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CLINICAL TRIAL

De novo sirolimus with low-dose tacrolimus versus full-dose tacrolimus with mycophenolate mofetil after heart transplantation—8-year results

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long-term study;
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nephrotoxicity;
malignancy

BACKGROUND: Although acute cellular rejection after heart transplantation (HTX) can be controlled by full-dose calcineurin inhibitor (CNI)–based immunosuppressive regimens, cardiac allograft vasculopathy (CAV), nephrotoxicity, and malignancy remain ongoing problems. To evaluate the potential beneficial effects of sirolimus and CNI reduction, we compared de novo low-dose tacrolimus and sirolimus with standard tacrolimus and mycophenolate mofetil (MMF)-based immunosuppression after HTX.

METHODS: We analyzed a long-term follow-up cohort of 126 patients who underwent HTX during the period 1998–2005 and received either de novo low-dose tacrolimus/sirolimus (lowTAC/SIR; $n = 61$) or full-dose tacrolimus/MMF (TAC/MMF; $n = 64$).

RESULTS: Freedom from treatment switch was less in the lowTAC/SIR group than in the TAC/MMF group (51.7% vs 73.0%, $p = 0.038$) 8 years after HTX. Freedom from acute rejection was 90.6% in the lowTAC/SIR group vs 80.3% in the TAC/MMF group ($p = 0.100$). There was no difference in freedom from International Society for Heart and Lung Transplantation CAV grade ≥ 1 (55.4% vs 60.0%, $p = 0.922$), time until CAV diagnosis (4.2 ± 2.0 years vs 3.2 ± 2.4 years, $p = 0.087$), and CAV severity ($p = 0.618$). The benefit of reduced early maximum creatinine for lowTAC/SIR treatment (1.8 ± 0.9 mg/dl vs 2.4 ± 1.1 mg/dl in TAC/MMF group, $p < 0.001$) did not continue 5 years and 8 years after HTX (1.4 ± 0.4 mg/dl vs 1.7 ± 1.2 mg/dl, $p = 0.333$, and 1.6 ± 1.1 mg/dl vs 1.6 ± 0.8 mg/dl, $p = 0.957$). The trend for superior survival at 5 years with lowTAC/SIR treatment (93.1% vs 81.3% in TAC/MMF group, $p = 0.051$) could not be confirmed after 8 years (84.7% vs 75.0%, $p = 0.138$). Multivariate analysis at 8 years did not reveal any benefit of lowTAC/SIR treatment.

CONCLUSIONS: Reduction of de novo CNI did not result in superior long-term renal function. Low-dose mechanistic target of rapamycin inhibition did not achieve any benefit in CAV prevention compared with full-dose TAC/MMF after HTX.

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According to the annual International Society for Heart and Lung Transplantation (ISHLT) registry reports, cardiac allograft vasculopathy (CAV), renal failure, and malignancies are the major contributors to mortality beyond 5 years after

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heart transplantation (HTX); after that follow up point, CAV and late graft failure (likely secondary to CAV) account for 32% of recipient deaths.[1–4] A benefit regarding development of CAV has been attributed to the newer immunosuppressive agent sirolimus (SIR, rapamycin), and its synthetic derivative everolimus (EVL), both mechanistic (formerly mammalian) target of rapamycin (mTOR) inhibitors.[1,5,6] At the present time, the use of the mTOR inhibitors SIR and EVL remains low (9% 1 year after HTX and 20% 5 years after HTX),[1] although the improved outcome of patients with a recent heart transplant and a diagnosis of CAV was interpreted as a result of the use of mTOR inhibitors[1] as well as newer approaches to CAV treatment such as drug-eluting coronary stents and targeting lower low-density lipoprotein cholesterol levels.[7–10]

In addition to CAV, calcineurin inhibitor(CNI)–related renal failure is a major problem after transplantation because renal dysfunction represents a significant mortality risk factor.[1] Because benefits of mTOR inhibitors regarding CAV and renal function after transplant were repeatedly proven in numerous studies, a combination of a CNI (cyclosporine A or tacrolimus [TAC], reduced dose to minimize renal disorders) with an mTOR inhibitor (SIR or EVL) could be an optimized de novo treatment after HTX. However, long-term results confirming the short-term follow-up studies are lacking. Because we had performed some of the early investigations using an mTOR inhibitor after HTX, we conducted a long-term follow-up analysis with the main focus on nephrotoxicity, CAV, malignancies, and survival within 8 years after HTX.

