Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Conversion to sirolimus for chronic allograft dysfunction: long-term results confirm predictive value of proteinuria

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Keywords
calcineurin inhibitor, chronic allograft dysfunction, mammalian target of rapamycin inhibitor, proteinuria, rapamycin, sirolimus, toxicity.

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Received: 23 July 2007
Revision requested: 17 August 2007
Accepted: 7 October 2007

doi:10.1111/j.1432-2277.2007.00592.x

Summary

The aim was to evaluate long-term graft survival and function after conversion to sirolimus (SRL) for chronic calcineurin inhibitor (CNI) toxicity and the predictive value of baseline proteinuria. This is a follow-up conversion study of 59 renal transplant patients with deteriorating graft function and histologic signs of CNI toxicity. Previously, baseline proteinuria <800 mg/day was identified as a short-term predictor for successful conversion. Follow-up was 5.3 ± 0.8 (3.7–6.8) years. Patient survival was 88%, graft survival 38%. Creatinine clearance at the last follow-up was 33.7 ± 14 ml/min, proteinuria 826 ± 860 mg/day. Baseline proteinuria <800 mg/day was associated with better graft survival. In a cox analysis including proteinuria >800 mg, glomerular filtration rate, age at conversion, chronic Banff score at conversion and time after transplantation at conversion, higher proteinuria was associated with a relative risk of graft loss of 3.98. Prognosis of chronic allograft dysfunction is poor. However, conversion to SRL remains an option for patients with low baseline proteinuria, which can slow down deterioration of graft function during a follow-up period of up to 5 years.

Introduction

Chronic allograft nephropathy (CAN) is the leading cause for late kidney graft loss except for death with a functioning graft [1]. Among the contributing factors to CAN – immunologic and nonimmunologic – chronic calcineurin inhibitor (CNI) toxicity is an important nonimmunologic factor [1]. Therefore, CNI withdrawal with or without subsequent introduction of another immunosuppressive agent, i.e. mycophenolate mofetil (MMF) or sirolimus (SRL) has been performed to preserve kidney function in the situation of chronic deterioration of graft function [2,3]. Conversion to SRL may have the potential to stabilize graft function during short-term follow-up periods of up to 1 or 2 years [3,4]. However, a considerable number of patients do not respond favorably to conversion to SRL [5,6]. In our previous study, we were able to demonstrate a predictive value of baseline proteinuria below 800 mg/day at time of conversion to be associated with a positive response as defined as stabilized or improved graft function 1 year after conversion (Δ creatinine ≤0.3 mg/dl or improved creatinine). During the first year after conversion, patient survival was 100% and graft survival 92%. Major adverse events were a transient decrease in hemoglobin – treated with erythropoesis stimulating agents – and dyslipidemia.

The aim of the present study was to evaluate long-term graft function and graft survival after conversion and the long-term predictive value of low baseline proteinuria for graft function and graft survival.

Study design and methods

All 59 kidney transplant patients evaluated in the previous study on predictive factors of success after conversion from CNI to SRL [6] from the transplant center of the Charité University Hospital Campus Mitte in Berlin,

Germany, and the Hospital Clínic in Barcelona, Spain, were included in this extension study. Inclusion criteria for the previous study were slowly deteriorating graft function with signs of chronic CNI toxicity in the absence of acute rejection. These patients had been converted from CNI-based therapy to SRL-based therapy for chronically declining graft function and chronic CNI toxicity as described earlier [6]. In all patients, a transplant biopsy had been performed to rule out acute rejection. The biopsy showed signs of chronic CNI toxicity in all patients. The conversion was performed by reducing the CNI to 50% of its original dose on the first day of application of SRL. As soon as the SRL target range of 8–12 ng/ml had been achieved, the CNI dose was further reduced until complete withdrawal after several weeks.

Follow-up visits according to local practice performed at least twice a year in the respective transplant center included a physical exam and laboratory parameters including kidney function [creatinine and calculated glomerular filtration rate (GFR) according to Cockcroft–Gault], proteinuria, hemograms as well as blood lipid concentrations.

Statistical analysis was performed using the nonparametric Mann–Whitney test or Chi square test where applicable and the Kaplan–Meier regression analysis. Furthermore, a Cox proportional hazards model analysis was performed.

