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ORIGINAL ARTICLE

An open-label randomized noninferior study of generic name and brand name of propafenone for rhythm control in patients with paroxysmal atrial fibrillation

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Abstract

Background: Propafenone is a class IC antiarrhythmic agent that is commonly used as the first-line therapy for patients with paroxysmal atrial fibrillation (AF) in Taiwan. This study compared the efficacy and safety of generic (Rhynorm) and brand name (Rytmonorm) propafenone for rhythm control of paroxysmal AF in Taiwan.

Methods: This was an open-label randomized multicenter noninferior study conducted in Taiwan. We enrolled 76 patients with AF. To investigate the efficacy of propafenone, we used a wearable electrocardiogram (ECG) event recorder to evaluate the daily burden of AF episodes in patients for 24 weeks. The primary efficacy endpoint was the frequency of AF with clinical significance, which was indicated by AF duration ≥30 seconds. The safety endpoints included proarrhythmic or hemodynamic adverse events.

Result: To analyze the efficacy and safety of these agents, 71 patients (five patients with screen failure) were randomized to two groups, specifically a Rhynorm group (n = 37) and a Rytmonorm group (n = 34), for 24 weeks of the treatment period. The baseline patient characteristics were comparable between the groups. However, the Rhynorm group was older (65.4 ± 8.40 vs 59.8 ± 10.8 years; $p = 0.02$). The primary efficacy endpoint at week 24 decreased by 4.76% ± 18.5% (from 24.3% ± 33.9% to 19.0% ± 28.7%; $p = 0.13$) in the Rhynorm group and by 3.27% ± 15.2% (from 16.9% ± 26.4% to 13.6% ± 19.2%; $p = 0.22$) in the Rytmonorm group, with an intergroup difference of 1.5% ± 17.0%; $p = 0.71$. This finding indicates that Rhynorm is not inferior to Rytmonorm ($p = 0.023$ for noninferiority). The safety profile of the agents was comparable between the two groups.

Conclusion: Our results verified that Rhynorm was noninferior to Rytmonorm in terms of efficacy and safety for treating paroxysmal AF in Taiwan (ClinicalTrials.gov Identifier: NCT03674658).

Keywords: Atrial fibrillation; Propafenone; Rhythm control

1. INTRODUCTION

Atrial fibrillation (AF) is the most common chronic arrhythmia in the clinical practice, and its prevalence is expected to increase along with the population aging in developed countries.[1] A previous study indicated that the incidence of AF increases progressively with age, predominantly in men.[2] If left untreated, AF is a significant risk factor for stroke and other morbidities. AF may be classified as newly detected, paroxysmal (ie, self-terminating episodes lasting <7 days), persistent (ie, nonterminating episodes lasting >7 days), or permanent (ie, no initial or further attempts to restore sinus rhythm were taken).[3,4] The underlying mechanism of AF is complex and is likely to differ among patients and in individual patients because of their cardiac condition.[5]

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Patients with AF may be asymptomatic or may present with palpitations, poor exercise tolerance, and symptoms of heart failure.

Treatment options in patients with AF include anticoagulation, rate control, and rhythm control. Rate control and stroke prevention are suitable for all patients with AF, whereas rhythm control is currently recommended for patients with symptoms.[6–9]

Propafenone is a class IC antiarrhythmic agent that blocks sodium channels, thereby reducing the speed of conduction velocity with a little or no effect on cardiac repolarization.[10,11] It also has mild β-blocking, calcium-channel blocking, and potassium current–blocking activities, with relative selectivity for I_{Kr}, which were demonstrated using voltage-clamp techniques.[12] Propafenone is used as first-line therapy for patients with paroxysmal AF who require long-term rhythm control for sinus rhythm restoration and maintenance. In these patients, the restoration and maintenance of sinus rhythm can alleviate the symptoms of AF and improve quality of life.[13] In Taiwan, propafenone is commonly used as the first-line therapy for sinus rhythm control in patients with paroxysmal AF. However, whether generic drugs are the optimal treatment in clinical practice is the subject of debate. Therefore, the present study was designed to evaluate the efficacy and safety of generic (Rhynorm) and brand name (Rytmonorm) propafenone for rhythm control in Taiwanese patients with paroxysmal AF.

