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ORIGINAL ARTICLE

Early cyclosporine withdrawal from a sirolimus-based regimen results in better renal allograft survival and renal function at 48 months after transplantation

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Summary

We report the 48-month results of a trial testing whether withdrawal of cyclosporine (CsA) from a sirolimus (SRL)-CsA-steroid (ST) regimen would impact renal allograft survival. Eligible patients receiving SRL-CsA-ST from transplantation were randomly assigned at 3 months to remain on triple therapy (SRL-CsA-ST, $n = 215$) or to have CsA withdrawn and SRL trough concentrations increased (SRL-ST, $n = 215$). SRL-ST therapy resulted in significantly better graft survival, either when including death with a functioning graft as an event (84.2% vs. 91.5%, $P = 0.024$) or when censoring it (90.6% vs. 96.1%, $P = 0.026$). Calculated glomerular filtration rate (43.8 vs. 58.3 ml/min, $P < 0.001$) and mean arterial blood pressure (101.3 vs. 97.1 mmHg, $P = 0.047$) were also improved with SRL-ST. Differences in the incidences of biopsy-proven acute rejection after randomization (6.5% vs. 10.2%, SRL-CsA-ST versus SRL-ST, respectively) and mortality (7.9% vs. 4.7%) were not significant. SRL-CsA-ST-treated patients had significantly higher incidences of adverse events generally associated with CsA, whereas those in the SRL-ST group experienced greater frequencies of events commonly related to higher trough levels of SRL. In conclusion, early withdrawal of CsA from a SRL-CsA-ST regimen rapidly improves renal function and ultimately results in better graft survival.

Introduction

New immunosuppressive agents have affected the incidence of acute rejection and early graft survival. Nonetheless, long-term renal allograft survival has improved only marginally [1]. While calcineurin inhibitors have been the mainstay of immunosuppressive therapy, their long-term use is associated with progressive

renal injury. Sirolimus (SRL) (rapamycin; Rapamune®, Wyeth-Ayerst, Collegeville, PA, USA) is a new immunosuppressant that is not a nephrotoxic calcineurin inhibitor [2]. Early studies showed the combination of SRL with cyclosporine (CsA), a calcineurin inhibitor, reduced acute rejection rates significantly compared with azathioprine (AZA) or placebo; however, renal function was not improved [3,4]. The Rapamune maintenance regimen (RMR) study has demonstrated improved renal function and blood pressure among kidney transplant patients who had CsA withdrawn early after transplantation [5–7]. We present the 48-month results of the RMR study.

Patients and methods

This randomized, open-label study was conducted at 57 centres in Europe, Canada and Australia. Approval was obtained from local ethics committees and the study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. The study design, methodology and eligibility criteria have been described previously [5]; there were no significant differences in recipient or donor demographic characteristics between randomized treatment groups. In brief, 525 renal transplant recipients received SRL (nominally 2 mg/day, trough >5 ng/ml), CsA (150–400 ng/ml) and steroids (ST) after transplantation. At 3 months ± 2 weeks after transplantation, eligible patients were randomly assigned to remain on triple therapy (SRL-CsA-ST group, $n = 215$) or to have CsA withdrawn and SRL trough concentrations increased to 20–30 ng/ml (immunoassay) during year 1, then decreased to 15–25 ng/ml thereafter (SRL-ST group, $n = 215$). Of the 95 patients who were not randomized, most discontinued for adverse events before the 3-month visit [5]; only 11 patients were not randomized because they did not meet the eligibility criteria at the 3-month visit [6]. The trial was originally planned for 36 months but was extended to 60 months after regulatory agency review of the 12-month results.

The primary endpoint was noninferiority of graft survival in the SRL-ST group compared with the SRL-CsA-ST group at 12 months. Secondary endpoints included graft survival through 60 months, patient survival, acute rejection and renal function. Noninferiority of the SRL-ST group at month 36 and thereafter would be established if the 95% confidence interval (CI) of the difference in graft survival (including death with a functioning graft and loss to follow up) between groups (SRL-CsA-ST minus SRL-ST) crossed zero and if the upper limit of the CI was not >10%. Graft survival was also determined using Kaplan–Meier estimates, censoring for loss to follow up from the time of this event, and the groups were compared using the log-rank test. Graft loss, death, acute rejection and malignancy occurring after discontinuation from the study were included in the analyses.

