Impact of Corticosteroid Use on the Clinical Response and Prognosis in Patients with Cardiac Sarcoidosis who Underwent an Upgrade to Cardiac Resynchronization Therapy

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Abstract

Aims Corticosteroids are widely used in patients with cardiac sarcoidosis (CS). In addition, upgrading to cardiac resynchronization therapy (CRT) is sometimes needed. This study aimed to investigate the impact of corticosteroid use on the clinical outcomes following CRT upgrades. Methods A total of 48 consecutive patients with non-ischemic cardiomyopathies who underwent CRT upgrades were retrospectively reviewed and divided into three groups: group 1 included CS patients taking corticosteroids before the CRT upgrade (n = 7), group 2, CS patients not taking corticosteroids before the CRT upgrade (n = 10), and group 3, non-CS patients (n = 31). The echocardiographic response, heart failure hospitalizations, and cardiovascular deaths were evaluated. Results The baseline characteristics during CRT upgrades exhibited no significant differences in the echocardiographic data between the three groups. After the CRT upgrade, responses regarding the ejection fraction (EF) and end-systolic volume (ESV) were significantly lower in CS patients than non-CS patients (ΔEF: group 1, 6.7% vs. group 2, 7.7% vs. group 3, 13.6%; p=0.039, ΔESV: 3.0 mL vs. -12.7 mL vs. -37.2 mL; p = 0.008). The rate of an echocardiographic response was lowest in group 1 (29%). There were, however, no significant differences in the cumulative freedom from a composite outcome among the three groups (p = 0.19). No cardiovascular deaths occurred in group 1. Conclusion CS patients taking corticosteroids before the CRT upgrade had lower echocardiographic responses but higher freedom rates from a composite endpoint. The timing of corticosteroid use would affect the clinical course following a CRT upgrade.

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Unstructed Abstract

This is the first study to investigate the impact of the corticosteroids therapy on the efficacy of an upgrade to cardiac resynchronization therapy (CRT) therapy in patients with cardiac sarcoidosis (CS). The echocardiographic response to an upgrade to CRT was lower in patients with CS than in those with other etiologies of non-ischemic cardiomyopathy. The patients with CS who had taken corticosteroids before the upgrade to CRT (group 1) demonstrated the lowest echocardiographic response. However, the cumulative freedom from hospitalizations from worsening heart failure and cardiovascular death did not significant differ between patients with CS and those with other etiologies. Especially, group 1 patients presented with the lowest rate of cardiovascular death and heart failure hospitalizations.

Abstract

Aims

Corticosteroids are widely used in patients with cardiac sarcoidosis (CS). In addition, upgrading to cardiac resynchronization therapy (CRT) is sometimes needed. This study aimed to investigate the impact of corticosteroid use on the clinical outcomes following CRT upgrades.

Methods

A total of 48 consecutive patients with non-ischemic cardiomyopathies who underwent CRT upgrades were retrospectively reviewed and divided into three groups: group 1 included CS patients taking corticosteroids before the CRT upgrade (n = 7), group 2, CS patients not taking corticosteroids before the CRT upgrade (n = 10), and group 3, non-CS patients (n = 31). The echocardiographic response, heart failure hospitalizations, and cardiovascular deaths were evaluated.

Results

The baseline characteristics during CRT upgrades exhibited no significant differences in the echocardiographic data between the three groups. After the CRT upgrade, responses regarding the ejection fraction (EF) and end-systolic volume (ESV) were significantly lower in CS patients than non-CS patients (ΔEF: group 1, 6.7% vs. group 2, 7.7% vs. group 3, 13.6%; p=0.039, ΔESV: 3.0 mL vs. -12.7 mL vs. -37.2 mL; p = 0.008). The rate of an echocardiographic response was lowest in group 1 (29%). There were, however, no significant differences in the cumulative freedom from a composite outcome among the three groups (p = 0.19). No cardiovascular deaths occurred in group 1.

Conclusion

CS patients taking corticosteroids before the CRT upgrade had lower echocardiographic responses but higher freedom rates from a composite endpoint. The timing of corticosteroid use would affect the clinical course

following a CRT upgrade.

Keywords Cardiac sarcoidosis, Corticosteroid, Cardiac resynchronization therapy, Upgrade and Heart failure.

