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STUDY DESIGN

Multicentre, randomized, double-blind, prospective study on the effects of ImmunoAdSorptiOn on cardiac function in patients with Dilated CardioMyopathy (IASO-DCM): Rationale and design

Marcus Dörr[1,2], Michael Böhm[3†], Erland Erdmann[4], Stefan Groß[1,2], Amir-Abbas Mahabadi[5], Matthias Nauck[2,6], Georg Nickening[7], Heinz-Peter Schultheiss[8†], Alexander Staudt[9†], Karl Werdan[10], Finn Waagstein[11†], Åke Hjalmarson[11†], and Stephan B. Felix[1,2*†]

[1]Department of Internal Medicine B, University Medicine, Greifswald, Germany; [2]DZHK (German Center for Cardiovascular Research), Partner site Greifswald, Greifswald, Germany; [3]Department of Internal Medicine III, Saarland University, Homburg, Germany; [4]Department of Internal Medicine III, University of Cologne, Cologne, Germany; [5]Department of Cardiology and Vascular Medicine, West German Heart and Vascular Center Essen, University Hospital Essen, Essen, Germany; [6]Institute of Clinical Chemistry and Laboratory Medicine, University Medicine, Greifswald, Germany; [7]Department of Internal Medicine II – Pneumology/Cardiology, University Hospital Bonn, Bonn, Germany; [8]Institute of Cardiac Diagnostics and Therapy, IKDT GmbH, Berlin, Germany; [9]Helios-Kliniken Schwerin, Department of Cardiology and Angiology, Schwerin, Germany; [10]Department of Internal Medicine III – Cardiology, Angiology and Internal Intensive Care Medicine, Mid-German Heart Center, University Hospital Halle (Saale), Halle, Germany; and [11]Wallenberg Laboratory, Sahlgrenska University Hospital, Göteborg, Sweden

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Aims Pilot studies indicate that immunoadsorption with subsequent IgG substitution (IA/IgG) induces beneficial effects in patients with dilated cardiomyopathy (DCM) and heart failure. This placebo-controlled study investigates whether IA/IgG treatment enhances left ventricular (LV) systolic function as compared to a control group receiving pseudo-treatment.

Methods This multicentre, randomized, double-blind, parallel-group trial aims to include 200 patients with heart failure due to DCM (LV ejection fraction [LVEF] <40%) on optimized guideline-directed heart failure medication. Participants are randomly assigned in a 1:1 ratio to IA/IgG using protein-A columns, or to pseudo-immunoadsorption followed by an intravenous infusion without IgG. Follow-up visits take place by telephone after 1 and 3 months and at the study centres after 6, 12 and 24 months. The primary efficacy endpoint is the change in LVEF from baseline to 6 months determined by contrast echocardiography, analysed at a core lab. In addition, LV end-diastolic and end-systolic volumes will be analysed as secondary endpoints over the entire study period to assess whether IA/IgG affects LV remodelling. As main secondary outcome, a composite of all-cause death, cardiac resuscitation, hospitalization for heart failure, and need for cardiac surgery to improve myocardial pump function will be evaluated after 24 months. In addition, exploratory outcomes as well as safety endpoints related to the treatment will be assessed throughout the whole study period.

*Corresponding author. Department of Internal Medicine B, University Medicine Greifswald, 17475 Greifswald, Germany. Tel: +49 3834 8680500, Fax: +49 3834 8680502, Email: stephan.felix@uni-greifswald.de

†Members of the Steering Committee are listed in the *Appendix*.

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Conclusion IASO-DCM is a randomized study which will provide comprehensive insights into the effects of immunoadsorption with subsequent IgG substitution in patients with DCM.

Keywords Dilated cardiomyopathy • Heart failure • Immunoadsorption • IgG substitution • Randomized controlled trial

Introduction

Dilated cardiomyopathy (DCM) is characterized by the enlargement of the left ventricle or both ventricles alongside with impaired systolic function not attributable solely to abnormal loading conditions (such as hypertension or valve disease) or significant coronary artery disease.[1,2] In industrialized countries, the prevalence is around 1 in 250 individuals, with an annual incidence ranging from 5 to 8 cases per 100 000 individuals.[1,2] As some cases might present asymptomatic, it is assumed that DCM is more prevalent and population-based estimates using less strict diagnostic criteria suggest that the prevalence of idiopathic DCM is likely 10-fold higher.

Dilated cardiomyopathy frequently leads to progressive heart failure (HF) due to declining left ventricular (LV) contractile function accompanied by various complications such as arrhythmias, and thromboembolism leading to high rates of sudden or HF-related death. DCM remains one of the most common causes of heart transplantation (HTx).[3] Improvements of medical treatment led to improved prognosis of DCM with 10-year survival free from all-cause mortality, HTx, and ventricular assist device (VAD) implantation of 42%.[3]

Clinical data indicate that in many cases viral infection and persistent inflammatory processes are involved in the pathogenesis of myocarditis and DCM, and may represent factors causing progression of ventricular dysfunction.[4,5] Hence, the term 'inflammatory cardiomyopathy' has been introduced.[1,4,5] Furthermore, genetic alterations can be identified in about 40% of cases of DCM and some patients have a positive family history indicating a genetic cause or modulatory effect of the genetic background.[1,6] Both myocarditis and DCM associate with abnormalities of the immune system.[4,7] Myocardial inflammation reflected by immunohistological findings in endomyocardial biopsies (EMBs) such as lymphocyte and mononuclear cell infiltration along with increased expression of cell adhesion molecules is frequent in DCM patients, suggesting ongoing immune activity.[4,7] Furthermore, activation of the humoral immune system with production of cardiac antibodies may play an important role in DCM as several antibodies against cardiac structures have been detected in these patients, directed against mitochondrial proteins, α- and β-cardiac myosin heavy chain isoforms, the cardiac β-receptor, the muscarinic acetylcholine receptor-2, and the sarcolemmal Na-K-ATPase.[4,7]

This randomized multicentre study will investigate with a placebo-controlled, double-blind design whether the removal of autoantibodies by immunoadsorption (IA) will influence the disease process and cardiac function of patients suffering from HF due to DCM.

