Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Three-year health-related quality-of-life outcomes for sirolimus-treated kidney transplant patients after elimination of cyclosporine

Graeme Russ,[1] Neville Jamieson,[2] Rainer Oberbauer,[3] Manuel Arias,[4] Maria G. Murgia,[5] Gilles Blancho,[6] Reiko Sato,[7] Maria Stoeckl[8] and Dennis A. Revicki[8]

1 The Queen Elizabeth Hospital, Woodville, Woodville South, SA, Australia
2 Department of Surgery, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK
3 Allgemeines Krankenhaus (AKH)-WienInnere Medizin Ill-Nephrologie, Vienne, Austria
4 Hospital Marques de Valdecilla, Servicio de Nefrologia Avda, Santander, Spain
5 U. O. Nefrologia e Dialisi, Ospedale S Michele, Piazzale A. Ricchi, Cagliari, Italy
6 CHU Nantes, Nantes University Hospital, Nantes, France
7 Global Health Outcomes Assessment, Wyeth Research, Collegeville, PA, USA
8 Center for Health Outcomes Research, United BioSource Corporation, Bethesda, MD, USA

Keywords
cyclosporine, health-related quality of life, immunosuppressive therapy, kidney transplantation, Kidney Transplant Questionnaire, randomized clinical trial, sirolimus.

Correspondence
Dr Dennis Revicki, Center for Health Outcomes Research, United BioSource Corporation, 7101 Wisconsin Ave., Suite 600, Bethesda, MD 20814, USA. Tel.: +1 301 654 9729; fax: +1 301 654 9864; e-mail: dennis.revicki@unitedbiosource.com

Received: 15 February 2007
Revision requested: 19 March 2007
Accepted: 30 July 2007

doi:10.1111/j.1432-2277.2007.00547.x

Abstract

This study compared 3-year health-related quality-of-life (HRQL) outcomes of sirolimus (SRL)-treated kidney transplant patients after elimination of cyclosporine (CsA) with patients continuing on a combined CsA and SRL regimen. A randomized, multi-country, open-label, clinical trial was performed. 430 kidney transplant patients were randomly assigned to SRL+corticosteroids (ST) ($n = 215$) or SRL+CsA+ST ($n = 215$) therapy after an initial 3-month period of combined SRL+CsA+ST treatment. HRQL was measured using the Kidney Transplant Questionnaire (KTQ) and the SF-36 Health Survey at month 3 (time of randomization) and months 12, 24, and 36 post-transplantation. Mixed-model ANCOVA was used to evaluate treatment differences in HRQL outcomes. HRQL scores were available for 361 (86.4%) eligible study patients. Significant treatment-by-assessment time interactions, favoring SRL+ST, were found on KTQ fatigue ($P = 0.0005$), emotions ($P = 0.028$), and appearance scores ($P = 0.006$). Statistically significant treatment-by-assessment time interactions were observed for SF-36 vitality ($P = 0.0001$), general health ($P = 0.011$), social function ($P = 0.020$), and role-physical scores ($P = 0.049$). Vitality scores improved in the SRL+ST group (mean 3.5-point change) over 36 months, compared with decreases in the SRL+CsA+ST group (mean –3.2-point change). SRL-based therapy with early CsA-elimination results in fewer appearance-related problems, less fatigue, greater vitality, and improved general health status and social functioning compared with continuous SRL+CsA+ST treatment.

Introduction

Kidney transplantation is the treatment of choice for end-stage renal disease (ESRD) [1]. Although it is generally known that health-related quality of life (HRQL) improves dramatically after a successful kidney transplant [1–5], less is known about which immunosuppressive regimen offers better HRQL outcomes. Side effects that have little or no impact on morbidity or mortality can be perceived by patients as highly distressing, which can lead to

lower HRQL [6]. Given the excellent short-term graft outcomes across different regimens [7] and the increasing number of available immunosuppressive agents, HRQL represents a unique and important outcome in addition to clinical parameters.

Although the introduction of calcineurin inhibitors (CNIs), either cyclosporine (CsA) or tacrolimus, has significantly reduced acute rejection rates and improved short-term graft survival rate, it has not led to an increase in long-term graft survival rate [8]. This discrepancy in short- versus long-term graft survival rate may partially be explained by the cumulative and irreversible nephrotoxicity associated with the prolonged use of CNIs [9]. As the evidence of CNI nephrotoxicity continues to grow, more research is examining therapeutic regimens that minimize or eliminate the negative effects of CNIs [10]. These newer regimens offer the possibility of a better renal function profile with improved long-term graft outcomes and, presumably, better HRQL outcomes.

Sirolimus (SRL) is an immunosuppressive mTOR inhibitor that has not been associated with nephrotoxicity in clinical trials [11–14]. It has been hypothesized that CNI-free regimens, based on mTOR inhibitors such as SRL, may provide effective long-term maintenance immunosuppression while also allowing improved kidney function after transplantation [13,14]. The Rapamune Maintenance Regimen (RMR) trial has shown that CsA withdrawal at month 3 after renal transplantation followed by SRL maintenance therapy has resulted in lower blood pressure, better renal function, and improved graft survival rate at 4 years, along with improved graft histology and less malignancy, compared with the CsA continuation group [12,15–17].