Results

Fifty-nine renal transplant patients (19 female, 40 male) aged 42.9 + 1.8 (23–79) years with chronic allograft dysfunction and histologic signs of chronic CNI toxicity were converted. At conversion, mean time after transplantation was 88.0 + 7.2 (3–189) months. Immunosuppression before conversion consisted of low dose corticosteroid and/or MMF or azathioprin in combination with CNI [6]. At the time of conversion, there had been no significant difference in calculated GFR between patients who responded to the treatment and nonresponders (31.1 ± 9.4 vs. 28.0 ± 12.2 ml/min) [6]. The mean follow-up after conversion was 5.3 ± 0.8 (3.7–6.8) years. Patient survival at the end of follow-up was 88% (52/59). Four patients died of a cardiovascular event, two of these with a functioning graft. One patient died of a bacterial infection, two died of unknown reasons. Overall 5-year graft survival was 36%, when graft survival was censored for death with a functioning graft, it was 38%. Graft survival in patients with baseline proteinuria at conversion <800 mg/day was 65%, whereas it was only 4% in patients with baseline proteinuria >800 mg/day at conversion ($P < 0.001$). Baseline proteinuria above 800 mg/day compared with baseline proteinuria below 800 mg/day was associated with a relative risk of graft loss after conversion of 3.05 (95% confidence interval 1.9–5.0). A Kaplan–Meier survival analysis is given in Fig. 1. Deterioration of renal function before conversion had not been significantly different over the 2 years preceding the conversion in patients with baseline proteinuria below or above 800 mg/day (ΔGFR −11.2 vs. −8.3 ml/min/year in patients with >800 mg/day versus patients with <800 mg/day at conversion). A cox proportional hazards model analysis for graft loss including as covariates proteinuria above 800 mg/day at conversion, estimated GFR, chronic Banff score, age at conversion and time elapsed after transplantation until conversion revealed a statistical significance only for proteinuria above 800 mg/day and estimated GFR (proteinuria >800 mg/day: odds ratio 3.982; 95% confidence interval 1.88–8.44, $P < 0.001$; estimated GFR: odds ratio 0.96 for each unit increase; 95% confidence interval 0.92–0.99; $P = 0.04$) with high proteinuria being by far the more important one.

In addition to the patients with graft loss, SRL therapy needed to be withdrawn in two patients after the first year (one because of wound healing problems and one because of refractory nephrotic range proteinuria). No

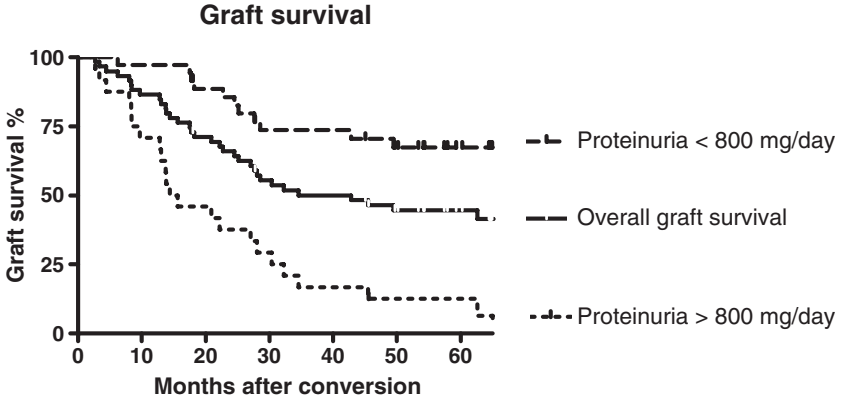

Figure 1 Graft survival as a Kaplan–Meier curve censored for death with a functioning graft. The interrupted line describes survival of patients with a baseline proteinuria at conversion of <800 mg/day. The continuous line shows overall graft survival, whereas the dotted line depicts those patients with baseline proteinuria >800 mg/day.

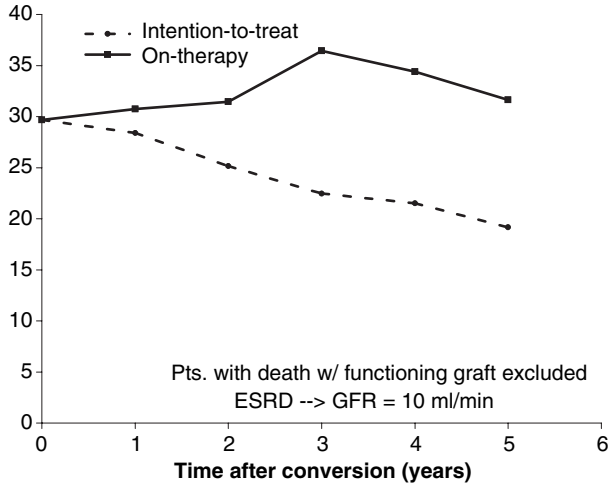

Figure 2 The development of calculated glomerular filtration rate (Cockcroft–Gault) at different time points after conversion in an intention-to-treat and in an as-treated analysis.

