Ten-Year Results of a Randomized Trial Comparing Tacrolimus Versus Cyclosporine A in Combination With Mycophenolate Mofetil After Heart Transplantation

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Background. Long-term results of prospective randomized trials comparing triple immunosuppressive strategies combining tacrolimus (TAC) or cyclosporine A (CsA) with mycophenolate mofetil (MMF) and steroids after heart transplantation (HTX) are rarely published. Therefore, we collected long-term follow-up data of an intervention cohort 10 years after randomization.

Methods. Ten-year follow-up data of 60 patients included in a prospective, randomized trial between 1998 and 2000 were analyzed as intention-to-treat (TAC-MMF n=30; CsA-MMF n=30). Baseline characteristics were well balanced. Cardiac allograft vasculopathy (CAV) was graduated in accordance with the new ISHLT classification.

Results. Survival at 1, 5, and 10 years was 96.7%, 80.0%, and 66.7% for TAC-MMF and 90.0%, 83.3%, and 80.0% for CsA-MMF (*P*=ns). Freedom from acute rejection (AR) was significantly higher in TAC-MMF versus CsA-MMF (65.5% vs. 21.7%, log-rank 8.3, *P*=0.004). Freedom from ISHLT$\geq$CAV$_1$ after 5 and 10 years was in TAC-MMF 64.0% and 45.8%, and in CsA-MMF 36.0% (log-rank 3.0, *P*=0.085) and 8.0% (log-rank 9.0, *P*=0.003). No difference in long-term results for freedom from coronary angioplasty or stenting, renal dysfunction, diabetes mellitus, CMV infection, or malignancy was detected.

Conclusion. Cross-over effects because of treatment switch may result in impairment of significance between the groups. The long-term analysis resulted in a significant difference in manifestation of CAV between the groups after 10 years. Less rejection in the TAC-group might have contributed to the lower incidence of CAV. Superior freedom from AR and CAV in the TAC-MMF group did not result in better long-term survival.

Keywords: Heart transplantation, Tacrolimus, Cyclosporine A, Cardiac allograft vasculopathy, Long-term.

S ince TAC was introduced into the clinic in 1989 (*1–5*), it progressively replaced CsA as calcineurin inhibitor (CNI) after HTX (*6*). One of the first prospective, randomized

studies comparing CsA and TAC after HTX demonstrated both CNI with the same efficacy and safety but with a trend to less acute rejections for treatment with TAC (*7*). MMF, clinically approved in 1995, was associated with a superior prevention of acute rejection compared with Azathioprine (AZA) in combination with CsA and corticosteroids (CS) in renal transplant recipients (*8*). The improvement of 1-year mortality and less acute rejection during the first year after HTX was verified for MMF as a substitute for AZA (*9*). In 1998, we designed a prospective randomized study to determine whether TAC or CsA is the better partner for MMF after HTX (*10*). The results 2 years after randomization presented both CNI as adequate and effective partners with MMF to prevent acute rejection in heart transplant recipients. In patients treated with TAC-MMF, significantly fewer rejections were observed. Patients treated with CsA-MMF needed significantly higher doses of MMF to achieve the MPA target levels. With respect to CAV, no significant difference between the treatment groups was discovered; however, a more pronounced intimal proliferation was detected in the CsA-MMF group. Despite no differences in 2-year survival, we concluded

that the short-term results of this randomized trial indicate the superiority of TAC over CsA as better partner for MMF after HTX (10).

Other prospective, randomized studies comparing TAC and CsA (10–20) also presented short- or mid-term results based on follow-up periods from 6 months to 3 years and in one case of 5 years (17).

The ISHLT registry detected a median survival of 11 years for the entire cohort of adult and pediatric heart recipients since initiation of the Registry in 1982 (6).

In view of the numerousness of heart recipients who fortunately live more than 5 years after transplantation, the question occurs whether the beneficial early results for TAC observed in our prospective, randomized study could be confirmed with longer follow-up and whether there will be an impact on long-term outcome.