There are few long-term follow-up studies comparing the HRQL outcomes associated with immunosuppressive therapies in the kidney transplant population. Such studies may assist physicians and their patients in understanding the longer-term outcomes of kidney transplantation. Oberbauer *et al.* [18] previously reported evidence from the RMR trial that a SRL-corticosteroid (ST) regimen with early and complete withdrawal of CsA improved appearance and fatigue outcomes over 2 years compared to the combination of SRL+CsA+ST. The current report, which summarizes the largest CsA withdrawal study that also assessed HRQL outcomes, highlights the analysis of HRQL endpoints over 3 years of follow-up from the RMR trial.

Methods

Study design and patient sample

A randomized, open-label, clinical trial was performed at 57 centers throughout Europe, Australia, and Canada. Beginning in May 1998, 525 de novo kidney transplant patients were enrolled. After 3 months of combined SRL+CsA+ST treatment for all patients, the patients were randomly assigned to two groups to receive continued treatment: Group A (or the CsA continuation group) with SRL+CsA+ST ($n = 215$), and group B (or the CsA withdrawal group) with SRL+ST ($n = 215$) with gradual elimination of CsA [12,18]. Study inclusion criteria allowed recruitment of patients with end-stage renal failure aged 13 years and older, and receiving either a primary or secondary graft organ from either a living or cadaveric donor. Exclusion criteria for randomization at 3 months included a Banff grade 3 acute rejection episode or vascular rejection within 4 weeks before randomization, post-transplant dialysis dependency, serum creatinine >400 μM, or inadequate renal function that in the opinion of the investigator precluded the elimination of CsA.

The patients in group A, randomly assigned to SRL+CsA+ST, treatment received a fixed dose of 2 mg/day SRL (trough concentrations >5 ng/ml) and CsA (dose adjusted to attain trough concentrations 50–200 ng/mL) The patients in group B, randomly assigned to SRL+ST treatment, had their SRL dose adjusted to attain SRL trough concentrations of 20–30 ng/ml through month 12, and 15–25 ng/ml thereafter. CsA was gradually tapered down starting at month 3, and eliminated fully over the course of 4–6 weeks thereafter [12]. Corticosteroid therapy was initiated within 24 h of transplantation, and was administered per local standard practice at each study center, and tapered to a dose of 5–10 mg/day by month 6. The average steroid dose at 6 months was tapered down to approximately 10 mg/day and remained between 5 and 10 mg/day for months 6 through 60 in both groups A and B, as stipulated by the protocol.

Local institutional review boards and ethics committees at all participating centers approved the study protocol, and written informed consent was obtained from each participating patient (or patient guardian) before entry into the study and initiation of treatment. The study was conducted in accordance with the Declaration of Helsinki.

HRQL assessments

Health-related quality-of-life is a multidimensional construct that represents the patient's perspective on the impact of treatment or disease on physical, psychological, and social functioning and well-being [19]. Because the use of both disease-specific and generic instruments are required for comprehensive assessment, HRQL was measured using the Kidney Transplant Questionnaire (KTQ) and the SF-36 Health Survey at month 3 (time of

randomization) and months 12, 24, and 36 after kidney transplantation. An endpoint HRQL assessment was also completed for patients who discontinued the study/treatment for whatever reason.

Kidney Transplant Questionnaire

The KTQ is a valid and reliable HRQL instrument designed specifically for use of the kidney transplant patients [20]. The instrument has been utilized effectively in previous clinical studies [18,21]. The 25-item KTQ assesses five domains: physical symptoms (six items), fatigue (five items), uncertainty-fear (four items), appearance (four items), and emotions (six items). The physical symptoms domain asks the patient to report on how bothersome a symptom or problem has been in the past 4 weeks. Through an interviewer-administered approach, patients report their responses on a 7-point Likert scale. Items pertaining to the remaining four domains are self-administered. Scores for all subscales range from 1 to 7, with higher scores indicating fewer problems and better health status [20].

SF-36 Health Survey

The SF-36 Health Survey, version 1, is a generic measure designed to evaluate self-reported health status, functioning, and well-being [22]. This self-administered 36-item instrument covers eight subscales including physical function, role limitations-physical, bodily pain, general health perceptions, vitality, social function, role limitations-emotional, and mental health. These subscales are scored from 0 to 100, with higher scores indicating better health status. The SF-36 has been extensively applied in research involving the primary care of the general population, and has been used to assess patients with chronic disease including ESRD [3,18,23].

Statistical methods

Study patient data were included in the analysis if they had an HRQL assessment at randomization and at least one follow-up HRQL assessment (at months 12, 24, 36, or at study termination). Of the 430 patients randomly assigned in the original study, 12 patients from Poland could not be included for further study, because no HRQL translations were available; therefore, 418 total patients were effectively included in this study. A total of 361 patients (86.4%) had a baseline and at least one follow-up HRQL assessment, and 186 patients (44.5%) had complete HRQL data over 36 months (Fig. 1). Study 'completers', such of the participants who stayed through the full course of the study, had no missing HRQL assessments at months 3, 12, 24, and 36 and this position was similar between groups A and B (SRL+CsA+ST, $n = 94$; SRL+ST, $n = 92$). Baseline demographic and clinical characteristics were compared between the treatment groups using chi-square tests for categorical variables and ANOVA for continuous variables. We compared the baseline demographic and selected clinical characteristics between the 'completers' and 'noncompleters' using chi-square and ANOVA. These analyses were conducted to assess any potential bias in the results because of differential follow-up or drop-out from study immunosuppressive therapy.