2. METHODS

2.1. Study design and population

This was an open-label randomized multicenter study conducted in Taiwan. We set a noninferiority margin (ie, the difference in favor of the standard treatment) of 20% in this trial. For an alpha level of 5% and a power of 80%, 58 patients (ie, 29 per group) were required in this trial according to the power calculator for the binary outcome for the noninferiority trial. We enrolled 76 patients in this study. The eligible patients were randomly divided into two groups. Patients with arrhythmia were screened for eligibility after providing written informed consent. These patients discontinued other prohibited class I or III antiarrhythmic agents for at least five half-lives (patients were required to discontinue amiodarone for 6 months) before being randomized. The patients were randomly assigned to the Rhynorm group (150 mg three times per day) or the Rytmonorm group (150 mg three times per day) for 24 weeks at a 1:1 ratio. The clinical evaluation was recorded during the study period. Before the two drugs were administered to the patients, a physical examination of their clinical condition was performed; they were monitored and recorded for at least 7 days. During the treatment period, the patients were scheduled for regular outpatient department visits for the evaluation of clinical symptoms, vital signs, blood work, and 12-lead ECG monitoring.

The following patients were included: (1) patients aged 20 to 80 years; (2) patients with recurrent paroxysmal AF; and (3) patients with AF that was diagnosed using ECG monitoring (eg, 12-lead ECG, 24-hour Holter monitoring, or long-term event recordings) within 12 months prior screening visit. The patients could receive propafenone at least 4 weeks before the screening visit. The following patients were excluded: (1) patients with permanent or persistent AF; (2) patients with any heart diseases, including New York Heart Association class III or IV angina pectoris or heart failure; second- or third-degree atrioventricular block with electrographic evidence; sinus node disease, atrioventricular conduction disturbance, or in the absence of an artificial pacemaker; hemodynamic moderate valvular heart disease (ie, stenosis and/or regurgitation); Brugada syndrome; left ventricular ejection fraction less than 50%; acute myocardial infarction or unstable angina within the past 12 months; cardiogenic shock (excluding arrhythmia shock) within the past 12 months; acute pericarditis or myocarditis within the past 6 months; cardiac or thoracic surgery within the past 6 months; symptomatic bradycardia (heart rate less than 50 beats/min); hemodynamic instability, defined as hypotension (systolic blood pressure less than 90 mmHg); hyperthyroidism; bronchospastic disorders or severe obstructive pulmonary disease; correctable AF for other reasons; and marked electrolyte imbalance; (3) patients with clinically significant abnormalities in laboratory parameters, including aspartate aminotransferase or alanine transaminase ≥3 times upper limit of normal, total bilirubin ≥2 times upper limit of normal, creatinine ≥2.5 mg/dL, hemoglobin <10 g/dL, and platelet <100,000/μL; (4) patients with known contraindication or history of allergy to propafenone; (5) pregnant or lactating women; (6) potentially pregnant women who did not agree to use contraception during the study; (7) patients who participated in any drug-related clinical trial within 30 days during the study period; and (8) patients with a propagating factor (eg, alcohol abuse–induced AF). The safety assessments of all patients included adverse events, vital signs, and laboratory tests (ie, hematology and biochemistry). Adverse events, symptoms, and concomitant medications/therapies were collected throughout the study using case report forms. We used the Micor A100 wearable ECG recorder (MiTAC International Corp., Taiwan) to investigate episodes of AF in patients.[14] The patients sent the ECG reports to the center at National Central University, Taiwan, at least twice per day using their cellphone. Each report was 30 seconds with one-lead ECG. All ECG reports were evaluated by the principal investigators.

2.2. Randomization procedure

A permuted block randomization method with 1:1 ratio was used to divide patients into Group A (Rhynorm, A drug) and Group B (Rytmonorm, B drug) for 24 weeks of treatment. Study participants were randomly assigned according to whether the patient has taken propafenone before stratification. The randomization code list was generated by the contract research organization and was provided to TSH Biopharm Co., Ltd, (Taipei, Taiwan) for packing and labeling the study drugs.