Abbreviations and acronyms

CS = cardiac sarcoidosis

CRT = cardiac resynchronization therapy

HF = heart failure

ICD = implantable cardioverter defibrillator

LA = left atrium

LV = left ventricular

LVEF = left ventricular ejection fraction

LVEDV = left ventricular end-diastolic volume

LVESV = left ventricular end-systolic volume

MR = Mitral regurgitation

NICM = non-ischemic cardiomyopathy

NYHA = New York Heart Association

PET/CT = positron emission tomography/computed tomography

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown etiology characterized by noncaseating granulomas in involved organs.[1] Cardiac involvement in sarcoidosis occurs in 20-27% of cases in the United States and may be as high as 58% in Japan.[2] Cardiac sarcoidosis (CS) manifestations include various types of tachy- and brady-arrhythmias, left ventricular (LV) systolic dysfunction, and sudden death, and it is increasingly recognized for its poor prognosis.[3-6]Corticosteroids are widely used as the first-line immunosuppressants for patients with CS, especially in patients who have active inflammation in the myocardium. However, patients with CS are sometimes not diagnosed in the early stage of the disease (e.g. during pacemaker or implantable cardioverter defibrillator [ICD] implantations for atrioventricular block or ventricular arrhythmias), and later are diagnosed with CS due to a cardiac function decline.[7] For those patients, it is not well known which therapeutic strategy should come first, corticosteroids therapy or an upgrade to CRT therapy from a pacemaker or ICD. Generally, the clinical response and long-term survival have been less favorable in patients undergoing CRT upgrades than de novo implantations.[8]However, the pathophysiology of CS greatly differs from that of other cardiomyopathies, and corticosteroid therapy would have a potential to affect the clinical response and long-term prognosis. Thus, in the present study, we investigated the echocardiographic response and long-term prognosis in patients with non-ischemic cardiomyopathy (NICM) who underwent CRT upgrade therapy and analyzed the impact of the timing of the initiation the corticosteroid therapy on the clinical outcomes in patients with CS.

Methods

Patients

We retrospectively reviewed the data bases of the CRT upgrade cases with NICM at Kobe University Graduate School of Medicine between 2006 and 2019 and Hyogo Brain and Heart Center between 2010 and 2019. The upgrade to CRT from a pacemaker or ICD was performed in patients with an LV ejection fraction (LVEF) of [?] 35% and New York Heart Association (NYHA) class of II-IV. The selection of CRT with or

without a defibrillator was determined by the attending physicians. The CRT procedure upgrade was carried out with the use of standard transvenous techniques.

CS was diagnosed according to the current guidelines.[11]Seven patients with CS had a histological diagnosis. The other patients with CS were diagnosed based on the clinical and imaging findings, including echocardiography, ^{67}Ga scintigraphy, myocardial perfusion scintigraphy (^{99m}Tc-tetrofosmin), positron emission tomography/computed tomography (PET/CT), and cardiac magnetic resonance.

The enrolled patients who underwent a CRT upgrade were divided into 3 groups: group 1 was comprised of patients with CS who had taken corticosteroids before the CRT upgrade; group 2 was comprised of patients with CS who had not taken corticosteroids before the CRT upgrade; and group 3 was comprised of patients with other NICMs. We compared the following outcomes among the three groups: 1) echocardiographic response to CRT (before and 6 months after the CRT upgrade), 2) sustained ventricular tachyarrhythmia events, 3) composite outcomes of cardiovascular death and hospitalizations for worsening heart failure.

This retrospective study complied with the principles of the Declaration of Helsinki. The study was approved by the ethics committee of Kobe University Hospital (No. B200243).

Consent

The patients consented to the use of their anonymized clinical data for research purposes by the opt-out fashion.

Assessment of Echocardiography

According to the recommendations from the American Society of Echocardiography, we measured the LV end-diastolic volume (LVEDV), LVESV, and LVEF using the biplane Simpson's method. Mitral regurgitation (MR) was categorized into five grades, as follows: none = grade 0; trace = grade 1; mild = grade 2; moderate = grade 3; and severe = grade 4. Two-dimensional echocardiography at rest was performed at baseline and 6 months follow-up to assess the LVEF and LVESV. Responders to CRT were defined as patients displaying a 15% reduction in the LVESV at least 6 months after the CRT implantation.

