American Journal of Transplantation 2002; 2: 100–104
Munksgaard International Publishers

ISSN 1600-6135

Cyclosporine Microemulsion and Tacrolimus are Associated with Decreased Chronic Allograft Failure and Improved Long-term Graft Survival as Compared with Sandimmune

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Tacrolimus and cyclosporine in the microemulsion formulation Neoral® have demonstrated improvements in acute rejection rates after renal transplantation compared with conventional cyclosporine formulation, Sandimmune®. To evaluate whether these drugs are also associated with improvements in chronic allograft failure (CAF) rates, we retrospectively analyzed 32 040 primary renal allograft recipients reported to the United States Renal Data System (USRDS) between 1994 and 1997.
Graft loss secondary to CAF was defined as graft loss beyond 6 months post-transplant, censored for death, acute rejection, thrombosis, infections and noncompliance. A Cox proportional hazard model was used to investigate the relationship between graft loss secondary to CAF and the use of conventional cyclosporine formulation, as opposed to cyclosporine microemulsion and tacrolimus (Prograf®). The analysis was corrected for confounding variables, such as acute rejection, sex, race, human leukocyte antigen (HLA) mismatch, % panel reactive antibodies (PRA), delayed graft function (DGF), cold ischemia time, induction therapy, dialysis time, etiology of end-stage renal disease, cytomegalovirus (CMV) risk group, donor source, era effect, and mycophenolate mofetil (MMF) use.
Cyclosporine microemulsion use was associated with a significantly lower relative risk (RR = 0.6, CI = 0.5–0.7) for CAF as opposed to conventional cyclosporine formulation. Likewise tacrolimus as compared with conventional cyclosporine formulation was associated with a significantly lower relative risk (RR = 0.7, CI = 0.6–0.8) for CAF. Conventional cyclosporine formulation treatment was associated with a 87.6% adjusted CAF-free survival rate at 4 years. Both tacrolimus and cyclosporine microemulsion were associated with a significantly better adjusted CAF-free survival at 4 years (91.4 and 92.4%, respectively).
Both cyclosporine microemulsion and tacrolimus are associated with improved graft survival and a decreased relative risk for CAF when compared with the older conventional cyclosporine formulation. This association is independent of the use of MMF or changes in era.

Key words: Cyclosporine, graft survival, tacrolimus, transplantation

Received 6 September 2001, revised and accepted for publication 14 September 2001

Introduction

The microemulsion formulation of cyclosporine, Neoral®, was developed to provide greater and more consistent exposure to cyclosporine (CsA) than the older Sandimmune® formulation. When compared with the conventional cyclosporine formulation, a very different pharmacokinetic profile and performance characterizes the cyclosporine microemulsion. As opposed to conventional cyclosporine formulation, cyclosporine microemulsion exhibits a significantly greater absolute bioavailability, a shorter time to maximum concentration, a greater maximal concentration, a greater correlation of trough to area under the concentration curve (AUC) and less day-to-day variability in total drug exposure (1–3). In general these are favorable changes; however, favorable changes in pharmacokinetic behavior may not necessarily be associated with improved short- and long-term clinical outcomes. One study had suggested that reduced cyclosporine variability might be associated with a lower incidence of chronic rejection (4). This study was limited to patients on conventional cyclosporine formulation, who intrinsically displayed differing degrees of variability in cyclosporine pharmacokinetics. This study suggested that lower conventional cyclosporine formulation variability was associated with a lower risk for chronic rejection, but the study could not ascertain a cause–effect relation between pharmacokinetics and chronic rejection, because they did not compare different formulations with intrinsically different pharmacokinetic properties. The association between lower variability and chronic rejection suggested in this study might have been very well mediated by better compliance in the patient who displayed lower variability or other confounding variables. A study directly comparing the two CsA formulations (Sandimmune® and Neoral®) would better answer the question of whether improved pharmacokinetics with cyclosporine translates into improved long-term outcomes.

A meta-analysis by Shah et al. (5) had indicated that use of the cyclosporine microemulsion of CsA is associated with a significantly lower rate of acute rejection episodes while not

increasing side-effects related to cyclosporine toxicity. In addition, one prospective study had suggested that cyclosporine microemulsion is associated with a decrease in acute rejection compared with the conventional cyclosporine formulation (6). However, no long-term data is available demonstrating a beneficial effect on long-term graft outcomes with the use of cyclosporine microemulsion as opposed to conventional cyclosporine formulation.