Renal function was determined via measurements of serum creatinine and calculated glomerular filtration rate (GFR) in patients who continued on therapy at 12, 24, 36 and 48 months and also by including values from discontinued patients [intent-to-treat (ITT) analysis]. Random coefficients regression analyses of calculated GFR versus time (slope analysis) were performed using on-therapy data over 6–48 months and by using all values over the same time period (ITT analysis). Calculated GFR was set to zero at the time of functional graft loss (subsequent values censored) for slope analyses.

Treatment-emergent adverse events (new events or those worsening after randomization) and other categorical variables were compared using Fisher's exact test. Analysis of covariance was used to analyse vital signs and laboratory data, including renal function, using baseline (last value before randomization) as the covariate. The number of antihypertensive drugs per patient was compared between treatments with a Cochran–Mantel–Haenszel test.

Results

When the noninferiority criteria were applied at 48 months, graft survival in the SRL-ST group was not inferior to that in the SRL-CsA-ST group (difference −11.2%; 95% CI = −18.5, −3.8). Conversely, noninferiority of the SRL-CsA-ST group would be established if the lower limit of the 95% CI was more than −10%; superiority of SRL-ST would further be established if the 95% CI did not include zero. Therefore, it may be concluded that graft survival (including loss to follow up) in the SRL-ST group was superior to that in the SRL-CsA-ST group. Figure 1 shows that the time to graft loss (including death with a functioning graft, but censoring for loss to follow-up) at 48 months was also significantly better in SRL-ST patients (91.5%) compared with SRL-CsA-ST patients (84.2%, log-rank $P = 0.024$). When censoring for both death with a functioning graft and loss to follow up, the difference remained statistically significant between SRL-CsA-ST and SRL-ST patients (90.6% vs. 96.1%, respectively, log-rank $P = 0.026$). At 48 months, 9.3% of the SRL-CsA-ST patients and 5.1% of the SRL-ST patients were lost to follow up for graft survival. The most common reason for functional graft loss in both groups was progressive renal dysfunction/nephropathy.

Figure 1 also illustrates overall graft survival, which includes the 95 patients who were enrolled but not randomized. The Kaplan–Meier estimate for graft survival censored for loss to follow up in all enrolled patients was 80.1%. By month 48, among the 95 nonrandomized patients, 35.8% had experienced functional graft loss,

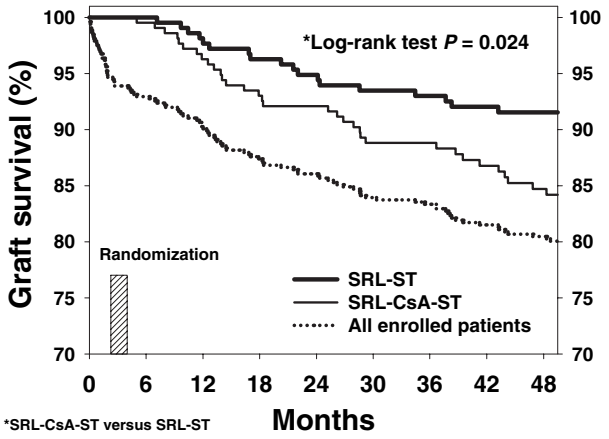

Figure 1 Kaplan–Meier plots of graft survival in the intent-to-treat (ITT) population at 48 months, censored for loss to follow up. The line for all enrolled patients ($n = 525$) includes the 95 patients who were not randomized as well as the 430 patients who were eligible for randomization ($n = 215$ per group).

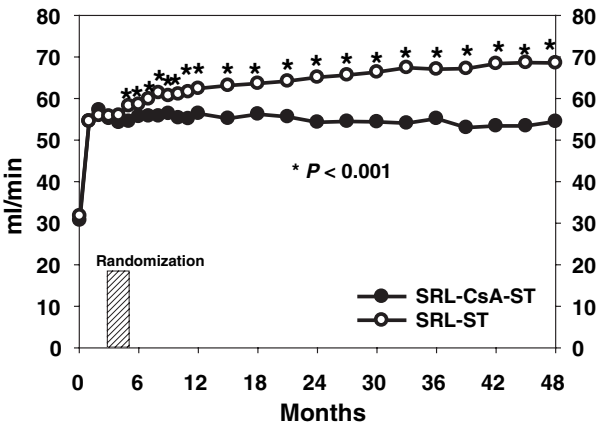

Figure 2 Calculated glomerular filtration rate (GFR), method of Nankivell: on-therapy population. At 48 months: $n = 97$, sirolimus (SRL)-cyclosporine (CsA)-steroid (ST) group; $n = 112$, SRL-ST group.

