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Steroid withdrawal and reduction of cyclosporine A under mycophenolate mofetil after heart transplantation ☆

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ABSTRACT

Survival and quality of life after heart transplantation are limited by a significant incidence of cardiovascular complications. Side effects of immunosuppressives contribute unfavorably. Aim of this study was to determine (1) whether withdrawal of corticosteroids and dose reduction of cyclosporine A can be performed safely under immunosuppressive therapy with mycophenolate mofetil and (2) if this is beneficial for renal function and cardiovascular risk reduction. Long term heart transplant recipients on steroids and cyclosporine A were examined in a monocentric, prospective, single-arm cohort study. Steroids were withdrawn, mycophenolate mofetil introduced and cyclosporine A dose reduced (target level 50–90 ng/ml). Follow up was 24 months. 23 patients were analyzed: Renal parameters (creatinine, urea, uric acid) improved significantly ($p<0.01$), as did cardiovascular parameters (heart rate [$p<0.05$], systolic and diastolic blood pressure [$p<0.01$]), HbA1c ($p<0.05$) and triglycerides ($p<0.05$). In contrast, the self-percepted state of health (SF36™) decreased. Drop outs occurred mostly due to steroid withdrawal syndrome [$n=7$]. The incidence of adverse events reflected the usual course after heart transplantation. We conclude that CS free immunosuppression comprising reduced cyclosporine levels and addition of MMF in long term heart transplant recipients is safe and improves the cardiovascular risk profile, carbohydrate metabolism and renal function.

1. Introduction

Adapting therapeutic protocols succeeded in reducing mortality after heart transplantation (HTX) during the first 6–12 months. Recently, a one-year survival rate of 86% and a HTX half-life of 11 years have been reported. However, the long term attrition rate and the survival curve appear unchanged [1]: Survival and quality of life are limited by chronic transplant rejection and an elevated risk of cardiovascular disease and mortality approximates to ~3.5% per year. Introduction of cyclosporine A (CsA) to the immunosuppressive therapy improved the outcome after HTX [2]. However, toxic side effects contribute to long term morbidity and mortality, frequently comprising severe cardiovascular and renal toxicity as early as 1.5 years post-cardiac transplant [3–5]. Preexistent ischemic cardiomyopathy was disclosed as a major cause for post cardiac transplant mortality, but the presence of ≥2 classical cardiovascular risk factors outweighed this effect [6]. Developing chronic allograft vasculopathy (CAV) is the most frequent cause for 5-year post cardiac transplant mortality [7]. Chronic renal insufficiency also leads to a significant increase of post cardiac transplant mortality (relative risk 4.55) [8], and calcineurin (CNI)-nephrotoxicity plays a major role in the development of chronic renal insufficiency [9]. CNI-associated nephrotoxicity seems to be irreversible once the serum-creatinine reached 3.5 mg/dl [10]. 10 years after transplantation (TX), the prevalence of maintenance renal replacement therapy is about 5% [7]. Corticosteroids (CS) have been crucial for successful organ transplantation both for prophylaxis and treatment of rejection [11]. Long term adverse effects comprise cardiovascular risk factors, e.g. hypertension, hyperlipidemia, obesity and diabetes and increased cardiovascular morbidity [12]. The risk of myocardial infarction in long term steroid treatment increased by >20% [13]. The increased cardiovascular risk seems to be related to the high prevalence of CAV [14,15]. Acknowledging the importance of harmful effects of CS and CNI, withdrawal strategies have been conceived,

Abbreviations: AE, adverse events; ANOVA, analysis of variance; AUC, area under curve; BMI, body mass index; BUN, blood urea nitrogen; CAV, chronic allograft vasculopathy; CNI, calcineurin inhibitors; CPET, cardiopulmonary exercise test; CRH, cortisol releasing hormone; CRS, cardio renal syndrome; CS, corticosteroids; CsA, cyclosporine A; ED, endothelial dysfunction; ESRD, end stage renal disease; GFR, glomerular filtration rate; HDL, high density lipoprotein; HTX, heart transplantation; ISHLT, International Society for Heart- and Lung Transplantation; IST, immunosuppressive therapy; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; MHH, Medizinische Hochschule Hannover; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; SAE, serious adverse events; SF-36, short form health survey; SWS, steroid withdrawal syndrome; TG, triglycerides; TX, transplantation.

