ORIGINAL ARTICLE

Efficacy of Add-on Therapy with Carvedilol and the Direct Renin Inhibitor Aliskiren for Improving Cardiac Sympathetic Nerve Activity, Cardiac Function, Symptoms, Exercise Capacity and Brain Natriuretic Peptide in Patients with Dilated Cardiomyopathy

Takuji Toyama, MD[1], Shu Kasama, MD[2], Yusuke Miyaishi, MD[3], Hakuken Kan, MD[3], Eiji Yamashita, MD[3], Ren Kawaguchi, MD[3], Hitoshi Adachi, MD[3], Hiroshi Hoshizaki, MD[3] and Shigeru Ohshima, MD[3]

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Abstract

***Purpose/Method*: Aliskiren is a direct renin inhibitor that has been reported to be effective for CHF, but the usefulness of combined therapy with carvedilol and aliskiren has not been reported. Forty-four patients with dilated cardiomyopathy (DCM) were randomized into a group receiving add-on therapy with carvedilol plus aliskiren and another group receiving carvedilol alone for 6 months.**

Nuclear imagings with ^{123}I-Metaiodobenzylguanidine (MIBG) and ^{99m}Tc-Sestamibi were performed. Exercise capacity using a specific activity scale (SAS) and the New York Heart Association (NYHA) class were evaluated. Cardiac sympathetic nerve activity was evaluated by ^{123}I-MIBG imaging, with the delayed heart-to-mediastinum activity ratio (H/M), delayed total defect score (TDS), and washout rate (WR).

***Results*: Combined add-on therapy with carvedilol and aliskiren improved several parameters much more than carvedilol alone ($p<0.05$) with respect to TDS, ejection fraction (EF), NYHA, SAS on 6 months and the changes in TDS, EF, end-diastolic volume and brain natriuretic peptide (BNP).**

***Conclusion*: Add-on therapy with carvedilol and aliskiren is more effective than carvedilol alone for improving cardiac sympathetic nerve activity, cardiac function, symptoms, exercise capacity, and brain natriuretic peptide in patients with DCM.**

Keywords: ^{123}I-metaiodobenzylguanidine imaging, Aliskiren, Brain natriuretic peptide, Cardiac sympathetic nerve activity, Carvedilol, Dilated cardiomyopathy

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The prognosis of patients with idiopathic dilated cardiomyopathy (DCM) remains poor. Activation of the sympathetic nervous system is one of the cardinal pathophysiologic abnormalities in patients with chronic heart failure (1). Studies performed in Sweden during the 1970s suggested that long-term beta-blocker therapy might have several hemodynamic and clinical benefits (2, 3). Controlled clinical trials then showed that beta-blocker therapy has consistent benefits for patients with chronic heart failure (4–7).

Aliskiren is a direct renin inhibitor that has a pharmacologically distinct mechanism of suppressing the renin-angiotensin-aldosterone system (RAAS), with the theoretical advantages of blocking an enzyme with only one known substrate (angiotensinogen) to inhibit the rate-limiting step of the RAAS cascade and thus reduce the synthesis of all subsequent components of this cascade (8). Similar to angiotensin

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1) Division of Cardiology, Toyama Cardiovascular Clinic, Maebashi, Japan
2) Clinical Research Center, Nara Medical University Graduate School of Medicine, Nara, Japan
3) Division of Cardiology, Gunma Prefectural Cardiovascular Center, Maebashi, Japan

Table 1 Clinical characteristics

Variable	Carvedilol alone (n=22)	Combined add-on (n=22)	p
Age, years	62 ± 13	62 ± 14	0.98
Male gender, n (%)	17 (77)	18 (82)	1
BMI, kg/m2	21.9 ± 3.9	23.7 ± 5.1	0.19
NYHA class			1
2	8	9	
3	14	13	
Atrial fibrillation, n (%)	4 (18)	7 (32)	0.49
Pacemaker implantation, n (%)	1 (5)	3 (14)	0.61
Sleep apnea syndrome, n (%)	4 (18)	4 (18)	1
Hypertension, n (%)	4 (18)	6 (27)	0.721
Diabetes Mellitus, n (%)	1 (5)	0	1
Dyslipidemia, n (%)	7 (32)	10 (45)	0.537
Smoking, n (%)	5 (23)	7 (32)	0.736
Chronic kidney disease, n (%)	11 (50)	7 (32)	0.358
eGFR, ml/min/1.73m^2	56 ± 24	65 ± 17	0.182
Medical treatment			
Beta-blocker, n (%)	22 (100)	22 (100)	1
ACEIs/ARBs, n (%)	0	0	1
Aliskiren, n (%)	0	22 (100)	<0.0001
Diuretics, n (%)	16 (73)	14 (64)	0.75
Aldosteron blocker, n (%)	6 (27)	8 (36)	0.75

BMI: body mass index, NYHA: New York Heart Association,
ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker.

receptor blockers (ARB), aliskiren may offer an alternative to angiotensin-converting enzyme (ACE) inhibitors or could be used in combination with an ACE inhibitor (or ARB) (9). The rationale for the latter approach is that ACE inhibitors (and ARBs) induce a compensatory increase of renin and downstream RAAS components that may eventually overcome their RAAS-blocking effect. Co-administration of aliskiren would be expected to block this compensatory increase of RAAS activity.

