Ten-years data of the first European clinical experience with once-daily tacrolimus extended release formulation in renal transplant recipients

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This study is an investigator-driven study without external funding.

The patients participated previously in an Astellas funded 10 week phase II multicenter study, in which the pharmacokinetics of tacrolimus before and after conversion from Tac BID to Tac QD was investigated (FG 12-02) and into the 4-year extension phase (FG 14-02). Approval for these studies were provided by the local medical ethics committee (study numbers: MEC03-048 and MEC 03-102).

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Abstract

Background: Clinical data about long-term use of tacrolimus QD are lacking.

Methods: Ten-years data were collected from 37 renal transplant recipients participating in a Tacrolimus BID (Prograf®) to QD (Advagraf®) conversion study. They were converted at a median of 4.1 years post-transplant (range 1.5-11.4) with a stable renal function (serum creatinine < 264 umol/L) on tacrolimus based immunosuppression (monotherapy 29, dual therapy 8). Thirty were first transplants and original renal disease was in 16 immunologic, 14 non-immunologic, and 7 unknown. Eleven received their kidney from a living donor.

Results: There were no acute rejections. Thirty-four recipients were on tacrolimus QD up to end of follow-up. Three patients were censored at 2, 3, and 4 years post-conversion. Actuarial 5- and 10-year patient survival rates were 92% and 85%, respectively. Five patients died with a functioning graft 1.2 - 9.2 years post-conversion. Actuarial 5- and 10-year death-censored graft survival rates were 100% and 83%, respectively. The 5 graft losses occurred at 8.2 - 9.0 years post-conversion (3 due to recurrence IgA nephropathy, chronic rejection, and renal failure after cardiac surgery). Serum creatinine was 128 umol/L (range 64-180) at conversion and 141 umol/L (range 66-304) at 10 years. All patients with a non-immunologic cause of renal failure had a stable creatinine, while the 8 patients with an increase in serum creatinine >20% had an immunological or unknown cause of renal failure.

Conclusion: Patients on tacrolimus QD have excellent 10-year renal function, patient - and graft survival.

Introduction:

The once-daily formulation of tacrolimus (Tac QD) has similar efficacy and safety as the twice-daily formulation (Tac BID) in de novo kidney transplant recipients [1,2] and in kidney patients converted from Tac BID to Tac QD [2,3]. Moreover Tac QD has added value, it improves adherence [4] and reduces intra (within-)patient variability in trough-level [5] and 24 hour exposure [6]. This improvement of intrapatient variability does not merely result from improved adherence but reflects different intrinsic pharmacokinetic properties of Tac QD [6]. This reduced intrapatient variability might be of clinical importance because there are indications that in kidney transplant patients using Tac BID a high intrapatient variability in trough-level is a risk factor for poor long-term outcome [7, 8]. Our center participated in 2003 in a 10 week phase II multicenter study, in which the pharmacokinetics of tacrolimus before and after conversion from Tac BID to Tac QD was investigated [3]. This was the first European clinical experience with Tac QD in renal transplant patients. The results of the 4-year extension phase was part of a publication about safety and efficacy of Tac QD in transplant patients [2]. As this follow-up was limited to a maximum of 4 years, long-term outcome of these patients were studied.

Methods:

The study was conducted in accordance with the Declaration of Helsinki and each patient gave written informed consent prior to enrollment into the study and the extension phase of this study. The founder study (FG12-02), registration number NCT00384137, and the extension phase (FG14-02), registration number NCT02118896 were approved by the local medical ethics committee (MEC03-048 and MEC 03-102).

Patients:

The in-and exclusion criteria have been published [3]. In short: male and female patients aged 18–65 years were eligible for inclusion if they were a recipient of a kidney transplant at least 6 months before enrollment, were receiving Tac BID-based immunosuppressive therapy and had serum creatinine levels <3 mg/dL (264 umol/L) at study entry. Patients were excluded if they had previously received an organ transplant other than a kidney, experienced a rejection episode within 90 days prior to study entry, experienced a rejection episode within the last 6 months that required anti-lymphocyte antibody therapy or had experienced >2 rejection episodes within the last 12 months.

