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BRIEF REPORT

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# Conversion from cyclosporin (Neoral®) to tacrolimus (Prograf®) in renal allograft recipients with chronic graft nephropathy: results of an observational study

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**Abstract** To evaluate the role of tacrolimus in the treatment of Chronic Graft Nephropathy (CGN), a pilot cross-sectional study was performed on 14 patients with deteriorating renal function and biopsy-proven CGN. Maintenance therapy was switched from cyclosporin to tacrolimus, and results of conversion on allograft function were assessed by estimated glomerular filtration rate (GFR) and clinical outcome. Minimum follow-up was 15 months. Two distinctive response patterns emerged: (i) continuing deterioration of renal function with no apparent benefit over the projected trend of GFR (nine patients), and (ii) unequivocal change in the GFR trend line equation with reduced rate of deterioration in one patient and sustained improvement of GFR in four patients (reversal of downward trend). Five out of 14 patients (36%) benefited from replacing Neoral with Prograf. All five patients exceeded their estimated time of return to dialysis by a median of 41 weeks (range: 29–52) and their grafts continue to function.

**Key words** Chronic graft nephropathy · Cyclosporin · Tacrolimus

## Introduction

The short-term results of renal transplantation have shown significant improvement since the introduction of cyclosporin to clinical transplantation. Nevertheless, despite a 30% increase in 1-year graft survival, the renal allograft half-life has remained unchanged since 1966 [12]. Thus, the impact on long-term results has been disappointing, with a large number of grafts still being lost to chronic graft nephropathy (CGN) [9]. In the United Kingdom, approximately 1,500 of the 15,000-strong renal allograft pool are lost every year. Of these losses, 450 (30%) are due to CGN (Dr R. Moore, personal communication). The Banff working party have set out specific criteria for the diagnosis of CGN including; interstitial fibrosis, tubular atrophy, and new onset arterial fibrous intimal thickening [14]. The incidence of CGN using these criteria has been estimated at 40% at 2-year protocol follow-up biopsy [4].

The effects of failing grafts on the renal community are two-fold. Firstly, is the huge financial burden directly attributable to CGN. The cost of dialysis for 1 year has been estimated at 20,000 whereas that of maintenance immunosuppression is 5,000 (Dr R. Moore, personal communication). The net cost of failing grafts attributable to CGN per year in the United Kingdom is therefore 6.75 million or 84.4 million over 5 years. Secondly, there is the increased numbers of patients returning to an already over-burdened dialysis community. The recommended annual target for acceptance onto dialysis programmes in the United Kingdom is 80 per million of the population per year. Allograft failure due to CGN is currently responsible for 10% of the total number of new patients entering dialysis programmes. Chronic graft nephropathy leading to renal failure is rapidly becoming one of the most common indications for patients requiring dialysis facilities.

Chronic graft nephropathy is a poorly understood and complex process of multifactorial etiology that

combines both immunological and non-immunological factors for which there is currently no proven treatment available. Undoubtedly, there is a great deal of inter-patient variability with regards to which particular factor or, more likely, combination of factors, exert their detrimental effects on graft function. The classical clinical picture of CGN is a slow progressive deterioration in renal function ultimately leading to graft failure. Such a scenario could be interpreted as a failure of a maintenance immunosuppressive therapy to maintain allograft function.

The rationale for this study is based on the principle that the failure of a treatment is an indication for a change of therapy. Until now there has been no alternative, however, the recent introduction of new immunosuppressive agents such as tacrolimus has presented an opportunity to investigate such a principle. Tacrolimus has been shown to be beneficial when compared to cyclosporin both *de-novo* and in refractory rejection [5, 7, 8, 13]. Its role in the treatment of chronic graft nephropathy has not been investigated.

This aim of this study, therefore, is to investigate the effect of changing maintenance therapy from Neoral-based immunosupression to Prograf-based therapy in patients suffering from chronic graft nephropathy.

## Materials and methods

A cross-sectional study of the cohort of renal allograft recipients attending the outpatient department in a period between February and April 1996 revealed 14 patients with progressive deterioration in renal allograft function associated with histological evidence of chronic graft nephropathy. Having obtained informed consent, the patients were converted from Neoral®- to Prograf®-based immunosuppression.