RESULTS

Baseline Characteristics and Patient Accounting

Patient demographic and baseline characteristics shown in Table 1 were equally distributed across both treatment groups. Because of death, the mean follow-up period was 9.1±3.3 years in TAC-MMF ITT and 8.8±4.0 years in CsA-MMF ITT (P=0.712). There was no dropout of the randomized 60 patients but missing data in subcategories. Switch to another immunosuppressive drug did not result in exclusion from the ITT analysis. Because one patient of the TAC-group moved to another transplantation center, only his survival data were analyzed. Baseline coronary angiography detected preexisting coronary artery disease in one patient of each group.

Survival

Causes of death in the TAC-group were cancer (n=4, 3.4, 4.0, 4.3, and 5.7 years), acute rejection (n=2, 5.6, and

7.2 years; the second case because of noncompliance in taking medications), systemic aspergillosis (n=1, 45 days), sepsis (n=1, 2.6 years), ileus (n=1, 2.0 years), and multi-organ failure (n=1, 8.2 years). Regarding the CsA group, there was death because of cardiovascular complications (n=3, 190 days, 2.9 and 3.7 years), systemic aspergillosis (n=2, 10 and 12 days) and cancer (n=1, 6.2 years).

There was no statistical difference in long-term survival between the treatment groups (Fig. 1). Survival after 1 year was 93.3% (log-rank 1.1, P=0.301): in TAC-MMF ITT 96.7% (n=29), and in CsA-MMF ITT 90.0% (n=27); after 5 years, 81.7% (log-rank 0.1, P=0.800): in TAC-MMF ITT 80.0% (n=24), and in CsA-MMF ITT 83.3% (n=25); and after 10 years, 73.3% (log-rank 1.0, P=0.308): in TAC-MMF ITT 66.7% (n=20), and in CsA-MMF ITT 80.0% (n=24). Patients who had never been switched to another immunosuppressive drug during treatment presented with inferior survival without statistical significance (69.8%, P=0.369).

Acute Rejection

TAC-MMF–treated patients had significantly lower rates of rejection episodes than the CsA-MMF–treated patients as shown in Figure 2. Freedom from acute rejection after 1 year was 47.5% in the study cohort with considerable benefit of TAC-MMF (log-rank 6.1, P=0.013): in TAC-MMF ITT 65.5% (n=19), and in CsA-MMF ITT 30.0% (n=9); after 5 years, 44.1% (log-rank 8.3, P=0.004): in TAC-MMF ITT 65.5% (n=19), and in CsA-MMF ITT 23.3% (n=7); after 10 years 42.4% (log-rank 8.2, P=0.004): in TAC-MMF ITT 65.5% (n=19), and in CsA-MMF ITT 21.7% (n=6). Mean freedom from acute rejection was in TAC-MMF ITT 6.6 y±0.8 years, and in CsA-MMF ITT 2.9±0.8 years (95% CI 4.9–8.3 and 1.4–4.4 years).

Variance analysis on AR onset detected for MPA levels during the first year a trend (P=0.051), and for ischemic time

TABLE 1. Patient demographic and baseline characteristics

Characteristics	TAC-MMF ITT	CsA-MMF ITT	P
No. of patients	30	30	1.0
Mean follow-up time (yr)	9.1±3.3	8.8±4.0	0.712
Mean donor age (yr)	38±14	42±13	0.297
Mean recipient age (yr)	55±1	55±12	0.824
Donor sex (M/F)	16/14	18/12	0.795
Recipient sex (M/F)	26/4	24/6	0.731
Sex mismatch (recipient M/F)	10/0	7/1	0.347
Primary diagnosis			
Dilated CMP	15	15	1.0
Ischemic CMP	15	15	1.0
CMV IgG Donor +	13	11	0.396
CMV IgG Recipient -	13	14	0.5
CMV Donor +/Recipient -	6	6	1.0
CMV prophylaxis postoperative	9	11	0.392
Mean ischemic time (h)	3.4±1.1	3.2±0.9	0.281
Operation duration (h)	4.7±0.9	4.4±1.0	0.480
ICU (d)	9.1±11.1	7.3±8.9	0.248
Ventilation postoperative (d)	2.5±2.9	3.2±5.4	0.627