Study design

ImmunoAdSorptiOn on cardiac function in patients with Dilated CardioMyopathy (IASO-DCM) is a multicentre, randomized, double-blind, parallel-group trial in patients with DCM randomly assigned 1:1 to IA and subsequent IgG substitution (IA/IgG), or to pseudo-IA (plasmapheresis but reinfusion of the plasma without passing of adsorption columns) followed by an intravenous infusion without IgG (control).

The main objective is to investigate whether IA/IgG enhances LV systolic function as compared to the control group, as determined by contrast echocardiography after 6 months. The main secondary objective is to ascertain whether IA/IgG compared to control improves the outcome (composite of all-cause death, cardiac resuscitation, hospitalization for HF, cardiac surgery) after 24 months.

Trial population

The IASO-DCM trial aims to include 200 patients with HF due to DCM and reduced ejection fraction diagnosed in accordance with current guidelines when the study was started.[8] Pre-defined inclusion and exclusion criteria were selected to ensure that only patients with defined DCM are enrolled and that there are no contraindications for carrying out an IA (*Table 1*). Briefly, DCM patients aged 18 to 70 years with symptomatic HF (New York Heart Association [NYHA] classes II–IV) and a LV ejection fraction (LVEF) <40% (determined by contrast echocardiography) are eligible to participate. Furthermore, onset of HF symptoms has to be ≥6 months and ≤7 years at the time of screening. The inclusion of eligible patients takes place after a detailed oral and written informed consent about the rationale, the procedure and potential risks of the study and after written consent has been obtained.

Concomitant therapy

Eligible patients must be treated with optimized HF therapy according to the European Society of Cardiology (ESC) guidelines from 2008 originally valid during the recruitment and follow-up phase.[8] These included angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, beta-blockers, mineralocorticoid receptor antagonists, and diuretics as clinically indicated. Treatment with angiotensin receptor–neprilysin inhibitors, however, took place during the course of the study due to an update of the ESC guidelines published in 2016.[9] HF medication must be initiated for at least 6 months with stable dosing for at least 2 months prior to the screening. It was recommended not to change the HF medication during the course of the investigation, with the exception of dosage adjustments of diuretics and of

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Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age 18–70 years • Dilated cardiomyopathy • NYHA class II–IV • LVEF <40% determined by contrast echocardiography (according to assessment of the local investigators) • Symptoms of heart failure ≥6 months and ≤7 years prior to screening • Treatment with ACE inhibitors or angiotensin II receptor blockers, beta-blockers, and aldosterone antagonists (the latter at the discretion of the attending physician), for at least 6 months and at stable doses for at least 2 months prior to screening date • Informed consent	• NYHA class IV patients who are bed-ridden and dependent upon parenteral medication • Cardiac insufficiency resulting from another cardiac disease (e.g. CAD defined by ≥50% stenosis of major vessel assessed by coronary angiography, hypertensive heart disease, valvular defects >second degree) • History of myocardial infarction • Acute myocarditis according to Dallas criteria • ICD implantation <1 month before screening date • CRT <6 months before screening date • Intravenous medication with inotropic drugs, vasodilators or repeated (>1/day) intravenous administration of diuretics • Active infectious disease, or signs of ongoing infection with CRP >10 mmol/L • Impaired renal function (serum creatinine >220 μmol/L) • Endocrine disorder excluding insulin-dependent diabetes mellitus • Any disease requiring immunosuppressive drugs • Anaemia (Hb <90 g/L) due to other causes than CHF • Pregnancy/lactation, or childbearing potential without appropriate contraception • Alcohol or drug abuse • Presence of a malignant tumour, or remission of malignancy <5 years • Another life-threatening disease with poor prognosis (survival <2 years) • Previous treatments with immunoadsorption or immunoglobulin • Contraindications for application of the echocardiography contrast agent used

ACE, angiotensin-converting enzyme; CAD, coronary artery disease; CHF, chronic heart failure; CRP, C-reactive protein; CRT, cardiac resynchronization therapy; Hb, haemoglobin; ICD, implantable cardiac defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

digitalis. The concomitant therapy may also include an implanted cardiac defibrillator (at least 1 month prior to screening) and cardiac resynchronization therapy if indicated according to the ESC guidelines (at least 6 months prior to screening).[8,9]

Study interventions

An overview of intervention procedures is given in *Figure 1*.

In the treatment group (IA/IgG), immunoglobulin extraction from the plasma will take place using Immunosorba® (Fresenius Medical Care, Bad Homburg, Germany), a protein A immunoadsorber for immunoglobulin removal. IA will be performed in one course of five sessions on consecutive days. Each session will continue until two- to three-fold of plasma volume has passed the IA columns. After the last IA session and subsequent IgG depletion, IgG will be substituted for safety reasons, to restore IgG plasma levels and to reduce the risk of infection. Six hours after the last IA session, patients of the IA/IgG group will accordingly receive 0.5 g/kg polyclonal IgG (Octagam®, Octopharma AG, Lachen, Switzerland, or Privigen®, CSL Behring GmbH, Marburg, Germany) intravenously. In the control group, a pseudo-IA is also carried out in one course of five sessions on consecutive days. Pseudo-IA consists of plasmapheresis with subsequent reinfusion of plasma but without previous passage through the IA columns. After the last session of pseudo-IA, the control patients will receive an intravenous infusion without IgG (saline).

All patients are hospitalized for the duration of the study interventions, and in both groups heart rate and respiratory rate are continuously recorded and blood pressure is measured at least every 30 min during each session of IA or pseudo-IA. For safety reasons, all patients will receive prophylactic antibiotics (e.g. amoxicillin intravenously once a day) to minimize the risk of infection during central venous catheterization.