2.3. Study endpoints

The primary endpoint was to compare the effect of Rhynorm and Rytmonorm over 24 weeks of treatment through event recorder monitoring and clinical evaluation. The effect was indicated by the frequency of episodes of paroxysmal AF that was recorded using an event recorder. Frequency of clinically significant recurrence of AF (ie, AF ≥ 30 seconds) was calculated as number of AF ≥30 s/total number of records. The secondary endpoints included the following: (1) proportion of patients with recurrent AF over 24 weeks; (2) frequency of recurrent AF (total number of AF/total number of records) at weeks 12 and 24; (3) frequency of recurrent AF ≥3 seconds (number of AF ≥3 s/total number of records) at weeks 12 and 24; (4) frequency of recurrent AF ≥5 seconds (number of AF ≥5 s/total number of records) at weeks 12 and 24; (5) frequency of recurrent AF ≥10 seconds (number of AF ≥10 s/total number of records) at weeks 12 and 24; (6) frequency of recurrent AF ≥20 seconds (number of AF ≥20 s/total number of records) at weeks 12 and 24; and (7) mean heart rate during AF episodes at weeks 12 and 24. The safety endpoints included the occurrence of clinical proarrhythmic and hemodynamic adverse events. Proarrhythmic adverse events were indicated by the occurrence of a new tachyarrhythmia of any origin and/or new bradyarrhythmia resulting from sinus or atrioventricular nodal dysfunction or other conduction disturbances. Hemodynamic adverse events were indicated by

any changes in arterial blood pressure or heart failure exacerbation not related to proarrhythmic events that required medical intervention.

2.4. Statistical analysis

A noninferiority clinical trial was designed to compare the efficacy of Rhynorm and Rytmonorm. We set a noninferiority margin at 20% in this trial. For an alpha level of 5% and a power of 80%, 58 patients (29 per group) were required in this trial based on the power calculator for a binary outcome. Continuous variables are expressed as mean ± standard deviation. Categorical variables are presented as frequency and percentage. Student's *t* test was used to analyze the differences in the frequency of AF episodes and the number of days with AF between the two groups. The Kaplan-Meier curve was used to determine the cumulative survival probability over time; the log-rank test was used to compare survival curves between different categories. Cox proportional hazards regression was used to calculate the hazard ratios (HRs) with 95% CI to evaluate the risk under time to events. Multivariate Cox proportional hazards models with adjustment for sex and age were used to estimate the HRs. Significance was indicated at $p < 0.05$. All statistical analyses were performed using SAS software, version 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

3. RESULTS

3.1. Baseline characteristics

We screened 76 patients for eligibility, and five patients were excluded (Fig. 1). Finally, 37 and 34 eligible patients were randomized into the Rhynorm and Rytmonorm groups, respectively. The baseline patient characteristics are shown in Table 1. All baseline patient characteristics in the two groups were comparable except for age; the Rhynorm group was significantly older than the Rytmonorm group (65.4 ± 8.40 vs 59.8 ± 10.8 years; $p = 0.02$).

3.2. Outcomes

3.2.1. Primary endpoint

Table 2 presents changes in the frequency of AF episodes (number of AF ≥ 30 s/total number of records) for the patients receiving Rhynorm or Rytmonorm at weeks 2, 12, and 24. No significant differences were noted between the two groups (all *p* values >0.05). Compared with the baseline, the frequency of clinically significant AF at week 24 decreased by 4.76% ± 18.5% (from 24.3% ± 33.9% to 19.0% ± 28.7%; $p = 0.13$) in the Rhynorm group and 3.27% ± 15.2% (from 16.9% ± 26.4% to 13.6% ± 19.2%; $p = 0.22$) in the Rytmonorm group; the intergroup difference was 1.5% ± 17.0% ($p = 0.71$). This finding indicates that Rhynorm is not inferior to Rytmonorm ($p = 0.023$

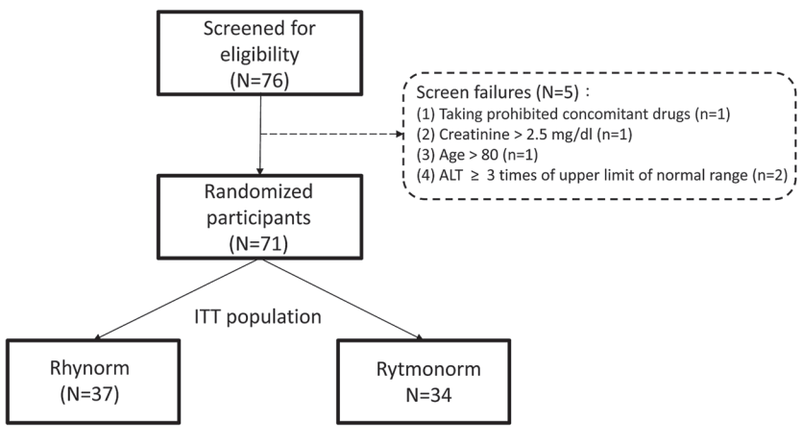

Fig. 1 The randomization of study population in two groups. Five patients are screen failures due to taking prohibited concomitant drugs in one patient, serum creatinine > 2.5 mg/dL in one, age older than 80 y in one and alanine transaminase greater than three times of upper limit of normal range in two. ALT = alanine transaminase; ITT = intent to treat; N = number.