However, there have been no reports about the effects of combined therapy with carvedilol and aliskiren on cardiac function, including cardiac sympathetic activity, in patients with chronic heart failure.

^{123}I-Metaiodobenzylguanidine (MIBG) imaging has been used to study cardiac sympathetic activity. Cardiac ^{123}I-MIBG uptake shows various changes in DCM patients compared with normal individuals (10, 11). Cardiac uptake of ^{123}I-MIBG and left ventricular ejection fraction (LVEF) are correlated (10, 11) and ^{123}I-MIBG imaging can be a useful prognostic marker in patients with DCM (11). The present study was undertaken to clarify the effectiveness of combined therapy with carvedilol and aliskiren versus carvedilol monotherapy on symptoms, cardiac function, and cardiac sympathetic activity in patients with DCM.

Methods

Study population

Between 2011 and 2013, we treated 44 consecutive DCM patients (9 women and 35 men with a mean age of 62 ± 14 years, range: 43 to 72 years) with either carvedilol plus aliskiren or carvedilol alone in addition to basal heart failure medications that included diuretics and aldosterone antagonists (Table 1). All patients had experienced at least one episode of heart failure requiring short-term hospitalization and all patients were symptomatic at the start of treatment. They were in New York Heart Association (NYHA) functional Class II or III and had LVEF ≤45% by quantitative gated SPECT (QGS) software. Twenty-two patients (4 women and 18 men, mean age: 62 ± 14 years) received add-on therapy with carvedilol plus aliskiren, while the other 22 patients (5 women and 17 men, mean age: 62 ± 13 years) received carvedilol alone. Patients were randomized to either group and all patients gave informed consent in accordance with the guidelines of the Human Clinical Study Committee of our hospital prior to participation in the study, which approved this study on February 2011. All patients completed therapeutic protocols

until follow-up study.

Coronary angiography showed normal coronary arteries in all patients. Acute or chronic myocarditis was excluded in all patients based on the results of left ventricular endomyocardial biopsy. None of the patients had a history of alcohol abuse. Moreover, congenital heart disease, moderate to severe valvular heart disease, and hypertensive heart disease were excluded by the findings on echocardiography and physical examination.

Study protocol

In patients receiving combined add-on therapy with carvedilol and aliskiren (combined add-on group), we started treatment with 150 mg/day of aliskiren and an initial carvedilol dose of 1.25 to 2.5 mg/day, and then increased carvedilol to the maintenance dose of 10 mg/day after 3 months. In patients receiving therapy with carvedilol alone (carvedilol alone group), we started the same treatment protocol for setting the dosage of carvedilol. A battery of tests were performed on both groups before treatment and after 6 months of treatment.

^{123}I-MIBG and ^{99m}Tc-MIBI imaging

^{123}I-MIBG and ^{99m}Tc-Sestamibi (MIBI) were obtained commercially (FUJIFILM Toyama Chemical Co., Ltd. Tokyo, Japan). Each patient was given an intravenous injection of 111 Mbq of ^{123}I-MIBG while in the upright position. Anterior planar and single photon emission computed tomography (SPECT) images were acquired at 15 min and 4 h after injection. SPECT imaging was performed with a dedicated 3-detector system (IRIX, Picker). The detectors were constantly corrected for energy, uniformity, and linearity. Projection images were acquired for 55 sec each in 5° increments over a 360° orbit and were recorded at a resolution of 64 × 64 pixels. On another day, each patient was injected with 720 MBq of ^{99m}Tc-MIBI in the upright position and imaging was performed 30 min later. ^{99m}Tc-MIBI SPECT images were acquired for 40 sec each in 5° increments over a 360° orbit. Energy discrimination was provided by a 20% window around the 159 keV photopeak for ^{123}I-MIBG and a 15% window around the 140 keV photopeak for ^{99m}Tc-MIBI imaging.