Endpoints

The primary endpoint is the change in LVEF from baseline to 6 months determined by contrast echocardiography as assessed by the core lab.

The main secondary endpoint is a composite of all-cause death, cardiac resuscitation, hospitalization for HF, cardiac surgery to improve myocardial pump function (HTx, VAD implantation, or bi-ventricular pacing) after 24 months. Hospitalization for HF is defined as unscheduled hospitalization ≥24 h due to progression of HF, which is characterized by increased symptoms of HF or change in medication in accordance to the criteria as defined in the EPHESUS study.[10] Further secondary, safety and exploratory endpoints are summarized in *Tables 2* and *3*.

Study plan and key measurements

An overview of the study schedule and assessments is shown in *Figure 2*. In brief, the intervention has to be started within 14 days

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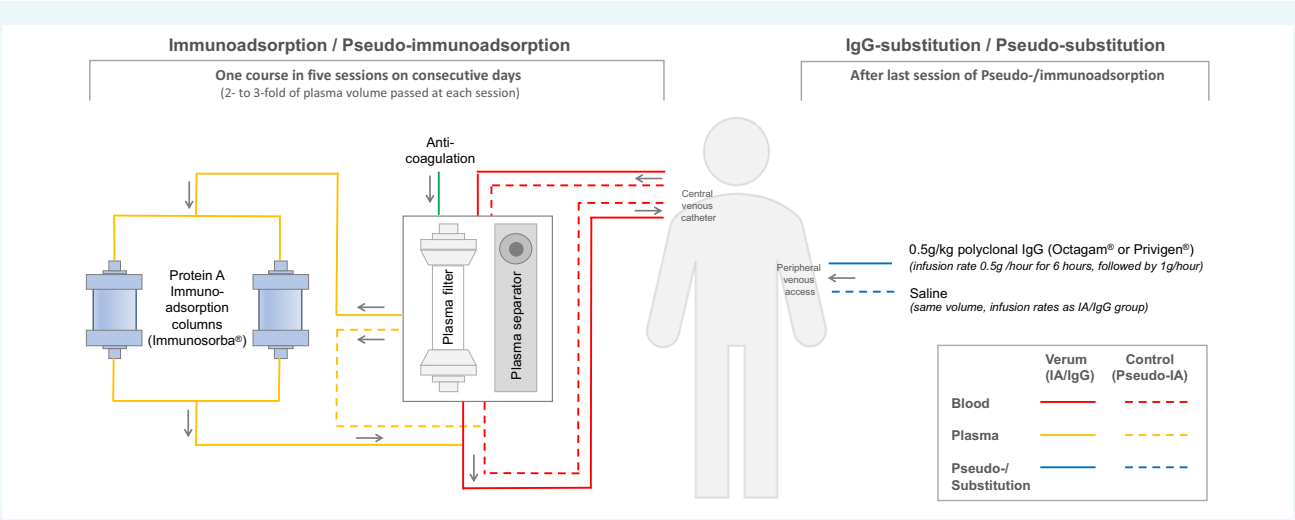

Figure 1 Study interventions. Protein A immunoadsorption is a technique that selectively removes antibodies from blood by exploiting the high affinity of protein A, derived from *Staphylococcus aureus*, for the Fc region of IgG antibodies. In this method, protein A is immobilized on a solid matrix, such as Agarose or Sepharose beads, creating an immunoadsorbent column. For this purpose, blood is first separated into plasma and cell components in a plasma separator. When the biological fluid is passed through the column, IgG antibodies bind specifically to protein A. The column is then washed to remove unbound substances, and the bound antibodies are eluted using a buffer that disrupts the protein A–IgG interaction. Plasma and cell components are then returned to the patient. In the study, the passage through the columns is omitted in the control group. In addition, IgG (verum group) or saline (control group) is substituted after the last treatment session as part of the study.

after randomization. The visits at the study centres at baseline and after 6, 12 and 24 months include a comprehensive examination programme including contrast echocardiography, cardiopulmonary exercise testing, assessment of quality of life and symptoms, blood sampling for local blood analyses and core lab biobanking. Information on adverse clinical events and endpoints is collected at every visit and by telephone after month 1 and 3.

Contrast echocardiography

Transthoracic echocardiography is performed at baseline and after 6, 12 and 24 months. All images from parasternal and apical views are obtained according to a standard operation procedure in accordance with the guidelines of the American Society of Echocardiography.[11] Cine loops are recorded in the apical four- and two-chamber view using contrast agents (Luminity®/Definity®, Lantheus Medical Imaging, Bedford, MA, USA; Optison™, GE Healthcare Inc., Milwaukee, WI, USA; SonoVue®, Bracco Imaging GmbH, Konstanz, Germany) to determine the LV volumes and calculate the LVEF. Data are stored digitally and analysed by the core lab.

Cardiac magnetic resonance imaging

Optionally, a cardiac magnetic resonance imaging is performed during the baseline and the follow-up examinations. The evaluation takes place in a core lab.

Cardiopulmonary exercise testing

Cardiopulmonary exercise capacity will be evaluated at baseline and after 6, 12 and 24 months using symptom-limited cardiopulmonary exercise test. All examinations are evaluated by an independent core lab.

Endomyocardial biopsy

Originally, in all patients, an EMB had to be obtained for diagnosis of DCM before study start. Following an amendment, EMBs will be performed optionally at the discretion of the investigators and treating physicians.

Genetic analyses

It is also planned to analyse the genetic background of all participants, as previous studies have identified a familial or genetic cause in many DCM cases.[6] Understanding the complex genetic architecture of DCM is crucial for tailoring treatment,[6] also for interventions targeting humoral immunity like IA therapy.