All analyses of treatment differences were performed based on intention-to-treat principles. Mixed model repeated-measures ANCOVA [24,25] was used to compare treatment differences in mean 3-, 12-, 24- and 36-month HRQL scores. The repeated-measures ANCOVA models included provisions for treatment group, assessment time, treatment-by-assessment time, donor source (i.e. living versus cadaveric donor) and covariates, including age, sex, and any rejection episode before randomization. The focus of the mixed-model ANCOVA analysis was on examining treatment-by-assessment time interactions to determine if there were differences in the trajectories of mean HRQL scores between the two treatment groups. If no statistically significant interaction was detected, the focus was on the respective treatment's main effects (i.e. average HRQL scores over the course of the study). These mixed model repeated-measures ANCOVA analyses were also conducted for a subset of patients who completed all HRQL assessments (i.e. study completers). A P-value of <0.05 was used to determine statistical significance unless otherwise specified. No adjustment was made for multiple statistical comparisons of the HRQL endpoints [26,27], and interpretation of statistically significant tests took multiplicity into account.

Results

Baseline demographic and clinical characteristics

Baseline demographic and clinical characteristics of the 361 patients (SRL+CsA+ST, $n = 178$; SRL+ST, $n = 183$) who had baseline and at least one follow-up HRQL assessment are summarized by treatment group in Table 1. There were no significant differences in baseline demographic and clinical characteristics between the treatment groups. No significant differences were found in baseline HRQL scores between the treatment groups (not shown).

Baseline demographic, clinical and HRQL data for completers and noncompleters

A total of 186 patients (44.5%) enrolled in the clinical trial had complete HRQL data over 36 months (Fig. 1), and this represents 51.5% of the HRQL intent-to-treat

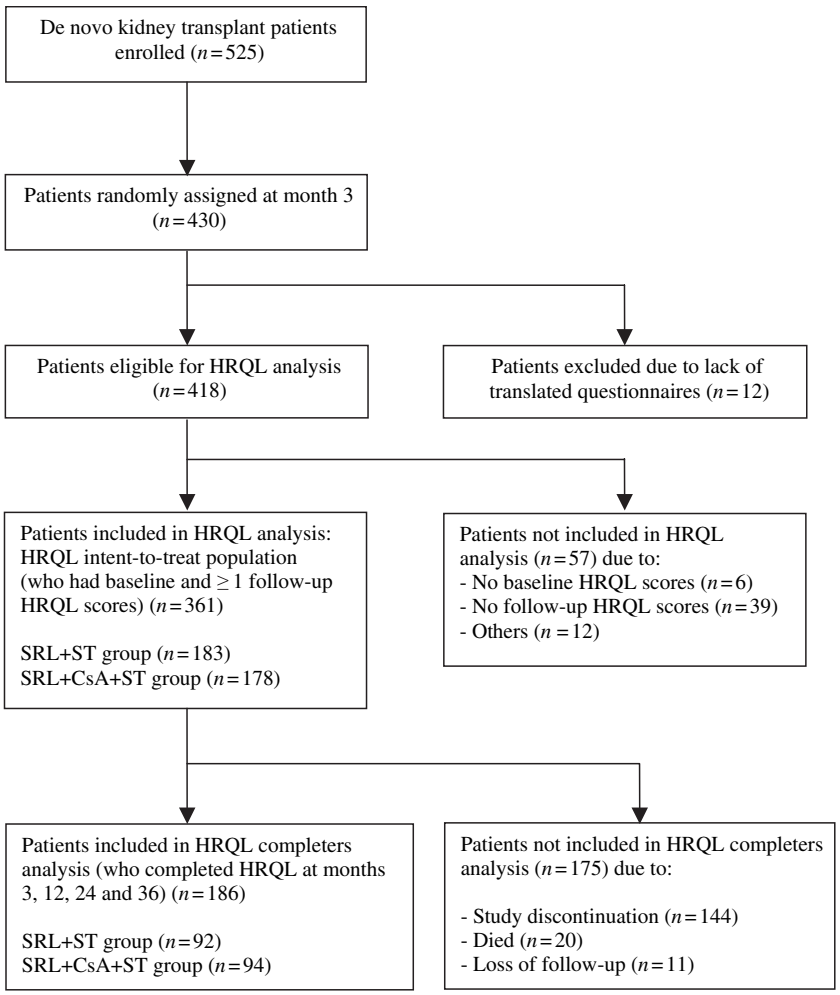

Figure 1 Patients included in health-related quality-of-life analyses.

Table 1. Baseline demographic and clinical characteristics: HRQL analysis.

