.5 ± 0.5	2.7 ± 0.8	2.8 ± 0.6	2.7 ± 0.7	0.535
Total EREFS score	3.1 ± 0.8	3.2 ± 1.0	3.3 ± 1.0	3.2 ± 1.1	0.929
Reflux esophagitis					
Absent	20 (90.9%)	32 (94.1%)	25 (100%)	31 (93.9%)	0.551
Present	2 (9.1%)	2 (5.9%)	0 (0%)	2 (6.1%)	
Atrophic gastritis					
Absent	20 (90.9%)	27 (79.4%)	17 (68%)	25 (75.8%)	0.291
Present	2 (9.1%)	7 (20.6%)	8 (32%)	8 (24.2%)	
Maximum number of eosinophils (/hpf)	52 ± 31	59 ± 42	47 ± 32	40 ± 31	0.367

Data are expressed as mean ± SD for continuous variables and as numbers (percentage) for categorical variables.
EoE, eosinophilic esophagitis; EPZ, esomeprazole; EREFS, endoscopic reference score; HPF, high power field; RPZ, rabeprazole; SD, standard deviation; VPZ, vonoprazan

Table 3. Efficacy of PPIs and P-CAB in endoscopic response

	RPZ10 (N=22)	RPZ20 (N=34)	EPZ20 (N=25)	VPZ20 (N=33)	p value
Changes in EREFS score					
Total EREFS score	-2 (-2, -1)	-2 (-3, -1)	-2 (-3, -1)	-2 (-3, -2)	0.644
Fibrostenotic EREFS score	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (-1, 0)	0.886
Inflammatory EREFS score	-2 (-2, -1)	-2 (-3, -1)	-2 (-3, -1)	-2 (-3, -1)	0.804
Exudates	-1 (-1, 0)	-1 (-1, 0)	-1 (-1, 0)	-1 (-1, 0)	0.786
Rings	0 (0, 0)	0 (0, 0)	0 (-1, 0)	0 (-1, 0)	0.781
Edema	-1 (-1, 0)	-1 (-1, -1)	-1 (-1, 0)	-1 (-1, -1)	0.637
Furrows	0 (-1, 0)	-0.5 (-1, 0)	-1 (-1, 0)	0 (-1, 0)	0.710
Stricture	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.262

Data are expressed as median (interquartile range).

EPZ, esomeprazole; EREFS, endoscopic reference score; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; RPZ, rabeprazole; VPZ, vonoprazan.

Figure legends

Figure 1. Study flow of the subjects. *1 Other causes including pemphigoid, SLE, and drug-induced eosinophilia. *2 Other therapy including H_2RA and antiallergic agents. EGE, eosinophilic gastroenteritis; EoE, eosinophilic esophagitis; EPZ, esomeprazole; H_2RA, histamine H_2 receptor antagonist; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; RPZ, rabeprazole; SLE, systemic lupus erythematosus; VPZ, vonoprazan.

Fig. 1

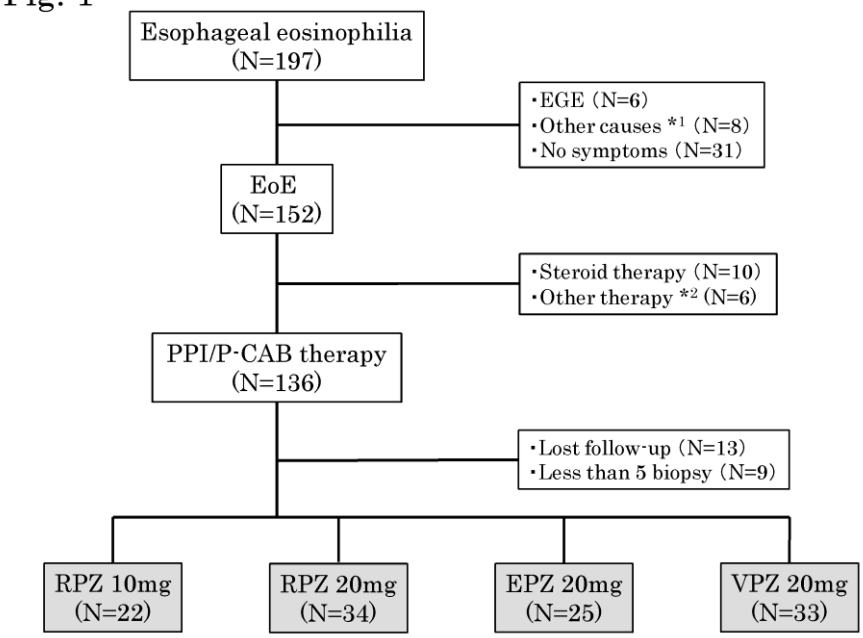

Figure 2. Efficacy of PPIs and P-CAB in symptomatic, endoscopic, and histological responses. (a) Symptomatic, (b) endoscopic, and (c) histological responses in each therapy group. There were no significant differences in symptomatic, endoscopic, and histological responses among the therapy groups. EPZ, esomeprazole; EREFS, endoscopic reference score; RPZ, rabeprazole; VPZ, vonoprazan.

Fig. 2