Randomization and blinding

Patients are randomized centrally by computer in a 1:1 ratio to either IA/IgG or control. The first patients will be randomized using block randomization. For the rest of the patients, optimal dynamic allocation according to Pocock's sequential treatment allocation method will be used. The randomization procedure will assure balance for seven prognostic factors: age (≤40/>40 years), sex (male/female), diabetes (yes/no), LVEF (mean and ≤25%/>25%), LV end-diastolic volume index (LVEDVI, mean), treatment duration for HF (≤2/>2 years), NYHA class (II/III/IV), implanted cardiac defibrillator (yes/no), cardiac resynchronization therapy (yes/no).

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Table 2 Secondary and safety endpoints

Secondary endpoints

- Main secondary endpoint: composite of all-cause death, cardiac resuscitation, hospitalization for heart failure and cardiac surgery to improve myocardial pump function (HTx, VAD implantation, myoplasty or bi-ventricular pacing) at 24 months
- Cardiac morbidity as determined by quality-of-life score (MLHFQ) and by the symptoms in accordance with NYHA classification at baseline and after 6, 12, and 24 months
- LVEF as determined by contrast echocardiography at baseline and after 12 and 24 months
- LVESVI as determined by contrast echocardiography at baseline and after 12 and 24 months
- LVEDVI as determined by contrast echocardiography at baseline and after 12 and 24 months
- Changes in cardiopulmonary exercise capacity: VO_{2max}, anaerobic threshold and VE/VCO_2 from baseline to 6, 12 and 24 months
- Changes in BNP and/or NT-proBNP from baseline to 6 months
- LVEF, as determined by MRI at rest at baseline, after 6, 12 and 24 months (optional)

Safety endpoints

- SAEs to be accounted for during the intervention period, at 1, 3 and 6 months
- A composite endpoint of all-cause death and hospitalizations due to any cardiovascular event or infections at 6 months (performed by the DSMB)

BNP, B-type natriuretic peptide; DSMB, Data Safety and Monitoring Board; HTx, heart transplantation; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SAE, serious adverse event; VAD, ventricular assist device; VE/VCO_2, ratio of minute ventilation and carbon dioxide production; VO_{2max}, maximum oxygen uptake.

Table 3 Exploratory endpoints and analyses

Exploratory analyses to characterize patient-specific factors by which it may be possible to predict the success of IA/IgG:

- Patients' age
- Symptom duration
- Extent of left ventricular systolic dysfunction as determined by LVEF at baseline
- Serum levels of specific cardiac autoantibodies at baseline
- Myocardial inflammation, as determined by expression of cellular adhesion molecules and HLA class II antigens and presence of lymphocytes and monocytes in myocardial biopsies at baseline (optional)
- Myocardial fibrosis in myocardial biopsies at baseline (optional)
- Virus persistence in myocardial biopsies at baseline (optional)

Immune parameters and parameters of LV remodelling at baseline and during follow-up:

- Changes in serum levels of specific cardiac autoantibodies and inflammatory cytokines obtained from baseline to day 6/7 as well as after 6, 12, and 24 months
- Changes in serum levels of IgG, IgA, IgM and IgG3 from baseline to treatment day 1 to 5 (twice every day: before treatment and within 1 h after treatment), day 6/7 and month 6, 12 and 24
- Changes in serum levels of specific cardiac autoantibodies from baseline to treatment day 5 (within 1 h after treatment) as well as after 6, 12, and 24 months
- Changes in LVEF from baseline to 12 and 24 months
- Changes in end-diastolic and end-systolic volume index assessed by MRI at baseline and after 6, 12, and 24 months (optional)
- Changes in LV end-systolic and end-diastolic diameters, as assessed by contrast echocardiography at baseline and after 6, 12, and 24 months
- Impact of concomitant drug treatment at baseline and of its changes during follow-up

HLA, human leucocyte antigen; IA/IgG, immunoadsorption with subsequent IgG substitution; IgG/G3/A/M, immunoglobulin G/G3/A/M; LV, left ventricular; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging.

Information on group assignment will be sent to an unblinded physician/technician responsible for the IA procedures. The other members of the local study team and the patients remain blinded for the entire duration of the study. Since it is not possible to produce a sham column that is identical to the IA column, special measures must be taken for the intervention phase. The IA/pseudo-IA is therefore performed behind a curtain and the unblinded physician/technician should make certain that both study team and patients cannot see the equipment used for the procedure. For the subsequent intravenous infusion of IgG solution (IA/IgG) or saline solution (control), identical glass bottles wrapped in black plastic foil and black plastic tubes are used. All analyses by core labs and by the Endpoint Committee will be performed without knowledge of the assignment of patients to the two treatment arms.

Statistical analysis

Sample size calculation is based on an expected standard deviation for the individual ejection fraction difference around 0.10 absolute percentages, and has been based on intervention studies with follow-up of more than 6 months.[12,13] A clinically significant ejection fraction difference of 0.045 is deemed relevant. Although no study had a follow-up of 6 months or more for the contrast echocardiography method when this study was designed, extrapolations from studies using common echocardiography measurements suggest a probable standard deviation of ejection fraction differences close to 0.092. With an alpha value of 0.05 and a power of 90%, the sample size suggests 180 participants. To accommodate loss to follow-up (less than 5%) and a blinded interim analysis after enrolment of 50% of the planned patients, a sample size of 200 has been chosen.