Characteristic	SRL + CsA + ST (*n* = 178)	SRL + ST (*n* = 183)	Total (*n* = 361)	*P*-value
Men (%)	121 (68)	114 (62)	235 (65)	0.257*
White (%)	166 (93)	174 (95)	340 (94)	0.448*
Age, mean (SD)	45.2 (11.4)	43.9 (13.0)	44.6 (12.3)	0.311†
Secondary transplants (%)	17 (10)	19 (10)	36 (10)	0.791*
Cadaver (%)	156 (88)	160 (87)	316 (88)	0.952*
Diabetes mellitus	7 (4)	14 (8)	21 (6)	0.131*
Acute rejection before randomization (%)	18 (10)	32 (17)	40 (13.6)	0.043*
Transplant hospitalization stay (days), mean (SD)	18.1 (12.7)	17.9 (12.0)	36 (12.4)	0.891†

HRQL, health-related quality of life; CsA, cyclosporine; SRL, sirolimus; SD, standard deviation.
*Pearson chi-square test.
†ANOVA with treatment as a factor.

sample. Baseline demographic and clinical characteristics were compared between completers and noncompleters. Although most characteristics were not significantly different between the groups, completers were more likely to be white ($P = 0.016$), younger ($P = 0.010$), and have a shorter hospital length of stay ($P < 0.0001$) than noncompleters.

Baseline HRQL assessments were also compared and significant differences were found on some KTQ and SF-36 subscales. Of the five subscales of the KTQ, significant

differences were found only in the fatigue subscale ($P = 0.012$) with completers reporting less fatigue than noncompleters (not shown). Completers and noncompleters differed in baseline SF-36 physical function ($P = 0.002$), role-physical ($P = 0.018$), general health ($P < 0.001$), vitality ($P < 0.001$), social function ($P = 0.001$), and mental health ($P < 0.001$) subscales (not shown). In all cases, the completers reported better baseline functioning and well-being than the noncompleters.

Between treatment group differences in HRQL outcomes

Mixed-model ANCOVA models were used to compare mean HRQL scores between the treatment groups over 3 years. There were significant treatment-by-assessment time interactions for the KTQ fatigue ($P = 0.0005$) and appearance ($P = 0.006$), as similar to earlier findings, as well as emotions scores ($P = 0.028$) (Table 2), indicating a significant between-treatment difference over time. In all three subscales, the SRL+ST group reported significantly greater improvements in or maintenance of KTQ scores compared with smaller improvements or deterioration in scores for the SRL+CsA+ST group (Table 2; Fig. 2). No statistically significant treatment-by-assessment time interaction or treatment main effects were seen for KTQ physical symptoms or uncertainty-fear scores.

The results from the mixed-model ANCOVAs for the SF-36 subscale scores are summarized in Table 3. Significant treatment-by-assessment time interactions were observed for vitality ($P = 0.0001$), as similar to earlier

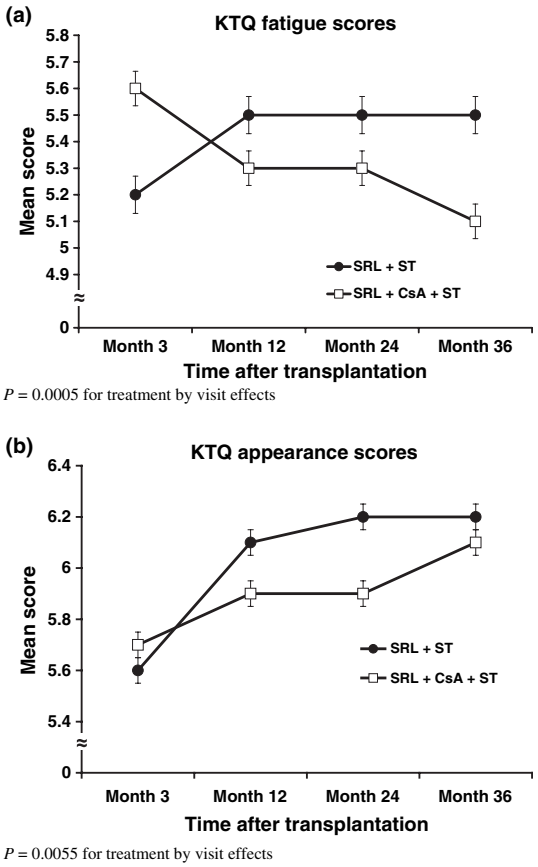

Figure 2 (a) Mean Kidney Transplant Questionnaire (KTQ) fatigue scores by Treatment Group and Study Visit. (b) Mean KTQ appearance scores by Treatment Group and Study Visit.

Table 2. Mean Kidney Transplant Questionnaire scores by Treatment Group and Study Visit: observed cases.

			Observed means (SE)					Repeated-measures ANCOVA‡	
Subscale*	Treatment	No.	Month 3	Month 12	Month 24	Month 36	Month 36–Month 3†	Treatment effect (*P*-value)	Treatment by time effect (*P*-value)
Physical Symptoms	SRL+ST	163	4.2 (0.21)	4.7 (0.17)	4.9 (0.19)	5.2 (0.2)	1		
	SRL+CsA+ST	151	4.4 (0.24)	4.7 (0.19)	4.7 (0.21)	5.2 (0.21)	0.8	0.9654	0.5596
Fatigue	SRL+ST	163	5.2 (0.14)	5.5 (0.12)	5.5 (0.12)	5.5 (0.13)	0.3		
	SRL+CsA+ST	151	5.6 (0.13)	5.3 (0.13)	5.3 (0.13)	5.1 (0.15)	−0.5	0.1625	0.0005
Uncertainty-fear	SRL+ST	163	5.2 (0.12)	5.4 (0.11)	5.5 (0.12)	5.5 (0.13)	0.3		
	SRL+CsA+ST	151	5.3 (0.14)	5.2 (0.11)	5.3 (0.12)	5.4 (0.13)	0.1	0.0828	0.4968
Appearance	SRL+ST	163	5.6 (0.13)	6.1 (0.08)	6.2 (0.07)	6.2 (0.08)	0.6		
	SRL+CsA+ST	151	5.7 (0.13)	5.9 (0.09)	5.9 (0.1)	6.1 (0.09)	0.4	0.0268	0.0055
Emotions	SRL+ST	163	5.5 (0.11)	5.5 (0.09)	5.5 (0.1)	5.6 (0.11)	0.1		
	SRL+CsA+ST	151	5.5 (0.11)	5.4 (0.09)	5.4 (0.11)	5.2 (0.13)	−0.3	0.0345	0.0278

