Effects of Pimobendan on Adverse Cardiac Events and Physical Activities in Patients With Mild to Moderate Chronic Heart Failure

— The Effects of Pimobendan on Chronic Heart Failure Study (EPOCH Study) —

The EPOCH Study Group*

The long-term beneficial effects of pimobendan in the treatment of chronic heart failure (CHF) have not been established, so the present trial compared pimobendan (1.25 or 2.5 mg twice daily) vs placebo in 306 patients with stable New York Heart Association class II or III CHF, and a radionuclide or echocardiographic left ventricular ejection fraction (LVEF) $\leq 45\%$ despite optimal treatment with conventional therapy, for up to 52 weeks in a double-blind protocol. At the end of the 52 weeks of treatment, combined adverse cardiac events had occurred in 19 patients in the pimobendan group (15.9%) vs 33 patients in the placebo group (26.3%). The cumulative incidence of combined adverse cardiac events was 45% lower (95% confidence interval of hazard ratio: 0.31–0.97, log-rank test: $p=0.035$) in the pimobendan group than in the placebo group. Death and hospitalization for cardiac causes occurred in 12 patients in the pimobendan group (10.1%), vs 19 patients in the placebo group (15.3%), but without significant difference. Treatment with pimobendan also increased the mean Specific Activity Scale score from 4.39 ± 0.12 at baseline to 4.68 ± 0.15 at 52 weeks ($p<0.05$). In conclusion, long-term treatment with pimobendan significantly lowered morbidity and improved the physical activity of patients with mild to moderate CHF. (*Circ J* 2002; 66: 149–157)

Key Words: Chronic heart failure; Inotropic drugs; Morbidity; Physical activity; Pimobendan

Chronic heart failure (CHF) is a complex clinical syndrome linked to abnormal cardiac function. Because it is characterized by depressed cardiac pumping, interventions that increase myocardial contractility would be expected to slow the progression of the disease and improve survival! The production of cyclic adenosine monophosphate (AMP) is impaired in patients with heart failure² and although pharmacologic agents that increase the concentration of intracellular cyclic AMP cause marked short-term hemodynamic improvement, several clinical trials have shown that chronic administration increased the mortality of patients with CHF!³ The mechanism of such accelerated mortality remains incompletely understood.

Pimobendan, a benzimidazole pyridazinone derivative, is positively inotropic through its combination of a calcium-sensitizing effect and a cyclic AMP-dependent mode of action^{4–6} In healthy young volunteers, pimobendan has a bioavailability of 70% and undergoes hepatic metabolism to an active metabolite, UDCG 212, which is more potent than the parent compound as a phosphodiesterase III inhibitor and an inotrope in vitro. This metabolite has also been

reported to have more effect on the calcium sensitivity of human ventricular myofilaments⁷ Early clinical studies of the acute hemodynamic effects of a single oral dose of pimobendan administered to patients with severe CHF have demonstrated a significant improvement in left and right ventricular function, peaking 3–5 h after drug intake^{8–10} Randomized, placebo-controlled trials in patients with CHF have also shown that pimobendan was therapeutically effective when added to conventional drug regimens, with or without digitalis!^{11–16} However, all these data are derived from relatively small samplings and the follow-up periods have not been sufficiently long, except for the PICO trial!¹⁵

In view of these findings, the present study was designed to examine the long-term effects of pimobendan with flexible doses within the approved daily dose range on adverse cardiac events and physical activity in Japanese patients with CHF.