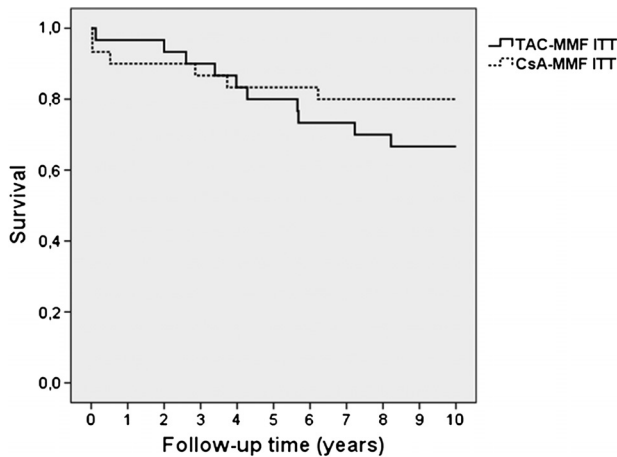mean±SD; CMP, cardiomyopathy; +, positive; -, negative.

FIGURE 1. Survival: Kaplan-Meier analysis for 10 years after HTX (difference between the ITT groups: log-rank 1.0, P=0.308).

a significant impact (P=0.027). Adjusted for early MPA levels and ischemic time, there was less AR in TAC-MMF ITT group (OR 5.1, 95% CI 1.4–18.3, P=0.013). Comparing patients with and without AR within the same ITT, there were no differences in MPA and TAC, respectively, CsA levels. Isolated analysis of patients treated continuously with the randomized immunosuppressive drug (n=43) showed comparable results with a freedom from AR of 46.5% 10 years after HTX (log-rank 9.8, P=0.002): in TAC-MMF 68.0% (n=17), and in CsA-MMF 16.7% (n=3).

Freedom From Treatment Failure

Treatment failure resulted in switch to another primary immunosuppressive drug. Four patients (13.8%) of the TAC group were switched to another immunosuppressive drug, three patients to sirolimus (SIR) because of renal dysfunction (3.9, 4.4, and 9.4 years), and one patient to CsA because of neuropathy (10 days). In the CsA group, 12 patients
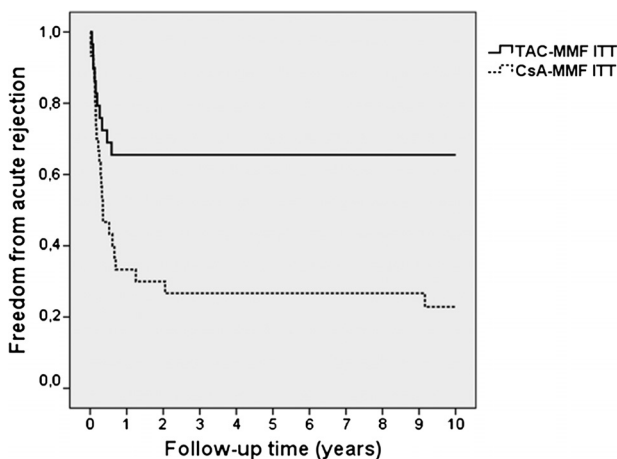
(40.0%) were changed, two patients to SIR because of renal dysfunction (1.9 and 3.2 years), five patients to TAC because of AR (8, 13, and 67 days, and 1.1 and 1.3 years), one patient to SIR because of AR but renal dysfunction (2.4 years), and one patient in each group to SIR because of neuropathy (4.9 years), to TAC because of gingival hyperplasia (1.5 years), to everolimus (EVE) because of CAV (7.0 years) and to TAC because of osteoporosis (2.0 years).