Table 1

The baseline characteristics of study population

Characteristics	Rhynorm (N = 37)	Rytmonorm (N = 34)	*p*
Age (y)	65.4 ± 8.40	59.8 ± 10.8	0.02
Gender, male, n (%)	30 (81.1)	26 (76.5)	0.77
Hypertension, n (%)	17 (45.9)	13 (38.2)	0.63
Dyslipidemia, n (%)	17 (45.9)	15 (44.1)	>0.99
Diabetes mellitus, n (%)	3 (8.1)	4 (11.8)	0.7
Coronary artery disease, n (%)	11 (29.7)	8 (23.5)	0.6
Stroke, n (%)	4 (10.8)	1 (2.9)	0.36
Heart failure, n (%)	6 (16.2)	6 (17.6)	>0.99
Body mass index (kg/m^2)	25.3 ± 3.53	26.5 ± 5.59	0.27
Heart rate (beats/min)	78.3 ± 16.9	75.7 ± 16.8	0.52
SBP (mmHg)	134.9 ± 17.1	130.6 ± 18.7	0.31
DBP (mmHg)	81.4 ± 12.4	77.5 ± 9.3	0.15
Previous propafenone use, n (%)	28 (75.7)	26 (76.5)	>0.99

DBP = diastolic blood pressure; SBP = systolic blood pressure.

Table 2

The frequency of AF episodes (≥30 s) in two groups (ITT)

Characteristics	Rhynorm (N = 37)	Rytmonorm (N = 34)	*p*
Frequency of AF episodes (%)			
Baseline	24.3 ± 33.9	16.9 ± 26.4	0.31
Week 2	25.1 ± 31.6	15.7 ± 22.3	0.15
Week 12	18.9 ± 27.9	14.4 ± 18.4	0.44
Week 24	19.5 ± 28.7	13.6 ± 19.2	0.32
Mean change of AF episodes compared with baseline (%)			
Week 2	0.79 ± 9.40	−1.66 ± 15.4	0.43
p between week 2 and baseline	0.40	0.54	
Week 12	−3.69 ± 17.0	−3.69 ± 14.3	>0.99
p between week 12 and baseline	0.19	0.16	
Week 24	−4.76 ± 18.5	−3.27 ± 15.2	0.71
p between week 24 and baseline	0.13	0.22	

AF = atrial fibrillation; ITT = intention to treat.

for noninferiority). In addition, total episodes of AF ≥30 seconds in the Rhynorm group were nonsignificantly higher than that in the Rytmonorm group, which was calculated using the Cox proportional hazards regression with adjustment for sex and age (adjusted HR, 1.23; CI, 0.69–2.43; $p = 0.47$).

3.2.2. Secondary endpoints

The number of patients with recurrent AF over 24 weeks was comparable between the two groups (88.6% in the Rhynorm group and 73.5% in the Rytmonorm group, $p = 0.13$). The time to first symptomatic AF recurrence (≥30 seconds) is shown in Fig. 2. The Kaplan-Meier curve indicates that the event-free survival rate of recurrent symptomatic AF ≥30 seconds did not significantly differ between the Rhynorm (median follow-up of 154 days) and Rhytmonorm groups (median follow-up of 161 days; log-rank test; $p = 0.66$). The changes in mean number of days of AF episodes are presented in Table 3. The mean number of days and the mean change of number of days with AF episodes at weeks 2, 12, and 24 did not significantly differ between the two groups. The total number of days with AF episodes increased significantly by 15.1 ($p < 0.001$) and 25.8 ($p < 0.001$) days in the Rhynorm group and increased significantly by 15.8 ($p < 0.001$) and 29.3 ($p < 0.001$) days in the Rytmonorm group at weeks 12 and 24, respectively, compared with the baseline. However, the total days with AF episodes did not differ significantly between two groups at week 12 ($p = 0.34$) and week 24 ($p = 0.11$). The mean heart rate during AF episodes at weeks 12 and 24 was 103.4 ± 20.4 and 99.0 ± 21.4 beats/min in the Rhynorm group