Methods

Patient Population

Patients between the ages of 20 and 85 years were eligible for enrollment into the study if they (1) had clinically stable, New York Heart Association (NYHA) functional class II in the subcategory of NYHA II, which means moderate limitation of physical activity, or NYHA functional class III chronic heart failure, (2) had remained symptomatic despite conventional therapy with digitalis, diuretics, angiotensin-converting enzyme (ACE) inhibitors, nitrates, Ca-blockers, β -blockers or antiarrhythmic etc for

(Received July 27, 2001; revised manuscript received November 2, 2001; accepted November 7, 2001)

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Table 1 EPOCH Patient Population

	Pimobendan	Placebo
No. patients considered for enrollment		306
Not eligible		8
Randomized (n)	147	151
Withdrawn before treatment initiation (n)		
Change in clinical status	5	5
Consent withdrawn	1	2
Protocol violation (loss of follow up)	2	1
Sudden death	0	1
Change in background treatment	0	1
Unexpected hospitalization	0	1
Total	8	11
Treatment initiated (n)	139	140
Withdrawn from analysis (n)	1	2
Full analysis data set	138	138
Treatment completed	111	113
Treatment discontinued		
Study exits	9	7
Drug-related adverse events	14	9
Non drug-related adverse events	4	9

at least 4 weeks without any changes in the drug regimen, and (3) had a radionuclide or echocardiographic left ventricular ejection fraction (LVEF) $\leq 45\%$ measured within 2 months of enrollment. Continuation of treatment with digitalis, diuretics, ACE inhibitors, nitrates, Ca-blockers and β -blockers was permitted, but other cardiotoxic agents, including vesnarinone, denopamine, and docalpamine were prohibited.

Exclusion criteria from enrollment included severe ventricular and atrial arrhythmias, advanced atrioventricular block, stenotic, obstructive or infectious heart disease, acute myocardial infarction within the previous 3 months, cardiac surgery within the previous 3 months, severe cerebrovascular, respiratory, hepatic, renal or hematological disease, or the presence of another life-limiting condition. Pregnant and nursing women were also excluded, as well as nonpregnant women of childbearing age unless they had been sterilized.

All patients gave written informed consent to participate in the study and the study protocol was approved by the Institutional Ethical Review Board of each participating institution.

Study Design

A preliminary patient evaluation was performed 2–4 weeks before the anticipated time of randomization into the study. Background medications remained unchanged, and patients were ultimately entered into the study if they had remained clinically stable during the pre-treatment period while baseline clinical tests were performed, including chest roentgenogram, 12-lead ECG, echocardiogram, measurement of serum atrionatriuretic peptide (ANP) level, routine blood chemistry and urinalysis. ANP was determined with the immunoradiometric assay method (IRMA).¹⁷ Echocardiographic and radionuclide methods^{18–20} were used to determine the LVEF in 93 and 9 patients, respectively, of the pimobendan group, and 96 and 14 patients, respectively, of the placebo group. Physical activity was determined from the Specific Activity Scale (SAS) questionnaire, which has been validated in patients with CHF.²¹

After gathering all baseline observations, the patients were randomly assigned to double-blind treatment for 52 weeks with pimobendan, 1.25 mg twice daily, vs matching

placebo. The dose could be increased to 2.5 mg twice daily if the patient had no improvement in the signs or symptoms of heart failure. Outpatient visits were scheduled every 4 weeks during which a physical examination was performed, the SAS questionnaire resubmitted, and adverse events were recorded. At weeks 4, 24 and 52 the evaluation also included an ECG, echocardiogram, chest roentgenogram, measurements of serum ANP levels, routine blood chemistry and urinalysis. The patients were treated with the study medication for up to 52 weeks, or until the primary endpoints (described later) occurred. At the end of 52 weeks, if the treatment was judged to have been clinically effective, its prescription could be continued with the written consent of the patient.

Randomization Procedure

The randomization code was prepared in sets of 6 patients according to a block design. Treatment was assigned by a registration office according to a code using a dynamic balancing method allowing adjustments for 4 variables, including LVEF ($>30\%$ vs $\leq 30\%$); underlying heart disease (dilated cardiomyopathy vs ischemic heart disease vs valvular insufficiency), NYHA functional class (II vs III) and enrolling institution.

Study Endpoints

The primary endpoints were adverse cardiac events, including death from heart failure, sudden/arrhythmic cardiac death, and hospitalization for worsening heart failure. The secondary endpoints were a decrease by ≥ 1 Mets in the SAS questionnaire score for at least 3 months as compared with the baseline, a need for modification of the background treatments with a new addition or an increase of the concomitant drugs for at least 4 weeks and/or with intravenous administration of a cardiotoxic agent for at least 4 h because of worsening heart failure, and death from non-cardiac and other cardiac causes. All adverse cardiac events were regularly reviewed by an independent Study Event Committee.