As shown in Figure 3, 1-year freedom from treatment failure was 93.2% in the study cohort without difference between ITT (log-rank 1.1, P=0.308): in TAC-MMF ITT 96.6% (n=28), and in CsA-MMF ITT 93.3% (n=27); and after 5 years 79.7% (log-rank 3.7, P= 0.054): in TAC-MMF ITT 89.7% (n=26), and in CsA-MMF ITT 70.0% (n=21); and after 10 years, freedom from treatment failure was 72.9% with significantly less switch in TAC-MMF ITT (log-rank 4.8, P=0.029): in TAC-MMF ITT 86.2% (n=25), and in CsA-MMF ITT 60.0% (n=18).

Cardiac Allograft Vasculopathy

As shown in Figure 4, freedom from CAV ISHLT$\geq$CAV$_1$ onset was 96.4% in the TAC group vs. 88.5% in the CsA group (log-rank 1.2, P=0.281) after 1 year, 64.0% in the TAC group vs. 36.0% in the CsA group (log-rank 3.0, P=0.085) after 5 years; and 45.8% in the TAC group vs. 8.0% in the CsA group (log-rank 9.0, P=0.003) after 10 years. The mean time until the first diagnosis of CAV confirmed by coronary angiography was 7.8±0.8 years in the TAC group and 4.6±0.7 years in the CsA group (95% CI 6.2–9.4 years and 3.3–5.9 years). Variance analysis on CAV onset could not prove any impact of the common risk parameters such as AR (P=0.566), donor age (P=0.124), diabetes mellitus (P=0.805), LDL and cholesterol levels (P=0.979 and P=0.355), systemic blood pressure (P=0.398), and positive CMV titer (P=0.792). In contrast, CsA-MMF was a significant risk factor in the multivariate analysis (OR 3.6; 95% CI 1.1–11.4; P=0.031).

One patient of the CsA group underwent coronary artery bypass grafting (7.89 years) because of severe CAV. The patient has a simvastatine intolerance.

FIGURE 2. Freedom from acute rejection: Kaplan-Meier analysis for 10 years after HTX (difference between the ITT groups: log-rank 8.2, P=0.004).
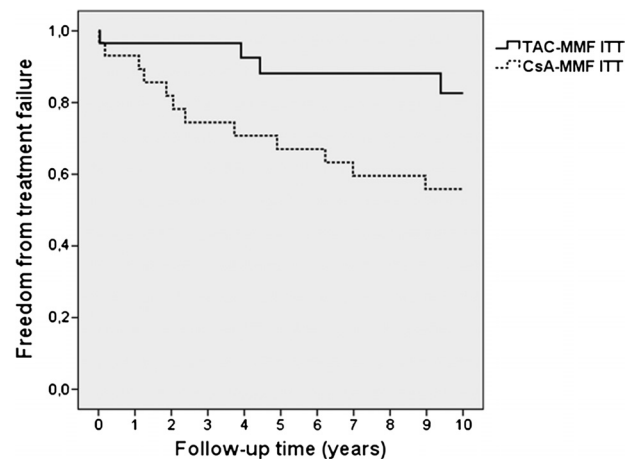

FIGURE 3. Freedom from treatment failure: Kaplan-Meier analysis for 10 years after HTX (difference between the ITT groups: log-rank 4.8, P=0.029).
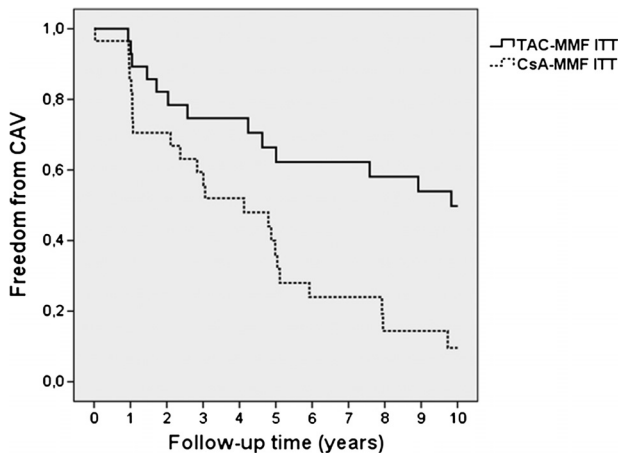
FIGURE 4. Freedom from CAV: Kaplan-Meier analysis for 10 years after HTX (difference between the ITT groups: log-rank 9.0, *P*=0.003).

