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Ig apheresis for the treatment of severe DCM patients

Sergey N. Pokrovsky [a,*], Marat V. Ezhov [a], Maya S. Safarova [a], Marina A. Saidova [a], Viktor N. Shitov [a], Marina I. Afanasieva [a], Andrew I. Khaustov [b], Irina Yu. Adamova [a], Olga I. Afanasieva [a], Gennady A. Konovalov [b]

[a] *Cardiology Research Center, 15a, 3rd Cherepkovskaya Street, 121552 Moscow, Russia*
[b] *MEDSI Clinic, 3A, Georgian Lane, 123056 Moscow, Russia*

Abstract

Background: Autoantibodies against β1-adrenoreceptor (AR) are considered by many authors to be the most significant in autoimmune process during DCM. Immunoadsorption (IA) of immunoglobulins (Ig apheresis) is a logic approach to remove autoantibodies against β1-AR and other antibodies. The effect of Ig apheresis and the role of anti-β1-AR in DCM are still an issue for discussion.

Methods: We have performed a prospective case–control study in 16 patients with DCM, NYHA Class II–IV congestive heart failure, positive and negative for anti-β1-AR.

Results: We observed a clinically significant mean change of exercise tolerance compared with controls (6 MWT distance increased from 420 ± 130 m to 550 ± 150 m, $p < 0.05$). Systolic function improved rapidly by increase in LVEF from 28.6 ± 5.2% to 33.0 ± 10.3%, LV end-systolic and end-diastolic volumes decreased from 166 ± 58 mL to 148 ± 50 mL and from 235 ± 73 mL to 220 ± 73 mL, respectively, whereas in the control group there was no significant change in clinical variables. The improved quality of life and cardiac function in apheresis group as well as negative changes in control group didn't correlate with the presence of anti-β1-AR.

Conclusions: Ig apheresis for the treatment of DCM patients is associated with the improvement of quality of life and cardiac function regardless of the presence of anti-β1-AR. We suggest that IgG apheresis is a safe and effective method for DCM patients.

Keywords: Dilated cardiomyopathy; Ig apheresis; Immunoadsorption; Heart failure; Cardiodepressive autoantibodies

1. Introduction

Dilated cardiomyopathy (DCM) is the myocardial disorder characterized by progressive dilatation and impaired ventricular systolic function [1]. DCM is the leading reason for heart transplantation worldwide [2]. Many studies suggest that humoral immunity contributes to the pathogenesis of DCM. A number of antibodies against various cardiac proteins have been identified in DCM. Antigens include sarcolemmal proteins (e.g. myosin, actin, troponin and tropomyosin), mitochondrial enzymes, heat-shock proteins, surface and muscarinic receptors [3–6]. Among these antigens the highly pathogenic role of autoantibodies against the β1-adrenergic receptors has been confirmed in numerous studies [7–9]. Immunoadsorption (IA) therapy is the logic approach for intervention into this autoimmune process. A variety of IA methods have been used to treat DCM patients: specific anti-β1-AR antibody binding columns [10], anti-sheep anti-human IgG columns [11,12], staphylococcal protein-A agarose columns [14], tryptophan columns [14]. In accordance with different protocols, IA treatments could be followed by intravenous

* Corresponding author. Laboratory of Atherosclerosis, Institute of Experimental Cardiology, Cardiology Research Center, 3rd Cherepkovskaya Street, 15a, 121552 Moscow, Russia. Tel.: +7 495 414 6732, +7 495 729 8223 (mobile); fax: +7 495 414 6820.
E-mail address: Dr.Pokrovsky@mail.ru (S.N. Pokrovsky).

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immunoglobulin (IVIG) substitution and number of treatment sessions varied from one to five. Positive therapeutic effect was not detected in the only one case of specific anti-β1-adrenoreceptor antibody adsorption. All the rest of the above mentioned methods are Ig apheresis which specifically remove total IgG from human plasma. Despite the negative results of anti-β1-AR trial, the presence of anti-β1-adrenoreceptor antibodies is still used by many investigators as the indication for IA treatment in DCM [15].