Statistical Analysis

All statistical analyses were performed with the statistical package SAS(r), version 8.0. The calculated sample

Table 2 Baseline Clinical Characteristics of Each Treatment Group

	Pimobendan (n=138)	Placebo (n=138)
Age (years) [range]	62.0±10.9 [24–84]	65.8±9.4 [32–84]
M/F (%)	104/34 (75.4/24.6)	99/39 (71.7/28.3)
Underlying heart disease, n (%)		
Dilated cardiomyopathy	86 (62.3)	85 (61.6)
Ischemic heart disease	46 (33.3)	47 (34.1)
Others	6 (4.3)	6 (4.3)
NYHA class, n (%)		
II _m	93 (67.4)	89 (64.5)
III	44 (31.9)	49 (35.5)
LVEF (%) [range]	33.1±8.6 [13–45]	32.6±8.6 [7–45]
SAS (Mets)	4.4±1.4	4.3±1.4
ANP (pg/ml)	52.4±2.7	54.8±2.5
CTR (%)	54.5±6.3	55.2±6.2
Duration of CHF (months)	44.9±47.4	41.6±47.7
Blood pressure (mmHg)		
Systolic	120.9±17.4	122.9±17.2
Diastolic	73.2±10.3	71.4±9.8
Heart rate (beats/min)	74.6±13.8	74.2±12.5
Concomitant medication		
Digitalis	81	82
Diuretics	116	109
ACE inhibitors	93	95
Nitrates	59	62
Ca-blockers	21	24
-blockers	35	27
Antiarrhythmic	46	40
Daily dose of study medication prescribed, n (%)		
Low dose (1.25 mg bid only for pimobendan group)	107 (77.5)	111 (80.4)
High dose (1.25 mg and 2.5 mg bid for pimobendan group)	31 (22.5)	27 (19.6)

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; SAS, specific activity scale; ANP, serum atrionatriuretic peptide; CTR, cardiothoracic ratio; CHF, congestive heart failure; ACE, angiotensin-converting enzyme. Values are mean±SD.

size was based on assumptions of 1-year cumulative incidence rates of 27–29% in the placebo group and hazard ratio of 0.4–0.5^{14,22} for combined primary and secondary endpoints. The target number of patients was calculated to be 130 per treatment group, based on a 5% type I error, a 2-sided test, and an 80% power, using Freedman's formula²³

The primary analysis was based on intention-to-treat, and included all primary and secondary adverse cardiac events which occurred in each patient during the 52-week treatment period. In this analysis, the cumulative incidence rates were calculated with respect to the time to the first combined primary and secondary endpoints by the Kaplan-Meier method in each treatment group and compared by log-rank test. The hazard ratio was estimated by Cox's regression.

Secondary efficacy analyses consisted of comparisons of treatment-associated changes in SAS, LVEF, ANP levels, cardiothoracic ratio (CTR) and NYHA functional class between the 2 groups of patients. An analysis of covariance using a baseline value as a covariate was used to examine the differences in response between the 2 treatment groups. The response at 52 weeks was used as the response variable and missing values were imputed using the Last-Observation-Carried-Forward approach.

Changes in NYHA functional class were summed in each group and the difference in response was tested by Wilcoxon's test. Unless specified otherwise, values are presented as mean±SD. P values <0.05 were considered statistically significant.

SAS Scores Analysis

Time trends for the SAS scores were analyzed by fitting

a general linear model for repeated measures. The least square means (LSMeans) were calculated for 14 time points, including baseline values, and a model with interaction terms between time points and groups, using a compound symmetry structure, was used for a working covariance matrix, and an empirical robust variance for the calculation of standard error. The overall type III effect of groups and time points, as well as interaction terms, was tested using a model with the baseline value as a covariate. Lower SAS scores corresponded to the worst physical condition.