Fourty stable recipients participated in the pharmacokinetic study. Thirty-nine recipients consented to be in the follow-up study with Tac QD as compassionate use. Within 4 months of the start of the follow-up study two recipients were converted back to Tac BID on their own wish because of respectively increased liver enzymes and dizziness. In both cases the complaints seemed to be unrelated to Tac QD and did not improve on Tac BID. These recipients were excluded from the long-term analysis.

The 37 remaining recipients had at conversion a median age of 55.3 years (range 20-64) and were at a median of 4.1 years (range 1.5-11.4) post-transplant. Their maintenance immunosuppression was Tac monotherapy in 29 (78%) and dual therapy in 8 (in addition to Tac Mycophenolate mofetil (MMF) in 5 and Pred in 3 recipients). Twenty-five were male (68%) and 12 (32%) were female.

Transplant-number: first 30 (81%), retransplant 7 (19%): 2^{nd} 5, 3^{rd} 1 and 5^{th} 1.

Original disease was '*Immunologic'* in 16 (43%, 7 due to IgA nephropathy, 11 due to other glomerulonephritis), '*Non-immunologic'* in 14 (38%, 9 due to Polycystic kidney disease, 2 due to Urologic, 2 due to Cardiovascular and 1 due to Oxalosis) and '*Unknown'* in 7 patients (19%).

The median age of the donors was 45,0 years (range 15-69). Eleven were living donors (related 7, unrelated 4) and 26 post-mortal (brain death 17, circulatory death 9).

Immunosuppression:

Before conversion immunosuppression was prescribed according to our local protocol. The main features of our center protocol are: Never induction therapy (also not for hyper-immunized patients). All patients receive from time of transplant Cyclosporine (< 1997) or Tac (since 1997) and (depending on era of transplantation) azathioprine, sirolimus or MMF. They start on prednisolone 10 mg/day. Within 3-6 months posttransplant all concomitant immunosupressive agents are withdrawn in immunological uncomplicated cases. In immunological high risk and complicated cases at least one concomitant agent is maintained. So, in our center most patients are after the first year post-transplant on Tac monotherapy (±70%) or on Tac-based dual therapy.

Endpoints.

The primary endpoints are patient and graft survival. Secondary endpoints are renal function (serum creatinine), and rejection.

Statistical methods:

The data were collected prospectively in first 4 years [2] and for the following years retrospectively from patient files up to graft failure or patient death (earliest event).There were no missing data. Data are given as numbers or median (range). Statistical analysis was performed by SPSS v 20. Patient and graft survival were analyzed using Kaplan-Meier estimates.

Results:

Thirty-four patients were on Tac QD during the follow-up period (24 up to end of study period with a functioning grafts and 10 up to graft failure or death). Three patients had to stop Tac QD and were censored at that time for the following reasons:

Patient 1 was retransplanted due to renal failure (unknown cause) 4 years before participating into the study. Due to recurrent skin cancers the patient was switched to sirolimus two years later. Due to intolerance to sirolimus (wound healing after skin biopsies due to recurrent skin cancer), she was switched back to Tac QD 5 years later and has a functioning graft with stable renal function up to 14 years after transplantation (serum creatinine 114 umol/L; no proteinuria).

Patient 2 was transplanted due to PCKD 5 years before participating into the study. She was switched to Tac BID after being in the study for 3 years by her own wish because of itching. Her itching did not improve after switch and disappeared after years. Later, after licensing Tac QD in the Netherlands, she restarted Tac QD without recurrence of the itching. She is now 15 years after transplantation with a good stable renal function (serum creatinine 120 umol/L; no proteinuria).