Tacrolimus is a macrolide calcineurin inhibitor, which has been in use for almost a decade (7). A number of studies have documented its efficacy in organ transplantation (8–15). For most studies in renal transplantation where tacrolimus has been compared with cyclosporine, the conventional cyclosporine formulation was utilized. In these studies, tacrolimus consistently demonstrated lower rejection rates and, in some cases, better 1-year graft survival rates. There are much fewer studies comparing tacrolimus to cyclosporine microemulsion; in these studies the differences in acute rejection rates were very small and inconsistent (8,9). In addition, studies attempting to compare long-term outcomes of tacrolimus to cyclosporine have considered the two formulations together creating a potentially large flaw in these studies.

Utilizing the United States Renal Data System (USRDS), we undertook a retrospective analysis to determine whether the use of either cyclosporine microemulsion or tacrolimus was associated with differences in long-term outcomes as compared with use of conventional cyclosporine formulation.

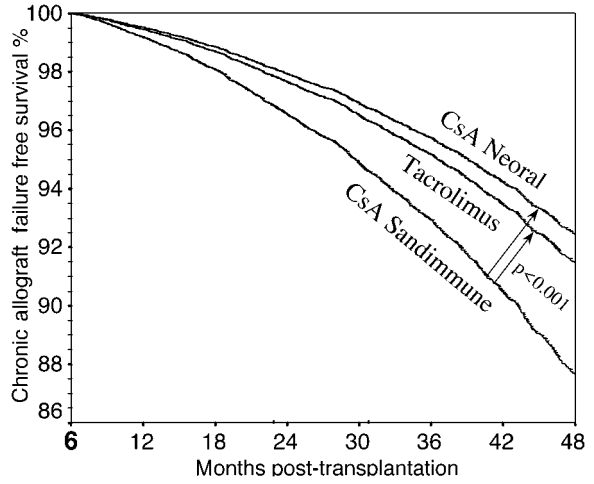

Figure 1: Chronic allograft failure-free survival by Cox proportional hazard in patients on two different cyclosporine (CsA) formulations versus tacrolimus.

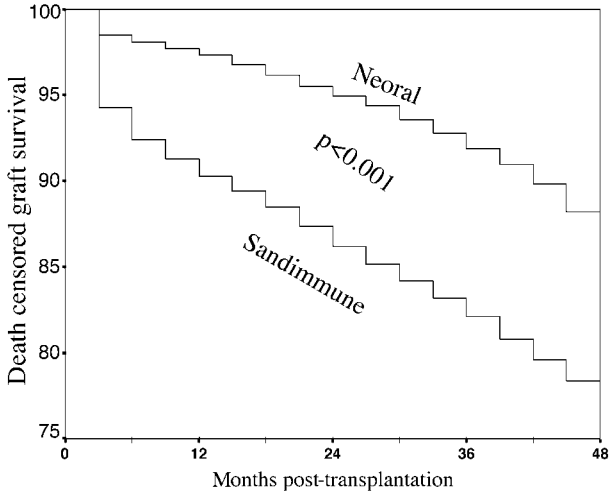

Figure 2: Graft survival by Kaplan–Meier.

Methods

This study was based on data collected by the US Renal Transplant Scientific Registry and supplemented with end-stage renal disease data in the US Renal Data System (USRDS). The study sample consisted of 32 040 patients who underwent solitary renal transplantation between January 01, 1994 and June 30, 1997.

The primary study end-point was chronic renal allograft failure (CAF) (16), defined as graft loss beyond 6 months post-transplant censored for death and all defined causes of graft loss with exception of chronic allograft nephropathy. When the primary cause of graft loss was indicated to be chronic allograft nephropathy, these patients were included in the group of graft loss secondary to chronic allograft failure. On the other hand, when the primary cause of graft loss was indicated as graft loss secondary to acute rejection, graft thrombosis, infection, surgical complications, or recurrent disease, these patients were not included in the group defined as chronic allograft failure. All patients with graft loss secondary to nonspecified cause were included in the definition of chronic allograft failure. The diagnosis of chronic rejection was not independently verified as it was based on follow-up data supplied by individual transplant centers to the Scientific Renal Transplant Registry. Secondary study end-points were graft and death censored graft survival. Patients were followed from transplant date until graft loss or death, or until the study end date of June 30, 1998.

Kaplan–Meier analysis was used to compare graft survival between the drug regimens. Breslow tests were used to investigate for statistically significant differences between survival curves.

