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Immunoadsorption therapy in refractory heart failure patients with dilated cardiomyopathy: a potential therapeutic option*

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SUMMARY

OBJECTIVE: Removal of cardiac autoantibodies by immunoadsorption might confer clinical improvement in dilated cardiomyopathy. In this pilot study, we investigated the efficacy and safety of immunoadsorption therapy in refractory heart failure patients with dilated cardiomyopathy.

METHODS: This study consisted of 9 heart failure patients with dilated cardiomyopathy, NYHA III-IV, left ventricular ejection fraction <30%, unresponsive to heart failure therapy, and with cardiac autoantibodies. Patients underwent immunoadsorption therapy for five consecutive days using a tryptophan column. Changes in cardiac function (left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular end-systolic diameter), exercise capacity (6-minute walk distance), neurohormonal (N-terminal pro-brain natriuretic peptide), proinflammatory (high-sensitive C-reactive protein), and myocardial (cardiac troponin-I), biochemical, and hematological variables were obtained at baseline and after 3 and 6 months of immunoadsorption therapy.

RESULTS: Mean left ventricular ejection fraction and 6-minute walk distance significantly increased at 3 months (from 23.27±5.09 to 32.1±1.7%, p=0.01 for left ventricular ejection fraction and from 353±118 to 434±159 m, p=0.04 for 6-minute walk distance) and further increased at 6 months after immunoadsorption therapy (to 34.5±7.7%, p=0.02 for ejection fraction and to 441±136 m, p=0.04 for 6-minute walk distance). NT-proBNP level reduced from 1161(392.8–3034) to 385(116.1–656.5) ng/L (p=0.04), and high-sensitive C-reactive protein decreased from 9.74±0.96 to 4.3±5.8 mg/L (p=0.04) at 6 months. Left ventricular end-diastolic diameter (66.1±5.8 vs. 64.7±8.9 mm) and left ventricular end-systolic diameter (56.1±8.6 vs. 52.3±10.8 mm) tended to decrease but did not reach statistical significance. No significant worsening was observed in creatinine, cardiac troponin-I, and hemoglobin levels after the immunoadsorption procedure.

CONCLUSION: In dilated cardiomyopathy patients with refractory heart failure, immunoadsorption may be considered a potentially useful therapeutic option to improve a patient's clinical status.

KEYWORDS: Plasmapheresis. Heart failure. Cardiomyopathy, dilated.

INTRODUCTION

Dilated cardiomyopathy (DCM) is a progressive myocardial disease characterized by systolic dysfunction and ventricular dilatation[1]. Genetic and autoimmune abnormalities as well as viral infections are thought to be involved in the underlying pathophysiological mechanisms of DCM. A number of autoantibodies (AAB) against various cardiac cell proteins including contractile proteins, mitochondrial proteins, sarcolemmal Na-K-ATPase, cardiac beta-1 adrenergic receptors (ARs), and muscarinic receptors have been identified in patients with DCM[2-9]. Accumulating evidence suggests that these AABs are able to disturb the normal physiological activity of the cardiomyocytes, may contribute to cardiac dysfunction, and play an active role in the pathogenesis of DCM[6-9]. Recent controlled small studies with a limited number of patients indicate that removal of these cardiac AABs by immunoadsorption (IA) therapy may decrease myocardial inflammation and induce improvements in cardiac function and quality of life in heart failure (HF) patients with DCM[10-14]. Therefore, in selected symptomatic HF patients with idiopathic DCM who do not respond to optimal standard medical therapy, IA therapy may be considered a potentially useful method for the improvement of the patient's clinical status. In this pilot study, we investigated the efficacy and safety of IA therapy in refractory HF patients with DCM.

METHODS

Study population

The present study included symptomatic HF patients with DCM, New York Heart Association (NYHA) functional class III-IV, left ventricular (LV) ejection fraction (EF) <30%,

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refractory to optimal evidence-based guidelines-recommended HF therapy including angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), beta blocker, diuretics, mineralocorticoid receptor antagonist (MRA), ivabradine, or digoxin treatment for at least 6 months. Coronary artery disease was excluded by coronary angiography. Patients with HF due to known origins such as primary valvular disease, congenital heart disease, or other cardiomyopathies and also those with severe chronic obstructive pulmonary disease, severe chronic kidney or liver disease, connective tissue disease, active infectious disease, chronic alcoholism, or malignancy were excluded from the study.

