Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Therapeutic effect of immunoadsorption and subsequent immunoglobulin substitution in patients with dilated cardiomyopathy: Results from the observational prospective Bad Berka Registry

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ARTICLE INFO

Article history:
Received 14 February 2016
Received in revised form 8 July 2016
Accepted 22 July 2016
Available online xxx

Keywords:
Dilated cardiomyopathy
Inflammatory
Immunoadsorption
Quality of life

ABSTRACT

Background: Elimination of cardiac autoantibodies, frequently detected in patients with dilated cardiomyopathy (DCM), with immunoadsorption (IA) improves functional capacity and left ventricular (LV) function. This study aimed to prospectively address this issue in a large cohort of unselected patients.

Methods: Consecutive patients undergoing IA followed by IgG substitution were included. Clinical and echocardiographic parameters were assessed at baseline (BL) and 12-month follow-up (FU). Patients were classified as IA responders when ≥2 of the following criteria were achieved: improvement in the Minnesota Living with Heart Failure Questionnaire (MLHFQ) ≥5 points, symptoms [≥1 New York Heart Association (NYHA) class], LV ejection fraction (EF) ≥10% or decrease in LV end-diastolic diameter (EDD) ≥10%, or N-terminal pro B-type natriuretic peptide (NT-pro-BNP) ≥50%.

Results: 93 patients (median age 61 years, LVEF 30%, duration of symptoms 14 months, 87% in NYHA class III/IV, >90% treated with β-blocker/angiotensin-converting enzyme inhibitor) were included. When the entire cohort was analyzed, a significant improvement in MLHFQ (50 vs. 26 points), NYHA-class (median 3.0 vs. 2.0), LVEF (30% vs. 38%), LVEDD (62 vs. 59 mm), NT-pro-BNP (892 vs. 523 pg/ml) was observed at FU ($p < 0.05$ for all). 48% ($n = 43$) were classified as responders. Those were characterized by a shorter disease duration (11 vs. 22 months), larger BL LVEDD (64 vs. 60 mm), presence of >1 viral genome, and higher values of mononuclear inflammatory cells at endomyocardial biopsy. Sixteen (17.2%) patients experienced IA related complications.

Conclusions: A positive response is observed in 48% of inflammatory DCM patients undergoing IA, and this translates into a significant improvement in clinical and echocardiographic parameters.

Introduction

Dilated cardiomyopathy (DCM) and inflammatory DCM (DCMi) refer to a heterogeneous group of conditions in which autoimmunity plays a major role and progressive cardiac chamber dilatation and remodeling finally leads to congestive heart failure [1]. Numerous autoantibodies against myocyte structural and functional proteins, muscarinic and β1-adrenergic receptors have been detected in patients affected from DCM/DCMi [1,2], and animal models have proved the pathogenic roles of autoantibodies [3,4]. In addition, plasmapheresis of cardiac autoantibodies in patients with DCM/DCMi and subsequent immunoglobulin (Ig) G substitution resulted in significant increase in cardiac index, left ventricular ejection fraction (LVEF), improvement in endothelial function [5], and symptom relief [6–9].

Because immunoadsorption (IA) outcomes on patients' physical status perception and emotional well-being has never been investigated, this observational study was aimed to prospectively assess the effects of IA on heart-related quality of life (QOL), cardiac performance, and clinical parameters in a large cohort of unselected patients.

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http://dx.doi.org/10.1016/j.jjcc.2016.07.014
0914-5087/

Materials and methods

Between January 2008 and January 2015, all consecutive patients with symptomatic [New York Heart Association (NYHA) classifications II to IV] LV dysfunction (LVEF $\leq$ 45%) undergoing IA at Zentralklinik Bad Berka Hospital were included. Relevant coronary heart disease was excluded in all by angiography. Patients were required to be under stable oral medication with maximal tolerated dose of angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, betablockers, and aldosterone antagonists, for at least 3 months to be enrolled in this registry. A relevant proportion of the patients were already under treatment with implantable cardiac devices [implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy (CRT), or cardiac contractility modulation (CCM)]. Cardiac contractility modulation is a treatment for patients with moderate to severe LV systolic heart failure (NYHA class II–IV) and acts on the cardiac muscle during the absolute refractory period via specific electrical signals generated by the pulse generator. Signals are applied approximately 30 ms after onset of the QRS complex. The signal consists of two bi-phasic pulses with an amplitude of $\pm$7.7 V and with a total signal duration of about 20 ms [10]. Exclusion criteria for IA were acute infectious diseases, cancer, chronic alcoholism, and heart failure due to known origins (e.g. valvular heart disease). The investigation conforms to the principles of the Declaration of Helsinki, written informed consent was obtained from each patient, and the protocol was approved by the Ethics Committee of the Zentralklinik Bad Berka, Germany.