On the anterior planar delayed ^{123}I-MIBG images, the heart-to-mediastinum (H/M) activity ratio was determined by using regions of interest (ROIs) positioned over the heart (H) and over the upper mediastinum (M). The ROI over the heart included the blood pool. Then the washout rate (WR) was calculated by using the following formula: (H-M) early- (H-M) delayed/(H-M) early × 100. At our center, the normal delayed H/M ratio was 2.32 ± 0.19 and the washout rate was 28.1 ± 7.0%.

The myocardial SPECT images of each patient were divided into 17 segments as follows. Short- axis images obtained at the basal and mid-ventricular levels were divided into 6 segments each, the apical ventricular level was divided into 4 segments, and the apical segment on the vertical long axis image formed 1 segment. Then semiquantitative assessment of regional uptake was done by assigning a five-point score (0＝normal uptake; 1＝slightly reduced uptake; 2＝moderately reduced uptake; 3＝severely reduced uptake; and 4＝defect) and the total defect score (TDS) was calculated as the sum of the scores for all 17 segments. TDS of the delayed ^{123}I-MIBG images and ^{99m}Tc-MIBI images was calculated. H/M activity ratio and TDS of the delayed ^{123}I-MIBG images were used to evaluate cardiac sympathetic activity (11).

Commercially available QGS software (Cedars-Sinai Medical Center, Los Angeles, CA) with a temporal resolution of 16 frames per R-R interval was used to create a 3-dimensional surface cinemode display. Then this display was employed to calculate the LVEF, left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV) throughout the cardiac cycle by using an automatic edge detection algorithm (12).

Cardiac symptoms and specific activity scale

Cardiac symptoms were scored according to the NYHA functional classification. Exercise capacity was estimated by using the specific activity scale (SAS). We asked all patients 21 questions of the SAS at the beginning of this study and after 6 months of treatment (13).

Cardiopulmonary exercise testing

All patients underwent symptom-limited cardiopulmonary exercise testing in the upright position on a calibrated bicycle ergometer (CPE2000, MedGraphics, St Paul, MN). Exercise started with warming up at 20 W for 4 min followed by a continuous increase of the workload until exercise was terminated by exhaustion. We evaluated exercise tolerance by determining the oxygen uptake at the anaerobic threshold (AT VO_2) and the peak oxygen uptake (peak VO_2) (14).

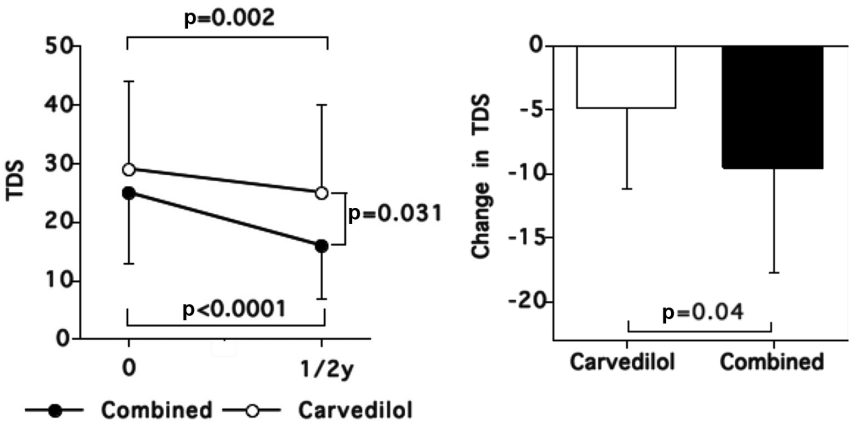
Statistical analysis

All examinations were performed and evaluated by investigators who had no information about which group the patients were enrolled in. Statistical analysis was performed with JMP software (SAS Institute Inc., Cary, NC) on a Macintosh computer. The paired two-tailed *t*-test was employed for comparison of parameters over time, while the unpaired two-tailed *t*-test was used for comparisons between the carvedilol alone and combined add-on groups. Results are expressed as the mean ± SD.

Table 2　Blood pressure and heart rate

Variable	Carvedilol alone (n=22)	Combined add-on (n=22)	p
Systolic BP, mmHg			
Baseline	124 ± 13	132 ± 16	0.087
6 months	115 ± 13**	119 ± 14**	0.375
Change in BP	-9 ± 12	-14 ± 12	0.204
Diastolc BP, mmHg			
Baseline	74 ± 10	80 ± 11	0.086
6 months	69 ± 11	70 ± 10**	0.962
Change in BP	-5 ± 12	-11 ± 10	0.086
HR, beats/min			
Baseline	81 ± 13	81 ± 14	0.952
6 months	69 ± 12**	71 ± 8**	0.554
Change in HR	-11 ± 13	-10 ± 11	0.675

BP: blood pressure, HR: heart rate.
**: p<0.01 vs baseline



(a)　(b)

Figure 1
a: TDS of ^{123}I-MIBG imaging.
b: The change in TDS of ^{123}I-MIBG imaging.
TDS: total defect score.