Freedom from coronary stenting after follow-up was 87.5% (log-rank 0.2, *P*=0.693).

Regarding the continuous treatment groups without switch to another immunosuppressive drug, there were 11 of TAC-treated patients and only three of CsA-treated patients without CAV after 10 years of follow-up.

Treatment Dosages and Resulted Trough Level

Within the first 5 years and within the 10 years of follow-up, administered TAC mean dosage of 4.1±2.0 mg/day and 3.8±2.2 mg/day resulted in mean trough levels of 10.7±0.9 ng/mL and 9.9±1.0 ng/mL, and a CsA mean dosage of 200±41 mg/day and 184±45 mg/day resulted in mean trough levels of 157±28 ng/mL and 132±39 ng/mL. Only within the first 3 months of study duration, the MPA levels (TAC-MMF ITT 3.1±1.0 vs CsA-MMF ITT 2.2±0.6 µg/mL; *P*=0.003) were significantly lower in the CsA-MMF–treated patients, despite higher MMF doses.

Cytomegalovirus

There was no difference between the ITT groups about preoperative CMV status and postoperative CMV prophylaxis (Table 1). Freedom from positive CMV titer was 58.6% in the TAC group and 73.3% in the CsA group (log-rank 1.8, *P*=0.186). In two cases of the TAC-MMF ITT and three cases of CsA-MMF ITT, there were severe CMV infections, which required hospital admission. There were no causes of death related to CMV infections.

Adverse Effects

Only at 5-year follow-up, there was a significantly higher creatinine detected in the CsA group (1.60±1.21 mg/dL in TAC-MMF ITT vs. 1.65±0.39 mg/dL in CsA-MMF ITT, *P*=0.014), which cannot be reconfirmed at 10-year follow-up (1.45±0.62 mg/dL in TAC-MMF ITT vs. 1.75±0.65 mg/dL in CsA-MMF ITT, *P*=0.120). After 5 and 10 years, creatinine levels of 2.0 mg/dL or greater were found in 13.0% and 22.2% in the TAC group and in 28.0% (*P*=0.180) and 41.7% (*P*=0.161) in the CsA group. Permanent hemodialysis was inevitable in one patient of the CsA group. Within the group of patients with drug application as randomized over the whole time of follow-up, there seemed to be a benefit for TAC-MMF over CsA-MMF in long-term creatinine measurement (5-year follow-up: 1.39±0.61 mg/dL vs. 1.74±0.36 mg/dL, *P*=0.005; and 10-year follow-up: 1.34±0.61 mg/dL vs. 1.91±0.63 mg/dL, *P*=0.012), despite comparable baseline creatinine levels (1.46±0.91 mg/dL vs. 1.15±0.23 mg/dL, *P*=0.298).

Antidiabetic treatment (oral and/or insulin) was necessary in 13.6% in the TAC group and in 16.7% in the CsA group (*P*=0.551) at 5-year follow-up, and in 22.2% and in 18.2% (*P*=0.528) at 10-year follow-up.

During follow-up, 16 patients (27.1 %) developed malignancy without statistical difference between the ITT (*P*=0.252); 10 patients (34.5%) in TAC-MMF ITT and 6 patients (20.0%) in CsA-MMF ITT. Neoplasm of the skin was found in five patients in the TAC group and three patients in the CsA group, lymphoma in one case in each group, and solid tumors in four patients in the TAC group and two patients in the CsA group.

Immunosuppressant-associated side effects were as follows: gastrointestinal disorders in the three cases in the TAC group and one case in the CsA group, neuropathy in two cases in the TAC group and three cases in the CsA group, and osteoporosis in two cases in the TAC group and four cases in the CsA group. In TAC-MMF ITT, one patient experienced restless leg syndrome, and four patients in the CsA group developed gingival hyperplasia.