In the present study we suggest that Ig apheresis provides the positive effect on the quality of life and cardiac function of DCM patients independently of the presence of antibodies against β1-adrenoreceptor.

2. Materials and methods

2.1. Study patients

Sixteen patients with DCM were included in this prospective randomized case–controlled study. All patients demonstrated left ventricular dysfunction with left ventricular ejection fraction (LVEF) ≤35%, symptoms of chronic heart failure according to the New York Heart Association (NYHA) class II–IV. We have excluded the patients with acute infection or inflammation, acute coronary syndrome or surgical intervention within 3 months prior to inclusion, heart failure due to known origin (e.g. arterial hypertension, myocardial infarction), cancer, chronic alcohol intoxication, life-threatening arrhythmia, clinically significant thyroid, renal or hepatic dysfunction. Written informed consent was obtained from each patient.

All patients received oral medications recommended for heart failure management including diuretics, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers and beta blockers (Table 1).

2.2. Echocardiography and exercise capacity

Echocardiographic parameters were determined by 2-dimensional echocardiography at baseline, after 1, 3 and 6 months according to a defined echocardiography protocol.

We used a commercially available cardiovascular ultrasound system (Vivid 7; GE Healthcare, Milwaukee, WI) with 3.5-MHz transducer. Two-dimensional, pulsed-Doppler, and Doppler tissue imaging were performed from standard parasternal and apical transducer positions with 2-dimensional frame rates of 60–100 frames/s and tissue Doppler frame rates >100 frames/s. Structural and functional measurements were made in accordance with current guidelines. Measurements of LV cavity size, LV ejection fraction, LV wall thickness, left atrial volume, right ventricular size, transmitral velocities, and pulsed-wave tissue Doppler velocities at the mitral annulus were reviewed by an echocardiography-trained cardiologist.

The 6 min walking distance (6MWD) test was also measured at baseline, after 1, 3 and 6 months of treatment.

Table 1
Baseline characteristics of patients.

	Apheresis group ($n = 9$)	Control group ($n = 7$)	p
Age (year)	50.1 ± 8.8	49.6 ± 9.8	0.73
Gender (male/female)	8/1	7/0	1
NYHA class, *n*			
II	1	2	–
III	4	3	–
IV	4	2	–
Body mass index, kg/m^2	30 ± 5	29 ± 4	0.42
Atrial fibrillation, *n* (%)	4 (44%)	3 (43%)	1.0
Left bundle branch block, *n* (%)	2 (22%)	3 (43%)	0.69
6MWT, m	260 ± 130	330 ± 110	0.23
hsCRP, mg/L	6.4 ± 4.6	5.6 ± 3.7	0.69
BNP, pg/mL	507 ± 279	443 ± 209	0.59
LVEF, %	29.7 ± 6.2	29.4 ± 6.8	0.92
LVEDD, cm	7.6 ± 0.7	7.5 ± 0.7	0.77
LVEDV, mL	259 ± 72	242 ± 81	0.64
Left atrium, cm	4.8 ± 0.8	4.9 ± 0.9	0.80
Anti-β1-AR, optical units	0.395 ± 0.145	0.425 ± 0.142	0.66
Patients with detected anti-β1-AR, *n* (%)	5 (55%)	3 (44%)	–
Medication			
ACE inhibitors	9	7	–
Beta blockers	9	7	–
Diuretics	8	7	–
Digoxin	5	5	–
Spironolactone	8	7	–

6MWT – 6 min walk distance, hsCRP – high sensitivity C-reactive protein, BNP – brain natriuretic peptide, LVEF – left ventricular ejection fraction, LVEDD – left ventricle end-diastolic dimension, LVEDV – left ventricle end-diastolic volume, Anti-β1-AR – antibodies against β1-adrenoreceptor.