Results

The clinical characteristics are shown in Table 1. It was found that the age, gender, BMI, NYHA class, the frequency of atrial fibrillation, pacemaker implantation, sleep apnea syndrome, hypertension, diabetes mellitus, dyslipidemia, smoking and chronic kidney disease, and eGFR were similar between the 2 groups. There were no significant differences of medications except for aliskiren between the 2 groups.

Blood pressure and heart rate before and 6 months of treatment are shown in Table 2. There were no significant differences between two groups in these parameters. Systolic blood pressure and heart rate in both groups significantly deceased after 6 months of treatment. And diastolic pressure only in combined add-on group significantly deceased after 6 months of treatment.

^{123}I-MIBG images data are summarized in Table 3. The TDS in the carvedilol alone group showed a significant decrease after 6 months of treatment (25 ± 15) in comparison with the baseline value (30 ± 12, p=0.002). In the combined add-on group, the total defect score also showed a significant decrease after 6 months (16 ± 9) in comparison with baseline (27 ± 12, p < 0.0001, Figure 1a). Moreover, the change of TDS was significantly lower in patients receiving combined add-on therapy than in patients receiving carvedilol alone (-10 ± 8 vs. -5 ± 6 p=0.04, Figure 1b).

The H/M ratio in the carvedilol alone group showed a non-significant increase after 6 months of treatment in comparison with the baseline value (1.74 ± 0.25 vs. 1.67 ± 0.25, p=0.051). In the combined add-on group, the H/M ratio was increased

Table 3 ^{123}I-MIBG and ^{99m}Tc-MIBI scintigraphies and cardiac function

Variable	Carvedilol alone (n=22)	Combined add-on (n=22)	p
TDS (MIBG)			
Baseline	30 ± 12	27 ± 12	0.434
6 months	25 ± 15**	16 ± 9**	0.031
Change in TDS	-5 ± 6	-10 ± 8	0.04
H/M ratio			
Baseline	1.67 ± 0.25	1.65 ± 0.17	0.689
6 months	1.74 ± 0.25	1.76 ± 0.19**	0.841
Change in H/M	0.07 ± 0.17	0.11 ± 0.17	0.443
WR (%)			
Baseline	47 ± 13	44 ± 9	0.464
6 months	42 ± 9*	38 ± 10**	0.212
Change in WR	-5 ± 8	-6 ± 9	0.607
TDS (MIBI)			
Baseline	4 ± 5	3 ± 4	0.248
6 months	3 ± 4	2 ± 3	0.11
Change in TDS	-1 ± 2	-1 ± 2	0.743
EDV (ml)			
Baseline	206 ± 64	204 ± 59	0.912
6 months	177 ± 63**	152 ± 59**	0.176
Change in EDV	-29 ± 32	-52 ± 44	0.049
ESV (ml)			
Baseline	149 ± 56	144 ± 60	0.792
6 months	118 ± 56**	92 ± 53**	0.118
Change in ESV	-30 ± 30	-52 ± 46	0.071
LVEF (%)			
Baseline	29 ± 9	30 ± 10	0.648
6 months	36 ± 10**	43 ± 12**	0.044
Change in LVEF	8 ± 8	13 ± 12	0.045

TDS: total defect score, H/M ratio: heart-to-mediastinum activity ratio, WR: washout rate, EDV: end-diastolic volume, ESV: end-systolic volume, LVEF: left ventricular ejection fraction.
*: $p<0.05$ vs baseline, **: $p<0.01$ vs baseline

significantly after 6 months in comparison with baseline (1.76 ± 0.19 vs. 1.65 ± 0.17, p=0.006).

The washout rate in the carvedilol alone group was decreased significantly after 6 months of treatment in comparison with baseline (42 ± 9% vs. 47 ± 13%, p=0.01). In the combined add-on group, the WR also showed a significant decrease after 6 months in comparison with baseline (38 ± 10% vs. 44 ± 9%, p=0.003).