All patients randomized into the study will be included in the intention-to-treat analysis set (ITT). The analysis of the primary endpoint will be the Fisher permutation test of two independent

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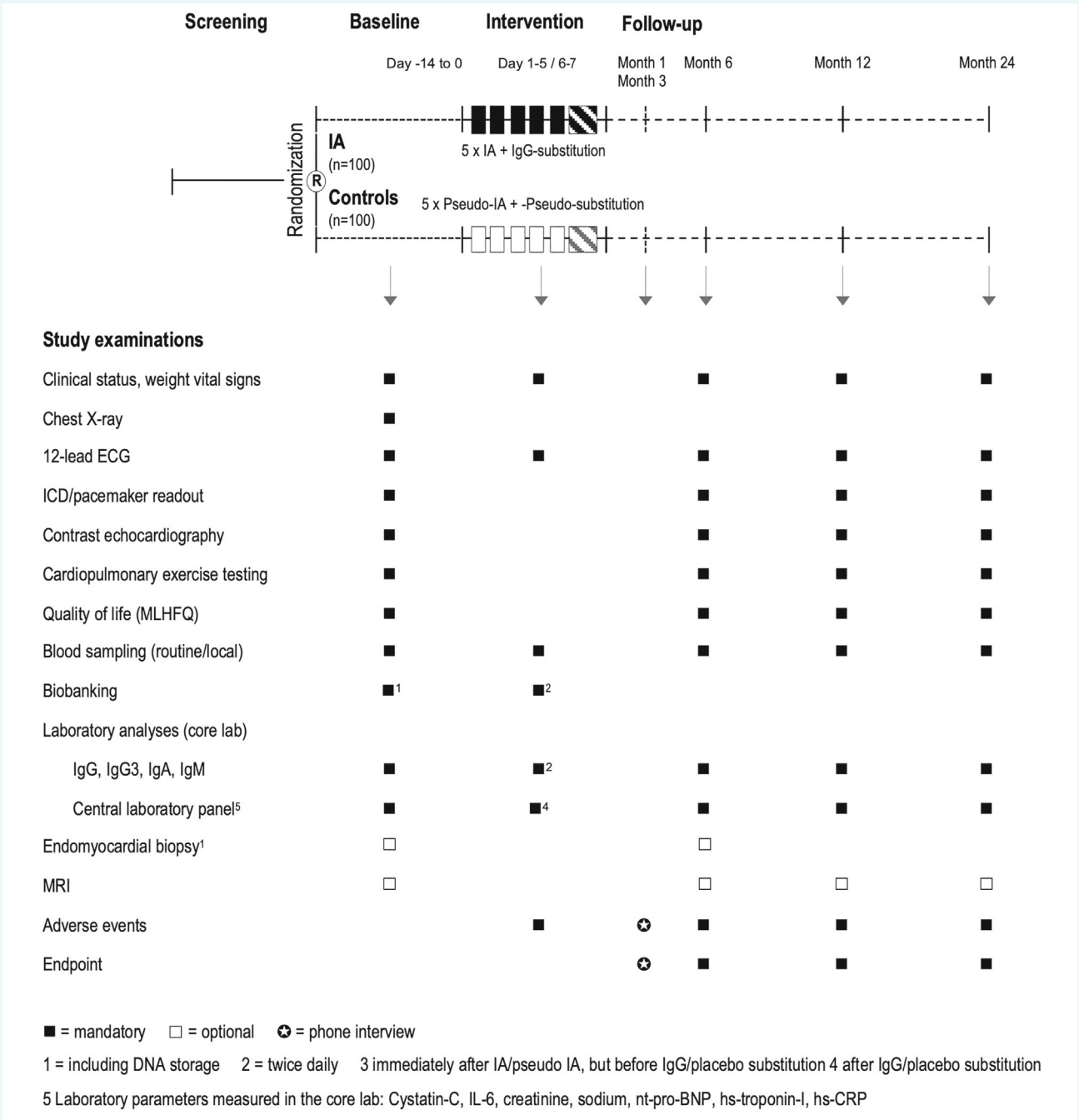

Figure 2 Study flow-chart. Overview of the study design, study visits and study measures in both study groups. CRP, C-reactive protein; ECG, electrocardiogram; hs, high-sensitivity; IA, immunoadsorption; ICD, implantable cardiac defibrillator; IgG/G3/A/M, immunoglobulin G/G3/A/M; IL-6, interleukin-6; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

groups. The final two-tailed test compares the ejection fraction change for IA/IgG to controls using all 200 patients, 100 in each group (alpha value 0.05, power ≥90%). For evaluation of the secondary objectives conventional statistical analyses will be used together with Cox proportional hazards model for time to event variables.

Study status

The first patient was randomized successfully into the study in November 2008. In the further course of the study, there were several delays in recruitment and temporary recruitment stops due to various reasons. Ultimately, recruitment was terminated

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at the end of 2018 by decision of the sponsor. At this timepoint, 171 randomized patients were available for analysis. According to the biostatisticians of this study, this number allowed a valid analysis of the primary endpoint. The last 24-month follow-up was completed in August 2021. The data are currently being analysed.

Discussion

Rationale of the study – The potential role of humoral immunity in dilated cardiomyopathy

Cardiac autoantibodies may play an active role in the pathogenesis of DCM by triggering the disease process rendering them as a treatment target. *In vitro* data indicate an adverse effect on cardiac performance for some antibodies. Cytotoxic autoantibodies against the ADP/ATP carrier cross-react with the calcium channel of cardiomyocytes in myocarditis and DCM.[14] In patients with clinically suspected or EMB proven myocarditis high-titre organ-specific anti-heart and anti-intercalated disk autoantibodies are independent predictors of death or HTx.[15] Purified antibodies obtained from DCM patients induce a negative inotropic effect in isolated rat cardiomyocytes by decreasing the calcium transients.[16,17] Immunization of rodents against peptides derived from cardiovascular G-protein receptors induces morphological changes of myocardial tissue resembling DCM.[18] Furthermore, recent data have provided evidence that antibodies against the β-receptor itself trigger DCM. Rats immunized against the second extracellular loop of cardiac β-receptors develop progressive LV dilatation and dysfunction. Interestingly, sera transferred from these immunized animals to unsensitized rats induced the similar cardiomyopathic phenotype, thus demonstrating the pathogenic potential of a particular antibody for development of DCM.[19] In addition, further models were able to support the hypothesis that autoantibodies contribute to the development and progression of DCM. For example, it has been shown that mice deficient in the programmed cell death-1 immunoinhibitory co-receptor develop autoimmune DCM with production of high-titre circulating IgG autoantibodies, identified as cardiac troponin I.[20]

