

SUCCESSFUL SRL USE

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Determinants of Successful Use of
Sirolimus in Renal Transplant Patients

Methods. All patients from 10 German centers that were switched to a sirolimus-containing maintenance immunosuppression in 2000 to 2008 after 3 months or later post-transplantation were enrolled (n = 726). Observation times after switching to sirolimus ranged from 4 days to 9 years (median: 24.3 months). With multinomial logistic regression, risk factors for the endpoints terminal graft failure and withdrawal of sirolimus therapy compared to successful therapy were identified.

Urinary protein determinations were recorded either by dipstick analysis, urine protein concentration, or daily protein excretion. For the analyses, dipstick results were imputed with the mean of protein concentrations (119 mg/L for negative dipsticks and 1588 mg/L for positive dipstick results). Dipstick results were considered only when no results on protein concentration were available.

Results. Successful sirolimus therapy was observed in 304 patients. Forty patients died with functioning graft. Therapy failures included graft loss (n ¼ 106) and sirolimus-discontinuation for various reasons (n ¼ 276). Successful sirolimus-use was predicted in 83% and graft failure in 65%, whereas prediction of deliberate sirolimus-discontinuation was poor (48%). Most favorable results for sirolimus-use were observed in patients switched in 2006 to 2008. Using ROC analysis, an estimated glomerular filtration rate (eGFR) below 32 mL/min was shown to be the cut-off in patients withdrawing from therapy as a result of renal reasons, as well as in patients with graft loss. Proteinuria above 151 mg/L was shown to be predictive for patients with graft failure.

Table 1. Demographic and Clinical Data of the Whole Study Population and in the Subgroups of Patients With Successful Use of Sirolimus and With Sirolimus Treatment Failure

| | Whole Population n = 726 | Successful Use n = 304 | Treatment Failure n = 422 | P Value |
|--|--------------------------|------------------------|---------------------------|---------|
| Recipient age at transplantation (years) | 43.3±13.6 | 44.0±13.3 | 42.7±13.7 | .129 |
| Recipient sex (% males) | 63.6 | 67.1 | 61.1 | .099 |
| Caucasian ethnicity (%) | 99.0 | 99.3 | 98.8 | .346 |
| Cause of ESRD (%) | | | | .875 |
| Diabetic nephropathy | 12.4 | 12.8 | 12.1 | |
| Hypertensive nephropathy | 3.6 | 4.0 | 3.3 | |
| Polycystic kidney disease | 11.4 | 10.4 | 12.1 | |
| Glomerulonephritis | 43.4 | 40.6 | 45.4 | |
| Tubulointerstitial disease | 14.3 | 14.8 | 14.0 | |
| Other inherited diseases | 3.6 | 4.4 | 3.1 | |
| Other diseases/unknown | 11.3 | 13.0 | 10.0 | |
| Living donor transplantation (%) | 16.4 | 15.9 | 16.8 | .740 |
| Kidney/pancreas transplantation (%) | 9.1 | 10.9 | 7.8 | .309 |
| Kidney plus other solid organ (%) | 1.4 | 1.3 | 1.4 | .945 |
| Kidney retransplants (%) | 25.5 | 26.4 | 24.8 | .644 |
| Donor age (years, range) | 44.3±15.9 (3-88) | 42.5±15.6 (4-88) | 45.5±15.9 (3-79) | .017 |
| Donor sex (% men) | 56.6 | 61.4 | 53.3 | .044 |
| HLA mismatches on locus A, B, DR (n) | 2.4±1.6 | 2.3±1.7 | 2.5±1.6 | .434 |
| Cold ischemia time (hours) | 14.2±8.0 | 14.5±7.8 | 14.0±8.1 | .371 |
| Panel reactive antibodies >10% (%) | 7.7 | 7.0 | 8.1 | .622 |
| Delayed graft function (%) | 25.0 | 25.0 | 24.9 | .984 |
| Initial immunosuppression (%) | | | | |
| Cytotoxic antibodies | 15.6 | 10.7 | 19.2 | .002 |
| IL-2 receptor antibodies | 20.3 | 22.7 | 18.5 | .160 |
| Cyclosporine | 62.0 | 66.2 | 59.0 | .049 |
| Tacrolimus | 26.8 | 24.7 | 28.3 | .291 |
| Azathioprine | 31.7 | 27.4 | 34.8 | .037 |
| Mycophenolate | 53.5 | 57.2 | 50.8 | .093 |
| Corticosteroids | 96.6 | 95.3 | 97.6 | .094 |
| Others | 2.1 | 2.0 | 2.2 | .889 |
| Acute rejection treatments before SRL initiation (%) | 39.7 | 35.9 | 42.6 | .099 |

Treatment failure included graft failure and termination of SRL therapy. Continuous data are given as means ± SD. Numbers in brackets represent range of values. Glomerulonephritis as cause of ESRD included non-biopsy confirmed suspected cases.