18.9% had died with a functioning graft and 6.3% were lost to follow up.

The incidence of biopsy-confirmed acute rejection after randomization was similar between groups at 48 months, although slightly lower in the SRL-CsA-ST group (6.5% vs. 10.2%, $P = 0.223$). All acute rejections after randomization were mild to moderate in severity. Moreover, the rate of first biopsy-proven acute rejection after transplantation was not significantly different between the SRL-CsA-ST (15.8%) and SRL-ST (20.5%) groups ($P = 0.260$). Patient survival at 48 months was also similar between groups when excluding loss to follow up (92.1% for SRL-CsA-ST, 95.3% for SRL-ST, $P = 0.232$). The causes of death in the SRL-CsA-ST group were cardiovascular events (3.7%), infections (2.3%), malignancies (0.9%) and diabetes (0.9%), whereas they were cardiovascular events (1.9%), infections (1.9%) and other (0.9%) in the SRL-ST group.

At 48 months, the difference in mean serum creatinine values was statistically significant between the SRL-CsA-ST and SRL-ST groups (165.5 vs. 121.6 μmol/l, respectively, $P < 0.001$; on-therapy values). An ITT analysis showed similar significant differences (174.0 vs. 135.7 μmol/l, $P < 0.001$). Serum creatinine values in the SRL-ST group were significantly lower beginning at month 6 and continued through 48 months. Similarly, mean on-therapy values for calculated Nankivell GFR (Fig. 2) were significantly better in SRL-ST patients from month 6 through month 48 (54.5 vs. 68.6 ml/min, $P < 0.001$). The ITT analysis of calculated GFR (including discontinued patients and setting GFR = 0 for graft loss) further confirmed superiority for the SRL-ST group (43.8 vs. 58.3 ml/min, $P < 0.001$). The slope of calculated GFR (ITT analysis) was significantly negative for the SRL-CsA-ST group (−2.71 ml/min/year, $P < 0.001$) and positive, although not statistically significant, for the SRL-ST group (0.53 ml/min/year, $P = 0.151$). The difference between slopes was statistically significant (−3.24 ml/min/year, $P < 0.001$) in favour of the SRL-ST group.

Figure 3 shows mean arterial blood pressure by treatment group. At most time points from 6 months through 48 months, the SRL-ST group had significantly better mean arterial blood pressure compared with patients receiving SRL-CsA-ST (101.3 vs. 97.1 mmHg, $P = 0.047$, at 48 months). Moreover, the SRL-ST group received significantly fewer antihypertensive medications (Fig. 4).

Discontinuation from assigned treatment, including those discontinuing at the 48-month visit, was significantly higher in the SRL-CsA-ST group (60.9% vs. 44.2%, $P < 0.001$). The main reason for discontinuation in both groups was adverse events. Patients who received SRL-CsA-ST had significantly higher incidences of increased creatinine (35.3% vs. 20%), hypertension (26.5% vs. 13%), hyperuricemia (17.7% vs. 8.8%), CsA

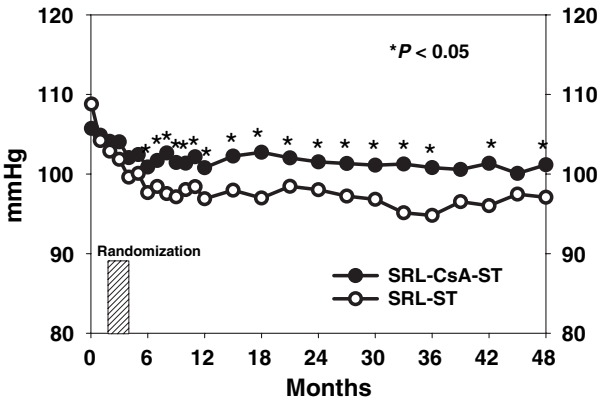

Figure 3 Mean arterial blood pressure: on-therapy population.