Patient 3 was transplanted because of renal failure due to reflux nephropathy 3 years before conversion. He had to be withdrawn from the study at 4 years post-conversion due to the impossibility to deliver the compassionate use Tac QD because he did not attend the scheduled outdoor visits; At that time he had a stable transplant function

(serum creatinine 133 umol/L; proteinuria 0.16 g/L). He restarted Tac BID and was treated 2 years later for chronic humoral rejection (biopsy proven). His renal function deteriorated slowly and he was retransplanted preemptive 10 year after conversion.

Tacrolimus dosages and trough levels

The median daily Tac dosages decreased over the years after conversion from 4.0 mg (at time of conversion) to 4.0 mg (at year 1), 3.75mg (at year 5) and 2.5mg (at year 10). The corresponding values for Tac trough levels were 7.1ng/ml, 6.5ng/ml , 5.8 ng/ml, and 5.7ng/ml respectively.

The dose normalized trough levels were comparable at time of conversion and at year 1 (1.775 ng/ml/mg and 1.625 ng/ml/mg, respectively). However they increased to 2.1 ng/ml/mg at year 5 and 2.28 ng/ml/mg at year 10.

Patient- and Graft Survival and Rejections

Five patients died with a functioning graft between 1.2 - 9.6 years after conversion (2.8 – 12.8 years after transplantation) due to pulmonary embolism, pulmonary adenocarcinoma, congestive heart failure, myocardial infarction, and Creutzfeldt-Jakob disease. In Figure 1a the actuarial patient survival curve (Kaplan-Meier) after conversion is depicted, showing a patient survival rate of 92% at 5 years and 85% at 10 years.

There were 5 graft losses between 8.2 - 9.7 years after conversion (10.3 - 14.7 years after transplantation) due to complicated cardiac surgery with good stable renal function before surgery, chronic rejection (not biopsy-proven), and 3 due to recurrent IgA nephropathy. In Figure 1b the actuarial death-censored graft survival (Kaplan-Meier) after conversion is depicted, showing a graft survival rate of 100% at 5 years and 83% at 10 years.

After conversion to Tac QD there were no early acute rejections. Two patients have had a late acute on chronic humoral glomerular rejection.

The first patient had a slow rise in serum creatinine and proteinuria. His biopsy (10 years post-transplant and 8 years after conversion) showed an acute and chronic glomerular rejection (C4d positive). After treatment with pulse methylprednisolone and intravenous Immunoglobuline, renal function stabilized at a serum creatinine of 205 umol/L and proteinuria decreased to 0.2-0.4 g/day on triple therapy (Tac QD, MMF and steroids).

The other patient is already mentioned as being censored (patient 3) due restarting Tac BID. He was diagnosed 4 years later (11 years post-transplant) with a chronic glomerular rejection (C4d positive), treated twice with methylprednisolone and intravenous Immunoglobuline, with a slow decrease of renal function for which he had a preemptive retransplant years two years later.

Renal function

In Figure 2, the median serum creatinine is depicted for the 27 patients without graft failure or death during follow up. These 27 patients consist of the 24 patients with a functioning graft while on Tac QD at year 10 and the data of the 3 censored patients up to date of stopping the Tac QD. The median serum creatinine was at time of conversion 127 umol/L (range 64-176) and at 10 year 145.5 umol/L (range 66-304). Patients who died during follow up had a comparable renal function at conversion (median creatinine 127 umol/L (range 11-131) and a stable renal function up to death (data not shown).

Compared to the other patients, the 5 recipients with graft failure already had a higher serum creatinine at time of conversion (median creatinine 163 umol/L, range128-180). As can be expected, in four serum creatinine increased during follow-up. The exception was the patient with an acute graft failure after cardiac surgery; he had a stable serum creatinine up to time of operation.