A total of 38 HF patients with DCM were screened for AABs directed against beta1-AR and M2-muscarinic receptors. Notably, 17 patients (44%) were positive for cardiac AABs, in which 16 patients have had AABs against beta1-AR and 3 patients have had AABs for M2-muscarinic receptors (2 of them were also positive for beta1-AR AAB). Nine patients with cardiac AABs who gave written informed consent were included in the study and underwent IA therapy (Figure 1). This study has been conducted between 2014 and 2018 in a university hospital, outpatient Heart Failure Unit with the capability of implantation of cardiac resynchronization therapy or implantable cardiac defibrillator and short-term mechanical circulatory support, which is affiliated with an institution with the availability of long-term ventricular assist devices or heart transplantation. The study protocol was approved by the ethics committee, and the study was performed in accordance with the guidelines of the Declaration of Helsinki.

Measurement of cardiac autoantibodies

The blood samples were tested by E.R.D.E – AAK – Diagnostik GmbH in Berlin, Germany. The test system is a bioassay of spontaneously beating neonatal rat cardiomyocytes. The presence of cardioactive receptor-AABs can be detected as a positive or negative reaction after the addition of the patient's immunoglobulin. The kind of ABB is verified using specific receptor antagonists. The blood samples of patients were sent to Berlin, Germany and it has taken 2–3 months to get the test results.

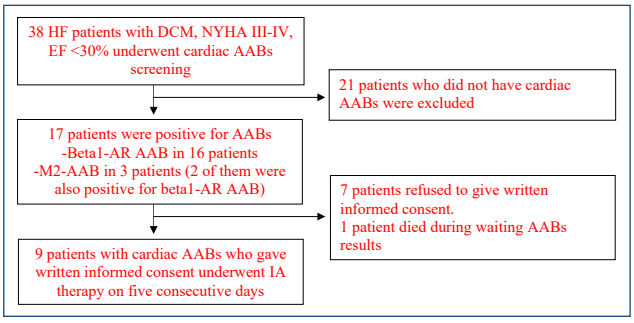

Figure 1. Flowchart of study design. AABs: autoantibodies; AR: adrenoreceptor; DCM: dilated cardiomyopathy; EF: ejection fraction; HF: heart failure; IA: immunoadsorption therapy; M2: muscarinic receptor2; NYHA: New York Heart Association.

Immunoadsorption protocol

All patients underwent IA therapy on five consecutive days in a total of five sessions and in one course. A catheter for blood access was inserted via the internal jugular vein. ACEI was switched to ARB (candesartan or valsartan in dose equivalence or maximally tolerated doses) at least 2 weeks before admission because ACEI inhibits the breakdown of the bradykinin, which is activated during IA. The patients received IA for 2–3 h in each session, and 1500–2000 mL of plasma was treated, using PLASAUTO Σ (Asahi Kasei Kuraray Medical, Tokyo, Japan). Immusorba TR-350 (Asahi Kasei Kuraray Medical, Tokyo, Japan) as IgG3-specific tryptophan column and Plasmaflo OP-05W (Asahi Kasei Kuraray Medical, Tokyo, Japan) to separate the plasma from whole blood were used. All patients received heparin during the IA procedure as an anticoagulant. After the final IA session, all patients also received intravenous Ig (IVIG) substitution (0.5 g/kg polyclonal IgG) to restore IgG plasma levels. All patients were admitted to the hospital for the entire course of therapy to avoid the risk of infection and bleeding. After IA therapy, changes in medication dosage were performed only for diuretics according to symptoms and signs of congestion. All other HF medications were continued without any change in dosages during the 6-month follow-up.

Measurements of cardiac function and exercise capacity

Transthoracic echocardiography was performed at baseline and after 3 and 6 months of IA therapy. left ventricular ejection fraction (LVEF), LV end-diastolic diameter (LVEDD), and LV end-systolic diameter (LVESD) have been determined. LVEF was measured according to the Simpson rule. Six-minute walk distance (6-MWD) was measured at baseline and after 3 and 6 months of IA therapy for the assessment of exercise capacity.

Neurohormonal, myocardial, inflammatory, and biochemical variables

N-terminal pro-brain natriuretic peptide (NTproBNP) as a neurohormonal biomarker of HF, high sensitive cardiac troponin-I (cTnI), and creatine kinase-MB isoenzyme (CK-MB) as myocardial markers, high sensitive C-reactive protein (hsCRP) as a marker of inflammation, serum creatinine as the markers of kidney function, serum electrolytes,

hemoglobin (Hgb) level, white blood cell (WBC) count, and platelet count were obtained at baseline and after 3 and 6 months of IA therapy.