2.3. Measurement of anti-β1-AR antibodies

The presence of antibodies against β1 AR was determined by ELISA using conjugate of two synthetic peptides [16]. The first one corresponded to the amino acid sequence number 125–133 of the first loop of human β1-adrenoreceptors (sequence H–Glu–Tyr–Gly–Ser–Phe–Phe–Cys–Glu–Leu–OH). The second synthetic peptide corresponded to the amino acid sequence number 208–218 of the second loop of human β1-AR (sequence H–Ala–Arg–Arg–Cys–Tyr–Asn–Asp–Pro–Lys–Cys–Cys–Asp–Phe–OH). A positive signal was defined as a signal which exceeded the background level by 1.5 times.

2.4. Ig apheresis

IA was performed according to the protocol established by Muller et al. [17]. We had used the columns containing polyclonal sheep antibodies against human IgG–IgAdsopak® (POCARD Ltd., Russia), designed for multiple use. Ig apheresis was performed within 5 consecutive days. The level of IgG and anti-β1-AR antibodies was monitored before and after each procedure. The daily treatment time was 3–5 h during which 5.2 ± 0.8 L of patient's plasma was passed through the

columns. 8–12 chromatography cycles were run during single procedure. IgG replacement therapy has not been performed.

2.5. Statistical analysis

Statistical analysis was performed using SPSS (version 16.0). Data are expressed as mean ± standard deviation. Continuous variables at baseline and follow-up in each group were compared by paired *t* test or Wilcoxon test. The differences were considered significant at $p < 0.05$.

3. Results

The clinical baseline characteristics of both groups are shown in Table 1. For both groups, age, NYHA class, LVEF and other parameters were comparable. Both groups included patients positive and negative for antibodies against β1-AR.

Patients from both groups reported the improvement in quality of life during the first three months. Optimization of medical therapy and regular in-hospital management might be the most probable causes of this finding. Initial improvement in the control group was followed by return to baseline levels after 3 months and further deterioration during follow-up period.

Fig. 1 demonstrates daily pre- and post-IgG and anti-β1-AR antibodies levels during the 5 consecutive days of treatment. Effective reduction of IgG level was achieved during the course of procedures, and anti-β1-AR antibodies were removed up to baseline level.

Examination on the basis of NYHA class revealed significant improvement in the apheresis group immediately after IA treatment. This effect persisted during 6 months of follow-up. In contrast, the patients from control group showed no significant relief from heart failure symptoms (Fig. 2). Similarly, the 6MWD test continued to improve