Methods

Patients

Between 1998 and 2005, 3 prospective, open-label, single-center studies comparing different immunosuppressive regimens after orthotopic HTX were performed consecutively; 2 studies were carried out by randomization,[11–13] and the third was a pilot study.[14] Exclusion criteria for study participants were comparable in all 3 studies: patients <18 years old, pregnancy or nursing, unwillingness or inability to use adequate contraception during study, cardiac retransplantation, previous or multiorgan transplantation, previous ventricular assist device, human immunodeficiency virus–positive donor or recipient, serum creatinine >2.5 mg/dl (2.0 mg/dl in the pilot study), elevated transaminases >1.5 times above reference value, and participation in any other investigational drug study within 28 days of study entry. All study protocols were approved by the local ethics committee and conformed to the Declaration of Helsinki. All patients gave written informed consent before inclusion and underwent routine follow-up examinations according to center practice as described previously.[11–14] Of these 171 study patients, 126 patients were enrolled in the current intention-to-treat (ITT) analysis because of the inclusion criteria, which included initial application of the intended de novo immunosuppressive therapy with TAC and SIR, both with reduced target trough levels (lowTAC/SIR group) or TAC and mycophenolate mofetil (TAC/MMF group). The main focus of this study was on the 8-year follow-up of each patient; the dates of the last observation range from 2006 to 2013 depending on patients' HTX dates; the previously published 1-year and 5-year follow-up data[11–14] were included in this analysis to describe the course of the follow-up (Figure 1). One male patient in the lowTAC/SIR group disappeared before follow-up a few months after HTX (fate unknown) and was excluded from the study analysis. Missing data in some sub-categories are due to the movement of 7 patients to another transplantation center.

Study medication and drug monitoring

Study medication (initially intravenously, subsequently orally) was administered as described previously.[11–14] All drugs were adjusted to defined target levels: in the lowTAC/SIR group, target TAC trough levels from 0 to 12 months 6 to 8 ng/ml, 2nd to 4th year 5 to 7 ng/ml, and 5th to 8th year 4 to 6 ng/ml and target SIR trough levels from 0 to 6 months 6 to 8 ng/ml and afterward 5 to 7 ng/ml; in the TAC/MMF group, target TAC trough levels from 0 to 6 months 13 to 15 ng/ml, 7 to 12 months 10 to 12 ng/ml, 2nd year 8 to 10 ng/ml, 3rd to 4th year 6 to 8 ng/ml, and 5th to 8th year 4 to 7 ng/ml, and target mycophenolic acid trough levels from 0 to 6 months 2.5 to 4.0 μg/ml, and 7 months to 8th year 1.5 to 2.5 μg/ml.

None of the patients received induction therapy. An intraoperative bolus of 500 mg methylprednisolone was administered intravenously followed by 3×125 mg within the initial 24 hours after HTX. Prednisolone was reduced stepwise and withdrawn after 6 months in patients without repeated rejection episodes. Statins were given routinely.[8]

Acute rejection

Acute rejection (AR) was defined as biopsy-proven grade ≥ 2 according to the 1990 ISHLT classification or $\geq 2R$ according to

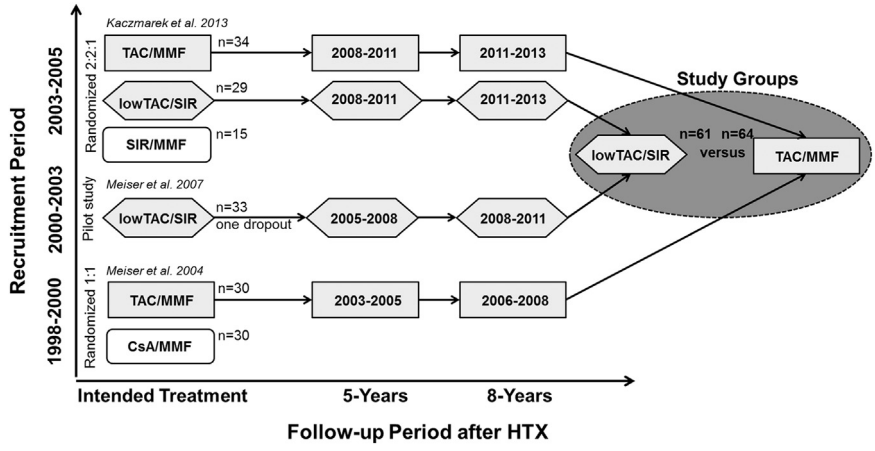

Figure 1 Study design.