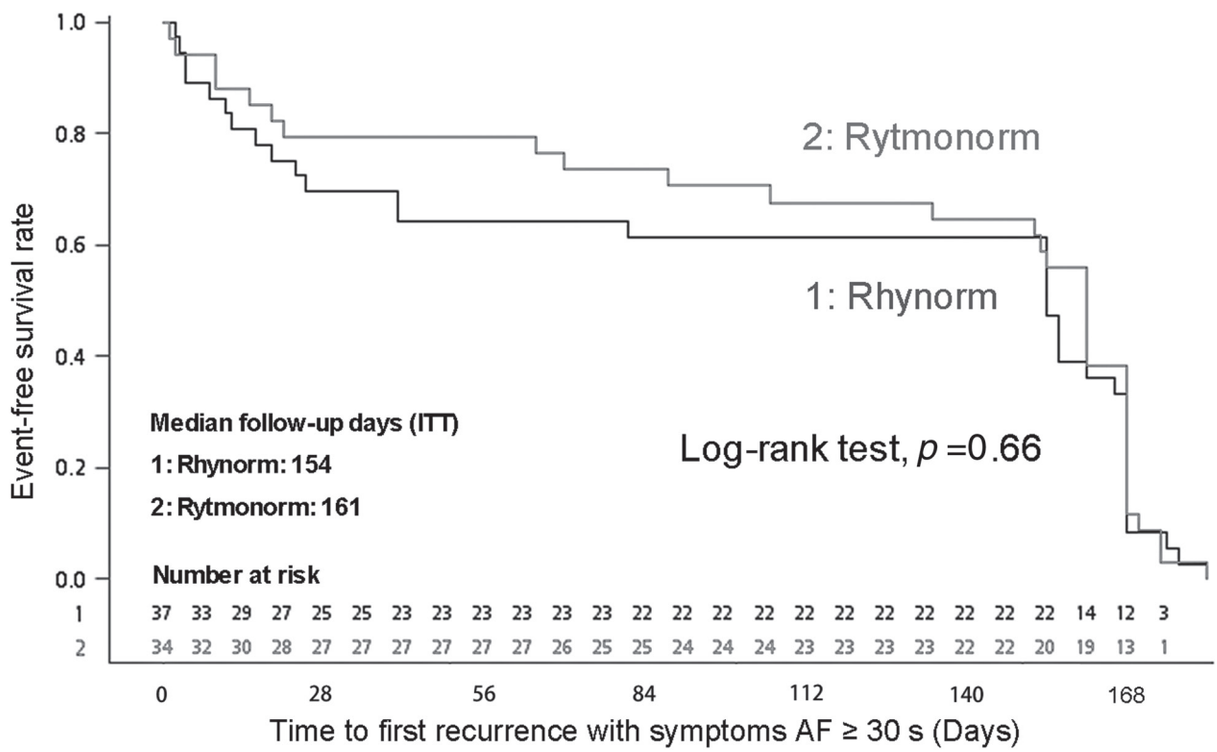

Fig. 2 The Kaplan-Meier survival curve of time to first symptomatic AF recurrence in study population (intention to treat) in two groups. AF = atrial fibrillation; ITT = intent to treat.

Table 3

The mean number of days with AF episodes (≥30 s) in two groups (ITT)

Characteristics	Rhynorm (N = 37)	Rytmonorm (N = 34)	*p*
Mean number of days with AF episodes (d)			
Baseline	3.30 ± 4.03	1.91 ± 2.50	0.09
Week 2	4.43 ± 4.96	3.9.1 ± 4.45	0.65
Week 12	18.2 ± 24.0	17.8 ± 19.7	0.95
Week 24	39.0 ± 53.3	31.2 ± 39.7	0.49
Mean change of number of days with AF episodes compared with baseline (d)			
Week 2	1.13 ± 2.32	1.94 ± 2.76	0.19
p value between week 2 with baseline	0.005	<0.001	
Week 12	15.1 ± 21.1	15.8 ± 17.8	0.34
p value between week 12 with baseline	<0.001	<0.001	
Week 24	25.8 ± 50.4	29.3 ± 37.9	0.11
p value between week 24 with baseline	<0.001	<0.001	

AF = atrial fibrillation; ITT = intention to treat.