Statistical Analysis

All data are presented as means, standard deviations (SDs), or proportions. The variables were compared with the one-way analysis of variance (ANOVA) followed by post hoc tests using the Bonferroni correction (Kruskal –Wallis test when appropriate) or chi-squared test (Fisher's exact test, if an inadequate number of assumptions). A Kaplan-Meier analysis was performed to assess the recurrence-free survival, and a log-rank test was used to compare the groups. All analyses were performed using IBM®SPSS® software, version 26 (IBM Corporation, Armonk, NY, USA), and a value of $p < 0.05$ was considered statistically significant.

Results

Baseline Patient Characteristics

A total of 48 patients with NICM who received an upgrade to CRT on the basis of the guidelines was reviewed. Of those, seventeen (35%) patients were diagnosed with CS. In the CS patients, 7 were administered corticosteroids before the CRT upgrade (group 1), and 10 were not (group 2). Thirty-one patients were diagnosed with non-CS (group 3).**Table 1** presents the patient characteristics during the upgrade to CRT. Although no significant differences were observed in the age, LVEF, LVEDV, LVESV, serum creatinine, plasma BNP, and previous frequency of right ventricular pacing, more female patients were included in group 1 than in groups 2 and 3. The LA diameter was largest in group 3.

Use of the Corticosteroids

Figure 1A shows the timing of the initiation of the corticosteroid therapy and maintenance dose in patients with CS (groups 1 and 2). In group 1, the steroid therapy was started at a median of 127 (12-176) months before the upgrade to CRT. In group 2, corticosteroids were not used in 4 patients, and corticosteroids were

introduced at a median of 3.2 (2.5-4.1) months after the upgrade to CRT in 6 patients.**Figure 1B** shows the comparison of the increased FDG uptake in the heart detected by the PET/CT scan between the group 1 and 2. The increased FDG uptake was significantly less seen in group 1 than group 2 at the time of the upgrade to CRT (14% vs. 70%, p = 0.0498). **Figure 1C** indicates the defect area of myocardial perfusion scintigraphy (^{99m}Tc-tetrofosmin) in groups 1 and 2 at the time of the CRT upgrade. A defect in the LV septum was more often seen in group 2 than group 1, but a defect in the LV lateral was more often seen in group 1.

Echocardiographic Response

A comparison of the echocardiographic changes following the CRT upgrade between the 3 groups is shown in **Figure 2** . A decrease in the LVESV (ΔLVESV) and increase in the LVEF (ΔLVEF) was most often seen in group 3. Also, the rate of an echocardiographic response rate was the highest in group 3 and lowest in group 1 (group 1: 2 of 7 patients [29%] vs. group 2: 5 of 10 patients [50%] vs. group 3: 21 of 27 patients [78%], p = 0.029).

Figure 3 shows the echocardiographic change between that before and six months after the upgrade to CRT in each group. There was a significant reduction in the ESV in group 3 (from 126 ± 34 mL to 91 ± 39 mL, p < 0.0001) but not in groups 1 and 2. There was a significant improvement in the EF in groups 2 and 3 (from 26 ± 7% to 34 ± 8%, p = 0.002 and from 26 ± 7% to 39 ± 9%, p < 0.0001, respectively) but not in groups 1.

Ventricular Arrhythmias

During the follow-up, ventricular arrhythmias (consisting of ventricular tachycardia or ventricular fibrillation, which needed anti-tachycardia pacing of defibrillation) after the upgrade to CRT were observed in 4 patients in group 1 (57%), 5 in group 2 (50%) and 12 in group 3 (39%) (p = 0.58).

Long-term Outcomes

A Kaplan-Meier analysis showed there was no significance difference in the composite outcome of hospitalizations from worsening heart failure and cardiovascular death among the three groups after the upgrade to CRT (p = 0.19). There were also no significant differences in cardiovascular death (p = 0.36) (**Figure 4)** . In group 1, however, the incidence of those adverse events tended to be lower than that in the other groups. No cardiovascular death occurred during the follow-up period in group 1. The mean recurrence-free period for the composite endpoint was longer in group 1 (2311 days, [95% CI; 1980–2642 days]) than group 2 (1989 days, [95% CI; 1494–2483 days]) and group 3 (1615 days, [95% CI; 1241 –1988 days]).

Discussion

This was the first study to investigate the impact of the corticosteroid therapy on the efficacy of an upgrade to CRT therapy in patients with CS. Previous studies showed that a high echocardiographic response to CRT therapy was associated with a good long-term prognosis.[9, 10]

The present study demonstrated that the echocardiographic response to an upgrade to CRT was lower in patients with CS than in those with other etiologies of NICM. The patients with CS who had taken corticosteroids before the upgrade to CRT (group 1) demonstrated the lowest echocardiographic response. However, the cumulative freedom from hospitalizations from worsening heart failure and cardiovascular death did not significantly differ between the patients with CS and those with other etiologies. In particular, the group 1 patients presented with the lowest cardiovascular death and hospitalizations.