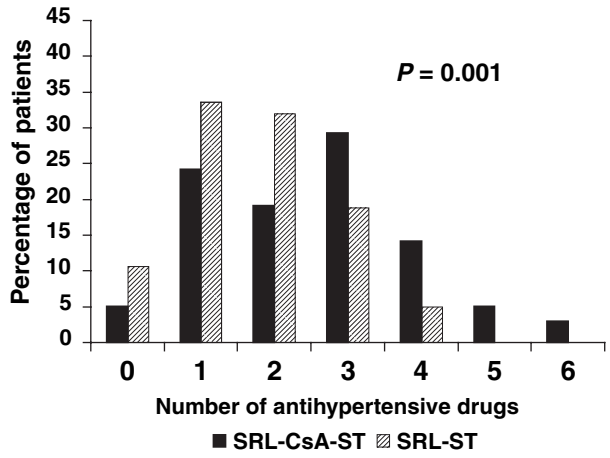

Figure 4 Number of antihypertensive agents at 48 months: on-therapy population.

toxicity (11.2% vs. 3.3%), oedema (0.7% vs. 4.2%), benign skin neoplasm (7.9% vs. 2.8%), gum hyperplasia (7.4% vs. 1.9%) and toxic nephropathy (6.5% vs. 0.9%). SRL-ST patients were reported to have significantly higher rates of increased ALT/SGPT (5.6% vs. 17.2%), increased AST/SGOT (3.7% vs. 13.0%), thrombocytopenia (3.7% vs. 13.0%), acne (6.0% vs. 12.1%), hypokalemia (5.1% vs. 10.7%), abnormal healing (1.4% vs. 5.6%), joint disorder (0.9% vs. 4.7%) and ileus (0.0% vs. 3.3%).

The overall incidence of stomatitis was low. During the prerandomization period (through month 3), the reported incidences of aphthous stomatitis, stomatitis and ulcerative stomatitis were 1.4%, 0.5% and 0.9% respectively. Following randomization, the incidences were 0.9% vs. 1.4% (SRL-CsA-ST vs. SRL-ST), 2.8% vs. 0.9% and 0 vs. 0.5%, respectively. Only one patient (SRL-ST group) discontinued for stomatitis. Neither the incidence of arthralgia (22.3% vs. 19.5%, SRL-CsA-ST versus SRL-ST, $P = 0.554$) nor the rate of discontinuation for this event (1.4% vs. 0.9%, $P = 1.000$) was significantly different between treatments. The incidence of clinically important infections was similar between groups, except for herpes zoster infections, which occurred more often in SRL-CsA-ST patients (7.0% vs. 0.9%, $P = 0.002$).

The overall incidence of malignancies was lower in the SRL-ST group, but the difference between groups did not reach statistical significance (12.1% vs. 7.4%, $P = 0.143$). Two patients in the SRL-CsA-ST group died of lung cancer, whereas no patient in the SRL-ST group died from cancer. By 48 months, 16 SRL-CsA-ST patients and 11 SRL-ST patients had reported cases of skin cancer. In the SRL-ST group, four skin cancer cases occurred more than 3 months (100 days) after the patients had been withdrawn from the SRL-ST group and returned to calcineurin inhibitor-based therapy. Of note, malignancy was diagnosed while patients were on therapy or within 100 days after discontinuing protocol-assigned treatment in 24 of the 26 patients (92%) with malignancy in the SRL-CsA-ST group and in nine of 16 (56%) in the SRL-ST group.