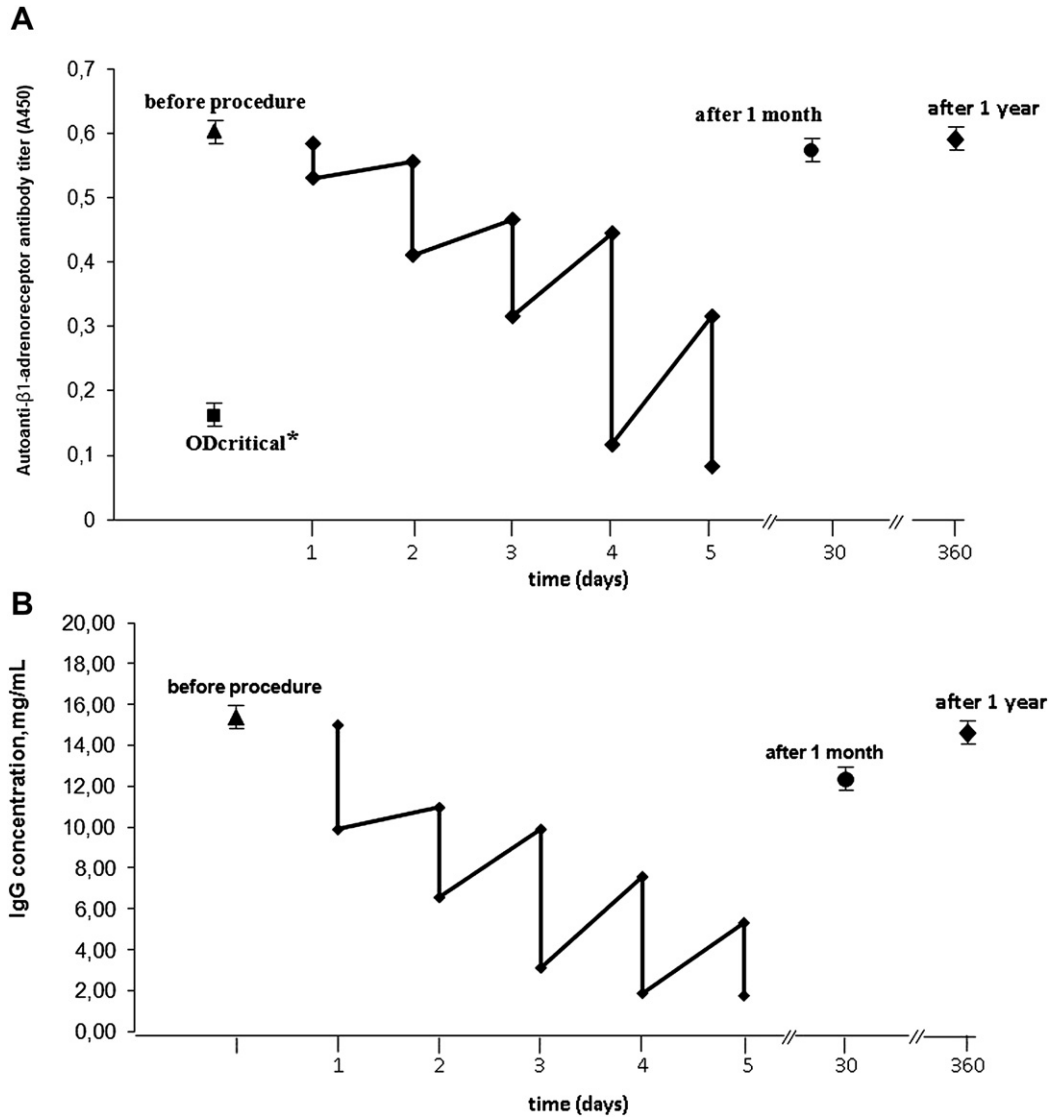

Fig. 1. Dynamic of autoanti-β1-adrenoreceptor antibodies titer (A) and total IgG concentration (B) during 5 consecutive Ig apheresis treatments.

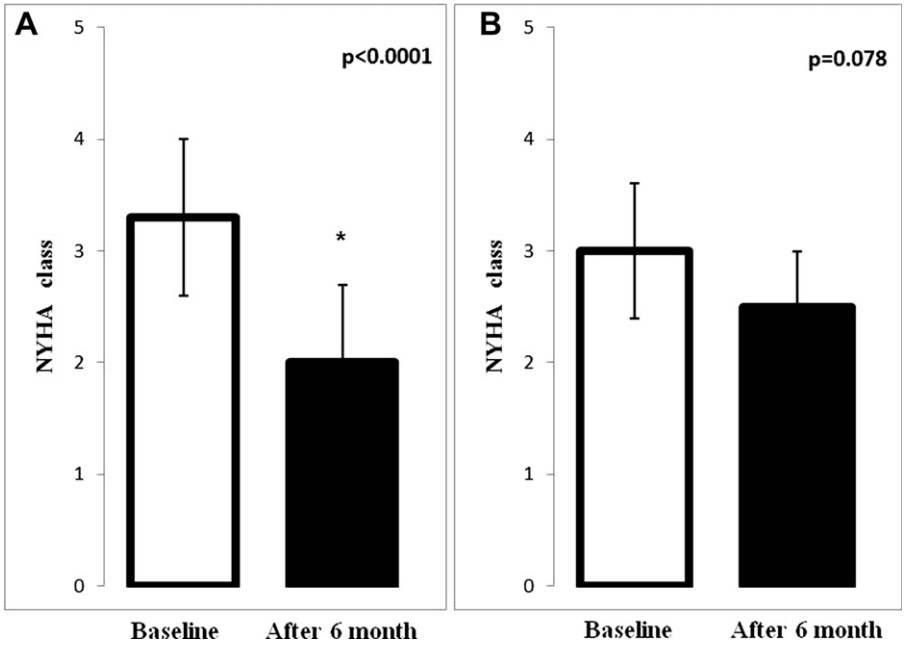

Fig. 2. NYHA class changes in Ig apheresis (A) and control group (B) at baseline and after 6 month follow-up.