Ten of the patients were on Neoral-based triple therapy at the time of conversion, whilst three were taking Neoral/prednisolone dual therapy, and one patient was on Neoral monotherapy. Thirteen of the patients taking Neoral had previously received Sandimmun whilst one patient had been on Neoral since the time of transplantation. The median duration of Neoral therapy for patients converted from Sandimmun was 9 months (range: 6–11 months), and all patients were considered to have stabilised on Neoral. Immunosuppression with Neoral aimed to maintain the levels within the therapeutic range of 100–200 ng/ml (Emit®assay). Eight of the patients had suffered a total of 15 rejection episodes whilst seven patients did not suffer any rejection of their allograft during the period of follow-up prior to conversion to Prograf. Patients were converted directly from Neoral to Prograf® at a dose of 0.15 mg/kg per day in 2 divided doses 12 h after discontinuing the Neoral, and were monitored according to clinical response and 12-h Prograf trough levels (Imx® assay). The desired maintenance level for Prograf was 5–15 ng/ml. The remaining immunosuppressive drugs were unchanged.

Pre- and post-conversion renal function was determined by means of a calculated glomerular filtration rate (GFR) using the Cockroft-Gault formula [1] to correct for age, weight and sex. A total of 1662 pre-conversion GFR estimations was performed in these 14 patients. The deterioration trend line was plotted from the point of best renal function prior to deterioration in renal function. The predicted time to return to dialysis was obtained by extrapolating the deterioration trend line to the point where it crossed the x-axis at the GFR level of 10 ml/min.

Statistical analysis was performed using a piecewise regression technique together with a Student's unpaired or paired *t* test to assess differences in means. A $P$ value of less than 0.05 was considered significant.

**Table 1** Mean glomerular filtration rates (GFR) for no-benefit group ($n = 9$), benefit group ($n = 5$) and for all patients ($n = 14$) prior to conversion, at conversion and during follow up

| Time | No benefit group ($n = 9$) | Benefit group ($n = 5$) | All patients ($n = 14$) |
|---|---|---|---|
| – 6 months | 23.7 ml/min | 39.8 ml/min | 29.5 ml/min |
| – 1 months | 19.8 ml/min | 31.0 ml/min | 24.5 ml/min |
| Conversion | 18.7 ml/min | 26.2 ml/min | 21.4 ml/min |
| + 1 months | 19.8 ml/min | 33.2 ml/min | 24.6 ml/min |
| End of study | 13.5 ml/min | 30.2 ml/min | 19.5 ml/min |

## Results

There were eight females and six males with a median age of 40 years (range: 19–60 years). Their median creatinine at the time of conversion was 438 mol/l (range: 262–677 μmol/l), and the median time from transplantation to conversion was 1750 days (149–4266 days). Medical history was well documented and revealed that in the period prior to the conversion (ranging from 7 to 24 months) these patients had been extensively investigated and had undergone a total of 1123 serum creatinine measurements (median 80 per patient), 43 ultrasound scan investigations ranging from 1–5 tests (median = 3), 28 biopsies ranging from 1–4 (median = 1), six patients had been investigated by angiography, and one by MRI angiography. All patients had a diagnosis of CGN in accordance with the Banff criteria [14], as assessed by a renal histopathologist. No patient gave evidence of acute rejection, cytomegalovirus infection, renal artery stenosis, ureteric obstruction or sepsis at the time of conversion, and none of the biopsies were considered to show evidence of cyclosporin nephrotoxicity. In the period leading to conversion, they had undergone no less than 191 adjustments of Neoral dose (median ten per patient), both increasing and decreasing, none of which succeeded in a sustained improvement in graft function. In addition, none of the patients were being treated with ACE inhibitors or had been treated with these agents in a 3-month period prior to conversion.