Upgrade to CRT in Patients with CS

CS has a complex etiology with granulomatous inflammation of the heart, and the pathogenesis includes the activation of the macrophages or lymphocytes, granuloma development, and fibrosis.[1] The published data regarding the outcome of CRT therapy in patients with CS is limited,[11-13] and the efficacy of an upgrade to CRT from a pacemaker or ICD in patients with CS is still controversial.[11, 12] The echocardiographic

response in patients with CS (groups 1 and 2) was lower than that in those with other etiologies (group 3). The possible mechanism was that the progression or fixation of the myocardial fibrosis from sarcoidosis exceeded the improvement in the cardiac function from the CRT therapy in patients with CS. Also, the echocardiographic response to an upgrade to CRT was the lowest in group 1. Corticosteroids are beneficial for suppressing inflammation from CS but have a potential to promote fibrotic changes in the myocardium.[14] It is notable that a defect area in the lateral LV was more often seen in group 1 than group 2. The greater fibrotic changes in the lateral LV area would interfere with appropriate bi-ventricular pacing and affect the echocardiographic CRT response. This could explain the lowest echocardiographic response being observed in group 1.

Corticosteroid Therapy and Long-term Prognosis

A prospective randomized trial to investigate the efficacy of corticosteroids in cardiac sarcoidosis is lacking. Several studies have shown that early initiation of corticosteroids results in better clinical outcomes.[15, 16] The results in the present study were concordant with that. Although the echocardiographic response in group 1 was poorer than that in the other groups, the cardiovascular death and heart failure hospitalizations in group 1 were low. Early initiation of the corticosteroid therapy could prevent recurrent inflammation and an expansion of sarcoidosis lesions. In fact, only 14% of the patients in group 1 had active inflammation (increased FDG uptake) of the heart, as compared to 70% in group 2. Progression of abnormal CS lesions could be delayed or suppressed by earlier corticosteroids therapy, which would improve their clinical outcomes.

Clinical Implications

In patients with CS, the echocardiographic response following a CRT upgrade should be carefully evaluated because of the complex etiology and effect of the corticosteroids. The echocardiographic response to an upgrade to CRT is not necessarily for predicting the long-term prognosis in patients with CS. The corticosteroid therapy should be preceded by an upgrade to CRT in CS patients who have cardiac dysfunction and are eligible CRT therapy.

Limitations

This was a retrospective study that involved a small sample size, which might have led to a statistical bias. Controlled studies are required to confirm the effects of CRT upgrades in patients with CS. There was a possibility that the differences in the baseline characteristics in each group (gender and LA diameter) affected the incidence of composite outcomes after the CRT upgrade. In general, women tend to have a better CRT response and clinical outcome than men.[17, 18]Although more female patients were included in group 1, the echocardiographic response in group 1 was the worst. Therefore, we considered that the good long-term prognosis despite the lack of a high echocardiographic response in group 1 was influenced by the corticosteroid therapy. Although we could not determine the outcome of the CRT upgrade in patients with CS in this study, further studies are warranted to evaluate the outcome of a CRT upgrade.

Conclusion

The timing of the initiation of the corticosteroid therapy in patients with CS would affect the echocardiographic response and long-term prognosis following an upgrade to CRT therapy. Earlier initiation of corticosteroids seems to improve the long-term outcomes in patients with CS. Unlike the patients with other NICMs, the echocardiographic response to an upgrade to CRT in patients with CS should be carefully evaluated because of the complex etiologies and impact of immunosuppressive therapy.