For the 24 patients still on Tac QD at year 10, the change in renal function at year 10 compared to time of conversion was analyzed. Therefore, patients were arbitrarily divided in groups depending on the relative change in serum creatinine (% change at year 10 compared to time of conversion) : Group 1 '*decrease>20%'* (n=2), group 2 '*decrease 0-20%'* (n=5), group 3 '*increase 0-20%'* (n=9), group 4*' increase 20-50%'* (n=4), group 5 '*increase >50%'* (n=4). Figure 3 shows per category the original diseases (immunologic, non-immunologic, not known). All patients with a non-immunologic cause of renal failure had a stable creatinine (category 1,2 and 3), while the patients with an increase in serum creatinine (category 4 and 5) all had either an ESRD due to immunological reasons or the reason was unknown.

Discussion

In this unique, observational conversion study of renal transplant patients, 10 years use of Tac QD shows a very good clinical outcome and was well tolerated.

Patient survival was excellent (92% and 85% at 5 and 10 years post conversion, respectively), especially if one considers the many years post-transplant that some patients were converted (up to 11.5 years). The causes of death in this small cohort is as can be expected in a renal transplant population.

The 10 year death-censored graft survival rate was 83 % and numerically higher than the death censored graft survival rate of a renal transplant group matched for donor source of the Netherlands (73,6 %). A better than average patient and graft survival can be expected because of the in- and exclusion criteria. On the other hand, many high risk patients were included as well: Seven patient were retransplants (up to the 5th transplant!) and 9 patients received a kidney from a circulatory death donor. Four recipients received an HLA-mismatched living unrelated donor kidney.

In our center, many recipients are successfully maintained on Tacrolimus monotherapy. The current group of recipients were at a median of 4.1 years post-transplant on monotherapy (78%) or dual therapy (22%) and subsequently maintained for 10 years on the same immunosuppressive therapy with Tac QD. Immunosuppression was changed in only 3 patients: 2 patients were on monotherapy Tac QD with a biopsy-proven recurrence of their IgA nephropathy. MMF was added in the hope to delay progression of this disease. The 3rd patient was treated for biopsy-proven humoral rejection and his immunosuppressive therapy was increased by adding MMF and steroids to TAC.

During Tac QD only one patient had biopsy-proven acute on chronic humoral rejection not leading to graft loss and one patient lost his graft because of (not biopsy-proven) chronic rejection.

The major reason for graft failure was recurrence of IgA nephropathy in 3 out of the 5 patients. As it has been reported that steroid use is strongly associated with a reduced rate of recurrence [9], these patients might have been benefitted if they had been kept on steroids.

All patients with an original non-immunological cause of kidney failure had 10

years after conversion a stable serum creatinine(increase <20% compared to pre-conversion creatinine value). The observation that an increase of creatinine >20% after 10 years occurred only in patients with original kidney failure due to an immunological cause or an unknown diagnosis, suggests that recurrence of kidney disease might be a causative factor for this decrease in renal function. This observation and the 3 graft losses because of recurrence of IgA nephropathy are compatible with the report that recurrence of original disease is now considered as an important determinant of graft survival [10, 11].

From conversion studies it is well known that *early* after conversion from Tac BID to Tac QD 24 hour exposure (and trough levels) decrease by about 10% [2, 3]. So, the fact that one year after conversion the dose-normalized trough levels were slightly decreased could be expected. However, that at 5 and 10 years after conversion the dose-normalized trough levels continuously increased, is unexpected and previously not described. Between 1 and 5 years after transplantation none of the factors normally associated with a decreased absorption or an increased clearance changed (e.g. hematocrit, albumin and concomitant use of steroids [12]). One can speculate that this increase in exposure is due to aging of our patients. However this interesting observation needs confirmation in a larger study.

Inevitably, the number of patients with such a long-term use of Tac QD is very limited, as these were the first patients included in Europe in trials on Tac QD. The strength of the study is, that all patients were studied in detail with a long follow-up in our own center and there were no missing data.