Two patterns of response emerged during the 15-month follow up: (i) continuing deterioration of renal function with no deviation from the projected trend of GFR ($n = 9$). Seven patients returned to dialysis between 6–42 weeks post-conversion, one died of a myocardial infarction and only one patient remains dialysis-

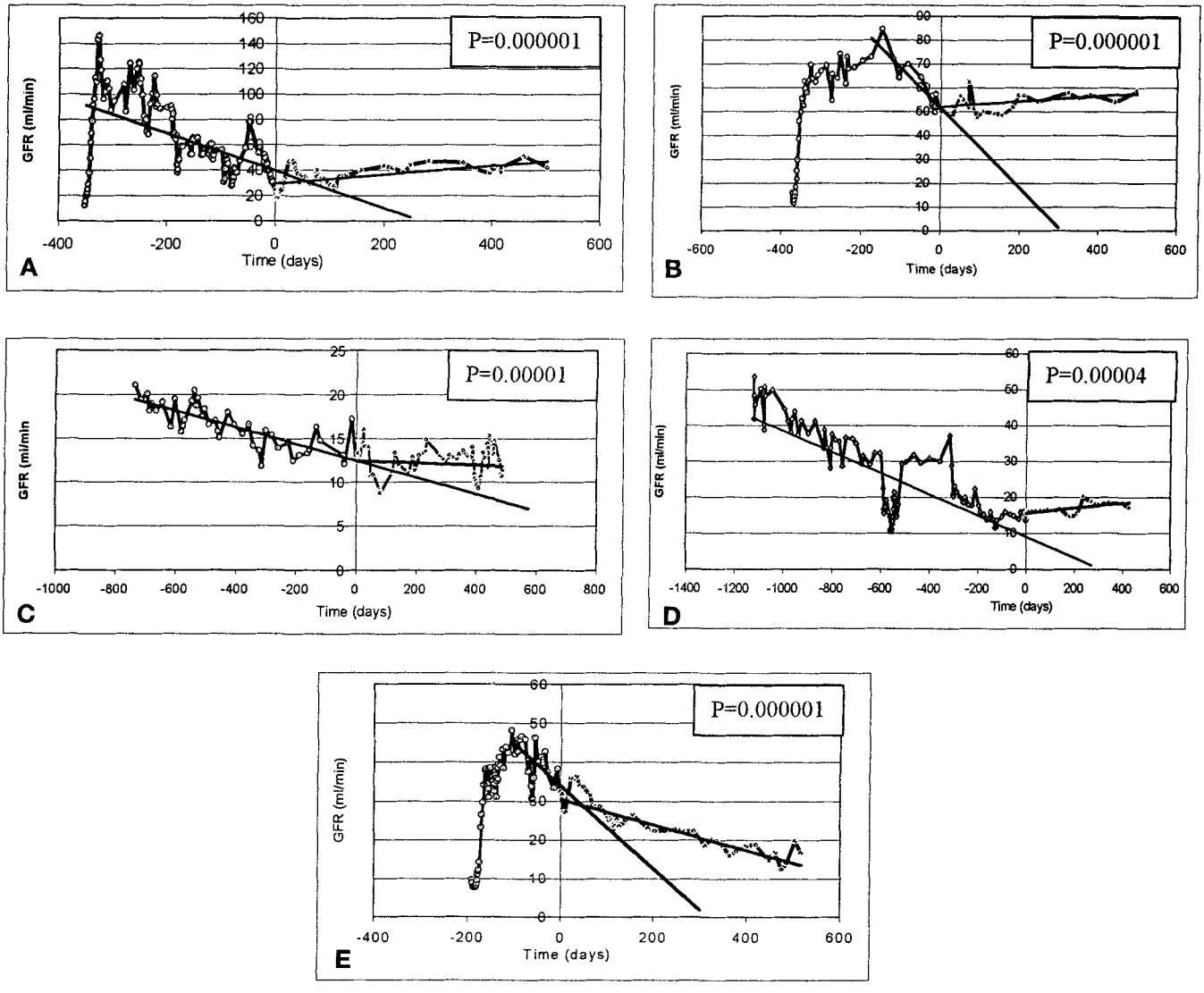


**Fig. 1** Graphs of GFR versus time for the five patients who benefited from conversion. Graphs **A–D** represent patients who showed a sustained improvement in GFR, and Graph **E** the patient demonstrating a reduced rate of deterioration. The negative values on the time *(x-axis)* signify GFR measurements prior to conversion and 0 is the time of conversion

independent, and, (ii) unequivocal change in the GFR trend-line equation with reduced rate of deterioration in one patient and actual sustained improvement of GFR (reversal of downwards trend) in four patients (Fig. 1). For both patient groups, the GFR at one month post-conversion demonstrated an improvement, a phenomenon we termed the 'one-month peak'. For patients that benefited, this peak is prolonged, but for those with no overall benefit the GFR soon returns to the predicted line of deterioration. Eleven patients (79%) were expected to have returned to dialysis by the end of the follow-up period i.e., 15 months from the time of conversion to Prograf. The actual number of failed grafts in that period was eight (57%).