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Table 1. Baseline characteristics

	group1 (n=7)	**group 2** (n=10)	**group 3** (n=31)	p value
Epidemiological background	**Epidemiological background**	**Epidemiological background**	**Epidemiological background**	**Epidemiological background**
Age, years	65 ± 6	71 ± 9	67 ± 11	0.27
Age [?] 75 years	1 (14)	5 (50)	7 (23)	0.23
Age by first device implantation, years	56 ± 5	66 ± 10	59 ± 11	0.13
Duration from first device implantation to CRT upgrade (days)	3508 (1980-6741)	2136 (1771-3884)	1914 (718-4274)	0.40
Male	1 (14)	6 (60)	21 (68)	0.041
Body mass index (kg/m^2)	22 ± 2	23 ± 3	22 ± 4	0.42
Comorbidities	**Comorbidities**	**Comorbidities**	**Comorbidities**	**Comorbidities**
Hypertension	1 (14)	2 (20)	9 (29)	0.7
Diabetes mellitus	0 (0)	3 (30)	8 (26)	0.37
Hyperlipidemia	1 (14)	1 (10)	7 (23)	0.86
Chronic kidney disease	2 (29)	2 (20)	9 (29)	0.9
COPD	0 (0)	0 (0)	0 (0)	
Stroke	0 (0)	1 (10)	3 (10)	0.61
High-grade atrio-ventricular block	6 (86)	10 (100)	21 (68)	0.12
Sick sinus syndrome	1 (14)	0 (0)	3 (10)	0.6
Previous frequent RV pacing	6 (86)	10 (100)	26 (84)	0.45
Previous device				
PM	5 (71)	10 (100)	23 (74)	0.19
ICD	2(29)	0 (0)	8 (26)	0.19
History of ventricular arrythmias	4 (57)	5 (50)	10 (32)	0.43
Prior VT ablation	1 (14)	3 (30)	2 (6)	0.083
Atrial fibrillation	1 (14)	3 (30)	16 (52)	0.15
Permanent	0 (0)	0 (0)	8 (26)	0.12
HF hospitalization	2 (29)	5 (50)	18 (58)	0.34
NYHA functional class	2 (2-3)	3 (2-3)	3 (3-3.5)	0.06

	group1 (n=7)	**group 2** (n=10)	**group 3** (n=31)	p value
Coronary Artery Disease	0 (0)	0 (0)	1 (3)	0.76
Valvular heart disease	0 (0)	0 (0)	4 (13)	0.6
Dilated cardiomyopathy	0 (0)	0 (0)	15 (48)	0.0015
Hypertrophic cardiomyopathy	0 (0)	0 (0)	2 (6)	0.56
Medication	**Medication**	**Medication**	**Medication**	**Medication**
β-blocker	6 (86)	9 (90)	26 (84)	0.89
ACEi/ARB	5 (71)	9 (90)	21 (68)	0.4
Spironolactone	4 (57)	6 (60)	19 (61)	0.98
Diuretics	4 (57)	8 (80)	23 (74)	0.64
Amiodarone	2 (29)	3 (30)	5 (16)	0.5
Cardiotonics	1 (14)	1 (10)	4 (13)	0.96
Corticosteroids	7 (100)	6 (60)	0 (0)	<0.0001
Dosage before CRT upgrade (mg)	5.0 (2.5-10)	0 (0-0)	0 (0-0)	0.001
Maintenance dosage (mg)	2.5 (2.5-10)	4.1 (0-10)	0 (0-0)	0.037
Electrocardiography	**Electrocardiography**	**Electrocardiography**	**Electrocardiography**	**Electrocardiography**
QRS duration (mm)	173 ± 20	178 ± 21	185 ± 32	0.56
Echocardiographic parameters	**Echocardiographic parameters**	**Echocardiographic parameters**	**Echocardiographic parameters**	**Echocardiographic parameters**
LA-diameter (mm)	40 ± 14	42 ± 4	49 ± 8	0.025
LVEF (%)	27 ± 9	26 ± 7	26.0 ± 7.0	0.98
LVEDV (mL)	168 ± 46	144 ± 46	175 ± 51	0.24
LVESV (mL)	127 ± 44	105 ± 33	127.2 ± 37.4	0.28
MR	3 (2-3)	2 (1.75-3.25)	2 (2-2.5)	0.16
Laboratory data	**Laboratory data**	**Laboratory data**	**Laboratory data**	**Laboratory data**
BNP (pg/mL)	321 (205-767)	271 (102-509)	188 (135-245)	0.7
Creatinine (mg/dL)	0.93 (0.68-1.29)	0.84 (0.79-1.20)	0.73 (0.69-1.28)	0.84
Hemoglobin (mg/dL)	12.4 ± 1.5	12.8 ± 1.6	12.1 ± 2.6	0.7
Type of device	**Type of device**	**Type of device**	**Type of device**	**Type of device**
CRT-P	3 (43)	4 (40)	13 (42)	0.99
CRT-D	4 (57)	6 (60)	18 (58)	0.99

Normal distribution data: means ± standard deviations.