Conclusion:

This study is the first long-term study of a renal transplant cohort converted from Tac BID to Tac QD. It demonstrates both a very good patient- and graft survival and preservation of renal function during the 10 year follow up. Seventy-eight percent of the patients were on Tac-monotherapy in accordance with our center policy on immunosuppression. Graft loss and decrease in graft function occurred mainly in patients with an immunological cause of renal failure.

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Figures and Legends.

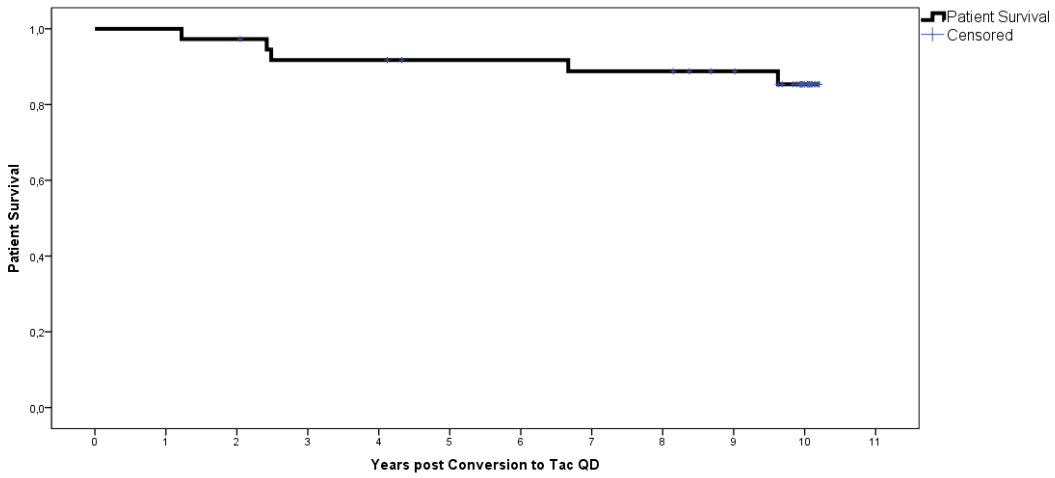

Fig 1a

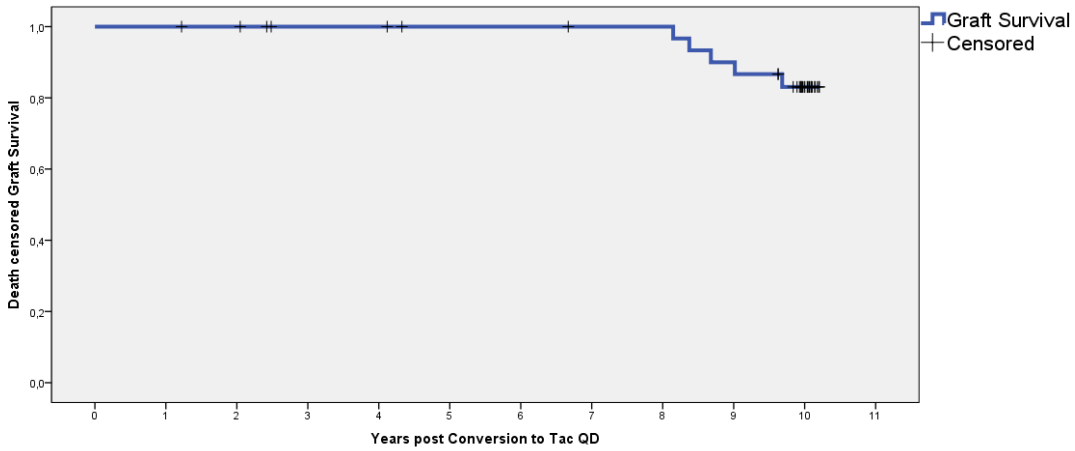

Fig 1b

Figure 1. Patient and Graft Survival.

Kaplan-Meier actuarial survival curves for Patient Survival (Fig 1a) and death-censored Graft Survival (Fig 1b). Patients switched from Tacrolimus QD to other immunosuppressants (n= 3) are censored at time of switch (see text).