Total defect scores obtained from the ^{99m}Tc-MIBI images were no significant changes of the score in either group in Table 3. The EDV, and ESV at baseline and after 6 months of treatment are compared in Table 3. All of these parameters showed significant improvement in both groups after 6 months of treatment ($p<0.01$). Moreover, the change of EDV (-52 ± 44%) of patients receiving combined add-on therapy was significantly larger than that of patients receiving carvedilol alone (-29 ± 32%, p=0.049)

LVEF in the carvedilol alone group increased significantly after 6 months of treatment (36 ± 10%) in comparison with the baseline value (29 ± 9%, $p<0.0001$). In the combined add-on group, LVEF also increased significantly after 6 months of treatment (43 ± 12%) in comparison with the baseline value (30 ± 10%, $p<0.0001$, Figure 2a). After 6 months of treatment, the LVEF of patients receiving combined add-on therapy was significantly higher than that of patients receiving carvedilol alone (p=0.044, Figure 2a). Moreover, the change of LVEF (13 ± 12%) of patients receiving combined add-on therapy was significantly larger than that of patients receiving carvedilol alone (8 ± 8%, p=0.045, Figure 2b).

Exercise capacity, BNP and NYHA functional class are summarized in Table 4. The SAS in the carvedilol alone group increased significantly after 6 months of treatment in

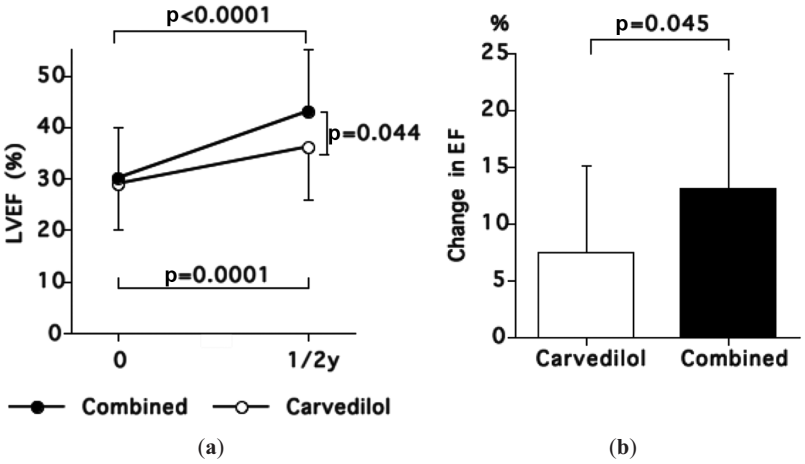


Figure 2
a: LVEF of QGS image.
b: The change in LVEF of QGS image.
LVEF: left ventricular ejection fraction, QGS: quantitative gated SPECT.

Table 4 Exercise capacity and BNP

Variable	Carvedilol alone (n=22)	Combined add-on (n=22)	p
SAS (Mets)			
Baseline	4.3 ± 1.5	4.6 ± 1.2	0.508
6 months	5.4 ± 1.4**	6.3 ± 1.3**	0.026
Change in SAS	1.1 ± 1.0	1.8 ± 1.5	0.096
Anaerobic threshold (AT VO_2)			
Baseline	13.1 ± 3.7	12.1 ± 2.3	0.408
6 months	13.3 ± 3.8	12.4 ± 3.2	0.502
Change in peak VO_2	0.25 ± 2.0	0.4 ± 2.6	0.855
Peak VO_2 (ml/min/kg)			
Baseline	16.8 ± 5.2	16.6 ± 3.2	0.893
6 months	16.6 ± 5.4	19.7 ± 4.7*	0.122
Change in peak VO_2	-0.4 ± 4.2	2.4 ± 3.3	0.079
BNP (pg/ml)			
Baseline	565 ± 949	836 ± 1135	0.401
6 months	615 ± 1186	157 ± 228*	0.089
Change in BNP	50 ± 521	-673 ± 1059	0.009
NYHA			
Baseline	2.6 ± 0.5	2.6 ± 0.5	0.764
6 months	2.0 ± 0.6**	1.6 ± 0.6**	0.03
Change in NYHA	-0.6 ± 0.5	-1 ± 0.6	0.037

SAS: specific activity scale, AT: anaerobic threshold, VO_2: oxygen uptake,
BNP: brain natriuretic peptide, NYHA: New York Heart Association class.
*: p<0.05 vs baseline, **: p<0.01 vs baseline

comparison with baseline (5.4 ± 1.5 METs vs. 4.3 ± 1.5 METs, p < 0.0001). In the combined add-on group, the SAS also showed a significant increase after 6 months compared with baseline (6.3 ± 1.3 METs vs. 4.5 ± 1.2 METs, p < 0.0001). Moreover, the SAS of patients receiving combined add-on therapy was higher than that of patients receiving carvedilol alone after 6 months of treatment (p=0.026).