Missing values were (1) death: a value of 0 was assigned after death; (2) hospitalization: the value at the hospitalization was imputed after the patient was admitted to the hospital. If the value was not available, the mean value for the hospitalization was calculated from all the available hospitalized cases; and (3) dropout or treatment discontinuation: a mean value was calculated from all data available for each patient before dropout or discontinuation.

NYHA Functional Class Analysis

Changes in NYHA functional class were categorized as improved, unchanged, or aggravated. Patients in NYHA class III heart failure at baseline were considered to have functionally improved if they were in NYHA class I, II_s or II_m at the end of the study, and to have worsened if they were in NYHA class IV or had experienced a primary adverse cardiac event by the end of the study. Likewise, patients in NYHA class II_m heart failure at baseline were considered to have improved if they were in NYHA class I or II_s at the end of the observation period, and to have worsened if they were in NYHA class III or IV, or had

Table 3 Cardiac Events Included in the Primary Analysis in Each Treatment Group

	No. of patients with events		
	Pimobendan	Placebo	Total
<i>Primary endpoints</i>			
Total	12 (1)	19 (4)	31 (5)
Sudden cardiac death	1	1	2
Hospitalization because of progressive CHF	11 (1)	18 (4)	29 (5)
Death from progressive CHF	0	0	0
<i>Secondary endpoints</i>			
Total	8	18	26
Decrease in SAS (≥ 1 Mets)	6	14	20
Addition or increase in doses of background medications	2	4	6
Non-cardiac and other cardiac deaths	0	0	0
Combined number of primary and secondary endpoints			
Total	19	33	52

CHF, chronic heart failure; SAS, specific activity scale. Events (primary endpoints) in parentheses occurred after secondary endpoints in the same patient and were not included in the combined number.

experienced a primary event by the end of the study period.

Safety Monitoring

Sequential safety monitoring was carried out throughout the study by an independent Safety and Data Monitoring Committee, but no interim analysis of efficacy was conducted. Adverse events were classified using the WHO-ART dictionary and adverse events for which a causal relationship with drug treatment was not excluded were treated as adverse drug reactions.

Results

Study Population

Between December 1995 and September 1998, 306 patients who gave written consent to participate were considered for enrollment (Table 1). Eight patients were found to be ineligible at the time of randomization and were excluded. Study medication was not initiated after randomization for miscellaneous reasons (Table 1) in 8 patients assigned to pimobendan, and in 11 assigned to placebo. Thus 279 patients were randomly assigned to

Fig 1. Kaplan-Meier estimations of cumulative rates of combined (primary + secondary endpoints) cardiac events in the pimobendan and placebo groups.

Fig 2. Kaplan-Meier estimations of cumulative rates of primary (primary endpoints) cardiac events in the pimobendan and placebo groups.

Table 4 Kaplan-Meier Analysis of the Cumulative Incidence Rates of Cardiac Events

Analysis	No. of events	Cumulative incidence	Estimated HR	95% CI	p value of log-rank test
<i>Combined primary and secondary endpoints</i>					
Pimobendan (n=138)	19	15.9%	0.55	0.31–0.97	0.035
Placebo (n=138)	33	26.3%			
<i>Primary endpoints</i>					
Pimobendan (n=138)	12	10.1%	0.63	0.30–1.29	0.202
Placebo (n=138)	19	15.3%			

HR, hazard ratio; CI, confidence interval.

treatment (139 to pimobendan and 140 to placebo). Three patients (1 with LVEF >60%, 1 with sinus arrest, and 1 with wide variations in the SAS scores during the pre-treatment period) were excluded from all analyses before unblinding of their treatment assignments. The baseline clinical characteristics of the 276 patients with full analysis data sets, evenly distributed between treatment with pimobendan and placebo, are summarized in Table 2. Nearly 80% of patients (107 patients in the pimobendan group and 111 patients in the placebo group) were treated with 1.25 mg twice daily of pimobendan or the equivalent dose of placebo throughout the entire period of study.