Table 4

The summary of adverse events in two groups (ITT)

Adverse events	Rhynorm (N = 37)	Rytmonorm (N = 34)	*p*
Adverse events			
Total adverse events, n (%)	14 (24.3)	13 (29.4)	>0.99
Number of Patients with SAE, n (%)	1 (2.7)	2 (5.9)	0.94
Number of Patients with AE, n (%)	9 (24.3)	10 (29.4)	0.83
Respiratory, thoracic, and mediastinal disorders	2 (5.4)	2 (5.9)	>0.99
Nervous system disorders	1 (2.7)	3 (8.8)	0.55
Cardiac disorders	4 (10.8)	2 (5.9)	0.75
Gastrointestinal disorders	0 (0.0)	1 (2.9)	0.97
Injury, poisoning and procedural complications	1 (2.7)	0 (0.0)	>0.99
Infections and infestations	4 (10.8)	2 (5.9)	0.75
Eye disorders	1 (2.7)	0 (0.0)	>0.99
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (2.9)	>0.99
Adenocarcinoma of prostate	0 (0.0)	1 (2.9)	0.97
ALT increase	0 (0.0)	1 (2.9)	0.97
Renal and urinary disorders	1 (2.7)	0 (0.0)	>0.99
Proarrhythmic events (%)	2 (5.4)	1 (2.9)	0.94
Hemodynamic events (%)	0 (0.0)	1 (2.9)	0.97

AE = adverse event; ALT = alanine transaminase; ITT = intention to treat; SAE = severe adverse event.

and 103.7 ± 19.3 and 101.9 ± 19.9 beats/min in the Rytmonorm group. No statistically significant differences were observed between the two groups at week 12 ($p = 0.99$) and week 24 ($p = 0.61$). In addition, frequency of recurrent AF of ≥3, ≥5, ≥10, and ≥20 seconds did not differ significantly between the two groups at weeks 12 and 24 (all p values >0.05).

3.2.3. Safety

The data of 71 patients were analyzed to evaluate the safety of the agents (Table 4). The safety profiles of Rhynorm and Rytmonorm were comparable. This finding suggests that patients tolerated both drugs. During the study period, 14 adverse events occurred in nine patients (24.3%) in the Rhynorm group, with one patient (2.7%) having a severe adverse event (ie, lens implantation). Among these patients, none had severe or life-threatening adverse events (ie, grade 4), and no adverse events led to death (ie, grade 5). Thirteen adverse events occurred in 10 patients (29.4%) in the Rytmonorm group, with two patients (5.9%) having severe adverse events (ie, cancer and palpitation). Among these patients, none had severe or life-threatening adverse events (ie, grade 4), and no adverse events led to death (ie, grade 5). In the Rhynorm group, the most common adverse events were cardiac and infection disorders (both 10.8%). In the Rytmonorm group, the most common adverse event was nervous system disorder (8.8%). In the aforementioned adverse events, the most common treatment-related adverse events that were confirmed by physicians were acute pharyngitis (5.4%) in the Rhynorm group and asthma (5.9%) in the Rytmonorm group. Regarding proarrhythmic adverse events, two patients (8.1%) in the Rhynorm group had sinus tachycardia and paroxysmal supraventricular tachycardia, one patient (2.9%) in the Rytmonorm group had paroxysmal supraventricular tachycardia, and one patient (2.9%) in the Rytmonorm group had hemodynamic adverse event (ie, hypotension).

Laboratory assessments of heart rate, systolic blood pressure, and diastolic blood pressure at baseline and week 24 were similar in both groups (Table 5). The baseline hematological parameters (ie, hemoglobin level, red blood cell, platelet, and white blood cell counts) did not differ significantly between the two groups. However, the hemoglobin level ($p = 0.04$), red blood cell count ($p = 0.01$), and white blood cell count ($p = 0.04$) were significantly lower in the Rhynorm group than in the Rytmonorm group at week 24. These differences were caused by significantly lower levels at week 24 compared with baseline in the Rhynorm group (hemoglobin level 14.1 ± 1.44 vs 14.5 ± 1.18 g/dL, $p = 0.004$; red blood cell count 4.50 ± 0.59 vs 4.72 ± 0.43 × 10^6/μL, $p = 0.002$;

Table 5

The laboratory assessments in two groups (ITT)

