Prospective Study of Everolimus With Calcineurin Inhibitor-Free Immunosuppression After Heart Transplantation: Results at Four Years

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Background. **Immunosuppression is necessary after transplantation but it is associated with distinct adverse side effects. These negative effects could at least partially be overcome with the mammalian target of Rapamycin (mTOR) inhibitor everolimus. Few studies have examined everolimus therapy with calcineurin inhibitor (CNI) withdrawal in maintenance heart transplant patients (HTx).**

Methods. **In this prospective, single-arm, single-center study, maintenance patients after HTx were converted from CNI to everolimus. They were followed for 48 months. Primary endpoints were kidney-function and arterial hypertension.**

Results. **Forty-eight patients were recruited (mean post-transplant time 5.4 ± 3.5 years). Of these, 36 were followed for the entire 4-year period. Median calculated glomerular filtration rate increased from 40.7 (32.4 to 59.1) mL/minute at baseline to 48.9 (29.7 to 67)) mL/minute at month 48 (p = not significant). Median systolic and diastolic blood pressure, triglycerides, and high-density lipoprotein and low-density lipoprotein cholesterol, did not change significantly in a comparison of the values at baseline and at 48 months. Early resolution of most non-renal CNI-related adverse events was sustained. Due to adverse events, CNI therapy had to be reintroduced in 6 patients (12.5%). No significant changes in cardiac function parameters were observed.**

Conclusions. **Calcineurin inhibitor-free immunosuppression with everolimus is an effective and safe option in selected maintenance HTx patients. Most adverse effects under everolimus occurred early after conversion and in most cases resolved without intervention within a few weeks. Refining selection criteria may help both in identifying patients who will profit most from switching and in alleviating the need to reintroduce CNI therapy.**

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Immunosuppression is a necessary requirement to prevent rejection after heart transplant (HTx). Calcineurin inhibitors (CNI) were introduced more than 30 years ago [1], resulting in a dramatic improvement in efficacy and thus a marked improvement in survival rates [2]. However, the adverse effects of CNI therapy, particularly renal dysfunction, became increasingly apparent [3]. In addition to their nephrotoxic effect, CNIs induce arterial hypertension, which requires medical therapy, in turn causing further adverse events and reducing therapeutic compliance [3]. Moreover, side effects such as tremor and cosmetic problems are quite common with CNI-based immunosuppression [3].

Patients given everolimus experience superior tolerability and fewer cytomegalovirus infections, compared with other regimens [4–6]. Initially, CNI-free immunosuppression with an mTOR-inhibitor in HTx focused on sirolimus (Rapamune), in combination with mycophenolic acid [7, 8]. After CNI withdrawal, renal function significantly improved in the majority of patients under a mTOR-inhibitor [7, 8]. Several studies show promising results for everolimus with reduced CNI-protocols [9, 10] but data on long-term everolimus-based CNI-free immunosuppressive regimens are still scarce [11].

In this prospective study, we evaluated the effect of switching maintenance HTx patients experiencing CNI-related adverse events or rejection to everolimus with CNI discontinuation. Patients were followed for 4 years after the switch. To the best of our knowledge, this is the first extended long-term follow-up of everolimus-based CNI-free immunosuppression in a large cohort of maintenance HTx recipients.

Patients and Methods

Study Design

This was a prospective, single-arm, single-center study in which maintenance HTx patients were switched from

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CNI therapy to everolimus. Patients receiving an immunosuppressive regimen including CNI with a clinical indication for switching immunosupression (renal impairment, other sever adverse events, or recurring acute rejections) were eligible to take part in the study unless they had severe preterminal chronic kidney insufficiency or were already receiving hemodialysis. Only patients transplanted for at least 1 year were included. A cohort of control patients remaining on a CNI-based regimen, pair-matched for age, sex, and time after transplantation, was used to comparatively assess the course of renal function in patients switched. Target trough levels of cyclosporine A for the control patients were as follows: Year 1 after transplantation, 200 to 250 ng/mL; years 2 to 5 after transplantation, 150 ng/mL; thereafter: 100 ng/mL. The study was conducted in accordance with the Declaration of Helsinki and the US Food and Drug Administration guidelines for good clinical practice, after approval by the local Medical Ethics Committee of our institution.