Also clinically important is the observation that the detection of organ-specific autoantibodies against the heart in asymptomatic relatives of DCM patients, both familial and non-familial cases, is an independent predictor of DCM progression during a 5-year follow-up.[21]

If cardiac antibodies are indeed impairing cardiac function, their removal should lead to an improvement in haemodynamic status and functional parameters in DCM patients. Cardiac antibodies, found in the IgG fraction, can be removed through IA therapy. Indeed, pilot studies have shown that IA improves cardiac function and symptoms in patients with DCM and advanced HF. After an initial uncontrolled pilot study had shown acute positive haemodynamic effects of IA with anti-IgG columns in patients with severe HF due to DCM,[7] this therapeutic principle, followed by immunoglobulin G substitution for safety reasons (IA/IgG), was investigated in a randomized study in 18 patients with DCM (NYHA class III–IV, LVEF <30%).[22] In contrast to controls, a significant increase in cardiac index was found in the IA/IgG group after 3 months. We could also show that IA/IgG therapy mitigates the inflammatory process in the myocardium of DCM patients.[23] In a study conducted by other researchers using a case–control design, it was demonstrated that performing IA once over five consecutive days, without subsequent IgG substitution, resulted in a similarly significant enhancement in LV systolic function compared to the control group that did not receive IA therapy.[24]

Additional evidence suggests that the cardiac effects of IA therapy such as an increased cardiac index and LVEF are linked to the removal of cardiodepressant antibodies.[16,17] Therefore, identifying these antibodies in the plasma of DCM patients with advanced HF before IA treatment can effectively predict haemodynamic enhancement after IA therapy.[17] It has also been shown that these cardiodepressant antibodies belong to the IgG-3 subclass.[25] Accordingly, removal of antibodies of the IgG-3 subclass may represent an essential mechanism in IA therapy of DCM.[25] Further prediction of the efficacy of IA may be obtained by the analysis gene expression patterns in EMBs of DCM patients.[26] Based on the experimental and clinical data on the role of cardiac antibodies in DCM, this study will examine whether IA/IgG has an impact on LV function in with DCM. In particular, we will also investigate whether the detection of cardiac-specific autoantibodies at baseline has an impact on the therapeutic effect of IA in DCM.

Trial population

Dilated cardiomyopathy is not restricted to younger patients as cardiomyopathies can present at any age and can affect individuals and families across the entire life course.[1] A broad range of up to 70 years was therefore selected as the inclusion criterion. The lower limit for the duration of HF symptoms of 0.5 years takes into account the data of the IMAC trial where patients with recent-onset DCM were included.[13] In this study, recent-onset DCM was characterized as DCM with no more than 6 months of cardiac symptoms at the time of randomization. This study clearly showed a high rate of spontaneous recovery of LV function in the whole study cohort with equal improvement of LVEF in the intervention and control group.

Rationale for intervention with a placebo-controlled protein A adsorption in one course

This study investigates the effects of IA/IgG in DCM patients using a placebo-controlled, double-blind design in which the control group undergoes pseudo-IA, that is plasmapheresis without passage of the plasma through adsorption columns. Both protein A and anti-IgG columns are approved for IA in Europe. We will use protein A columns synthesized by bacteria, which are not associated with side effects associated with mammalian antibodies, unlike anti-IgG Sepharose, which is obtained from immunized sheep. While anti-IgG Sepharose eliminates all IgG subclasses, including IgG-3, protein A selectively binds to human IgG-1, -2, -4 and has a lower affinity for IgG-3. However, a previous study could demonstrate that optimizing the treatment regime by prolonging

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IA sessions and reducing protein column loading volume enhances IgG-3 removal with protein A and leads to significant acute and sustained haemodynamic improvement in advanced DCM patients with HF, comparable to the use of IgG columns.[27] For the treatment of autoimmune diseases IA or plasmapheresis is usually repeated at regular intervals. For DCM, however, case-controlled and a prospective open-controlled study confirmed that an IA treatment in one course over five consecutive days leads to a similarly effective improvement in LVEF as repeated IA treatments.[28]

Endpoints and exploratory analyses

Small randomized studies show that IA/IgG provides favourable effects on cardiac function of DCM patients as assessed by cardiac output or LVEF as a surrogate of outcome, particularly those with severe HF.[22,23,27,28] However, confirmation through a larger randomized, prospective, placebo-controlled, and double-blind multicentre study is needed to assess the short-term as well as the long-term effects of IA/IgG on LV function. There is an ongoing debate as to which parameter is the best to assess LV function. LVEF reliably measures both LV function and structure and remains the best method for assessment of the ventricular phenotype and most HF studies still use LVEF as the inclusion criterion.[29] The objective of this study is to investigate whether IA/IgG improves LVEF as proxy of LV systolic function as compared to controls from baseline to 6 months with follow-up measurements at 12 and 24 months and the primary endpoint is the change in LVEF from baseline to 6 months determined by contrast echocardiography. In addition, changes in LV end-systolic and end-diastolic volumes will be used as parameters for LV remodelling.[30] Therefore, LV end-systolic volume index and LV end-diastolic volume index will be analysed as secondary endpoints over the entire study period to assess whether IA/IgG influences LV remodelling.

A multicentre study confirmed that contrast-enhanced echocardiography offers comparable accuracy and less variability than magnetic resonance imaging for assessing global LV systolic function and volumes.[31] It also provides significantly lower variability than unenhanced echocardiography, making it suitable for comparing baseline and follow-up studies in large multicentre trials due to its wide availability, affordability, and accuracy. The main secondary endpoint is a composite of all-cause death, cardiac resuscitation, hospitalization for HF, and cardiac surgery to improve myocardial pump function at 24 months.