Laboratory assessments	Rhynorm (N = 37)	Rytmonorm (N = 34)	*p*
Vital sign			
Baseline			
Heart rate (bpm)	78.3 ± 16.9	75.7 ± 16.8	0.52
SBP (mmHg)	134.9 ± 17.1	130.6 ± 18.7	0.31
DBP (mmHg)	81.4 ± 12.4	77.5 ± 9.3	0.15
At week 24			
Heart rate (bpm)	78.5 ± 17.7	75.2 ± 12.8	0.38
SBP (mmHg)	129.0 ± 16.2	128.8 ± 14.5	0.96
DBP (mmHg)	77.5 ± 9.6	77.2 ± 10.6	0.91
Hematology			
Baseline			
Hemoglobin (g/dL)	14.5 ± 1.18	14.6 ± 1.2	0.84
Red blood cell ($\times 10^6$/uL)	4.72 ± 0.43	4.82 ± 0.42	0.36
Platelet ($\times 10^3$/uL)	210.3 ± 414.9	211.4 ± 385.6	0.91
White blood cell	6055 ± 1756	6461 ± 1770	0.34
At week 24			
Hemoglobin (g/dL)	14.1 ± 1.44	14.7 ± 0.97	0.04
Red blood cell ($\times 10^6$/uL)	4.50 ± 0.59	4.82 ± 0.41	0.01
Platelet ($\times 10^3$/uL)	212.6 ± 508.1	213.7 ± 426.2	0.93
White blood cell	4866 ± 2560	5942 ± 1502	0.04
Biochemistry			
Baseline			
Sodium (mmol/L)	140.1 ± 2.8	141.1 ± 1.9	0.24
Potassium (mmol/L)	4.3 ± 0.4	4.3 ± 0.3	0.80
Creatinine (mg/dL)	1.03 ± 0.26	1.02 ± 0.30	0.80
Total bilirubin (mg/dL)	0.68 ± 0.03	0.62 ± 0.25	0.37
ALT (U/L)	21.4 ± 15.3	23.0 ± 9.8	0.61
AST (U/L)	22.3 ± 10.1	20.7 ± 5.6	0.39
Alkaline phosphatase (U/L)	69.9 ± 19.2	77.6 ± 31.7	0.23
At week 24			
Sodium (mmol/L)	139.8 ± 3.4	140.9 ± 2.1	0.12
Potassium (mmol/L)	4.2 ± 0.4	4.2 ± 0.3	0.82
Creatinine (mg/dL)	1.03 ± 0.24	1.03 ± 0.33	0.99
Total bilirubin (mg/dL)	0.73 ± 0.35	0.75 ± 0.29	0.73
ALT (U/L)	20.0 ± 10.0	23.2 ± 11.4	0.23
AST (U/L)	21.0 ± 8.8	21.2 ± 6.6	0.94
Alkaline phosphatase (U/L)	67.1 ± 19.9	76.2 ± 40.8	0.25

ALT = alanine transaminase; AST = aspartate aminotransferase; DBP = diastolic blood pressure; ITT = intention to treat; SBP = systolic blood pressure.

and white blood cell count 4866 ± 2560 vs 6055 ± 1756, p = 0.001). No significant differences in the aforementioned hematological parameters at week 24 and baseline were observed in the Rytmonorm group. In addition, the biochemistry parameters (ie, sodium, potassium, creatinine, alanine transaminase, aspartate aminotransferase, and alkaline phosphatase levels) at baseline or week 24 were similar between the two groups.

4. DISCUSSION

4.1. Major findings

This study demonstrated that in terms of efficacy and safety, the generic (Rhynorm) propafenone is not inferior to the brand name (Rytmonorm) propafenone for rhythm control in patients with paroxysmal AF. Both drugs could nonsignificantly decrease the AF burden (≥30 seconds; primary efficacy endpoint) at week 24 compared with baseline, with similar adverse events.