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many of these involving the use of mycophenolate mofetil (MMF) that does not induce hypertension and is supposedly not nephrotoxic [16]. Addition of MMF to reduce CNI significantly improved renal function [17] and other co-morbidities relevant to the development of CAV [10,18,19]. Studies on post-transplant steroid reduction using MMF also showed improved metabolic parameters [20–22], and proved that a safe steroid withdrawal is possible [20,22–27].

Withdrawal of CS and reduction of the CNI dose may improve long-term survival in post-cardiac transplant patients. The aim of this study was to investigate the effectiveness, safety and compatibility as well as preservation of kidney function, influence on cardiovascular risk profile and effects on health status and quality of life of a steroid free immunosuppressive regimen comprising a reduced cyclosporine A dose in combination with MMF in long term HTX.

2. Materials and methods

The study was designed as a non-randomized, prospective, single-armed monocentric conversion treatment study. The study protocol was approved by the ethics committee of the Hannover Medical School (MHH) and conducted according to the declaration of Helsinki. The study was registered at www.clinicalTrials.gov [Identifier NCT00359658]. After the recruitment period of 18 months, patients were followed-up for 24 months at the MHH, Germany. Inclusion criteria were: Heart transplantation more than 3 years prior to inclusion, current immunosuppressive therapy with CsA and CS since at least 6 months, age between 18 to 75 years, serum-creatinine <3.5 mg/dl (310 μmol/l) and blood urea nitrogen (BUN) ≤150 mg/dl, CsA trough concentration 50–250 ng/ml during the last 12 months prior to inclusion, and a written informed consent by patient or legal representative. Exclusion criteria were: Malignancy during the last 3 years, acute rejection ≥3A or 2R according to The International Society of Heart & Lung Transplantation (ISHLT)-criteria (31, 33) within the last 6 months, acute infection, hepatitis B, −C, or HIV, leucopenia <3000/μl, hemoglobin <9 g/dl, platelets <70.000/μl, acute gastric ulcerative disease, need for renal replacement therapy during the last 4 weeks, pregnancy, breast-feeding, taking of immunosuppressive drugs other than cited within the inclusion criteria, current participation in different study, history of allergic reaction to MMF and psychiatric disorder. Study participation was terminated if one of the following criteria became obvious: Sepsis or acute rejection ≥ ISHLT 3A or 2R (biopsy proven) or decline of TX function, consent withdrawal or significant impairment of any of the above given endpoints noticed at the intermediate analysis after 6 and/or 12 months. Myocardial biopsies were performed at regular intervals according to standard procedures during the first year after TX. During the study interval Bx were conducted if rejection was suspected. Immunosuppressive therapy (IST) was prescribed as following: CS were tapered by 0.5 mg weekly until withdrawal. MMF was started on day one with 2×250 mg and increased by 250 mg/week to a final dose of 2–3 g/d (intended trough level 2–4 mg/l and mini area-under curve (AUC) 30–60 $ng \times ml^{-1} \times h^{-1}$ followed by a CsA dose reduction to a blood trough level of 50–90 ng/ml). Patients were followed-up for 24 months; interim analyses were performed after 6, 12 and 18 months. Outcome measures: Primary endpoint was improved preservation of kidney function. Secondary endpoints were: first, improvement of cardiac risk profile as determined by blood pressure, lipid status (cholesterol, HDL, LDL, triglycerides), blood glucose (Hba1c), uric acid, and BMI; second, safety of immunosuppressive therapy as determined by occurrence of acute rejection, LVEF, gastrointestinal adverse events, opportunistic infections, organ dysfunction, neoplasia and further severe adverse events; third, improvement of health status and quality of life as documented by the SF-36™ questionnaire [28] and improvement of physical fitness shown by cardiopulmonary exercise testing (CPET). The endpoint related variables were determined as: TX-heart function/-rejection: Echocardiography, 12-channel electrocardiography, heart biopsy in case of suspected rejection; kidney function: serum creatinine and BUN; safety: documentation of possible severe adverse events and its therapy; general performance: CPET; and health status and quality of life: SF-36™-questionnaire. In addition a complete blood count and a broad panel of clinic-chemical parameters were determined. During the follow-up outpatient visits, therapy was initiated if needed for achievement of the following clinical goals: blood pressure below 135/85 mmHg, total cholesterol <5.0 mmol/l, LDL-cholesterol <3.0 mmol/l, HDL-cholesterol >1.0 mmol/l, triglycerides <2.0 mmol/l, control and regulation of glucose metabolism, control of uric acid (prescription of allopurinol if >500 μmol/l), control of body weight and providing of individual diet sheet. Statistical analysis was done per protocol. Independent data of equal variance were tested by two-tailed Student's *t*-test. Independent data of non-equal variance were tested by Wilcoxon-matched-pairs test. MacNemar-test was used for qualitative testing of dependent variables. Distribution of qualitative variables was compared by Chi-Square test with Fisher's exact test. Calculation of AUCs was used for longitudinal comparison of quantitative data as was one-sided ANOVA for comparison of univariate mean values. Significance was accepted as $p<0.05$. Quality of data was depicted by calculation of 95% confidence intervals.