AT VO_2 in both groups did not changed after tretment. Peak VO_2 in the carvedilol alone group did not change significantly (from 16.8 ± 5.2 to 16.6 ± 5.4, p=0.57). On the other hand, the peak VO_2 of the combined add-on group significantly improved after 6 months of treatment compared with baseline

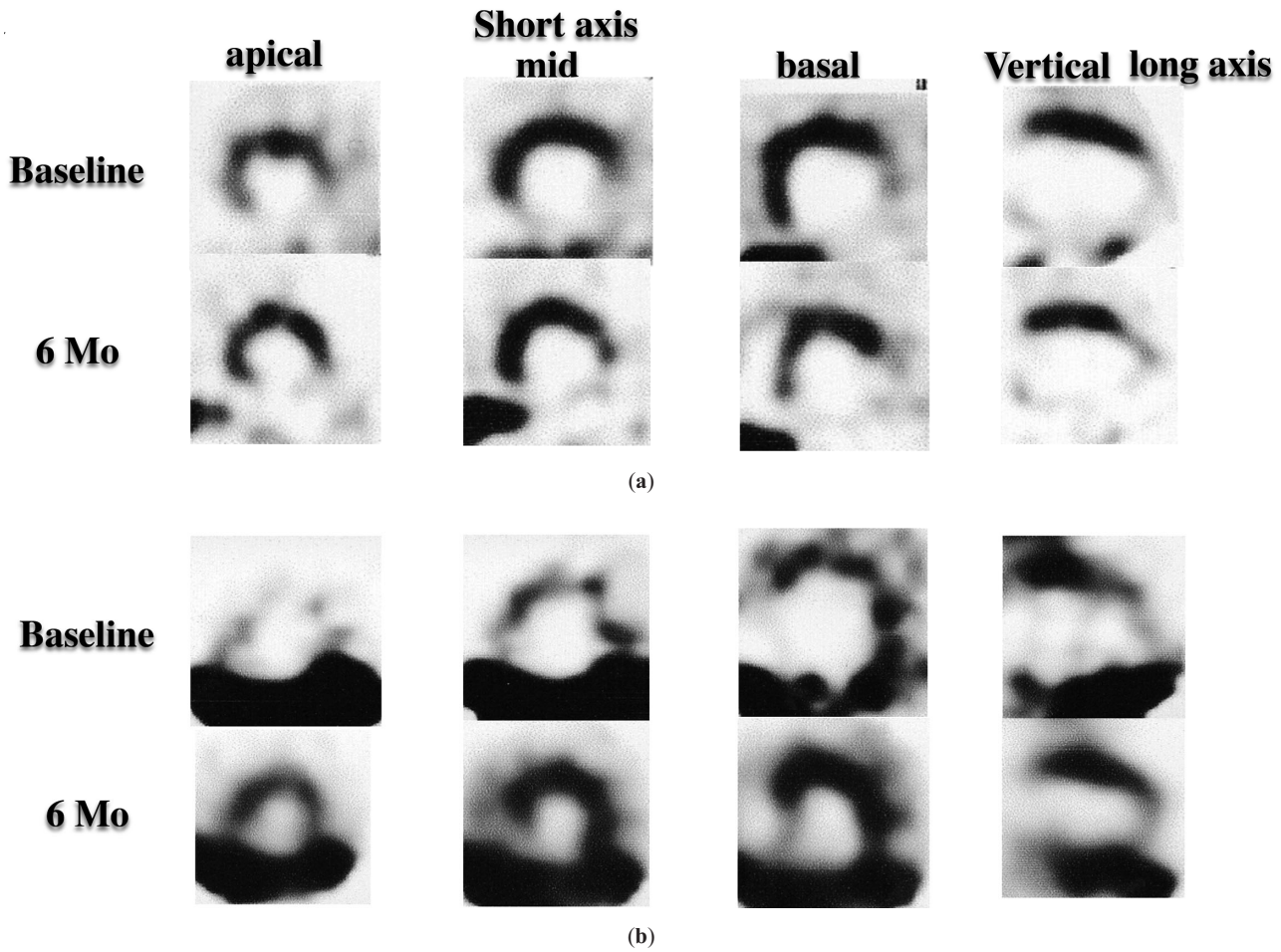


Figure 3

a: Representative case from the carvedilol alone group. ^{123}I-metaiodobenzylguanidine (MIBG) images obtained from short-axis and vertical long-axis reconstructions. ^{123}I-MIBG uptake decreased in many segments at the beginning, and improved mildly after 6 months' carvedilol alone treatment. TDS changed from 34 to 29, H/M ratio changed from 1.7 to 1.82.

b: Representative case from the combined add-on group. ^{123}I-MIBG uptake was decreased in all segments at the beginning. ^{123}I-MIBG uptake in the same area has improved after 6 months' combined add-on treatment. TDS improved from 42 to 22. H/M ratio increased from 1.55 to 2.05.

6Mo: 6 months.