SE, standard error; ANCOVA, analysis of covariance; SRL, sirolimus; CsA, cyclosporine; ST, steroids.

*Scores range from 1 to 7, with higher scores indicating better health status.

†Mean score difference between month 3 and month 36.

‡Two-tailed *P*-values from mixed-model repeated-measures ANCOVA, including treatment, assessment time, treatment × assessment time, donor source, age, sex, and presence of acute rejection episode before randomization.

Table 3. Mean SF-36 health survey scores by Treatment Group and Study Visit: observed cases.

			Observed means (SE)					Repeated-measures ANCOVA‡	
Subscale*	Treatment	No.	Month 3	Month 12	Month 24	Month 36	Month 36–Month 3†	Treatment effect (*P*-value)	Treatment by time effect (*P*-value)
Physical functioning	SRL+ST	181	75.1 (1.65)	81.5 (1.55)	79.7 (1.96)	82.4 (1.97)	7.3		
	SRL+CsA+ST	176	74.9 (1.84)	77.1 (1.93)	78 (2.07)	81.1 (2.18)	6.2	0.3992	0.4577
Role-physical	SRL+ST	179	49.9 (3.07)	70.6 (3.23)	73.4 (3.38)	74.8 (3.46)	24.9		
	SRL+CsA+ST	174	54.7 (3.1)	64 (3.27)	66.5 (3.56)	66.9 (4.09)	12.2	0.3430	0.0488
Bodily pain	SRL+ST	181	73.1 (1.95)	74.8 (2.06)	77.3 (2.36)	79.2 (2.41)	6.1		
	SRL+CsA+ST	175	73.8 (1.95)	72.8 (2.15)	73.3 (2.38)	77.5 (2.53)	3.7	0.5187	0.6285
General health	SRL+ST	179	65.7 (1.43)	65.3 (1.67)	67.1 (1.86)	65.5 (2.1)	−0.2		
	SRL+CsA+ST	175	67.5 (1.41)	65 (1.62)	62.6 (1.72)	60.2 (2.05)	−7.3	0.2624	0.0107
Vitality	SRL+ST	180	63.3 (1.62)	65.2 (1.83)	68.2 (1.97)	66.8 (2.02)	3.5		
	SRL+CsA+ST	176	66.5 (1.58)	64.2 (1.78)	61.5 (1.91)	63.3 (2.01)	−3.2	0.2874	0.0001
Social functioning	SRL+ST	181	77.6 (1.88)	83.6 (1.83)	81.1 (2.03)	85.6 (1.96)	8		
	SRL+CsA+ST	176	80.2 (1.77)	81.4 (1.82)	82.3 (1.83)	79.1 (2.21)	−1.1	0.3592	0.0204
Role-emotional	SRL+ST	180	77 (2.69)	79.8 (2.87)	81.2 (3.08)	84.4 (3.14)	7.4		
	SRL+CsA+ST	172	71.2 (2.92)	76.4 (2.92)	76.7 (3.27)	81.6 (3.42)	10.4	0.1369	0.9672
Mental health	SRL+ST	180	76.8 (1.27)	76.1 (1.51)	76.1 (1.64)	75.7 (1.74)	−1.1		
	SRL+CsA+ST	176	76.8 (1.27)	74 (1.51)	71.8 (1.76)	72.3 (1.86)	−4.5	0.0538.	0.1236

SE, standard error; ANCOVA, analysis of covariance; SRL, sirolimus; CsA, cyclosporine; ST, steroids.

*Scores range from 0 to 100, with higher scores indicating better health status.

†Mean score difference between month 3 and month 36.

‡Two-tailed *P*-values from mixed-model repeated-measures ANCOVA, including treatment, assessment time, treatment × assessment time, donor source, age, sex, and presence of acute rejection episode before randomization.

findings, as well as role-physical ($P = 0.049$), general health ($P = 0.011$), and social function ($P = 0.020$) scores. No other statistically significant treatment-by-assessment time interactions were observed (all $P > 0.05$) for the other SF-36 subscale scores. For vitality scores, the SRL+ST group improved from month 3 to month 36 compared with decreases in the SRL+CsA+ST group (Fig. 3a). For general health, decreases were seen in the SRL+CsA+ST group compared with stable scores in the SRL+ST group over 36 months (Fig. 3b). For social function, the SRL+ST group demonstrated improvements, while the SRL+CsA+ST treated group had slight decreases (not shown).