during the observation period in the apheresis group. There was significant increase in distance covered in 6MWD in comparison with control group (Fig. 3). Brain natriuretic peptide (BNP) level decreased significantly in apheresis group (507 ± 279 pg/mL and 272 ± 185 pg/mL ($p < 0.05$)) and did not changed in control group (449 ± 209 pg/mL and 330 ± 122 pg/mL ($p = 0.1$)) during the study.

Although the differences in LVEF between apheresis and control groups did not reach statistical significance, mean LVEF tended to improve steadily in the apheresis group during 3 months of follow-up. A tendency toward relative decrease in LVEF was seen after 6 months in both groups. However in patients from the apheresis group LVEF was still higher (Fig. 4).

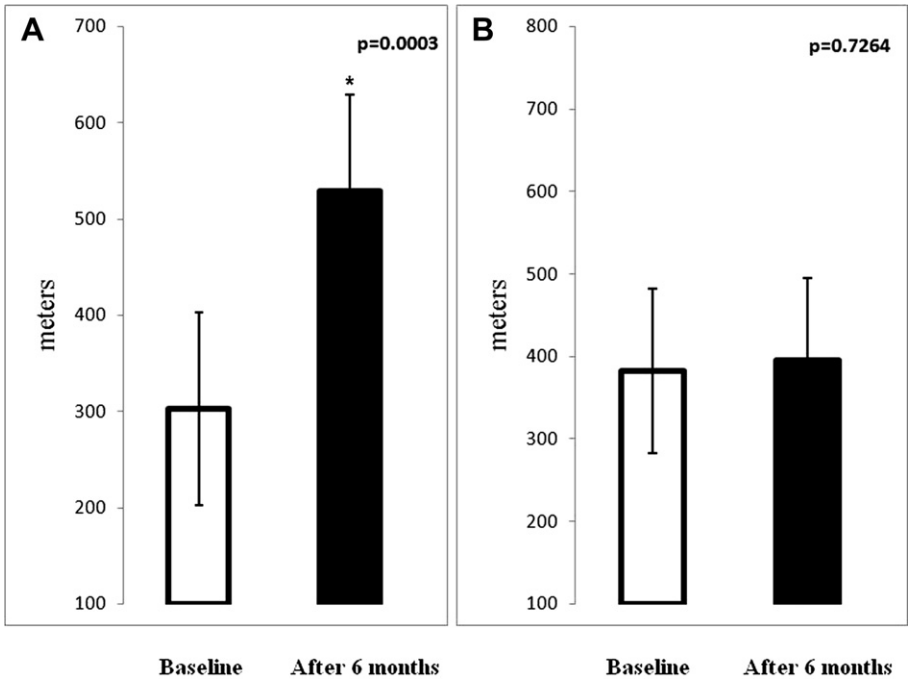

Fig. 3. Time dependent of walking distance by 6 min test assessment in the IgG apheresis group (A) and control group (B).

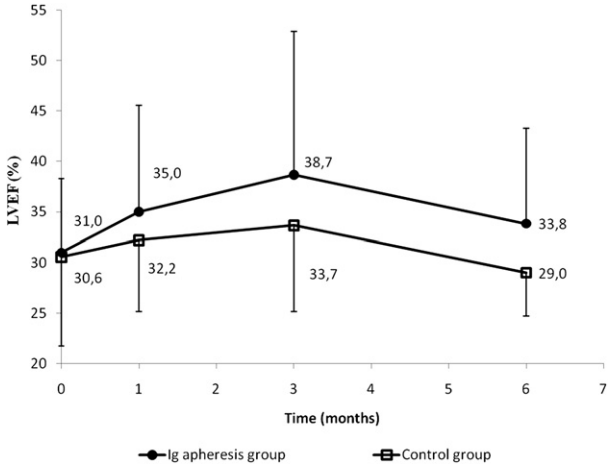

Fig. 4. Dynamic of LVEF in patients with DCM during 6 months of follow-up. LVEF – left ventricular ejection fraction, DCM – dilated cardiomyopathy.