Non-normal distribution data: medians and interquartile ranges.

CS = cardiac sarcoidosis, COPD = chronic obstructive pulmonary disease, PM = pacemaker, ICD = implantable cardioverter defibrillator, VT = ventricular tachycardia, HF = heart failure, NYHA = New York Heart Association, ACEi =angiotensin-converting enzyme inhibitor, ARB = angiotensin-receptor blocker,

CRT = cardiac resynchronization therapy, LA = left atrium, LVEF = left ventricular ejection fraction, LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, MR = mitral regurgitation, BNP = brain natriuretic peptide, CRT-P = cardiac resynchronization therapy pacing with a pacemaker, CRT-D = cardiac resynchronization therapy with a defibrillator.

Figure legends

Figure 1. Differences between group 1 and group 2. (A) Timing the initiation of the corticosteroids and maintenance dose in patients with CS. Each blue dot indicates the time from the initiation of corticosteroids and the maintenance dose in each patient. (B) Comparison of the increased FDG uptake in the heart detected by the PET/CT scan between groups 1 and 2 at the time of the CRT upgrade. (C) Defect area on the myocardial perfusion scintigraphy (^{99m}Tc-tetrofosmin) between the two groups at the time of the CRT upgrade. CS = cardiac sarcoidosis, CRT = cardiac resynchronization therapy. FDG = fluorodeoxyglucose, PET/CT = positron emission tomography/computed tomography, Positive = increased FDG uptake in myocardium on PET/CT, Negative = not increased FDG uptake in myocardium on PET/CT.

Septum = septum of left ventricle, Lateral = lateral wall of the left ventricle, Inferior =, inferior wall of the left ventricle, Anterior = anterior wall of left ventricle.

Figure 2. The comparison of the echocardiographic response among the CS patients taking corticosteroids before the CRT upgrade (group 1), CS patients not taking corticosteroids before the CRT upgrade (group 2), and non-CS patients (group 3).

CS = cardiac sarcoidosis, LVEF = left ventricular ejection fraction, LVESV = left ventricular end-systolic volume.

Figure 3. The change in the LVESV and LVEF before and after the CRT upgrade in each group (CS patients taking corticosteroids before the CRT upgrade [group 1], CS patients not taking corticosteroids before CRT upgrade [group 1] and non-CS patients [group 3]).

LVEF = left ventricular ejection fraction, LVESV = left ventricular end-systolic volume, pre = before the CRT upgrade, post = six months after the CRT upgrade.

Figure 4. Kaplan-Meier curve demonstrating the freedom from (A) the composite endpoint of cardiovascular death and hospitalizations for worsening heart failure and (B) cardiovascular death after a CRT upgrade among the CS patients taking corticosteroids before the CRT upgrade (group 1), CS patients not taking corticosteroid before the CRT upgrade (group 1), and non-CS patients (group 3).

CS = cardiac sarcoidosis, CRT = cardiac resynchronization therapy.

Figure 1.