Cox proportional hazard regression was used to estimate the independent association of different calcineurin inhibitor use with chronic allograft failure while controlling for relevant risk factors. To account for bias of a longer follow-up time in the Sandimmune-treated patients and a potentially dominant era effect, the year of transplantation was included as an explanatory variate in the Cox proportional hazard analysis. Other independent variables studied in the Cox model were: azathioprine vs. mycophenolate mofetil (MMF) treatment; induction versus no induction treatment; recipient age; donor age; donor and recipient race, gender and cytomegalovirus (CMV) IgG antibody status; primary cause of end-stage renal disease (ESRD); donor source (cadaveric vs. living); cold and warm ischemia times; human leukocyte antigen (HLA) mismatch; presensitization; acute rejection; and delayed graft function (DGF). DGF was defined as a need for one or more dialysis treatments in the first post-transplant week or lack of urine output in the first 24 h post-transplant. Immunosuppressive therapy was evaluated on an 'intent to treat' basis, by assigning patients to groups based on the medications they were on at discharge from the hospital. All patients studied were on one calcineurin-based immunosuppressive regimen with

Table 1: Demographics of renal transplant recipients by calcineurin inhibitor therapy

	CsA	Neoral	Tacrolimus
Number (n)	12899	15624	3,517
Recipient age (years)	40.0 ± 12.8	44.9 ± 12.8	43.5 ± 12.3
Recipient gender (male)	61.3%	61.0%	57.5%
Donor age (years)	35.0 ± 15.7	35.3 ± 15.5	34.5 ± 16.4
Recipient race (African-American)	26.5%	23.6%	24.7%
% PRA > 30%	4.9%	3.8%	4.6%
0 HLA mismatch	5.8%	6.5%	3.3%
Cold time (h)	16.0 ± 11.4	14.8 ± 11.2	17.5 ± 11.3
Delayed graft function	5.3%	5.0%	5.8%
Living donor	27.1%	30.1%	17.9%
Cause of ESRD			
Glomerulonephritis	22.5%	21.3%	17.7%
Hypertension	19.0%	18.0%	13.9%
Diabetes	26.0%	27.2%	35.4%
Polycystic kidney disease	4.3%	3.2%	2.7%
Time on dialysis (months)	23.4 ± 27.5	22.8 ± 27.3	22.6 ± 27.8
MMF	10.2%	36.4%	41.4%
Follow-up	33.2 ± 15.7	27.2 ± 11.5	23.7 ± 11.7

CsA, cyclosporine; ESRD, end-stage renal disease; MMF, mycophenolate mofetil; PRA, panel reactive antibodies.

one of the three calcineurin inhibitors studied (i.e. Sandimmune® vs. Neoral® vs. Prograf®).

A probability of type 1 error ($\alpha < 0.05$) was considered to be the threshold of statistical significance. For multiple comparisons, the threshold of statistical significance was adjusted by the Bonferroni procedure, i.e. comparing Neoral® vs. Prograf® vs. Sandimmune® treatment; a probability of type 1 error ($\alpha < 0.017$) was considered to be the threshold of statistical significance in this analysis. All statistical analysis was performed using SPSS software (version 10.05 for Windows 95, SPSS, Inc., Chicago, IL).

Results

The demographic characteristics of the patients analyzed are displayed in Table 1. Between 1994 and 1997, 15624 patients had been reported to be treated with cyclosporine microemulsion, 12899 patients with conventional cyclosporine formulation and 3517 patients had been reported to have been treated with tacrolimus at discharge from the hospital.

Table 2: Cox proportional hazard model for the relative risk (RR) of chronic allograft failure

Variable	RR	95% CI	p-value
Calcineurin inhibition (Sandimmune)			< 0.001
Neoral	0.6	0.5–0.7	< 0.001
Tacrolimus	0.7	0.5–0.8	< 0.001
MMF (AZA)	0.8	0.7–0.9	0.02
African-American recipient (Caucasian)	1.5	1.4–1.7	< 0.001
Primary disease (glomerulonephritis)			< 0.001
Hypertension	1.3	1.1–1.5	0.001
Diabetes	1.18	1.1–1.4	0.017
Polycystic kidney disease	0.7	0.5–0.9	0.011
Living donation (cadaveric donation)	0.8	0.7–0.9	0.003
Acute rejection (no acute rejection)	3.6	3.2–3.9	< 0.001

AZA, azathioprine; MMF, mycophenolate mofetil.
Additional variables corrected for in the model but not displayed in the table are: donor and recipient age and gender, donor race, cold ischemia time, human leukocyte antigen (HLA) mismatch, panel reactive antibodies (PRA), cytomegalovirus (CMV) serology, time on dialysis pretransplant, year of transplant and antibody induction. Reference groups are in parenthesis.