4. Discussion

This study adds to the current knowledge regarding the use of IA for the management of DCM patients. Ig apheresis treatment in our small group of patients was associated with a significant improvement of quality of life and amelioration of cardiac performance. Unlike most previous studies with IA for DCM, we have included in the apheresis group patients who were also negative for anti-β1-AR antibodies.

Numerous authors suggest that the measurement of specific autoantibodies (e.g. anti-β1-AR antibodies, anti-human M2-muscarinic acetylcholine receptors) is helpful for the monitoring of clinical status in patients with DCM [13,14,18]. According to current data, anti-β1-AR antibodies are associated with reduced cardiac function and predict sudden death in patients with DCM. Apparently, anti-β1-AR antibodies are not key molecules responsible for DCM manifestation. They were found only in 26–46% of patients diagnosed with dilated cardiomyopathy. The results of the treatment with anti-β1-adrenoreceptor antibody adsorption showed negative results. The clinical effects observed after IA treatment do not correlate with the presence of these specific antibodies in the blood. The concentration of anti-β1-AR antibodies increased up to the pretreatment levels during the first month after IA treatment, whereas improvement in cardiac function persisted up to 6, and in several cases up to 12 months. Some authors also report that the effect of hemodynamic improvement during IA was similar among patients positive and negative for β1-AR antibodies [19].

It was shown that a lot of other autoantibodies are involved in pathologic process during DCM [20]. Specific autoantibodies for the M2-muscarinic acetylcholine receptor correlate with the greater incidence of atrial fibrillation in DCM patients. Autoantibodies to the α-myosin were detected in 23%–66% of patients with DCM, and their presence correlates with the deterioration of left ventricular systolic function and increased diastolic stiffness. In more than half of patients with severe DCM the elevated level of cardiac troponin I is detected and antibodies to it. Autoantibodies specific for the sarcolemmal Na–K–ATPase are shown to be independent predictors of poor systolic function, ventricular tachycardia, and sudden cardiac death [20]. The list of autoantibodies found in DCM patients is constantly updated by new autoantibodies measured by different methods. According to published data, the concentration of cardiodepressive antibodies measured by biological methods only shows the strong correlation with clinical outcomes of DCM patients.

Cardiac index and LVEF improvement induced by IA are strongly correlated with the level of antibodies measured by these methods [21,22]. It may be related with cardiodepressive activity of autoantibodies "pool" as well as with pathogenic role of some particular molecules. It remains still an unsolved question.

Unfortunately, biological methods based on the use of primary culture of neonatal rat cardiomyocytes or chicken embryos, are too complex for routine diagnostic purposes. The simple, reproducible assay for the measurement of target molecules is still missing. This makes it difficult to identify a subset of patients who will benefit from IA therapy.

Despite the many open questions regarding possible mechanisms of IA action, the clinical improvement after IA therapy was shown by all investigators. IA was first proposed to use in clinical practice as the bridge to heart transplantation. The currently available data show that this method could be an alternative treatment of DCM patients. Although high initial treatment costs for IA are incurred, significantly better survival rates lead to reasonable costs per life year gained [23]. As compared with surgery approach of the DCM treatment, Ig apheresis is a simple and widely used method. So, its application to the general population of patients with DCM is justified.

5. Conclusions

Ig apheresis is the promising therapeutic option in patients with DCM without sufficient benefit of

conventional medical therapy. Clinical improvement after Ig apheresis can be directly associated with the removal of numerous autoantibodies against cardiac proteins circulating in plasma. Application of Ig apheresis treatment to the general population of in DCM patients offers an effective and low-risk treatment.

Conflicts of interest

The authors have no financial interests to disclose. This study was supported by the Fund No 8/3-280n-10 from the Moscow State Government, Russian Federation.

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