All 5 patients that benefited from conversion to tacrolimus exceeded their estimated time of return to dialysis by a median of 41 weeks (range: 29–52). Even if all 5 grafts had failed then, the mean time to failure would have increased from 30.6 (+/–8.6) to 70.2 (+/–3.7) weeks ($P < 0.0004$, Student's unpaired $t$-test). In view of the fact that all five patients remain dialysis-independent, this benefit is going to be even greater. The median calculated GFR for all patients at the time of conversion was 16.2 ml/min (range: 8.5–49.7 ml/min), the mean values are shown in Table 1. There was no significant difference between the median GFR for the patients that benefited, compared to those that did not benefit from conversion ($P = 0.06$).

There was no difference in the Neoral levels between groups at the time of conversion (92 ng/ml vs. 100 ng/ml). The tacrolimus level in the benefit group at 1 month post conversion was higher than in the no benefit group (13.3 ng/ml vs. 9.6 ng/ml), but the difference did not reach statistical relevance ($P = 0.099$, Student's paired $t$ test; CI–18.8 to + 0.4).

The benefit group showed a significant ($P < 0.04$, Student's unpaired $t$ test) increase in serum albumin from 35.4 g/l at the time of conversion to 41.0 g/l at the end of the study. Interestingly, rise in serum albumin was observed even in those patients who did not benefit from conversion in terms of the GFR. In total, 10 of 14 patients had better serum albumin levels following the conversion, and the mean values for all 14 patients increased from 32.7 g/l to 35.7 g/l ($P < 0.02$, Student's paired $t$ test).

## Discussion

We believe this is the first study indicating that a change of Neoral-based maintenance immunosuppression to Prograf-based therapy is capable of changing the irreversible decline in renal function in patients with failing grafts due to chronic graft nephropathy. The mechanism by which tacrolimus improves graft function in the context of CGN is uncertain. It is possible that the simple act of removing cyclosporin, a potent renal vasoconstrictor [2, 10] may be responsible, at least in part, for the sustained improvement seen in the glomerular filtration rates of five of these patients post-conversion. This may also explain the 'one-month peak' phenomenon that was observed. However, the continuing improvement in GFR of four of the patients (Fig. 1) cannot be explained simply by the removal of the nephrotoxic effect of cyclosporin, as there is substantial evidence that the mechanism of tacrolimus nephrotoxicity is similar to that of cyclosporin [6, 11]. For those in the non-benefit group who failed to show an improvement, the explanation for a lack of response may simply be that this group had a more advanced nephropathy which was not distinguishable simply on the basis of the Banff scoring.

Injury sustained by the renal allograft, both immunological and non-immunological, represents only one aspect of the pathogenesis of CGN. Defence mechanisms of the graft designed to withstand the "attack", such as the expression of protective proteins, together with mechanisms of subsequent repair and regeneration have not been adequately investigated, and deficiencies in these systems may well play crucial roles in the development of CGN.

The importance of serum albumin levels on patient- and graft outcome has only recently been recognised. Guijarro et al. [3] reported that serum albumin is a strong independent risk factor for all-cause mortality after renal transplantation. In our study, conversion from Neoral to Prograf resulted in a significant improvement in the levels of serum albumin, thus potentially reducing the risk of death with a functioning graft for these patients.

In conclusion, this small observational study has suggested an important role for tacrolimus in the salvage of patients with progressive deterioration in function due to CGN. Five out of 14 patients (36%) clearly benefited from replacing Neoral with Prograf. If these findings were confirmed in a prospective randomised trial it would be the first instance of effective treatment for chronic graft nephropathy. Further studies are required to establish the mechanism responsible for the observed improvement.

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