Abbreviations: ESRD, end-stage renal disease; SD, standard deviation; SRL, sirolimus.

Table 2. Clinical and Laboratory Data at the Time of Sirolimus Initiation

| | Whole Population n = 726 | Successful Use n = 304 | Treatment Failure n = 422 | P Value |
|---|--------------------------|------------------------|---------------------------|---------|
| Age at SRL initiation (years, range) | 49.8±13.4 (15-78) | 50.4±12.7 (15-77) | 49.4±13.8 (16-78) | .383 |
| Time interval between transplantation and SRL initiation (years, range) | 6.1±6.1 (0.03-28) | 5.9±5.9 (0.03-28) | 6.2±6.3 (0.03-27) | .735 |
| Diabetes (%) | 23.6 | 21.6 | 25.0 | .292 |
| Hypertension (%) | 84.7 | 82.8 | 86.1 | .226 |
| Body weight (kg, range) | 73.8±15.5 (32-127) | 75.3±15.7 (41-127) | 72.7±15.3 (32-119) | .050 |
| Body mass index (kg/m ² , range) | 24.9±4.2 (16.1-42.3) | 25.2±4.4 (16.1-42.3) | 24.8±4.1 (16.4-42.2) | .151 |
| eGFR (mL/min, median) | 39±19 (35) | 45±18 (42) | 35±19 (30) | <.001 |
| Proteinuria without dipstick (mg/L; median) | 348±751 (108) | 112±130 (68) | 510±937 (145) | <.001 |
| Proteinuria with dipstick (mg/L; median) | 431±726 (119) | 225±400 (119) | 587±867 (126) | <.001 |
| Reasons for SRL initiation (%) | | | | |
| Study | 11.1 | 10.0 | 11.8 | .409 |
| Malignancy | 24.9 | 32.0 | 19.9 | <.001 |
| Graft-related reasons | 51.5 | 43.7 | 57.1 | <.001 |
| "Creeping creatinine" | 22.9 | 17.7 | 26.5 | .004 |
| Acute rejection | 12.0 | 10.3 | 13.3 | .214 |
| Chronic allograft nephropathy | 16.9 | 10.0 | 21.8 | <.001 |
| Renal calcineurin inhibitor toxicity | 26.6 | 23.7 | 28.7 | .115 |
| Extrarenal side effects of immunosuppression | 12.3 | 12.0 | 12.6 | .784 |
| Infection | 1.0 | 0.7 | 1.2 | .473 |
| Others | 4.3 | 3.3 | 5.0 | .271 |
| Unknown | 10.5 | 10.0 | 10.9 | .654 |
| SRL dosing at initiation | | | | |
| Loading dose (mg) | 6.4±4.8 | 5.5±4.0 | 7.0±5.2 | .042 |
| Maintenance dose (mg/d) | 2.9±1.6 | 2.8±1.5 | 3.0±1.7 | .128 |
| Maintenance dose at 3 months (mg/d) | 2.7±1.8 | 2.5±1.5 | 2.8±2.0 | .122 |
| SRL trough level at 3 months | 8.1±3.8 | 8.0±3.3 | 8.2±4.1 | .967 |
| Immunosuppressive regimen before SRL | | | | .906 |
| Triple (%) | 39.4 | 40.4 | 38.7 | |
| Dual (%) | 51.9 | 50.9 | 52.5 | |
| Mono (%) | 8.7 | 8.6 | 8.8 | |

Table 3. Outcome of Patients After Sirolimus Initiation

| Outcome | N | % |
|---|-----|------|
| Successful treatment | 304 | 41.9 |
| Death with functioning graft on SRL treatment | 40 | 5.5 |
| Graft failure on SRL treatment | 108 | 14.6 |
| thereof death afterwards | 8 | 1.1 |
| SRL discontinuation with functioning graft | 276 | 38.0 |
| thereof death afterwards | 5 | 0.7 |

Death with functioning graft was related to malignancy (n = 18), cardiovascular disease (n = 10), infection (n = 3), and to other (n = 4) or unknown causes (n = 5). Death after graft failure was related to cardiovascular disease (n = 2), infection (n = 3), and to other (n = 1) or unknown causes (n = 2). Death after discontinuation of SRL was related to malignancy (n = 1), cardiovascular disease (n = 1), and infection (n = 3).