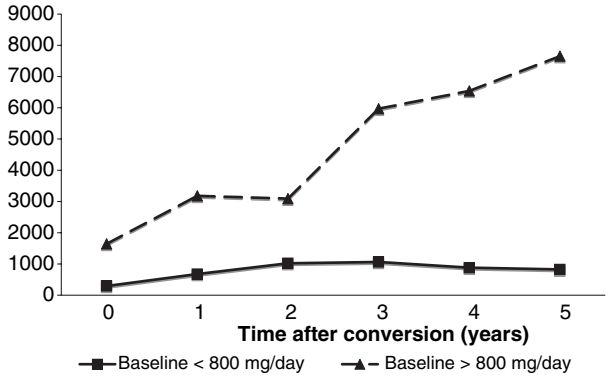

Figure 3 The development of proteinuria at different time points after conversion in an as-treated analysis in the groups of patients with less or more than 800 mg/day of baseline proteinuria at conversion ($P < 0.05$ at conversion and up to 3 years postconversion).

acute rejections were observed after the first year after conversion. Kidney function and proteinuria are depicted in Figs. 2 and 3. Creatinine clearance at last follow-up was 33.7 ± 14 ml/min, proteinuria 826 ± 860 mg/day in patients with a functioning graft.

After the first year, anemia requiring treatment with erythropoesis stimulating agents (22%) and ankle edema (20%) were the adverse events with an incidence of more than 5%. At the end of follow-up, the mean hemoglobin concentration was 11.4 ± 1.7 g/dl, the mean triglyceride and cholesterol concentrations were 214 ± 68 and 248 ± 49 mg/dl, respectively. Mouth ulcers and other clinical signs of over-immunosuppression did not become apparent after the first year. At the last follow-up, the daily SRL dose was 2.2 ± 1.0 mg with a mean whole blood trough concentration of 9.3 ± 2.2 ng/ml.

Discussion

This is one of the few studies providing a 5-year follow-up, after conversion from a CNI-based therapy to a mammalian target of rapamycin (mTOR) inhibitor therapy for chronic allograft dysfunction. So far, many studies on conversion to an SRL-based protocol are encouraging, but they cover shorter follow-up periods of only 1 year [3,7].

In our previous conversion study, we demonstrated the predictive value of low proteinuria for a beneficial outcome after 1 year [6]. Bumbea *et al.* [4] were able to identify the absence of proteinuria at time of conversion as a predictive parameter. This study confirms the predictive value of proteinuria for long-term results. The relative risk of graft loss, during a follow-up of 5 years after conversion, was threefold elevated in patients with baseline proteinuria higher than 800 mg/day compared with those with lower proteinuria. Proteinuria might be a surrogate parameter for established and ongoing structural damage to the graft.

The present data demonstrate that a stabilization of kidney function can be achieved in patients with a low baseline proteinuria; however, the data also demonstrate that despite late conversion to SRL, many grafts fail during long-term follow-up. To some extent, this reflects the limits of long-term outcomes in kidney transplantation regardless of the individual patient's immunosuppressive therapy with graft half-life approaching only 10 years [8]. One can speculate that for the patients with failed grafts, the conversion came either too late or was not the appropriate measure. Nankivell *et al.* [9] were able to characterize histologically the natural history of CAN. They showed that – presumably as a result of ongoing immunologic and nonimmunologic damage – CAN was histologically universal in their patients after 3 years, although these patients had mean creatinine values of 1.62 mg/dl 6–10 years after transplantation, values that under many circumstances would still be considered more than satisfactory, i.e. today's routine biochemical parameters lack the specificity to detect early structural damage. Once creatinine values start to rise, structural damage and especially glomerular sclerosis might just be too advanced leaving only little functional nephron mass to be preserved. This hypothesis is also confirmed by the findings of Watson *et al.* [3] showing that better baseline GFR yields more improvement in renal function 1 year after conversion. Therefore, if a conversion to a CNI-free mTOR inhibitor-based regimen is taken into account, this should be done as soon as possible.

On the other hand, it can also be speculated that undetected chronic immunologic damage might have contributed to late graft loss in some of our patients. Nankivell *et al*. [9] were also able to show that subclinical rejection leads to a higher degree of histologic damage. Therefore, a biopsy to exclude an immunologic cause for chronic deterioration of graft function should always be considered before conversion and later on in case of accelerated deterioration of graft function.

The major drawback of this study is the absence of a control group. Therefore, this study does not pretend to demonstrate or discard superiority of late conversion to SRL compared with another regimen or compared with an unchanged CNI-based maintenance therapy. Most probably, these aspects will be answered by other studies such as the CONVERT trial [10]. However, once a decision for conversion has been contemplated, our long-term results might help identify patients who are likely to have a long-term benefit.

In summary, our data show that stabilization of graft function after late conversion to SRL can last during the follow-up period of 5 years in two-thirds of patients with low baseline proteinuria. Furthermore, low baseline proteinuria predicts a long-term graft survival after conversion.

Authorship

FD, KB, JMC: designed the study; FD, KB, TS, FO, LF, HHN, JMC: performed the study; FD, KB, JMC: collected data; FD, LF, JMC: analyzed data; FD: wrote the paper.

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