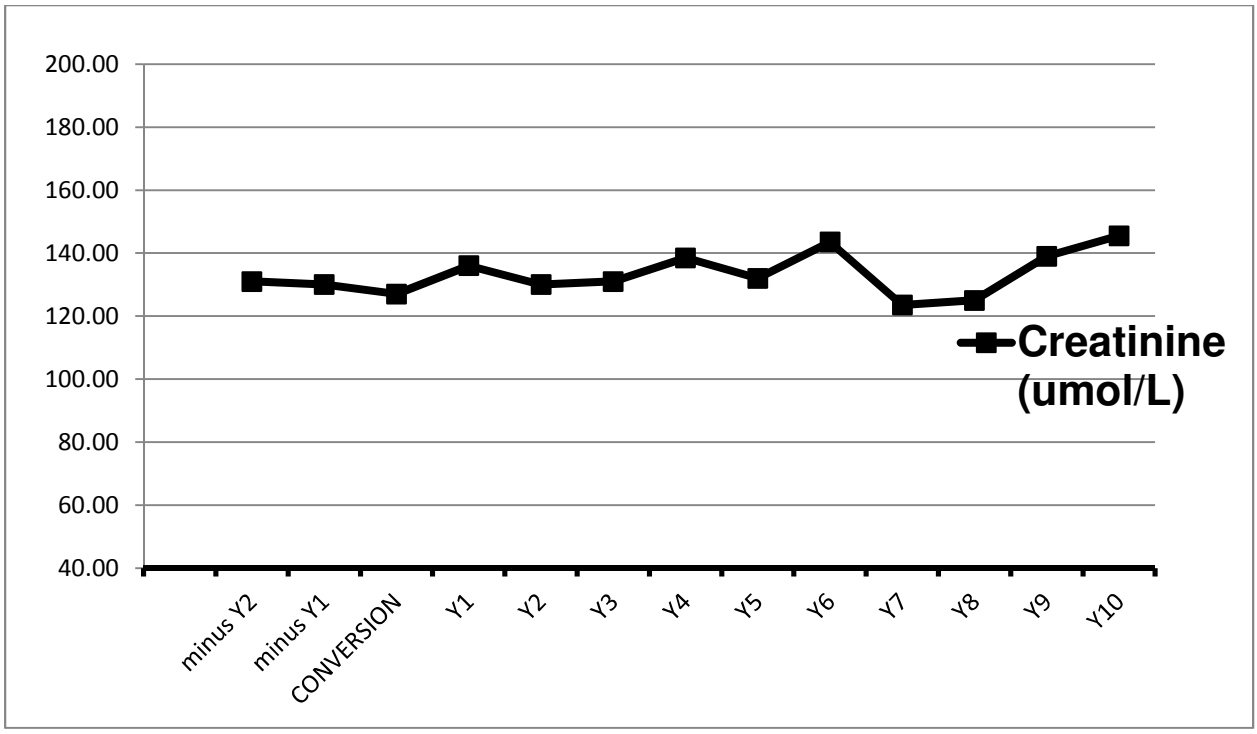

Figure 2. Serum creatinine before and after conversion during the 10 years of follow-up.

Median serum creatinine (umol/L) for the 27 patients with a functioning graft during follow up (24 patients on Tac QD at year 10 and for the 3 censored patients last creatinine before switch from Tacrolimus QD to other immunosuppressants). Function of patients who died had also stable renal function up to death (see text).