Abbreviation: SRL, sirolimus.

Table 4. Quantile of the Time (Days) to Events (Overall Treatment Failure, Survival, Graft Failure, and Deliberate Discontinuation From Sirolimus)

| Quantile | Overall Treatment Failure (n = 422) | Survival (n = 40) | Graft Failure (n = 106) | Discontinuation (n = 276) |
|----------|-------------------------------------|-------------------|-------------------------|---------------------------|
| 0.1 | 38.6 | 72.5 | 54.9 | 29.7 |
| 0.2 | 73.6 | 137.6 | 105.4 | 55.0 |
| 0.3 | 120.0 | 278.1 | 178.2 | 98.3 |
| 0.4 | 189.0 | 547.8 | 253.6 | 147.0 |
| 0.5 | 338.5 | 739.5 | 439.5 | 249.0 |
| 0.6 | 501.4 | 898.0 | 554.4 | 397.0 |
| 0.7 | 624.4 | 1231.3 | 740.3 | 554.8 |
| 0.8 | 924.0 | 1576.0 | 992.2 | 808.8 |
| 0.9 | 1454.4 | 1785.4 | 1471.2 | 1237.7 |

Table 5. Causes for Sirolimus Discontinuation in the 276 Patients With Functioning Graft

| Reason for Discontinuation | n | % |
|-----------------------------|----|------|
| Graft-related reasons | 97 | 35.1 |
| Infection/pulmonary reasons | 47 | 17.0 |
| Patient's wish | 30 | 10.9 |
| Side effects | 52 | 18.8 |
| Skin, muscles, joint | 22 | 8.0 |
| Gastrointestinal tract | 15 | 5.4 |
| Others | 10 | 3.6 |
| Planned operation | 14 | 5.1 |
| Unknown | 26 | 9.4 |

Graft-related reasons for SRL discontinuation include deteriorating GFR, chronic rejection and proteinuria; skin/muscle/joint includes arthralgia, edema, aphthous ulcerations and pruritus; gastrointestinal reasons include diarrhea, vomiting, and alterations in clinical chemistry such as elevated lipase or hyperlipidemia. Reasons with a frequency of less than 5 are summarized in Others.

Abbreviations: GFR, glomerular filtration rate; SRL, sirolimus.

Table 6. Receiver Operator Characteristic Analysis of Estimated Glomerular Filtration Rate for Successful Use of Sirolimus vs the Whole Patient Group With Treatment Failure and the Different Subgroups With Treatment Failure

| | AUC | Confidence Interval | | P Value | Sensitivity | Specificity | Youden Index | eGFR Cut-off (mL/min) |
|------------------------|-------|---------------------|-------|---------|-------------|-------------|--------------|-----------------------|
| All treatment failures | 0.703 | 0.662 | 0.744 | <.001 | 0.727 | 0.621 | 0.348 | 33.4 |
| Graft failure | 0.869 | 0.830 | 0.908 | <.001 | 0.78 | 0.842 | 0.617 | 31.3 |
| Discontinuation | 0.639 | 0.591 | 0.687 | <.001 | 0.62 | 0.624 | 0.248 | 37.8 |
| Graft-related | 0.675 | 0.606 | 0.744 | <.001 | 0.76 | 0.565 | 0.325 | 32.0 |
| Other reasons | 0.620 | 0.564 | 0.676 | <.001 | 0.62 | 0.606 | 0.226 | 37.9 |

The lower and upper limit of the 95% confidence interval is given.

Abbreviations: AUC, area under the curve; eGFR, estimated glomerular filtration rate; ROC, receiver operating characteristic.

Table 7. Adjusted Odds Ratios With 95% Confidence Intervals Associated With Successful Treatment With Sirolimus vs Treatment Failure From Graft Failure, or Termination From Graft-related Reasons and Other Reasons.