Exploratory analyses will characterize patient-specific factors predicting response to IA/IgG treatment. We will furthermore analyse clinical data including symptom duration, age, sex, and concomitant HF medications. This study will also use the subgroup with optional myocardial biopsies to investigate whether patients with or without viral persistence as well as patients with or without immunohistochemical evidence of myocardial inflammation indicating persistent immune system activation respond differently to IA/IgG therapy. We will explore whether parameters of systemic inflammation at baseline such as high-sensitivity C-reactive protein associate with changes in LV function after intervention. Finally, the genetic background for possible correlations with the response to treatment on an exploratory basis will be assessed.[6]

Conclusion

The IASO-DCM trial will provide insights on the effects of immunoadsorption with subsequent IgG substitution on LV systolic function and remodelling in patients with DCM based on a randomized placebo-controlled design. Moreover, potential predictors for the individual response to this treatment will be evaluated.

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Appendix

Trial organization

The study coordinator and the legal sponsor are responsible for all aspects of the study protocol and amendments. The Steering Committee is responsible for the clinical and scientific conduct of the study and publication of the results. An independent Endpoint Review Committee reviews and adjudicates all pre-specified events according to established definitions. Both committees only have access to blinded data while the study is underway. In addition, the trial is supervised by an independent Data Safety and Monitoring Board (DSMB). Members of the committees are listed in the *Appendix*. The trial is registered with ClinicalTrials.gov (www.clinicaltrials.gov NCT00558584), conformed to CONSORT guidelines for cluster-randomized trials, and is approved by the local ethics committees. The trial is conducted in accordance

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with national laws, Good Clinical Practice, and the Declaration of Helsinki.

Coordinating Investigator: Stephan B. Felix (Greifswald, Germany).

Legal sponsor: University Medicine Greifswald (Greifswald, Germany).

Steering Committee: Åke Hjalmarson (Göteborg, Sweden) Chair, Stephan B. Felix (Greifswald, Germany), Coordinating Investigator, Michael Böhm (Homburg/Saar, Germany), Heinz-Peter Schultheiss (Berlin, Germany), Finn Waagstein (Göteborg, Sweden), Alexander Staudt (Schwerin, Germany), Gert Baumann (Berlin, Germany), Hans Wedel (Frölunda, Sweden).

Endpoint Review Committee: Karl Werdan [chair] (Halle/Saale, Germany), Axel Schlitt (Halle/Saale, Germany).

Data Safety and Monitoring Board: Erland Erdmann [chair] (Köln, Germany), Georg Nickenig (Bonn, Germany), Walter Lehmacher (Köln, Germany).

Biometry: Hans Wedel (Frölunda, Sweden), Stefan Groß (Greifswald, Germany).

Core labs: Echocardiography: Mair Mahabadi (Essen); CPET: Ralf Ewert, Sabine Kaczmarek (Greifswald); central laboratory analyses and biobanking: Matthias Nauck (Greifswald), MRI: Evangelos Giannitsis, Henning Steen (Heidelberg).

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References

1. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, *et al.* 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J* 2023;**44**:3503–3626. https://doi.org/10.1093/eurheartj/ehad194
2. Heymans S, Lakdawala NK, Tschope C, Klingel K. Dilated cardiomyopathy: Causes, mechanisms, and current and future treatment approaches. *Lancet* 2023;**402**:998–1011. https://doi.org/10.1016/S0140-6736(23)01241-2
3. Merlo M, Cannatà A, Pio Loco C, Stolfo D, Barbati G, Artico J, *et al.* Contemporary survival trends and aetiological characterization in non-ischaemic dilated cardiomyopathy. *Eur J Heart Fail* 2020;**22**:1111–1121. https://doi.org/10.1002/ejhf.1914
4. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, *et al.* Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013;**34**:2648a–2648d. https://doi.org/10.1093/eurheartj/eht210
5. Tschöpe C, Ammirati E, Bozkurt B, Caforio ALP, Cooper LT, Felix SB, *et al.* Myocarditis and inflammatory cardiomyopathy: Current evidence and future directions. *Nat Rev Cardiol* 2021;**18**:169–193. https://doi.org/10.1038/s41569-020-00435-x
6. Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: The complexity of a diverse genetic architecture. *Nat Rev Cardiol* 2013;**10**:531–547. https://doi.org/10.1038/nrcardio.2013.105
7. Felix SB, Beug D, Dörr M. Immunoadsorption therapy in dilated cardiomyopathy. *Expert Rev Cardiovasc Ther* 2015;**13**:145–152. https://doi.org/10.1586/14779072.2015.990385
8. Dickstein K, Cohen-Solal A, Filippatos G, McMurray J, Ponikowski P, Poole-Wilson PA, *et al.*; ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008;**29**:2388–2442. https://doi.org/10.1093/eurheartj/ehn309
9. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, *et al.*; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200. https://doi.org/10.1093/eurheartj/ehw128
10. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, *et al.*; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–1321. https://doi.org/10.1056/NEJMoa030207
11. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, *et al.* ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography – summary article: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). *J Am Coll Cardiol* 2003;**42**:954–970. https://doi.org/10.1016/s0735-1097(03)01065-9
12. Groenning BA, Nilsson JC, Sondergaard L, Fritz-Hansen T, Larsson HB, Hildebrandt PR. Antiremodeling effects on the left ventricle during beta-blockade with metoprolol in the treatment of chronic heart failure. *J Am Coll Cardiol* 2000;**36**:2072–2080. https://doi.org/10.1016/s0735-1097(00)01006-8
13. McNamara DM, Holubkov R, Starling RC, Dec GW, Loh E, Torre-Amione G, *et al.* Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. *Circulation* 2001;**103**:2254–2259. https://doi.org/10.1161/01.cir.103.18.2254
14. Schultheiss HP, Kuhl U, Janda I, Melzner B, Ulrich G, Morad M. Antibody-mediated enhancement of calcium permeability in cardiac myocytes. *J Exp Med* 1988;**168**:2105–2119. https://doi.org/10.1084/jem.168.6.2105
15. Baritussio A, Schiavo A, Basso C, Giordani AS, Cheng CY, Pontara E, *et al.* Predictors of relapse, death or heart transplantation in myocarditis before the introduction of immunosuppression: Negative prognostic impact of female gender, fulminant onset, lower ejection fraction and serum autoantibodies. *Eur J Heart Fail* 2022;**24**:1033–1044. https://doi.org/10.1002/ejhf.2496
16. Felix SB, Staudt A, Landsberger M, Grosse Y, Stangl V, Spielhagen T, *et al.* Removal of cardiodepressant antibodies in dilated cardiomyopathy by immunoadsorption. *J Am Coll Cardiol* 2002;**39**:646–652. https://doi.org/10.1016/s0735-1097(01)01794-6
17. Staudt A, Staudt Y, Dörr M, Böhm M, Knebel F, Hummel A, *et al.* Potential role of humoral immunity in cardiac dysfunction of patients suffering from dilated cardiomyopathy. *J Am Coll Cardiol* 2004;**44**:829–836. https://doi.org/10.1016/j.jacc.2004.04.055
18. Matsui S, Fu ML, Katsuda S, Hayase M, Yamaguchi N, Teraoka K, *et al.* Peptides derived from cardiovascular G-protein-coupled receptors induce morphological cardiomyopathic changes in immunized rabbits. *J Mol Cell Cardiol* 1997;**29**:641–655. https://doi.org/10.1006/jmcc.1996.0307
19. Jahns R, Boivin V, Hein L, Triebel S, Angermann CE, Ertl G, *et al.* Direct evidence for a beta 1-adrenergic receptor-directed autoimmune attack as a cause of idiopathic dilated cardiomyopathy. *J Clin Invest* 2004;**113**:1419–1429. https://doi.org/10.1172/JCI20149
20. Okazaki T, Tanaka Y, Nishio R, Mitsuiye T, Mizoguchi A, Wang J, *et al.* Autoantibodies against cardiac troponin I are responsible for dilated cardiomyopathy in PD-1-deficient mice. *Nat Med* 2003;**9**:1477–1483. https://doi.org/10.1038/nm955
21. Caforio AL, Mahon NG, Baig MK, Tona F, Murphy RT, Elliott PM, *et al.* Prospective familial assessment in dilated cardiomyopathy: Cardiac autoantibodies predict disease development in asymptomatic relatives. *Circulation* 2007;**115**:76–83. https://doi.org/10.1161/CIRCULATIONAHA.106.641472