Completer analysis of between-group differences in HRQL outcomes

Among 186 patients who completed all HRQL assessments, there were comparable rates of completion between the SRL+CsA+ST group ($n = 92$, 49.5%) and the SRL+ST group ($n = 94$, 50.5%, $P = 0.883$). The mixed model ANCOVAS performed on the HRQL completer population mostly confirmed results from the larger intent-to-treat HRQL population. Statistically significant treatment-by-assessment time interactions were observed for the KTQ fatigue ($P = 0.0005$), appearance ($P = 0.013$), and emotions ($P = 0.048$) scores (not shown), favoring the SRL+ST group. There were no statistically significant interaction or treatment main effects for KTQ physical symptoms and uncertainty-fear scores. For the SF-36, significant treatment-by-assessment time interactions were observed for the subscales of general health ($P = 0.002$), vitality ($P < 0.0001$), and social function ($P = 0.034$) (not shown), favoring the SRL+ST group. There were no significant treatment-by-assessment time (all $P > 0.05$) or treatment main effects (all $P > 0.05$) for the remaining SF-36 subscale scores.

Discussion

This clinical trial compared the long-term HRQL outcomes of renal transplant patients who received SRL+CsA+ST for the first 3 months after transplant and were then randomly assigned to either continue SRL+CsA+ST or SRL+ST with CsA withdrawal. This is the largest CsA withdrawal study that also assessed HRQL outcomes [18,28]. Treatment differences favoring SRL+ST were found using the KTQ on areas like fatigue, appearance, and emotions scores, and likewise using SF-36 vitality, general health, and social function scores. Combined with comparable and excellent graft and patient survival rate [12,15,17,28], these results suggest that SRL-based therapy with elimination of CsA

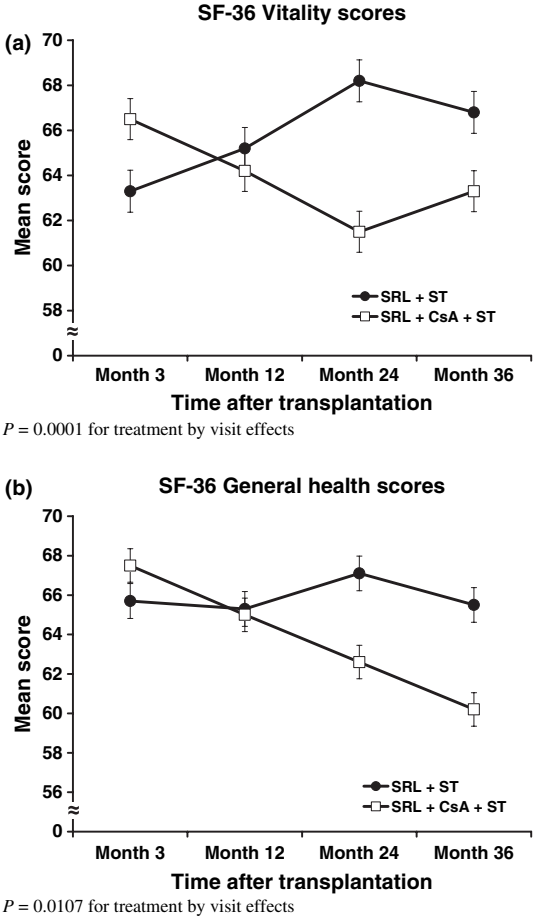

Figure 3 (a) Mean SF-36 vitality scores by Treatment Group and Study Visit. (b) Mean SF-36 general health scores by Treatment Group and Study Visit.

provides HRQL benefits. The HRQL findings are consistent with the clinical results after 3 years, which demonstrably improved serum creatinine, glomerulation filtration rate, and graft survival rate in the SRL-ST compared with the SRL-CsA-ST group [12,16]. Renal function continued to improve in the SRL-ST group after 1 year, while in the SRL-CsA-ST group renal function declined after 1 year.

The most important findings from this study are the consistent treatment differences on measures of fatigue and vitality, which further support the findings from the 2-year HRQL analyses [18]. The SRL+ST group reported reduction in fatigue, while the SRL+CsA+ST group reported significant increases in fatigue. These treatment differences correspond to a between-treatment difference of 0.8 points, which is clearly clinically significant on a 7-point scale [29]. This difference represents a 0.59 effect size. Based on comparative data from other studies [3,30], patient-reported fatigue and vitality at 3 months in this study were greatly improved over pretransplantation assessments. The patient-reported outcomes are consistent with the observation of significantly better hemoglobin values in the SRL-ST compared with the SRL-CsA-ST group after 3 years of follow-up [12,16].

The mean SF-36 vitality scores at 36 months were 63 to 67 for both treatment groups, and these findings are consistent with those reported elsewhere for renal transplant recipients [3]. The between-treatment difference emerged after CsA withdrawal at 3 months. The vitality scores improved 3.5 points during the 3-year follow-up in the SRL+ST group, but decreased more than 3.2 points in the SRL+CsA+ST group. Differences between the two groups of more than five points on the SF-36 vitality scores are considered clinically significant [22,31].

The significant differences between the treatments over time in SF-36 general health and social functioning scores may also be attributable in part to the effects on fatigue and vitality. It is likely that those patients who are experiencing greater fatigue report more impaired perceptions of their general health status and less participation in social and recreational activities with family and friends. For general health, the mean scores remained stable in the SRL+ST group, while these scores decreased significantly in the SRL+CsA+ST group. For social functioning, the mean scores increased in the SRL+ST treated group but remained largely stable in the SRL+CsA+ST group. Further research is needed to understand the complex relationships between fatigue and other HRQL outcomes in renal transplant patients.