At 48 months, on-therapy values for mean serum cholesterol were significantly higher in SRL-ST patients than in patients receiving SRL-CsA-ST (5.7 vs. 6.3 mmol/l, respectively, $P = 0.022$). Six patients (2.8%) in each group discontinued because of hypercholesterolemia. Mean triglyceride (2.4 vs. 2.5 mmol/l, SRL-CsA-ST versus SRL-ST), high-density lipoprotein cholesterol (1.6 vs. 1.7 mmol/l) and low-density lipoprotein cholesterol (3.5 vs. 3.5 mmol/l) values were not significantly different between groups at 48 months. Five patients (2.3%) in the SRL-CsA-ST group and eight (3.7%) in the SRL-ST group discontinued because of hypertriglyceridemia. Mean haemoglobin values were significantly higher in the SRL-ST group at 48 months (127.3 vs. 134.5 g/l, $P < 0.001$), although the difference was not clinically important. Haemoglobin values in the SRL-ST group were significantly lower at most times between randomization and 9 months, but became significantly higher from 18 months. This trend may be secondary to the gradual improvement in renal function over time in SRL-ST patients. White blood cell (8.0 vs. 7.4×10^9/l, SRL-CsA-ST versus SRL-ST) and platelet (230 vs. 214×10^9/l) counts were similar between groups at 48 months.

Compliance was excellent in obtaining target trough levels for both SRL and CsA. Median SRL whole blood trough levels, as measured by monoclonal immunoassay (median daily doses) in the SRL-CsA-ST group, were 10.6 ng/ml (2.0 mg) and 10.3 ng/ml (2.0 mg) at months 36 and 48 respectively. In the SRL-ST group, these parameters were 17.8 ng/ml (5.0 mg) and 17.6 ng/ml (4.0 mg) at months 36 and 48 respectively. Median CsA whole blood trough levels as measured by monoclonal immunoassay (median daily doses) in the SRL-CsA-ST group were 95 ng/ml (175 mg) and 91 ng/ml (150 mg) at months 36 and 48 respectively. There was no significant difference between groups in the daily ST doses [5,6].

Discussion

The 48-month results from this study show that patients who had CsA withdrawn from a SRL-CsA-ST regimen had significantly better calculated GFR, mean arterial blood pressure and graft survival with no significant difference in the cumulative incidence of biopsy-confirmed acute rejection. An earlier report of the 36-month results showed an increasing difference between groups in the rate of graft survival [7]. This difference continued to increase after 36 months and was statistically significant

at 48 months, either when including patients' loss to follow-up or when using Kaplan–Meier estimates and censoring patients' loss to follow up. Kaplan–Meier methodology is that typically employed for estimating long-term renal allograft survival using registry databases and is accurate if sufficient patients have follow up through the point of analysis [1].

At 36 months, three SRL-CsA-ST and two SRL-ST patients had been lost to follow up. The number of patients lost to follow up increased to 20 and 11 (SRL-CsA-ST and SRL-ST, respectively) at 48 months, principally because 14 patients in the SRL-CsA-ST group and seven in the SRL-ST group did not agree to participate in the study beyond 36 months, which was the original duration of the protocol. Nonrandomized patients generally experienced poor early outcomes or adverse events and it should be noted that graft survival among the 95 nonrandomized patients was much lower than either of the randomized groups, resulting in an overall graft survival of 80.1% at 4 years for the 525 enrolled patients.

Similarly, the renal function advantage associated with CsA withdrawal persisted through 48 months, as indicated by improved serum creatinine and calculated GFR values. Furthermore, slope analyses revealed that renal function remained unchanged during 2–4 years in the SRL-ST group, whereas it declined in the SRL-CsA-ST group. Mota and colleagues reported the results of blinded, central pathologist readings from protocol-mandated biopsies that were performed during this trial, at engraftment and at 12 and 36 months after transplantation [8]. Mean chronic allograft damage index scores were significantly lower at 36 months in SRL-ST patients (4.7 vs. 3.2, $P = 0.003$), with tubular atrophy scores showing the greatest difference (0.77 vs. 0.32, $P < 0.001$). Thus, the results from our trial suggest that the improvement in graft survival in the SRL-ST group was a natural consequence of the preservation of renal structure and function.