DISCUSSION

The study (*10*) was primarily designed for the first 2 years after HTX. This long-term results are predicated on routine examinations during follow-up period. Regarding long-term survival, there was no significant difference between the treatment groups. Because of the small study cohort, the study may be underpowered to detect differences in survival. Based on ITT analysis, it has to be considered that the additive shorter patient-years for randomized treatment with CsA versus TAC (190 versus 211 patient-years) improved long-term outcome including long-term survival by early switch to an individual beneficial primary immunosuppressive drug.

The definition of AR as ISHLT (*21*) grade II (2R) and higher or grade IB (1R) combined with clinical symptoms, which necessitated steroid therapy is based on clinical experiences in our transplantation center and was suitable to other randomized studies (*14, 16*). The benefit of TAC over CsA preventing AR after HTX was presented before (*13, 14, 16, 18, 20*). The ISHLT stated in the recommendations on the principles of immunosuppressive regimens in heart transplant recipients that the result of clinical trials suggest that TAC-based regimens may be associated with lower rejection rates but not with superior survival compared with CsA-based regimens (*22*). Our results emphasize this recommendation even with long-term results 10 years after HTX. The lower MPA level during the first 3 months after HTX in CsA-treated patients and the relatively high TAC levels maintained throughout the first year (11.8±1.9 ng/mL) may have contributed the significant difference in freedom from AR between the ITT groups. Antibody-mediated rejection was not routinely tested at our center.

The development of CAV is deemed to be one of the leading causes of posttransplant mortality particularly with increasing follow-up time: between 1 and 3 years after HTX, approximately 10% of deaths were shown to be associated with CAV (6), and 5 years after HTX, 32% of deaths were caused by CAV in addition with late-onset graft failure, which could be related to undetected CAV (23, 24). Prospective, randomized studies comparing TAC- and CsA-based immunosuppressive regimens after HTX reported a trend toward superior of preventing CAV for TAC (25, 26). However, no significant difference between both CNI regimens in angiographically detected CAV could be documented 5 years after HTX (17, 27). Reichenspurner (28) characterized CAV as histologic manifestation of chronic rejection after HTX, and he recognized the lack of long-term data for incidence of CAV in TAC- and CsA-treated heart recipients. In fact, and contrary to the current opinion because of absent evidence (27), our randomized study could unmask a significantly better freedom from CAV in the TAC-MMF ITT group but not until 10 years after HTX.

The duration and array of rejection episodes were described as risk for CAV development (29, 30). Both were not determined in this study. Stoica et al. (31) demonstrated that acute moderate and severe cellular rejection had a cumulative impact on CAV onset, whereas mild, untreated rejection was not associated with CAV. This subdivision was not considered in our study.

After 5 years of follow-up, there was a better creatinine level in TAC-MMF–treated patients, and almost twice the number of patients in CsA-MMF group had creatinine levels of 2.0 mg/dL or greater. Analysis of continuous randomized treatment indicated that TAC-MMF treatment resulted in lower creatinine levels, but a selection bias must be considered. Although the study cohort may be undersized to show differences between the treatment groups, we disclose a trend for TAC-MMF as beneficial therapy in renal function like presented by Kobashigawa et al. (18).

CONCLUSION

In 2000, 23% of heart recipients achieved TAC; in 2009, its use increased to 73%, whereas the use of CsA has decreased below 20% (6). There is no general preference about CsA or TAC as CNI-based therapy after HTX in the current ISHLT recommendations (22). Furthermore, no evidence of different CAV rates between CsA- and TAC-based therapies is documented by the ISHLT (27). We conclude that the lack of evidence is based on insufficient follow-up duration of randomized studies published so far. Despite the limitation because of the small study cohort, this study represents the first published prospective, randomized study comparing TAC versus CsA in combination with MMF over 10 years of follow-up including the new ISHLT nomenclature for CAV (32). Our long-term analysis resulted in a significant difference in manifestation of CAV between TAC-MMF– and CsA-MMF–treated patients. However, cross-over effects because of treatment switch may result in impairment of significance between the groups. However, superior freedom from AR and CAV in the TAC group did not result in better long-term survival.