4.2. Efficacy

Propafenone hydrochloride is a class 1C drug and can be useful in restoring and maintaining sinus rhythm in patients with AF.[15] However, the clinical efficacy of generic (Rhynorm) and brand name (Rytmonorm) propafenone had not been compared in Taiwan. A previous study suggested that propafenone is an effective drug for the prophylaxis of recurrences of AF in patients with recent-onset AF.[16] In previous studies with a follow-up ranging from 6 to 18 months, 39% to 64% of patients were free from AF recurrences under propafenone treatment.[17–22] In our study, we compared the efficacy of Rhynorm and Rytmonorm after 24 weeks of treatment in patients with paroxysmal AF in Taiwan and demonstrated that both drugs nonsignificantly reduced the AF burden with similar efficacy. In addition, the Kaplan-Meier curve showed that the event-free survival rate of recurrent symptomatic AF ≥30 seconds was not significantly different between the Rhynorm and Rytmonorm groups. For other secondary endpoints, the number of total days with AF episodes was 25.8% in the Rhynorm group and 29.3% in the Rytmonorm group at week 24. No significant differences between the two groups were observed. Therefore, our study demonstrated that the efficacy of generic (Rhynorm) and brand name (Rytmonorm) propafenone for rhythm control of patients with paroxysmal AF in Taiwan is similar.

4.3. Safety

The safety profile of the generic and brand name propafenone was similar. This finding indicates that patients tolerated both drugs. The incidence of adverse events in the Rhynorm group was 24.3% and in the Rytmonorm group was 29.4%. One patient in the Rhynorm group and two patients in the Rytmonorm group had severe adverse events, and no drug-related severe adverse events were observed in the two groups. These findings are comparable with those in previous studies.[23–25] In our study, proarrhythmic or hemodynamic adverse events were rare (5.4% vs 2.9%, respectively) in both groups. No severe, life-threatening proarrhythmic events were noted in the two groups. Notably, several significant differences in the laboratory assessments of the two drugs were observed. We found that the hemoglobin level and red blood cell and white blood cell counts were significantly lower in the Rhynorm group at week 24 compared with baseline. These laboratory data were significantly different between the two drugs at week 24. Previous studies have demonstrated that although propafenone or flecainide can cause blood dyscrasias, this adverse effect is relatively uncommon.[26,27] Drug-induced blood dyscrasias can be caused by the toxicity of the drug, inborn problems with metabolism, and immunological reactions. Drug-induced antibodies are directed at target cells, such as platelets (thrombocytopenia) or granulocytes (agranulocytosis).[28] We found that Rhynorm significantly reduced the hemoglobin levels and red blood cell and white blood cell counts after 24 weeks of treatment, but Rytmonorm did not. After Rhynorm therapy, although these parameters slightly decreased, they were all within normal range. Therefore, additional attention is not required. In addition, abnormal liver function is another relatively rare side effect of propafenone, and only one patient treated with Rytmonorm had such adverse event.

4.4. Generic drugs

We used the randomization method to compare the efficacy and safety of generic and brand name propafenone. Although generic drugs are commonly used around the world, the number of randomized control trials comparing the efficacy and safety of generic and brand name drugs is limited. Most clinicians are repeatedly exposed to studies claiming that generic drugs are not as effective or safe as their brand name counterparts.[29,30] Our previous retrospective study compared the clinical efficacy and safety of brand name and generic fenofibrate in patients with hypertriglyceridemia.[31] We found that both drugs could

effectively reduce triglyceride levels with little difference in the safety of renal or hepatic functions. In this open-label randomized study, generic Rhynorm was comparable to brand name Rytmonorm in terms of the clinical efficacy of rhythm control in patients with paroxysmal AF in Taiwan. Overall, the safety of the two drugs was comparable, with the exception of mildly reduced hematological parameters in the Rhynorm group after 24 weeks of treatment. These results may encourage physicians and primary health-care providers to treat paroxysmal AF with a generic drug, specifically Rhynorm, rather than the brand name drug in Taiwan.

This study has several limitations. First, we enrolled a small sample size. Second, because we used a permuted block randomization method with a 1:1 ratio, less satisfactory random distribution might have occurred in this trial. Third, after randomization, because the Rhynorm group was significantly older than the Rytmonorm group, we used a multivariate model to evaluate the HRs with adjustment for age and sex. In addition, we used a wearable ECG device to detect clinically significant AF episodes of the patients every day. Thus, the AF burden might be underestimated if the patient did not activate the recordings when the AF episodes were asymptomatic. Finally, bias may have occurred because of the open-label design of this study.

In conclusion, for the rhythm control of paroxysmal AF in patients in Taiwan, we verified that generic propafenone (Rhynorm) was not inferior to brand name propafenone (Rytmonorm) in terms of efficacy and safety in this open-label randomized control study. Our study may encourage physicians to prescribe the generic to treat paroxysmal AF in patients in Taiwan.

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