Based on outcomes in a population of >100 000 renal transplant patients, Hariharan *et al.* found that creatinine at 12 months combined with the change in creatinine over 6–12 months had a significant association with long-term graft survival [9]. Our data support their findings; however, it is recognized that renal function may be of limited predictive value for graft loss both in individual patients [10] as well as for some regimens associated with initially improving renal function but lacking adequate long-term follow up. Patients who had an early withdrawal of CsA from an SRL-CsA-ST regimen experienced significant benefits not only in renal function, but also in significantly better graft survival at 48 months after transplant compared with patients who remained on CsA. This contrasts with the meta-analysis findings that CsA withdrawal from AZA- or mycophenolate mofetil (MMF)-based regimens resulted in a significantly increased risk of acute rejection (difference 11%; 95% CI = 7%, 15%) without a graft-survival benefit (relative risk of graft loss 1.06, 95% CI = 0.81, 1.29) [11]. More recently, Abramowicz and colleagues reported that CsA withdrawal from a CsA-MMF-ST regimen 12–30 months after transplantation resulted in significantly higher acute rejection ($P = 0.026$) and numerically lower graft survival (92% CsA-MMF-ST versus 88% MMF-ST) 4 years later, despite a trend for improved renal function with MMF-ST [12]. In that trial, nine grafts were lost to chronic rejection in the MMF-ST group compared with three in the CsA-MMF-ST cohort.

When given with CsA, both SRL [3,4] and everolimus [13], the other inhibitor of mammalian target of rapamycin (mTOR) under clinical investigation, decrease renal function. These data, combined with other results showing better renal function with SRL compared with CsA [2], indicate that both mTOR inhibitors enhance the nephrotoxicity of CsA. The results from the present study demonstrate the clear advantages of discontinuing CsA immunotherapy, and consequently, the protocol was amended to discontinue protocol-assigned therapy in the SRL-CsA-ST group. Seven patients in the SRL-CsA-ST group discontinued therapy at the 48-month visit because of the protocol amendment, but none did so prior to 48 months. All patients will be followed through 60 months.

The rate of discontinuation from assigned treatment and the potential impact on the findings merit commentary. Including discontinuations occurring during the 36- and 48-month visits, 52.1% vs. 62.3% (SRL-CsA-ST versus SRL-ST, $P = 0.041$) and 39.1% vs. 55.8% (SRL-CsA-ST versus SRL-ST, $P < 0.001$) of patients continued on protocol-assigned therapy beyond these time points respectively. Although the rate of discontinuation may seem high, these results are consistent with the usual findings from multicentre trials. At 36 months in the Tricontinental Mycophenolate Mofetil Renal Transplantation Study [14], 51.2% of the CsA-AZA-ST, 49.7% of the CsA-MMF (2 g)-ST and 50.6% of the CsA-MMF (3 g)-ST treated patients remained on assigned treatment. Similar success was observed in a trial comparing tacrolimus (TAC)-MMF-ST, CsA-MMF-ST and TAC-AZA-ST [15]; at 36 months, 55.6%, 48.0% and 47.4% of patients, respectively, were still receiving randomized therapy.

With regard to the impact of discontinuation, it is well known that most discontinuing patients receive standard therapy (principally CsA without SRL in the present study) and a lesser percentage crossover to the comparator group. Thus, discontinuation tends to diminish treatment effects and minimize differences in major outcome

variables. Accordingly, ITT analyses are the most conservative with regard to testing superiority. In our trial, the ITT analyses of both renal function and graft survival were significant in favour of the SRL-ST despite an approximately 50% rate of discontinuation, further underscoring the benefit of early CsA withdrawal compared with a continuous regimen of SRL-CsA-ST.

A limitation of this study is the lack of an additional CsA-based, SRL-free treatment group for comparison, as indeed much has been learned about the nephrotoxicity of mTOR inhibitor-CsA combinations after the first patient was enrolled in May 1998. Consequently, direct comparisons of SRL with CsA without the confounding factors of combining them needs to be tested in other trials. Kreis and colleagues have reported a direct comparison of SRL-MMF-ST with CsA-MMF-ST in renal transplantation [16] and Flechner, subsequently, showed that this therapeutic approach could be improved by adding basiliximab induction [17]. The latter study found that both renal function and structure were significantly better with the SRL-based regimen at 2 years [18]. These phase 2 studies involved a limited number of patients, but established the merit of undertaking future multicentre phase 3 trials comparing SRL directly with CsA.

In conclusion, withdrawing CsA from SRL-CsA-ST therapy at 3 months after transplantation rapidly improves renal function, attenuates the progression of histological damage and ultimately results in better graft survival. The 48-month data from our study further confirm that early, progressive and complete withdrawal of CsA from a combination of SRL, CsA, and ST is safe and effective.

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