MATERIALS AND METHODS

Patients

Complete 10-year follow-up data of 60 adult orthotopic heart transplant recipients of a prospective, open-label, single-center, randomized trial were analyzed. Between 1998 and 2000, all patients were 1:1 randomized to treatment with TAC (n=30) or CsA (n=30) both in combination with MMF as described previously (10). Exclusion criteria were age younger than 18 years, pregnancy or nursing, unwillingness or inability to use adequate contraceptions during the study, cardiac retransplantation, previous or multiorgan transplantation, human immunodeficiency virus–positive donor or recipient, serum creatinine greater than 2.5 mg/dL or elevated transaminases greater than 1.5 times above reference value, or participation in any other investigational drug study within 28 days of study entry. The study protocol was approved by the local ethics committee and was conformed to the Declaration of Helsinki. All patients gave written informed consent before inclusion.

University of Wisconsin solution was used as preservation medium. Patients underwent routine follow-up examinations including drug level monitoring, transvenous endomyocardial biopsy, echocardiography, and coronary angiography according to center practice.

Study Medication and Drug Monitoring

Study medication (initial intravenously, subsequent oral) was administered as described previously (10). Both CNIs and MMF were adjusted to target levels (TAC: month 0–6=13–15 mg/mL, month 7–12=10–12 mg/mL, second year=8–10 mg/mL, third to fourth year=6–8 mg/mL, fifth to tenth year= 4–7 mg/mL; CsA: month 0–6=200–300 mg/mL, month 7–24=150–200 mg/mL, third to tenth year=100–150 mg/mL; MPA: month 0–6=2.5–4.0 μg/mL, month 7 to tenth year: 1.5–2.5 μg/mL).

All patients received an intraoperative bolus of 500 mg methylprednisolone intravenously followed by 3×125 mg within the initial 24 hours after HTX. Prednisolone was weaned standardized without difference between the treatment groups; the therapy was given for 6 months and withdrawn in patients without repeated rejection episodes. None of the patients received induction therapy. Because statins are beneficial for survival after HTX (33), all patients received simvastatine routinely at a minimum dose of 5 mg/day or in case of persistent hypercholesterolemia (total cholesterol, >200 mg/dL or low-density lipoprotein cholesterol >140 mg/dL) at a maximum dosage of 20 mg/day.

Acute Rejections

Transvenous endomyocardial biopsies were performed routinely after 1, 2, 3, 4, 6, 8, and 10 weeks; after 3, 4, 5, 6, 9, 12, and 24 months; and when clinically indicated. Rejection was defined in adherence with the ISHLT (21) as histologic grade II (2R) and higher or grade IB (1R) combined with clinical symptoms, which necessitated steroid therapy or any treated rejection. According to the protocol in patients experiencing three rejection episodes, a switch of the primary immunosuppressant was mandatory.

Cardiac Allograft Vasculopathy

Diagnosis of CAV was based on coronary angiography. There was a baseline coronary angiography 1 month after transplantation for detecting preexisting coronary artery disease. Afterward, the examinations were carried out annually during the first years and increasingly infrequent when clinically not indicated. CAV was graduated in accordance with the new nomenclature for CAV published by the ISHLT in 2010 (32).

Statistical Analysis

Data are presented as ITT analysis unless otherwise indicated. Survival, freedom from acute rejection, treatment switch, and CAV were calculated using Kaplan-Meier analysis, and differences were assessed using log-rank test. As nonparametric test, the Wilcoxon rank-sum test was used. The chi-square test was performed to evaluate differences in adverse events. Influence of risk factors on AR and CAV onset were analyzed using logistic regression analysis. Numerical data are listed as mean±standard deviation (SD). A $P<0.05$ was considered significant.

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