Table 2 displays the relative risk for chronic allograft failure in this cohort of patients. Both cyclosporine microemulsion (RR = 0.6, CI = 0.5–0.7) and tacrolimus (RR = 0.7, CI = 0.5–0.8) were associated with a lower relative risk for chronic allograft failure as compared with conventional cyclosporine formulation. Similarly, treatment with MMF (RR = 0.8, CI = 0.7–0.9) was associated with a significantly reduced relative risk for chronic allograft failure. Also living donation (RR = 0.8, CI = 0.7–0.9) and polycystic kidney as primary kidney disease (RR = 0.7, CI = 0.5–0.9) were associated with a significant protective effect from chronic allograft failure.

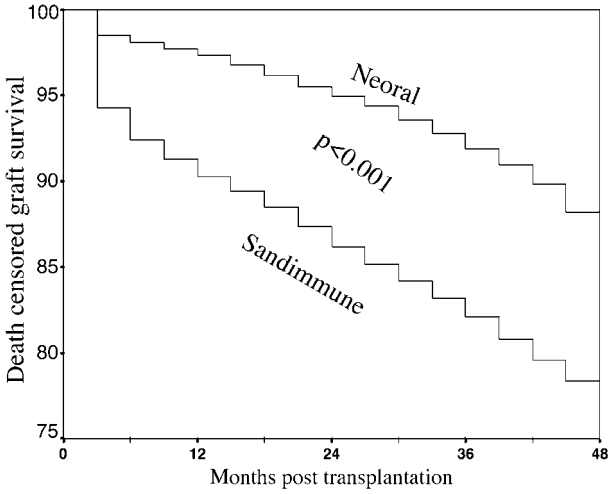

Figure 3: Death censored graft survival by Kaplan–Meier.

African-American recipient status (RR = 1.5, CI = 1.4–1.7), hypertension (RR = 1.3, CI = 1.1–1.5) and diabetes (RR = 1.2, CI = 1.1–1.4) as primary disease, and acute rejection (RR = 3.6, CI = 3.2–3.9) were all variables associated with a significantly increased risk for chronic allograft failure.

Figure 1 displays the adjusted 4-year projected CAF-free survival in patients on conventional cyclosporine formulation as compared with tacrolimus and cyclosporine microemulsion. Both cyclosporine microemulsion and tacrolimus were associated with a statistically significantly better CAF-free survival ($p < 0.001$) as compared with conventional cyclosporine formulation.

By Kaplan–Meier analysis, both graft survival and death censored graft survival were significantly improved in patients receiving cyclosporine microemulsion as compared with conventional cyclosporine formulation (Figures 2 and 3).

Discussion

Our data demonstrate that both the cyclosporine microemulsion and tacrolimus are associated with superior 4-year death censored graft survival when compared with the conventional cyclosporine formulation. This holds true for both the univariate analysis (for cyclosporine microemulsion) and the multivariate analysis (for both tacrolimus and cyclosporine microemulsion) with chronic allograft failure as end-point. As the multivariate analysis accounts for factors such as year of transplant, utilization of MMF and other factors known to affect long-term graft survival, we feel that this association is a true and strong one.

In the multivariate analysis, it appears that both cyclosporine microemulsion and tacrolimus confer approximate equal protection against the risk of CAF. As these data are complete only through 1997 and as the confidence interval for the decreased relative risk for CAF is nearly identical for both immunosuppressants, we are very hesitant to conclude a clear associative benefit of one agent over the other. In addition, we would like to reinforce that the focus of this analysis was on the comparison of cyclosporine microemulsion and tacrolimus versus conventional cyclosporine formulation, and not cyclosporine microemulsion versus tacrolimus. To this end, we chose not to include tacrolimus in the univariate analysis. As it was possible that a changing pattern of tacrolimus use was occurring, we felt that the multivariate analysis would best correct for this change and best avoid an unintentional comparison between tacrolimus and cyclosporine microemulsion.

It is unlikely that the differences noted here between cyclosporine microemulsion and conventional cyclosporine formulation are reflective of different eras, as the eras of the use of both agents is largely overlapping and the multivariate analysis is corrected for a potential era effect. As the major difference between these formulas is the more predictable pharmacokinetics for cyclosporine microemulsion, it is likely that at least part of this benefit is reflective of this improvement in cyclosporine pharmacokinetics.

In summary, the change in formulation of cyclosporine from the traditional oil-based conventional cyclosporine formulation to the newer microemulsion formulation cyclosporine microemulsion was associated with improvements in renal graft survival and a decreased risk of CAF. In a similar fashion, tacrolimus was also associated with a decreased risk of CAF when compared with conventional cyclosporine formulation.

The relative effect of these agents when analyzed as combination therapy with other immunosuppressants such as MMF, sirolimus and IL-2 receptor antibodies will take a greater follow-up and more extensive analysis.

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