Statistical analysis

The statistical analysis was performed using the Statistical Package for Social Sciences software 20.0 (IBM SPSS 20, SPSS Inc., Chicago, US). Differences in parameters before and after IA were compared using an independent sample *t*-test or paired sample *t*-test for the analysis of normally distributed variables; otherwise, the Wilcoxon signed rank test was used for the analysis of non-normally distributed variables and described using medians (interquartile ranges [IQRs]). Normally distributed variables were expressed as mean ± standard deviation. Categorical data were presented as frequencies and percentages and were analyzed by Pearson chi-square or continuity correction chi-square. Changes in clinical parameters were compared over time (baseline, 3 months, and 6 months) using a linear mixed model. $p < 0.05$ were considered statistically significant.

RESULTS

Baseline clinical characteristics of the study population including HF medication are shown in Table 1. The mean age of the study population was 44.1±7.8 years, and 55.5% were male. Four (44.4%) patients had a history of hypertension, and 2 (22.2%) had diabetes mellitus. Baseline mean EF was 23.27±5.09%, NT-proBNP was 1192±1015 pg/mL, 6-MWD was 353±118 m, creatinine level was 0.82±0.17 mg/dL, and Hgb level was 13.4±2 g/dL. At the time of screening, all patients were receiving ACEI or ARB, beta-blockers, and loop diuretics, and 88.9% were using MRA.

Changes in cardiac function, exercise capacity, neurohormonal, myocardial, proinflammatory, biochemical, and hematological variables after 3 and 6 months of IA therapy are shown in Table 2. Mean LVEF and 6MWD significantly increased at 3 months (from 23.27±5.09 to 32.1±1.7%, p=0.01 for LVEF and from 353±118 to 434±159 m, p=0.04 for 6MWD) and further increased at 6 months after IA therapy (to 34.5±7.7%, p=0.02 for LVEF and to 441±136 m, p=0.02 for 6MWD). Although LV end-diastolic (66.1±5.8 vs. 64.7±8.9 mm) and end-systolic diameters (56.1±8.6 vs. 52.3±10.8 mm) tended to decrease at 6 months, these decreases did not reach statistical significance. Reduction in NTproBNP and high-sensitive C-reactive protein (hs-CRP) was not significant at 3 months, but at the end of the 6-month follow-up, the NT-proBNP level reduced from 1161(392.8–3034) at baseline to 385(116.1–656.5) ng/L (p=0.04), and hsCRP decreased from 9.74±0.96 at baseline to 4.3±5.8 mg/L (p=0.04). Myocardial markers of hs-cTnI and CK-MB did not change significantly during the 6-month follow-up of IA therapy.

Table 1. Clinical characteristics of the patients.

Age, years	44.1±7.8
Male gender, n (%)	5 (55.5)
Body mass index, kg/m^2	32.2±9.6
Heart rate, bpm	74.2±15
Systolic BP, mm Hg	108.7±14.6
Diastolic BP, mm Hg	67.5±8.2
Diabetes, n (%)	2 (22.2)
Hypertension, n (%)	4 (44.4)
Smoking, n (%)	2 (22.2)
Atrial fibrillation, n (%)	3 (33.3)
LBBB/RBBB, n (%)	0 (0)
Anemia, n (%)	3 (33.3)
ASA, n (%)	1 (11.1)
Beta blocker, n (%)	9 (100)
RAAS inhibitors, n (%)	9 (100)
Spironolactone, n (%)	8 (88.9)
Loop diuretics, n (%)	9 (100)
Ivabradine, n (%)	4 (44.4)
Digoxin, n (%)	2 (22.2)
CRT, n (%)	0 (0)
ICD, n (%)	3 (33.3)

ASA: acetylsalicylic acid; BP: blood pressure; CRT: cardiac resynchronization therapy; ICD: implantable cardioverter-defibrillator; LBBB: left bundle branch block; RAAS: Renin-Angiotensin-Aldosterone System; RBBB: right bundle branch block.

All patients had completed IA without any major complications. No adverse event was observed during and after IA therapy. Overall, patients did not experience hypotension, tachycardia, bleeding, fever, or signs of infection during and after the procedure (Table 3). No significant worsening in renal function was found, and Hgb level or WBC count remained stable after IA (Table 2).

During 6-month follow-up, 1 patient was hospitalized with acute decompensated HF at 4 months, experienced progressive clinical deterioration, and died despite optimal HF management. Rest of the patients did not need hospital admission, implantation of ventricular assist devices, or heart transplantation during the 6-month follow-up period.

Table 2. Changes in clinical parameters after 3 and 6 months of immunoadsorption therapy.