Study medication was discontinued because of adverse events in 18 patients from each group. Four adverse events in the pimobendan-treated group were unrelated to drug therapy and were noncardiovascular. Nine adverse events in the placebo-treated group were unrelated to drug therapy, and included 2 hospitalizations for acute myocardial infarction. In addition, 9 patients in the pimobendan-treated group and 7 in the placebo-treated group exited the study. The reasons for exiting the study that were not related to safety problems included withdrawal of informed consent or loss of follow up etc. Therefore, treatment was completed per protocol by 111 patients treated with pimobendan and 113 patients treated with placebo.

Cardiac Events

During the 52-week study period, one patient died suddenly in each treatment group, there were 12 hospitalizations for worsening heart failure in the pimobendan-treated group vs 19 in the placebo-treated group, and 26 secondary adverse cardiac events (secondary endpoints) occurred. The secondary adverse cardiac events were a decrease in SAS score and the addition or increase in doses of concomitant treatment in 8 pimobendan-treated vs 18 placebo-treated patients. Because 5 hospitalizations for worsening heart failure (1 in the pimobendan, 4 in the placebo group) occurred after the secondary adverse cardiac events (secondary endpoints) in the same patients, the primary analysis of combined primary and secondary endpoints included a total of 52 events: 19 in the pimobendan-treated group, and 33 in the placebo-treated group (Table 3).

The cumulative incidence rates of combined primary and secondary endpoints were 15.9% in the pimobendan-treated group and 26.3% in the placebo-treated group (Fig 1, Table 4), corresponding to an estimated 45% risk reduction (95% CI of hazard ratio: 0.31–0.97, logrank test: $p=0.035$). The cumulative incidence rates of the primary endpoints were 10.1% and 15.3%, respectively (Fig 2, Table 4), corresponding to an estimated hazard ratio of 0.63 without significant difference, but comparable to that of the combined primary and secondary endpoints.

Changes in SAS

Fig 3 and Table 5 show the time course of the SAS scores, expressed as LSMeans $\pm$ SE, in each treatment group. There was no significant difference at baseline between the 2 groups. The analysis of covariance using the baseline values as covariates revealed a significant overall improvement in the pimobendan-treated group compared with the placebo-treated group ($p=0.045$) and this improvement was judged to be nearly uniform over the study period, because the interaction between the 2 groups and the time points was not significant ($p=0.18$). The difference in SAS scores between baseline and 52 weeks was significant in the pimobendan-treated group ($p=0.024$), consistent with a treatment-related increase in daily physical activities. In contrast, the difference in the placebo-treated group was not statistically significant ($p=0.318$).

Changes in NYHA Functional Classification

In the placebo-treated group, NYHA functional class improved in 20.9% of patients from the baseline, remained unchanged in 54.5% and was aggravated in 24.6%, whereas in the pimobendan-treated group the NYHA improved in 34.6%, remained unchanged in 54.1% and was aggravated in 11.3% of the patients. The difference between the 2 groups was statistically significant ($p=0.0013$).

Changes in LVEF, ANP and CTR

Table 6 summarizes the treatment-related changes in the indices of LVEF, ANP and CTR measured between baseline and the end of the study period. Mean LVEF at baseline and 52 weeks was $32.8 \pm 8.1\%$ vs $38.7 \pm 13.0\%$ in the pimobendan-treated group, and $32.7 \pm 8.5\%$ vs $35.8 \pm 11.2\%$ in the placebo-treated group. Analysis of covariance revealed that the increase in LVEF by 52 weeks was signif-

Fig 3. Time course of the Specific Activity Scale (SAS) scores expressed as LSMeans $\pm$ SE in each treatment group.