| Parameter Estimate | | | | | |
|--|--|------------|-------------------------|-------------|--------------|
| Outcome | Factor | Odds Ratio | 95% Confidence Interval | | Significance |
| | | | Lower Bound | Upper Bound | |
| Graft failure | Intercept | | | | 0.363 |
| | Time from Tx to SRL initiation (years) | 0.981 | 0.914 | 1.053 | 0.594 |
| | Age at transplantation (years) | 0.989 | 0.963 | 1.016 | 0.418 |
| | eGFR before SRL initiation (mL/min) | 0.916 | 0.887 | 0.946 | 0.000 |
| | Proteinuria before SRL initiation (mg/L) | 7.332 | 2.697 | 19.933 | 0.000 |
| | SRL initiation years | | | | |
| | 2000-2002 | 18.080 | 4.600 | 71.053 | 0.000 |
| | 2003-2005 | 5.585 | 1.475 | 21.148 | 0.011 |
| | 2005-2008 | | | | |
| | Main reason for SRL initiation | | | | |
| | Study | 0.831 | 0.144 | 4.774 | 0.835 |
| | malignancy | 0.445 | 0.082 | 2.414 | 0.348 |
| | Creeping creatinine | 1.507 | 0.656 | 3.462 | 0.334 |
| | Chronic allograft nephropathy | 1.868 | 0.765 | 4.562 | 0.170 |
| | Renal CNI toxicity | 1.659 | 0.666 | 4.136 | 0.277 |
| | Other CNI side effects | 1.190 | 0.351 | 4.036 | 0.780 |
| | Acute rejections | 2.883 | 0.936 | 8.883 | 0.065 |
| Other reasons | 5.523 | 1.787 | 17.071 | 0.003 | |
| Discontinuation due to graft-related reasons | Intercept | | | | 0.005 |
| | Time from Tx to SRL initiation (years) | 1.025 | 0.981 | 1.070 | 0.272 |
| | Age at transplantation (years) | 1.012 | 0.993 | 1.031 | 0.229 |
| | eGFR before SRL initiation (mL/min) | 0.985 | 0.972 | 0.999 | 0.037 |
| | Proteinuria before SRL initiation (mg/L) | 3.145 | 1.176 | 8.413 | 0.022 |
| | SRL initiation in the years | | | | |
| | 2000-2002 | 2.800 | 1.371 | 5.718 | 0.005 |
| | 2003-2005 | 1.787 | 1.024 | 3.116 | 0.041 |
| | 2005-2008 | | | | |
| | Main reason for SRL initiation | | | | |
| | Study | 3.560 | 1.583 | 8.007 | 0.002 |
| | Malignancy | 1.242 | 0.590 | 2.616 | 0.568 |
| | Creeping creatinine | 1.107 | 0.556 | 2.204 | 0.773 |
| | Chronic allograft nephropathy | 1.138 | 0.536 | 2.416 | 0.737 |
| | Renal CNI toxicity | 1.406 | 0.702 | 2.818 | 0.336 |
| | Other CNI side effects | 2.175 | 1.014 | 4.662 | 0.046 |
| | Acute rejections | 1.550 | 0.610 | 3.943 | 0.357 |
| Other reasons | 3.294 | 1.408 | 7.705 | 0.006 | |

| | | | | | |
|--|--|-------|--------|--------|-------|
| Discontinuation due to extra-renal reasons | Intercept | | | | 0.001 |
| | Time from Tx to SRL initiation (years) | 1.075 | 1.017 | 1.136 | 0.010 |
| | Age at transplantation (years) | 1.001 | 0.975 | 1.027 | 0.949 |
| | eGFR before SRL initiation (mL/min) | 0.974 | 0.954 | 0.994 | 0.011 |
| | Proteinuria before SRL initiation (mg/L) | 9.590 | 3.536 | 26.010 | 0.000 |
| | SRL initiation in the years | | | | |
| | 2000-2002 | 1.443 | 0.541 | 3.847 | 0.464 |
| | 2003-2005 | 0.924 | 0.447 | 1.910 | 0.830 |
| | 2005-2008 | | | | |
| | Main reason for SRL initiation | | | | |
| | Study | 4.396 | 1.399 | 13.815 | 0.011 |
| | Malignancy | 3.433 | 1.329 | 8.869 | 0.011 |
| | Creeping creatinine | 1.771 | 0.734 | 4.270 | 0.203 |
| | Chronic allograft nephropathy | 0.800 | 0.297 | 2.154 | 0.659 |
| | Renal CNI toxicity | 3.968 | 1.635 | 9.628 | 0.002 |
| | Other CNI side effects | 2.531 | 0.871 | 7.354 | 0.088 |
| | Acute rejections | 8.429 | 3.018 | 23.544 | 0.000 |
| Other reasons | 6.316 | 1.998 | 19.970 | 0.002 | |

The reference category is: Successful use.

Abbreviations: CNI, calcineurin inhibitors; eGFR, estimated glomerular filtration rate; SRL, sirolimus; Tx, transplantation.

THANK YOU