Immunoadsorption and subsequent immunoglobulin G substitution

Patients underwent IA on five consecutive days using protein-A columns (Immunosorba, Fresenius Medical Care AG, Bad Homburg, Germany) with an improved treatment regimen for IgG-3 reduction [8,9]. After the last IA session, all patients received 0.5 g/kg polyclonal IgG (Privigen, CSL Behring, Germany) to restore IgG plasma levels [8,9] (Fig. 1).

Histological and immunohistological analyses and detection of viral genomes

Whenever possible, patients underwent endomyocardial biopsy before IA, and nested PCR/RT-PCR (polymerase chain reaction/reverse transcription polymerase chain reaction) was performed to detect viral genomes [11]. Myocarditis/DCMi was diagnosed at immuno-histochemical analysis, and identification of cardiac immune cells (CD3+ and CD45+ T lymphocytes and/or CD68+ macrophages), and measurement of human leukocyte antigen class I and II expression was performed as previously described [12].

For immunohistological staining, paraffin-embedded tissue sections were treated with an avidin-biotin-immunoperoxidase method according to the manufacturer's protocol (Vectastain Elite ABC Kit, Vector, Burlingame, CA, USA). The following monoclonal antibodies were applied for identification, localization, and characterization of mononuclear cell infiltrates: CD3 for T cells (DAKO, Hamburg, Germany), CD45RO clone UCHL1 for activated T-cells (DAKO), MAC 387 for macrophages and natural killer cells (Linares, Dossenheim, Germany), HLA-ABC clone w6/32, and HLA-DP clone CR3/43 (DAKO) to assess HLA class I or II expression in professional antigen-presenting immune cells, respectively. For assessment of CD54/ICAM clone 1304 (Biologo, Kronshagen, Germany) was used. CD54/ICAM is an endothelial- and leukocyte-associated transmembrane protein long known for its importance in stabilizing cell–cell interactions and facilitating leukocyte endothelial transmigration. The amount of endothelial or interstitial HLA activation was graded by the pathologist into 4 grades (1: low activation; 2: low-intermediate activation; 3: intermediate activation; 4: strong activation).

To quantify the inflammatory cell infiltration, we examined sections using a high-power objective and counted the number of

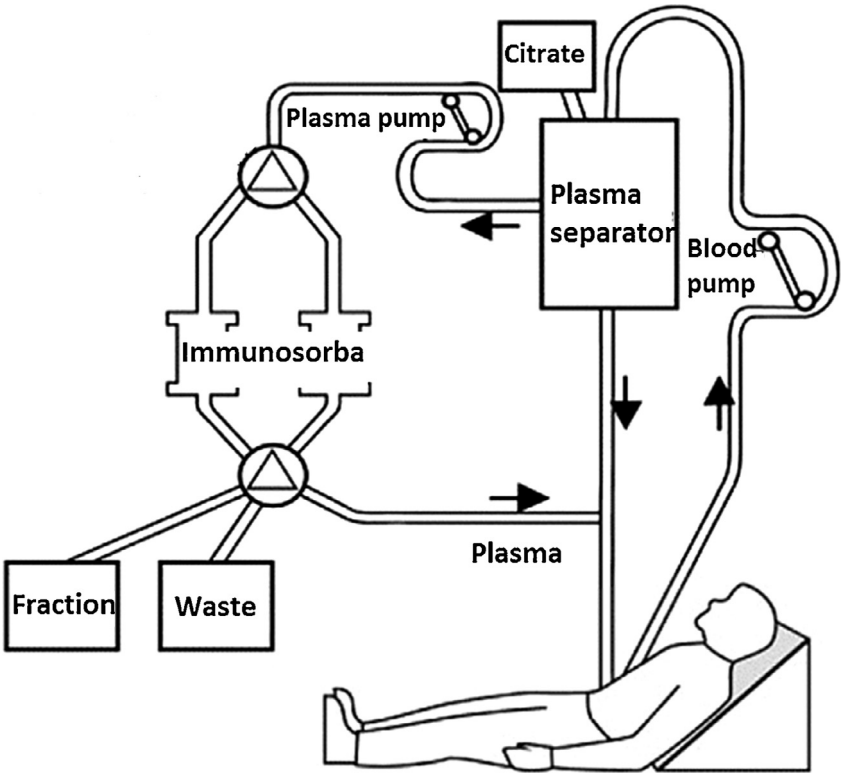

Fig. 1. Immunoadsorption using the Immunosorba column (Fresenius Medical Care, Bad Homburg, Germany).

Please cite this article in press as: Ohlow M-A, et al. Therapeutic effect of immunoadsorption and subsequent immunoglobulin substitution in patients with dilated cardiomyopathy: Results from the observational prospective Bad Berka Registry. J Cardiol (2016), http://dx.doi.org/10.1016/j.jjcc.2016.07.014