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22. Felix SB, Staudt A, Dörffel WV, Stangl V, Merkel K, Pohl M, *et al.* Hemodynamic effects of immunoadsorption and subsequent immunoglobulin substitution in dilated cardiomyopathy: Three-month results from a randomized study. *J Am Coll Cardiol* 2000;**35**:1590–1598. https://doi.org/10.1016/s0735-1097(00)00568-4
23. Staudt A, Schäper F, Stangl V, Plagemann A, Böhm M, Merkel K, *et al.* Immunohistological changes in dilated cardiomyopathy induced by immunoadsorption therapy and subsequent immunoglobulin substitution. *Circulation* 2001;**103**:2681–2686. https://doi.org/10.1161/01.cir.103.22.2681
24. Müller J, Wallukat G, Dandel M, Bieda H, Brandes K, Spiegelsberger S, *et al.* Immunoglobulin adsorption in patients with idiopathic dilated cardiomyopathy. *Circulation* 2000;**101**:385–391. https://doi.org/10.1161/01.cir.101.4.385
25. Staudt A, Böhm M, Knebel F, Grosse Y, Bischoff C, Hummel A, *et al.* Potential role of autoantibodies belonging to the immunoglobulin G-3 subclass in cardiac dysfunction among patients with dilated cardiomyopathy. *Circulation* 2002;**106**:2448–2453. https://doi.org/10.1161/01.cir.0000036746.49449.64
26. Ameling S, Herda LR, Hammer E, Steil L, Teumer A, Trimpert C, *et al.* Myocardial gene expression profiles and cardiodepressant autoantibodies predict response of patients with dilated cardiomyopathy to immunoadsorption therapy. *Eur Heart J* 2013;**34**:666–675. https://doi.org/10.1093/eurheartj/ehs330
27. Staudt A, Dörr M, Staudt Y, Böhm M, Probst M, Empen K, *et al.* Role of immunoglobulin G3 subclass in dilated cardiomyopathy: Results from protein A immunoadsorption. *Am Heart J* 2005;**150**:729–736. https://doi.org/10.1016/j.ahj.2004.11.002
28. Staudt A, Hummel A, Ruppert J, Dörr M, Trimpert C, Birkenmeier K, *et al.* Immunoadsorption in dilated cardiomyopathy: 6-month results from a randomized study. *Am Heart J* 2006;**152**:712.e1–712.e6. https://doi.org/10.1016/j.ahj.2006.06.027
29. Bristow MR, Kao DP, Breathett KK, Altman NL, Gorcsan J III, Gill EA, *et al.* Structural and functional phenotyping of the failing heart: Is the left ventricular ejection fraction obsolete? *JACC Heart Fail* 2017;**5**:772–781. https://doi.org/10.1016/j.jchf.2017.09.009
30. Abboud A, Januzzi JL. Reverse cardiac remodeling and ARNI therapy. *Curr Heart Fail Rep* 2021;**18**:71–83. https://doi.org/10.1007/s11897-021-00501-6
31. Hoffmann R, von Bardeleben S, ten Cate F, Borges AC, Kasprzak J, Firschke C, *et al.* Assessment of systolic left ventricular function: A multi-centre comparison of cineventriculography, cardiac magnetic resonance imaging, unenhanced and contrast-enhanced echocardiography. *Eur Heart J* 2005;**26**:607–616. https://doi.org/10.1093/eurheartj/ehi083

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