Table 5 Time Trends of the Specific Activity Scale (SAS)

	Pimobendan (n=134) LSMean $\pm$ SE	Placebo (n=135) LSMean $\pm$ SE	95% CI of difference
Baseline	4.39 $\pm$ 0.12	4.30 $\pm$ 0.12	-0.23, 0.43
4 weeks	4.66 $\pm$ 0.12	4.36 $\pm$ 0.12	-0.04, 0.64
24 weeks	4.79 $\pm$ 0.13	4.43 $\pm$ 0.15	-0.05, 0.75
52 weeks	4.68 $\pm$ 0.15*	4.14 $\pm$ 0.17	0.09, 0.98

CI, confidence interval. * $p=0.024$ vs baseline. F test of analysis of covariance using baseline values as covariates: Drug ($F=4.04$, $df=1$, $p=0.045$), Week ($F=1.73$, $df=12$, $p=0.054$), Drug/Week ($F=1.35$, $df=12$, $p=0.18$).

Table 6 Treatment-Related Changes in LVEF, ANP and CTR

	Pimobendan	Placebo	Test
LVEF (%)	(n=102)	(n=110)	
Baseline	32.8±8.1	32.7±8.5	p=0.044
52 weeks	38.7±13.0	35.8±11.2	
ANP (pg/ml)	(n=97)	(n=91)	
Baseline	47.1±2.7	54.0±2.5	p=0.0001
52 weeks	36.5±2.7	60.9±3.0	
CTR (%)	(n=98)	(n=98)	
Baseline	54.7±6.2	55.2±6.1	p=0.002
52 weeks	54.3±6.9	56.6±7.2	

Analysis of covariance using baseline values as covariates. LVEF, left ventricular ejection fraction; ANP, serum atrionatriuretic peptide; CTR, cardiothoracic ratio. Values are mean±SD.

Table 7 Severe Adverse Events in Each Treatment Group During the Study Period

Event	Pimobendan (n=138)	Placebo (n=138)
Musculo-skeletal system disorder	2	0
Nervous system disorder	2 (1)	2
Visual disorder	0	1
Psychiatric disorder	0	1
Gastrointestinal system disorder	2	3 (1)
Liver and biliary system disorder	2	0
Metabolic and nutritional disorder	1	3 (1)
Cardiovascular disorder, general	0	1 (1)
Myo-, endo-, pericardial or valvular disorder	1 (1)	2
Heart rate and rhythm disorder	3 (1)	2 (2)
Vascular (extracardiac) disorder	1	1
Respiratory system disorder	4 (1)	6
Red blood cell disorder	1	0
Urinary system disorder	0	2
Neoplasm	1	1
Resistance mechanism disorder	2	0
Whole body disorder	16 (5)	24 (2)
Total no. of severe adverse events	38 (9)	49 (7)
Total no. of patients with severe adverse events	30 (9)	44 (7)

Numbers in parentheses indicate severe adverse drug reactions.

icant in favor of the pimobendan-treated group ($p=0.044$). Furthermore, serum ANP levels significantly decreased from 47.1 ± 2.7 to 36.5 ± 2.7 pg/ml in the pimobendan-treated group, but increased from 54.0 ± 2.5 to 60.9 ± 3.0 pg/ml in the placebo-treated group by 52 weeks ($p=0.0001$). Finally, CTR increased from $55.2\pm6.1\%$ to $56.6\pm7.2\%$ in the placebo-treated group, but remained unchanged in the pimobendan-treated group ($54.7\pm6.2\%$ to $54.3\pm6.9\%$), the difference that was highly significant ($p=0.002$).

Adverse Events

Pimobendan was well tolerated. There were no significant differences between the pimobendan- and placebo-treated groups with regard to blood pressure and heart rate during the entire study period. Adverse events were reported in 103 patients (74.6%) in the pimobendan-treated group and 100 patients (72.5%) in the placebo-treated group. Severe adverse events were observed in 30 patients (21.7%) in the pimobendan-treated group and 44 patients (31.9%) in the placebo-treated group (Table 7). Severe adverse drug reactions were reported in 9 patients (6.5%) in the pimobendan-treated group and in 7 patients (5.1%) in the placebo-treated group. Pimobendan treatment was not associated with an increased incidence of arrhythmias.

Discussion

Against recent pessimism expressed with respect to the long-term safety and efficacy of existing cardiostimulant drugs^{24,25} the present study found that long-term treatment with pimobendan, an inotropic agent, reduced the incidence of adverse cardiac events, including worsening of heart failure and a decrease in functional capacity, without a significant effect on mortality in patients with NYHA functional classes II and III CHF.