(from 16.6 ± 3.2 to 19.7 ± 4.7, p = 0.026). Moreover, the change of peak VO_2 of patients receiving combined add-on therapy was tended to be higher than that of patients receiving carvedilol alone (2.4 ± 3.3 vs. -0.4 ± 4.2, p=0.079).

BNP in the carvedilol alone group did not change significantly (from 565 ± 949 to 615 ± 1186). On the other hand, the BNP level of the combined add-on group significantly improved after 6 months of treatment in comparison with baseline (from 836 ± 1135 to 157 ± 228, p< 0.02). Moreover, the change of BNP value of patients receiving combined add-on therapy was significantly larger than that of patients receiving carvedilol alone (-673 ± 1059 vs. 50 ± 521, p=0.009).

The carvedilol alone group showed improvement of the NYHA functional class after 6 months of treatment in comparison with baseline (from 2.6 ± 0.5 to 2.0 ± 0.6, p< 0.0001). The combined add-on group also showed significant improvement after 6 months of treatment (from 2.6 ± 0.5 to 1.6 ± 0.6, p<0.0001). At 6 months, the NYHA functional class of patients receiving combined add-on therapy was significantly higher than that of patients receiving carvedilol alone (p=0.03). Moreover, the change of the NYHA functional class of patients receiving combined add-on therapy was significantly larger than that of patients receiving carvedilol alone (-1 ± 0.6 vs. -0.6 ± 0.5, p=0.037).

About the adverse effects, hypotension that was defined as the decrease of the systolic blood pressure under 100 mmHg during 6 months of treatment was found in 4 patients in the carvedilol alone group and 6 patients in the combined add-on group. There were no other adverse effects. Two representative cases were shown in Figure 3.

Discussion

Myocardial scintigraphy with ^{123}I-MIBG, an analog of

norepinephrine, has been reported to provide images that reflect the function of the cardiac sympathetic nervous system (10, 11), and assessment of ^{123}I-MIBG uptake is considered to be useful for evaluating the severity of heart failure. In addition, the heart-to-mediastinum ratio and total defect score obtained from ^{123}I-MIBG images are correlated with the LVEF. ^{123}I-MIBG imaging can be used for both assessment of the prognosis and evaluating the response to treatment (11). Merlet P reported that H/M ratio was the best predictor for life duration more than LVEF (11). In this study, we did not clarify the usefulness of H/M ratio as a predictor. But the good prognosis could be expected in the patients whose H/M ratio improved after treatment.

Several large-scale trials of beta-blockers such as bisoprolol (4), metoprolol (5), and carvedilol (6, 7) have been performed in patients with chronic heart failure, and the effectiveness of beta-blocker therapy for chronic heart failure has been well established. Aliskiren has also been reported to have neurohormonal effects in patients with chronic heart failure (15), but the influence of combined therapy with carvedilol and aliskiren on chronic heart failure has not been compared with that of beta-blockers alone (including carvedilol). In the present study, we investigated the effect of combined add-on therapy with carvedilol and aliskiren compared to carvedilol alone in patients who had dilated cardiomyopathy.

The mechanisms by which beta-blockers improve dilated cardiomyopathy include the following: 1) improved diastolic relaxation, filling, and compliance; 2) inhibition of sympathetically mediated vasoconstriction via prostaglandin and renin release; 3) protection against catecholamine-induced myocardial damage and necrosis; and 4) up-regulation of beta-adrenergic receptors, leading to restoration of catecholamine responsiveness (16–18). Beta-blockers enhance the expression of beta adrenergic receptor kinase and reduce the expression of beta 1-receptors (19). Beta-blockers also have hemodynamic and energetic benefits (20), as well as enhancing cell-mediated immunity and improving T cell function (21).

It has been reported that beta-blocker therapy for patients with chronic heart failure is effective at decreasing cardiac deaths due to heart failure and improves the LVEF (2–7, 22–24). In this study, we used carvedilol, which is a nonselective beta-blocking agent. Gilbert reported that there are no significant differences of hemodynamic effects between carvedilol and the beta1-selective blocking agent metoprolol. However, metoprolol treatment is associated with an increase of cardiac beta-receptor density, whereas carvedilol does not alter cardiac beta-receptor expression (25), suggesting that carvedilol allows cardiac function to recover without up-regulation of beta-adrenergic receptors. Furthermore, carvedilol can improve cardiac performance to the same extent (23, 24) or a greater extent (25) than metoprolol in patients with heart failure.

Aliskiren, the first orally active direct renin inhibitor to become available, is as effective as other RAAS inhibitors at reducing blood pressure, has an incremental BP-lowering effect when added to ARB therapy (26), and is approved for the treatment of hypertension worldwide at doses of 150 and 300 mg/day. Because aliskiren blocks the upstream RAAS, it prevents the reactive increase of plasma renin activity that accompanies treatment with downstream RAAS inhibitors, including ACEIs and ARBs, and blocks the resulting increase of angiotensin I and angiotensin II (27–30).