	Baseline	3-month FU	6-month FU	P
LVEF, %	23.27±5.09	32.1±1.7	34.5±7.7	0.02
LVEDD, mm	66.1±5.8	65.7±3.2	64.7±8.9	0.71
LVESD, mm	56.1±8.6	55.7±3.5	52.3±10.8	0.92
6MWD, m	353±118	434±159	441±136	0.04
NTproBNP, pg/mL	1161(392.8–3034)	846(399.5–883.5)	385(116.1–656.5)	0.04
hs-CRP, mg/L	10.1(1.85–14.7)	3.15(0.90–21.1)	1.82(0.82–7.85)	0.04
Troponin-I, ng/mL	0.02±0.03	0.008±0.003	0.005±0.001	0.36
CK-MB, ng/mL	1.62±0.63	2.1±1.06	1.84±0.41	0.20
Na, mEq/L	138±2.86	141±2.7	138±2.8	0.75
K, mEq/L	4.48±0.4	4.6±0.28	4.45±0.22	0.90
Creatinine, mg/dL	0.82±0.17	0.84±0.14	0.86±0.18	0.31
Hgb, g/dL	13.7±1.37	14.4±2	14.1±1.6	0.38
WBC, $10^3/\mu L$	8.30 (7.7–9.6)	7.8(7.4–9.15)	9.05(7.37–10.05)	0.32
Platelet count, $10^3/\mu L$	222 .0(193.0–235.5)	229.0±60.2	247.6±55.1	0.31

*Data are presented as median (IQR) or mean±SD. CK-MB: creatine kinase myocardial band; Hgb: hemoglobin; hs-CRP: high sensitive c-reactive protein; K: potassium; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; 6MWD: 6-minute walk test; Na: sodium; NTproBNP: N-terminal pro-b-type natriuretic peptide; WBC: white blood count.

Table 3. Fever, heart rate, and systolic and diastolic blood pressure during immunoadsorption sessions.

	Before the procedure	After the procedure	p
Body temperature, °C			
First session	36.2±0.27	36.3±0.55	0.8
Second session	36.1±0.15	36.1±0.1	0.7
Third session	36.5±0.41	36.3±0.45	0.02
Fourth session	36.2±0.49	36.1±0.32	0.34
Fifth session	36.3±0.5	36.3±0.44	1
Heart rate, bpm			
First session	77±15	79±8.5	0.66
Second session	77±18	79±16	0.39
Third session	77±16	77±16	0.91
Fourth session	76±13	77±13	0.69
Fifth session	86±18	83±15	0.7
Systolic BP, mm Hg			
First session	119±11.7	110±14.5	0.02
Second session	113±13.8	116±9	0.63
Third session	119±13.3	117±11.3	0.74
Fourth session	114±18	119±19.2	0.48
Fifth session	113±14.6	119±18.2	0.33
Diastolic BP, mm Hg			
First session	73.1±7.8	63.5±10.6	0.1
Second session	66.5±8.6	66.6±10.7	0.94
Third session	72.5±10.6	71.5±9.1	0.82
Fourth session	67.6±10.9	74±12.3	0.28
Fifth session	74±11	70.6±7.8	0.27

BP: blood pressure.

DISCUSSION

The results of this study showed that IA therapy in DCM patients with refractory HF significantly improves cardiac function and exercise capacity through increases in LVEF and 6MWD. In addition, NTproBNP and hs-CRP levels were found to significantly decrease during the 6-month follow-up. Furthermore, IA was well tolerated and appeared to be feasible in patients with DCM as no adverse event was observed during and after the procedure.

Removal of AABs by IA has been shown to be a new potential therapeutic approach in treating DCM. In the first uncontrolled pilot study in 8 patients with DCM, Wallukat et al. reported that this technique efficiently removed cardiac beta-1 AR AABs and improved symptoms and cardiac function in this group of patients[10]. In 9 patients with DCM and LVEF <25%, Felix et al. randomized 18 DCM patients with LVEF <30% who have cardiac beta-1 AR AABs to IA or conventional therapy and reported that initially, 3 consecutive days and then monthly 2 consecutive days of IA therapy with IVIG substitution for 3 months resulted in a significant increase in LVEF, cardiac index, and stroke volume index, a significant decrease in systemic vascular resistance and beta-1 AR AAB level, and significant improvement in NYHA functional capacity[11]. In the other small randomized study by Muller et al. in 34 DCM patients with NYHA II-IV, LVEF <29% who have cardiac beta-1 receptor autoantibodies, and 17 patients who underwent IA on 5 consecutive days without IVIG substitution showed a significant increase in LVEF (from 22.3±3.3 to 37.9±7.9%, p<0.0001), and improvement in NYHA functional class compared showed no significant changes in the control group[12]. These single-center small studies suggested hemodynamic and clinical improvements of IA therapy in DCM patients with HF. The results of our study are consistent with the findings of previously published small studies in improving LVEF and functional capacity and reducing NTproBNP levels. 6MWD that we used in our study is a much more objective measure than the NYHA classification for the assessment of functional capacity. Different from other studies, we were also able to show a beneficial effect of IA on inflammatory state with a significant reduction in hs-CRP levels.