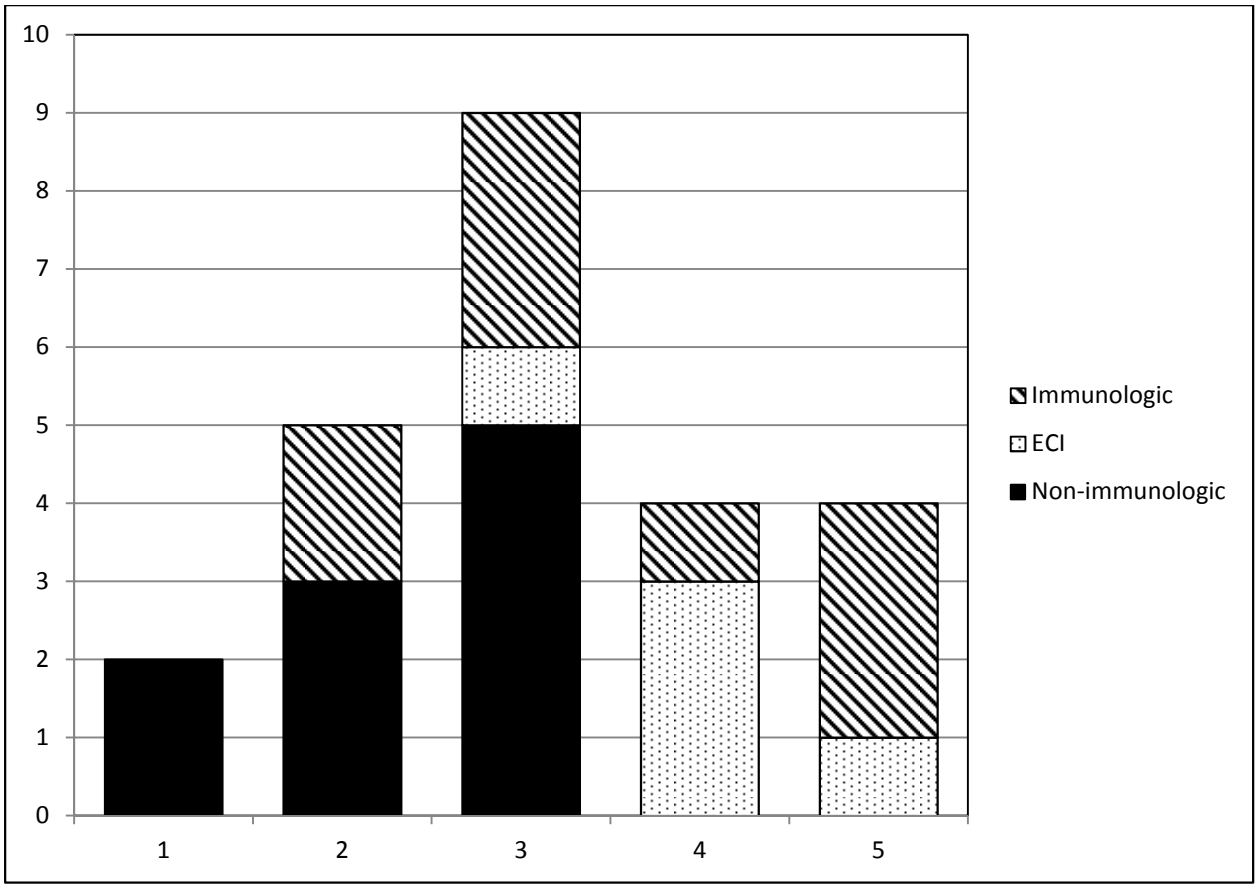

Figure 3. Change in serum creatinine from time of conversion to year 10 in relation to original renal disease category.

The 24 patients on Tac QD for 10 years were divided arbitrarily according to their relative change in creatinine at year 10 compared to at its value at conversion. On the X-axis are given five groups: group 1 'decrease > 20%' (n=2), group 2 'decrease 0-20%' (n=5), group 3 'increase < 20%' (n=9), group 4 'increase 20-50%' (n=4), and group 5 'increase > 50%' (n=4). On the Y-axis the number of patients are shown. In addition in each bar the original renal disease is depicted by different patterns: 'non-immunologic' (solid section), 'immunologic' (striped section),or 'unknown' (dotted section).