3. Results

40 patients (33 males, 7 females) at mean age of 56.5 years were included. Mean time after transplantation was 13.2 ± 2.9 years. CAV was present in 21 patients, no patient had a coronary artery bypass, and 7 had coronary stents at baseline (Table 1). 17 participants dropped out early. 7 of these dropped-out due to CS withdrawal syndrome, four due to MMF intolerance, in three patients pre-existing co-morbidities aggravated, and two due to suspected acute rejection. In one of these, MMF blood levels were low and fluctuating giving reason to suspect non-compliance. 23 patients completed the study (Fig. 1). Immunosuppressive therapy: Adjusting IST levels according to the study protocol was successfully performed: Mean CsA blood levels were lowered about 15% from 107 to 81.4 ng/ml. The MMF daily dose was 2 g after 8 weeks and 2.1 g after 2 years. The trough levels rose from 1.5 to 2.0 mg/l. The mini-AUC was 44.6 $ng \times h^{-1} \times ml^{-1}$ after 3 and 45.5 $\times h^{-1} \times ml^{-1}$ after 6 months. Hence MMF was adjusted well to the intended blood levels. The mean daily steroid dose was 4.9 mg at baseline. Primary endpoint: Reduction of CsA significantly improved kidney function. Serum creatinine decreased from 146.3 ± 40.3 to 129.5 ± 33.3 μmol/l ($p<0.01$). Estimated GFR therefore increased by about 14%. Accordingly, plasma urea and uric acid decreased from 12.1 ± 4.67 to 10.2 ± 3.47 mmol/l, ($p<0.01$) and 450.2 ± 103 to 354 ± 59.8 μmol/l ($p<0.001$) respectively (Fig. 2). Secondary endpoints: The cardiac risk profile was improved after two years. Calculated by a

Table 1
Characteristics of the study population.

		N (%)	Mean	SD
Age	Total	40	56.5	11.3
	Male	33 (82.5)	56.2	11.7
	Female	7 (7.0)	57.7	9.6
HTX-age		40	13.2	2.9
Last coronary angiography (y)		40	1.7	1.2
Underlying condition				
	DCM	28 (70.0)		
	ICM	10 (17.5)		
	Myocarditis	1 (2.5)		
	Valvular	1 (2.5)		
CAV		21 (52.5)		
Bypass		0 (0)		
Stent		7 (17.5)		

HTX: Heart transplantation; CAV: transplant vasculopathy; DCM: dilatative cardiomyopathy; and ICM: ischemic cardiomyopathy.