Immunosuppression

Everolimus was introduced using a standardized protocol described elsewhere [12, 13]. All patients received antihypertensive therapy (beta-blockers, calcium-antagonists, angiotensin converting enzyme inhibitors or angiotensin-I blockers), adjusting the doses as required. In the minority of patients who were not receiving statins at baseline, statins therapy could be initiated as necessary after the introduction of everolimus.

Evaluation

Study visits took place at baseline and every 3 months thereafter up to 48 months post switch. At each visit, a physical examination was performed and blood (electrolytes, kidney and liver function tests, C-reactive protein, interleukin-6, NT-proBNP, lipid status, etc) and urine (creatinine, global protein, albumin, alpha1-microglobulin, alpha2-macroglobulin) biochemistry were analyzed. In addition, the trough concentration of everolimus was measured by liquid chromatography with mass spectrometry [14]. A standard echocardiographic examination and Doppler echocardiography were performed by experienced cardiologists at each study visit. Coronary angiograms and right-heart catheterization, with measurement of cardiac output and pulmonary artery pressure, were undertaken before switching and after 12 months. Catheterization results were analyzed by specialized cardiologists, blinded to the medical treatment, who qualitatively graded (normal, coronary artery disease, or allograft vasculopathy) each vessel. Right ventricular biopsy was performed yearly, when rejection was clinically suspected, and before and after larger operations with deep surgical wounds, because these operations required patients to temporarily revert to CNI-based protocols. Myocardial single photon emission computed tomography was performed before conversion to everolimus and 12 months after switching.

Study Endpoints

In previous studies [13, 15], renal function and blood pressure after 24 months served as the primary endpoints. Accordingly, in this follow-up study we continued to observe these primary endpoints up to 4 years from the time of conversion. Secondary endpoints for this study were changes in CNI-related adverse events (tremor, hirsutism, gingival hyperplasia, and peripheral edema), changes in lipid status, and the occurrence of adverse events, hospital readmissions, and rejection episodes after the switch to everolimus.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics 20 (IBM Corporation, Armonk, NY). Due to the small sample size and the partial lack of a normal distribution of our data, nonparametric methods were applied. A Friedman test with post hoc analyses for multiple comparisons was used to determine differences between the time intervals of assessment, both for continuous and for ordinal data. The Mann-Whitney U test was performed to compare the 2 groups, regarding the effect of changes at 1-year intervals, beginning at baseline and ending 48-months later. The McNemar χ^2 test was used to compare the dichotomous proportions of the presence and absence of different periods at baseline and after 48 months. Changes in parameters over all 5 time intervals were investigated by means of the Cochran Q, followed by post-hoc analyses in case of overall significance. A p value less than 0.05 was considered statistically significant.

Results

The results of the first 6 and 24 months after switching to everolimus, including adverse events, have already been published before [13, 15, 16]. In the following, the results from month 25 to month 48 and the overall course of a 4-year follow-up are presented.

Patient Population

A total of 48 patients were recruited, of whom all could be followed for 12, 44 for 24, 38 for 36, and 36 for the full 48 months. Six patients (12.5%) discontinued everolimus due to adverse events. Five patients died during the study period. There was no indication of an acute or chronic rejection as the reason for these deaths. One patient was lost to follow-up.

The study population consisted of 43 males and 5 females, with a mean age of 54.4 years (range: 22 to 74 years) at inclusion. At the time of conversion, the mean posttransplant time was 5.4 $\pm$ 3.5 years. In all but 1 case, the indication for switching was CNI-related adverse events, comprising mostly renal impairment and allograft vasculopathy. One patient was switched due to recurrent rejection episodes that developed despite several immunosuppressive regimens.

A control group of 34 patients remaining on a CNI-based regimen was used to comparatively assess renal