CHF is treated on the basis of its severity, cause and pathology in individual patients with priority given to the prevention of mortality and the improvement in the quality of life (QOL). That is, in patients with mild CHF, the primary objective is prevention of mortality and a decrease in incidence of clinical interventions such as hospitalization and the addition or increased dosage of therapeutic drugs. On the other hand, in patients with moderate to severe CHF who develop symptoms affecting their physical activities and eventually affecting their social life, the primary objective of treatment is not only prevention of mortality and a decrease in incidence of the clinical interventions, but also improvement in the level (threshold) of physical activity causing the symptoms and improvement of QOL. In the present trial, in order to assess the effect of long-term administration of pimobendan on the mortality

and morbidity of patients with CHF, cardiac events such as heart failure death, sudden death and hospitalization because of worsening heart failure were defined as the primary endpoints, and a decrease in physical activity, the addition or dosage increase of concomitant drugs because of worsening heart failure and non-cardiovascular deaths were secondary endpoints. The primary analysis was carried out with regard to cardiac events combining primary and secondary endpoints, and the results showed that the cumulative incidence of combined adverse cardiac events was 45% lower in the pimobendan group than in the placebo group ($p=0.035$), suggesting that pimobendan has a long-term beneficial effect in the treatment of CHF.

In a study of 52 ambulatory patients in NYHA functional class III–IV heart failure, adding 5 or 10 mg/day of pimobendan to a conventional drug regimen for 4 weeks was associated with a significant increase in maximal exercise duration and peak oxygen uptake compared with placebo.¹¹ Furthermore, in a multicenter randomized trial of pimobendan, 2.5, 5.0 or 10 mg/day vs placebo for 12 weeks, including nearly 200 patients with moderate heart failure, active therapy significantly increased exercise capacity and QOL, and was associated with fewer hospitalizations for heart failure than placebo.¹² It is noteworthy that the effects of pimobendan did not follow a simple dose–response relationship, as maximum efficacy was associated with the 5 mg/day dose, and a lesser efficacy was observed with the 10 mg/day dose.

Long-term therapy was evaluated in the Pimobendan in Congestive Heart Failure (PICO) trial, which randomly assigned 317 outpatients with NYHA functional class II–III CHF to receive placebo vs pimobendan 2.5 or 5 mg/day for 6 months.¹⁵ Though pimobendan increased exercise duration significantly compared with placebo, no significant effects were observed on peak oxygen consumption or QOL. There were 11 deaths among the 108 placebo-treated patients (10.2%) and 36 among the 209 pimobendan-treated patients (17.2%). In contrast, in a smaller, 6-month, double-blind randomized study of patients with symptomatic heart failure, 5 of 11 patients who received placebo were withdrawn because of worsening heart failure, compared with none of the patients treated with pimobendan.¹⁶ In addition, pimobendan significantly improved physical activity, manifesting as a significant increase in mean SAS score at the end of therapy, whereas in the placebo-treated group, the mean SAS score remained unchanged throughout the study period.

In the present study, one patient treated with pimobendan died. The present study had a smaller proportion of patients with severe CHF than in the PICO trial, as indicated by a higher mean LVEF of 33% vs 26–28% in PICO. Also, more patients (80%) were treated with a lower dose of pimobendan as compared with the PICO trial.

The most direct evaluation of heart failure consists of inquiring about symptoms at rest and during exertion. Because the symptoms are usually accentuated during exertion, it has been suggested that the functional status of patients with CHF could be reliably indicated by exercise capacity.^{26–28} However, daily activities do not demand a maximal energy expenditure. Several clinical trials of CHF have included the ‘Living With Heart Failure’ questionnaire as a measure of QOL.^{29,30} Although changes in exercise capacity and in physical activity assessed from the overall questionnaire score have been shown to correlate weakly, though significantly, discrepancies between these

2 parameters have been regularly noted, illustrating the distinction between objective measures and subjective assessment of disability.¹² SAS, the clinical scale used here, has been shown to predict exercise capacity more reliably, with a correlation coefficient between SAS and peak oxygen consumption of 0.78 ($p<0.001$) measured in 51 patients.²¹ This reproducible score was associated with a mean difference of 0.4 ± 0.5 Mets in inter-observer variability, prompting us to consider changes in functional capacity ≥ 1 Mets as reliable and clinically relevant.