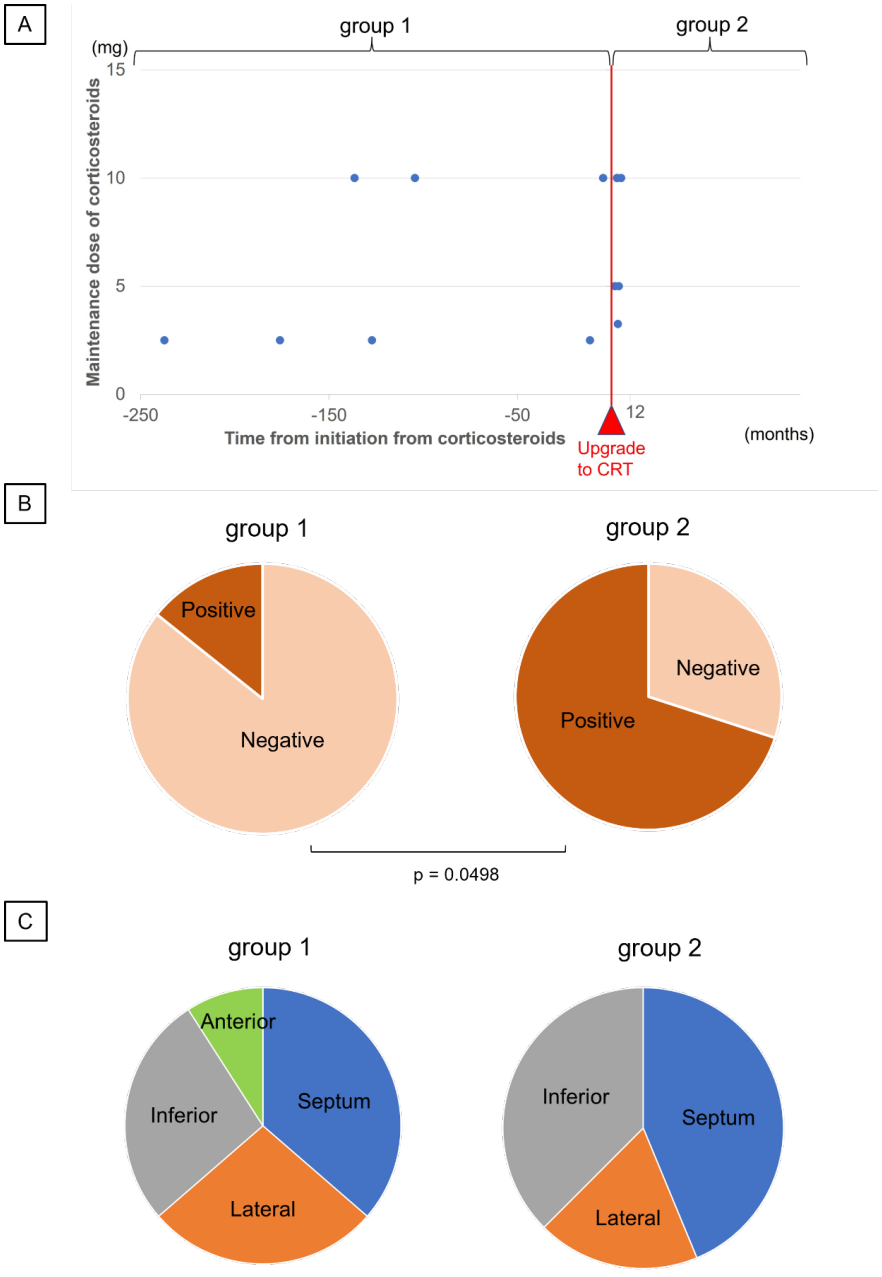

Figure 2.

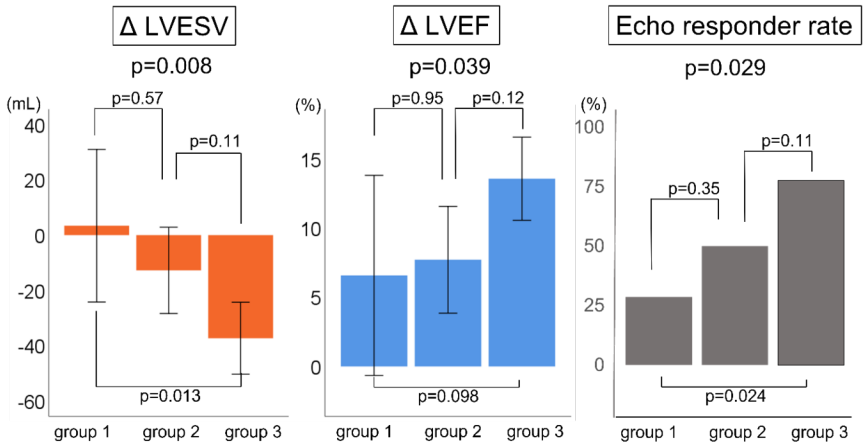

Figure 3.

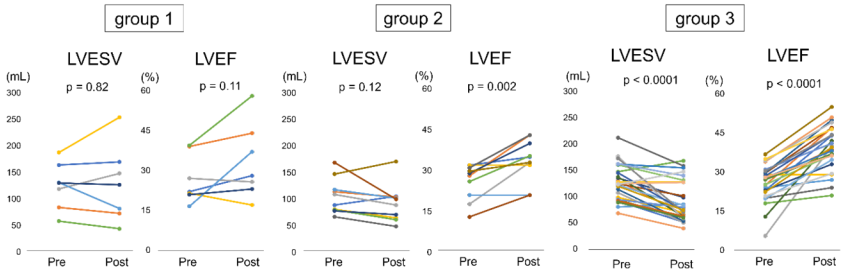

Figure 4.