Increased fatigue and lower vitality in the SRL+CsA+ST group may be attributable to insufficient renal function, drug-induced electrolyte imbalance, concomitant use of drugs such as β-blockers or simply an adverse effect of CsA [18]. Fatigue is common in chronic renal disease and other chronic diseases. Further research on fatigue outcomes associated with transplantation is needed to confirm this finding.

In this study, patients in the SRL+ST group reported slightly fewer appearance-related problems by 12 months than patients in the SRL+CsA+ST group, although these differences were less apparent by 36 months. KTQ appearance scores improved in the SRL+ST group within 9 months after CsA withdrawal, an improvement that was maintained over the next 2 years of follow-up. By 36 months, however, these differences were found unlikely to be clinically significant. Other clinical studies [3,32] also found differences in appearance-related measures favoring tacrolimus-treated compared with CsA-treated kidney transplant patients.

Interpretation of these HRQL findings should consider several limitations associated with this clinical trial. Firstly, although 86% of patients participating in this trial provided at least one follow-up HRQL assessment and

45% provided all four assessments (i.e. 52% of the HRQL intent-to-treat analysis sample), the completers were more likely to be white, younger, and have shorter hospital lengths of stay than noncompleters. Patients with complete HRQL assessments were more likely to report better baseline HRQL, and this may affect the generalizability of the results to the broader population of kidney transplant recipients. Because the rates of completers and noncompleters by treatment group were comparable, the treatment comparisons may not be biased. Moreover, the results from the completer analysis and the broader HRQL population in this trial produced largely similar results. Secondly, it may not be possible to generalize these HRQL results completely, given that study patients were randomly assigned only if they did not experience a Banff grade 3 or vascular rejection episode during the previous 4 weeks. Although these limitations may affect generalizability to all renal transplant recipients, there is no reason to believe that the HRQL results favoring the regimen without CsA are affected. Thirdly, the HRQL outcomes reported in this study are based on patients' subjective reports, which may be biased by different events, especially emotions and other psychosocial scores. Different patients may experience fatigue and other symptoms differently over the course of the study. However, patients' report of this subjective experience is the only way to measure these problems. Fourthly, this study was open-label and there may be some bias introduced in patient-reported outcomes associated with receiving fewer immunosuppressive medications. However, the HRQL results are consistent with objective clinical endpoints and it is difficult for patients to maintain a positive bias over 3 years in the absence of some positive clinical effects. Finally, the issue of multiplicity of endpoints is common to most HRQL studies [26]. Given the importance of 3-year outcome data, we did not adjust the statistical tests for multiplicity. However, we did account for multiplicity in interpreting statistically significant results for the HRQL endpoints giving more weight to differences that reached less than $P = 0.01$.

Given the number of available immunosuppressive treatment regimens, physicians should consider the potential effect of these regimens on long-term patient functioning and well-being [6]. Further, there are available alternative strategies for reducing immunosuppressive treatment, but all require careful monitoring of toxicities and renal function [33]. These HRQL findings indicate that the elimination of CsA from a combined SRL, CsA, and ST regimen at 3 months after kidney transplantation results in decreased fatigue, and improved vitality, general health perceptions, and social functioning compared with continuous treatment with CsA over 3 years. The current study results further confirm and extend the earlier HRQL findings based on 2 years of follow-up [18]. The HRQL results are consistent with the clinical outcomes and reduced toxicities associated with CsA withdrawal. SRL-based therapy with CsA elimination is a safe and effective treatment compared with continuous SRL+CsA+ST, and has been shown to maintain patient energy and vitality, social activities, and general health.

Acknowledgements

This study was supported by a grant from Wyeth Research, Collegeville, Pennsylvania, and Paris, France. The authors would like to acknowledge the contributions of all the clinical centers that participated in this study (see reference 12 for a complete list), as well as Magali Lelong (Wyeth Research, Paris, France) for her key contributions to the management of this trial.

Authorship

GR, NJ, RO, MA, MGM, GB performed the research/study, collected the data, and reviewed the manuscript. RS designed the research/study and reviewed the manuscript. MS analyzed the data and wrote the manuscript. DAR designed the research/study, analyzed the data, and wrote the manuscript.

References

1. Humar A, Denny R, Matas AJ, Najarian JS. Graft and quality of life outcomes in older recipients of a kidney transplant. *Exp Clin Transplant* 2003; **1**: 69.
2. Karam VH, Gasquet I, Delvart V, *et al.* Quality of life in adult survivors beyond 10 years after liver, kidney, and heart transplantation. *Transplantation* 2003; **76**: 1699.
3. Shield CF III, McGrath MM, Goss TF. Assessment of health-related quality of life in kidney transplant patients receiving tacrolimus (FK506)-based versus cyclosporine-based immunosuppression. *Transplantation* 1997; **64**: 1738.
4. Dew MA, Switzer GE, Goycoolea JM, *et al.* Does transplantation produce quality of life benefits? A quantitative analysis of the literature 3. *Transplantation* 1997; **64**: 1261.
5. Jofre R, Lopez-Gomez JM, Moreno F, Sanz-Guajardo D, Valderrabano F. Changes in quality of life after renal transplantation. *Am J Kidney Dis* 1998; **32**: 93.
6. Keown P. Improving quality of life – the new target for transplantation. *Transplantation* 2001; **12**(Suppl.): S67.
7. U.S. Department of Health and Human Services 2004. *Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1995–2002*. Rockville, MD: Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation,