McMurray et al. investigated the effects of aliskiren in patients with symptomatic heart failure (15). The primary efficacy outcome was the difference of N-terminal pro-BNP (NT-proBNP) and they reported that the plasma NT-proBNP level increased by 762 ± 6123 pg/mL with placebo therapy and decreased by 244 ± 2025 pg/mL with aliskiren therapy ($p = 0.0106$). BNP and urinary aldosterone were also reduced by aliskiren. In the present study, BNP was decreased in the combined add-on group receiving carvedilol plus aliskiren (from 836 ± 1135 to 157 ± 228, $p < 0.02$), but not in control group receiving carvedilol alone. Moreover, the change of BNP value (-673 ± 1059) of the combined add-on group was significantly lower than that of the carvedilol alone group (50 ± 521, $p = 0.009$). There were some differences between the results of McMurray's study and our findings. McMurray et al. found no differences between treatments with regard to the changes of symptoms or signs up to the end of the study. There were also no differences of echocardiographic wall thickness, LVESV, LVESV, and LVEF. On the other hand, LVESV, LVESV, and LVEF, and NYHA functional class all improved significantly ($p < 0.01$) in both groups after 6 months of treatment in our study. Moreover, the LVEF after 6 months and the change of LVEF were significantly higher in the combined add-on group than the carvedilol alone group, while NYHA functional class after 6 months was significantly lower in the combined group. These different findings might be related to the different patient populations and methods of the two studies. McMurray et al. assessed the effect of adding aliskiren to basal treatment with an ACE inhibitor and beta-blocker in patients with heart failure and over 50% of their patients had ischemic heart disease (15). On the other hand, we compared add-on therapy with carvedilol plus aliskiren with carvedilol alone in patients with idiopathic dilated cardiomyopathy who seemed to respond better to treatment than the subjects of McMurray's study.

Assessment of cardiac sympathetic function by ^{123}I-MIBG imaging showed that improvement of the TDS and the H/M ratio was greater in the combined add-on group than in the carvedilol alone group after 6 months of treatment. In addition, the improvement of cardiac symptoms (NYHA functional

class) and exercise capacity (specific activity scale and peak VO_2), as well as cardiac function, were also greater in the combined add-on group. Based on our findings, combined add-on therapy with aliskiren and carvedilol is more effective than carvedilol alone for improving cardiac symptoms, exercise capacity, cardiac function, and cardiac sympathetic activity in patients with DCM. Therefore, aliskiren combined with carvedilol may be a useful regimen for the treatment of heart failure.

All three ^{123}I-MIBG imaging parameters improved after treatment in both groups, but the TDS and H/M ratio showed a difference between the combined add-on group and the carvedilol alone group. Because TDS showed more difference than the H/M ratio, it was the most sensitive of the 3 parameters

Several limitations of this study should be considered. First, it was a single-center study in a small number of patients, so it was difficult to identify differences between combined add-on therapy and carvedilol alone. Second, we did not treat the patients with ACE inhibitors or ARBs, although these drugs are usually added to beta-blockers for the management of heart failure. Ideally, aliskiren or placebo should have been added to basal heart failure treatment including ACE inhibitors or ARBs, but these drugs all inhibit the RAAS and it would be difficult to clarify the effectiveness of aliskiren if other RAAS blockers were used for heart failure treatment. This is why we did not use ACE inhibitors and ARBs. Third, the doses of both carvedilol and aliskiren were not optimized. A high dose of carvedilol may cause hypotension and bradycardia, while high doses of aliskiren can also cause hypotension. For Japanese patients, 10 mg of carvedilol and 150 mg of aliskiren are generally effective daily doses, so we used these low doses of carvedilol and aliskiren in the present study.

In the future, we need to study the long-term effects of our add-on regimens and compare them in a large number of patients by performing a multicenter trial.

Conclusion

In patients with DCM, combined add-on therapy with carvedilol plus aliskiren was superior to carvedilol alone with respect to improving cardiac symptoms, exercise capacity, cardiac function, and cardiac sympathetic activity. Therefore, combined therapy with carvedilol and aliskiren may be useful for treating DCM.

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Conflicts of interest

The authors have no conflicts of interest to declare in relation to this article.

Reprint requests and correspondence:
Takuji Toyama, MD
Toyama Cardiovasucular Clinic, 2-33-9, Aramaki-machi, Maebashi, 371-0044, Japan
E-mail: t.toyama@toyama-clinic.jp

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