The primary objective of the present clinical trial was to evaluate the effect of long-term administration of pimobendan on the prognosis of heart failure. Taking the therapeutic purpose for heart failure into consideration, it is also necessary to examine improvements in symptoms or function in the areas of QOL, cardiac function etc, in addition to the evaluation of events corresponding to aggravation of prognosis. In view of this, SAS, NYHA functional classification, LVEF, ANP and CTR were analyzed as the secondary variables. Treatment with pimobendan was associated with improvement in physical activity, suggested by an increase in SAS score and improvement of NYHA functional classification. The analysis of LVEF, ANP and CTR also showed a treatment-related improvement in each variable.

Much attention has been focused on a possible direct toxic effect of pimobendan on myocytes, exacerbating arrhythmias, enhancing neurohormonal activity, and increasing the mortality of patients with CHF. However, a beneficial effect of pimobendan has been found in several experimental studies.^{4–7,31,32} In the skinned myocardial fiber, calcium sensitizers shifted the Ca^{2+} -force curve to the left, increasing the degree of contractile force generated at a given Ca^{2+} concentration;^{4,5,7,31} however, Ca^{2+} sensitizers may adversely inhibit cardiac relaxation by the slow detachment of Ca^{2+} from troponin C, with elevated myocardial tension during diastole.^{33,34} Pimobendan offsets this impairment of diastolic relaxation by its low-level inhibitory effect of phosphodiesterase.³⁵ When initial heat liberated from guinea pig papillary muscles and the integral stress-time were measured simultaneously using myothermal equipment, both were substantially increased by pimobendan, whereas the slope of the function relating to initial heat and the developed integral tension-time remained unchanged.⁶ In patients with idiopathic dilated cardiomyopathy and moderate CHF, the systemic hemodynamic actions induced by pimobendan were associated with advantageous effects on myocardial oxygen consumption.³⁶ Therefore, the increase in myocardial oxygen force by pimobendan is accomplished in a more economical way, making this agent better suited for long-term treatment of heart failure.

There is growing evidence that immunologic responses mediated by certain cytokines, including tumor necrosis factor- α , interleukin-1, interleukin-6 etc, may play an important pathogenic role in the development of heart failure.^{37–41} Several clinical studies have demonstrated that patients with CHF express excessive levels of those cytokines in plasma;^{42–45} and on the basis of those observations, great interest has been generated in new therapies to modulate those cytokines.⁴⁶ Pimobendan inhibits the production of tumor necrosis factor- α in human peripheral mononuclear cells;⁴⁷ and of NO in cultured macrophages *in vitro*.⁴⁸ More recently, it was reported that myocardial protein levels of tumor necrosis factor- α , interleukin-1, and interleukin-6 were substantially reduced by pimoben-

dan, together with a significant reduction in intracardiac NO production and inducible nitric oxide synthase (iNOS) gene expression.⁴⁹ Although the mechanism by which pimobendan inhibits the production of proinflammatory cytokines and iNOS gene expression has not been elucidated, it has recently been reported that pimobendan inhibits the activation of transcription factor nuclear factor- κ B.⁵⁰ These data suggest that the therapeutic effects of pimobendan observed in the present study may be attributable, in part, to its immunomodulating or anticytokine properties.

In conclusion, the present study demonstrated that long-term concurrent treatment with a low dose of pimobendan (1.25 mg twice daily) in patients with moderate CHF is well tolerated, reduces morbidity, and improves physical activity without a significant increase in adverse effects. However, it does not influence the risk of mortality.

Acknowledgments

The investigators would like to thank the patients who participated in this study. This study was supported by a grant from Nippon Boehringer Ingelheim, Japan.

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