2004. Available at: http://www.unos.org/data/. Accessed on 25 November, 2005.
8. Meier-Kriesche HU, Schold JD, Srinivas TR, Kaplan B. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. *Am J Transplant* 2004; **4**: 378.
9. Vincenti F, Ramos E, Brattstrom C, *et al.* Multicenter trial exploring calcineurin inhibitors avoidance in renal transplantation. *Transplantation* 2001; **71**: 1282.
10. Flechner SM. Minimizing calcineurin inhibitor drugs in renal transplantation. *Transplant Proc* 2003; **3**(Suppl.): 118S.
11. Hamdy AF, El-Agroudy AE, Bakr MA, *et al.* Comparison of sirolimus with low-dose tacrolimus versus sirolimus-based calcineurin inhibitor-free regimen in live donor renal transplantation. *Am J Transplant* 2005; **5**: 2531.
12. Kreis H, Oberbauer R, Campistol JM, *et al.* Long-term benefits with sirolimus-based therapy following early cyclosporine withdrawal. *J Am Soc Nephrol* 2004; **15**: 809.
13. Morales JM, Wramner L, Kreis H, *et al.* Sirolimous does not exhibit nephrotoxicity compared to cyclosporine in renal transplant recipients. *Am J Transplant* 2002; **2**: 436.
14. Flechner SM, Kurian SM, Solez K, *et al.* De novo kidney transplantation without use of calcineurin inhibitors preserves renal structure and function at two years. *Am J Transplant* 2004; **4**: 1776.
15. Oberbauer R, Segoloni G, Campistol JM, *et al.* Early cyclosporine withdrawal from a sirolimus-based regimen results in better renal allograft survival and renal function at 48 months after transplantation. *Transplant Int* 2005; **18**: 22.
16. Mota A, Arias M, Taskinen EI, *et al.* Sirolimus-based therapy following early cyclosporine withdrawal provides significantly improved renal histology and function at 3 years. *Am J Transplant* 2004; **4**: 953.
17. Campistol JM, Eris J, Oberbauer R, *et al.* The Rapamune Maintenance Regimen (RMR) Study Group. Sirolimus therapy after early cyclosporine withdrawal reduces the risk of cancer in adult renal transplantation. *J Am Soc Nephrol* 2006; **17**: 581.
18. Oberbauer R, Hutchison B, Eris J, *et al.* Health-related quality-of-life outcomes of sirolimus-treated kidney transplant patients after elimination of cyclosporine A: results of a 2-year randomized clinical trial. *Transplantation* 2003; **75**: 1277.
19. Patrick DL, Chiang YP. Measurement of health outcomes in treatment effectiveness evaluations: conceptual and methodological challenges. *Med Car* 2000; **38**(Suppl II.): II14.
20. Laupacis A, Pus N, Muirhead N, Wong C, Ferguson B, Keown P. Disease-specific questionnaire for patients with a renal transplant. *Nephron* 1993; **64**: 226.
21. Fiebiger W, Mitterbauer C, Oberbauer R. Health-related quality of life outcomes after kidney transplantation. *Health Qual Life Outcomes* 2004; **2**: 2.
22. Ware JE, Snow KK, Kosinski M, Gandek B. *SF-36 Health Survey: Manual and Interpretation Guide*. Boston: The Health Institute, New England Medical Center, 1993.
23. Wight JP, Edwards L, Brazier J, Walters S, Payne JN, Brown CB. The SF-36 as an outcome measure of services for end stage renal failure. *Qual Health Care* 1998; **7**: 209.
24. Verbeke G, Molenberghs G, eds. *Linear Mixed Models in Practice: A SAS-Oriented Approach*. New York: Springer, 1997.
25. Fairclough DL. *Design and Analysis of Quality of Life Studies in Clinical Trials*. Boca Raton, FL: Chapman & Hall/CRC, 2002.
26. Perneger TV. What's wrong with Bonferroni adjustments. *BMJ* 1998; **316**: 1236.
27. Fayers PM, Machin D. *Quality of Life: Assessment, Analysis and Interpretation*. New York: John Wiley & Sons, 2000.
28. Johnson RW, Kreis H, Oberbauer R, Brattstrom C, Claesson K, Eris J. Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. *Transplantation* 2001; **72**: 777.
29. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to explain the clinical significance of health status measures. *Mayo Clin Proc* 2002; **77**: 371.
30. Laupacis A, Keown P, Pus N, *et al.* A study of the quality of life and cost-utility of renal transplantation. *Kidney Int* 1996; **50**: 235.
31. Edgell E, Coons S, Carter WB, *et al.* A review of health-related quality-of-life measures used in end-stage renal disease. *Clin Ther* 1996; **18**: 887.
32. Reimer J, Franke GH, Philipp T, Heemann U. Quality of life in kidney recipients: comparison of tacrolimus and cyclosporine-microemulsion. *Clin Transplant* 2002; **16**: 48.
33. Kirk AD, Mannon RB, Swanson SJ, Hale DA. Strategies for minimizing immunosuppression in kidney transplantation. *Transpl Int* 2005; **18**: 2.