The removal of AABs against cardiac beta-1 AR by IA therapy has been proposed as a potential mechanism for the improvement of cardiac functions in patients with DCM. The presence of specific cardiodepressant AABs in plasma prior to IA is referred to as a predictor of the possible efficacy of this therapeutic approach. Staudt et al. reported that DCM patients with cardiodepressant AABs demonstrated significant hemodynamic benefits from IA therapy, whereas, in the non-cardiodepressant group, hemodynamics did not change significantly throughout 3 months of repetitive IA courses[15]. These data suggested that the presence of cardiodepressant AABs predicts the hemodynamic benefits of IA therapy. Most studies enrolled beta1-AR AAB-positive patients. We, therefore, enrolled patients with DCM who had either AAB against beta1-AR or muscarinic receptors in our study.

There has been no consensus on the ideal protocol for IA therapy. In various studies, patients underwent repeated IA treatment courses at monthly intervals for 3 months, while in some studies, IA therapy has been performed as a single treatment course on 5 consecutive days. Both treatment regimens are comparable, provide acute and prolonged hemodynamic and clinical benefits, and also result in a prolonged reduction in cardiac AABs[10-17]. Since IA is an invasive and expensive treatment, a single treatment course on 5 consecutive days might be thought to be a more suitable option. So, in our study, we used the protocol of a single IA course on 5 consecutive days and were able to show the beneficial effects of one course IA protocol over 6-month follow-up period. In addition, IVIG therapy following each IA course has been given as a part of the protocol in most studies in order to reduce the risk of infection; however, in some studies, IA therapy has been performed without IVIG substitution[13]. We preferred to use IVIG substitution after the final IA session in order to avoid the risk of infection that may arise from inappropriate lowering circulating IgG levels.

Autoantibodies that are most likely to be involved in immunoregulatory activity are IgG-3 and IgG-1 subclasses. IgG-3 is referred to as the most active IgG subclass and is thought to play a key role in cardiac dysfunction as a mediator of antibody-dependent cellular cytotoxicity[18]. It is considered that AABs belonging to the IgG-3 subclass play a pivotal role in the therapeutic efficacy of IA. IA with tryptophan columns causes a marked reduction of plasma levels of IgG-3 with a low immunogenicity and a high affinity for the IgG-3 subclass[19]. In 16 patients with DCM who have refractory HF, Nagatomo et al. showed that IA therapy using IgG-3 specific tryptophan column significantly increased LVEF and 6MWD and significantly decreased NTproBNP levels and autoantibody titers against beta-1 AR and M2 muscarinic receptors with a greater extent removal of IgG3 subclass than the other IgG subclasses[19]. Due to low immunogenicity and a high affinity for the IgG-3 subclass, we used the tryptophan column in the IA procedure. Although substitution of IVIG is considered not to be required after

IgG-3 specific IA, IVIG substitution has been performed in our patients because antibody and IgG3 titers have not been obtained in our study.

Limitations

This was a single-center pilot study including only a limited number of patients. However, previously published studies with IA in DCM also included small samples with 8 to 34 patients. Furthermore, the present study was not a randomized, controlled study. However, in many studies, a repeated IA protocol at monthly intervals had been performed, and a nonspecific protein-A column or anti-IgG column had been used. Different from previous studies, the present study also provides complementary information about the protocol of a single IA course on 5 consecutive days and the IgG-3-specific tryptophan column that we used in our study. Considering that IA is an emerging, invasive, and expensive therapy, findings that come from even small-scale studies would contribute to further studies.

CONCLUSION

In idiopathic DCM patients with refractory HF who do not respond to optimal standard medical therapy, IA therapy may be considered a potentially useful method to improve the patient's clinical status. Although IA therapy is a new and promising therapeutic option in the treatment of DCM, more data from larger, randomized, prospective, multicenter studies are needed before the routine use of this therapy in this patient population.

AUTHORS' CONTRIBUTIONS

YC: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. **SM:** Data curation, Formal Analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. **ST:** Conceptualization, Data curation, Formal Analysis, Investigation, Software, Validation, Visualization, Writing – original draft, **OMA:** Investigation, Methodology, Validation, Visualization.

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