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A Randomized Controlled Trial on Safety of Steroid Avoidance in Immunologically Low-Risk Kidney Transplant Recipients

Jana Ekberg[1,4], Seema Baid-Agrawal[1,4], Bente Jespersen[2], Ragnar Källén[3], Ehab Rafael[3], Karin Skov[2] and Per Lindnér[1]

[1]Transplant Institute, Sahlgrenska University Hospital, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden; [2]Department of Nephrology, Aarhus University Hospital, Aarhus, Denmark; and [3]Department of Transplantation, Skane University Hospital, Malmoe, Sweden

Introduction: Steroid-based immunosuppression after transplantation increases the risk of post-transplant diabetes mellitus (PTDM), with adverse effects on patient and graft survival. In the SAILOR study, we investigated the safety and efficacy of complete steroid avoidance in immunologically low-risk kidney recipients without diabetes on the current standard-of-care maintenance regimen with tacrolimus/mycophenolate mofetil (MMF).

Methods: In this 2-year, multicenter, open-label trial, a total of 222 patients were randomized to receive either steroid avoidance protocol (tacrolimus/MMF/antithymocyte globulin [ATG] induction [$n = 113$]) or steroid maintenance protocol (tacrolimus/MMF/prednisolone/basiliximab-induction [$n = 109$]).

Results: At 1 year, no significant differences were found between steroid avoidance and steroid maintenance arms in the incidence of PTDM, the primary end point (12.4% vs. 18.3%, respectively, $P = 0.30$, CI: 16.3–4.4), or in overall biopsy-proven rejections (15% vs. 13.8%, respectively, $P = 0.85$). At 2 years, the composite end point of freedom from acute rejection, graft loss, and death (81% vs. 85%, respectively, $P = 0.4$), kidney function, or adverse events was comparable between the 2 arms. Moreover, 63.9% of the patients in the steroid avoidance arm remained free from steroids at 2 years.

Conclusion: The SAILOR study provides further evidence for the feasibility, safety, and efficacy of early steroid-free treatment at 2 years in immunologically low-risk kidney recipients with tacrolimus/MMF maintenance regimen.

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Kidney transplantation remains the best possible option for eligible patients with kidney failure, as it offers better quality of life and longer survival compared with dialysis. Despite excellent short-term results with declining acute rejection rates, long-term results have not improved considerably. Premature death with a functioning graft mainly related to cardiovascular (CV) disease remains one of the major causes of graft loss in the long term.[1]

PTDM is associated with an unfavorable CV risk profile[2] and is an independent predictor of CV disease,[3] graft failure, and mortality after kidney transplantation.[4–6] Incidence of PTDM varies in the literature, mainly because of the different immunosuppressive protocols used and the lack of uniform diagnostic criteria. In a study analyzing data from 2 randomized controlled trials (RCTs) in kidney transplant recipients using a composite definition of PTDM based on the American Diabetes Association criteria, the 1-year incidence of PTDM reached 30% to 37% with standard-dose tacrolimus/MMF/steroid-based maintenance regimens.[7,8] Both steroids and tacrolimus, in interaction with other variables, such as age, ethnicity, and overweight, are considered to be risk factors for PTDM.[4] Steroids are believed to cause insulin resistance, whereas tacrolimus impairs insulin secretion in a dose-related manner.[9]

In the past 2 decades, several RCTs with steroid-sparing protocols, including steroid avoidance and steroid withdrawal, have been conducted worldwide to

Correspondence: Jana Ekberg, Transplant Institute, Sahlgrenska University Hospital, Bruna stråket 5, 413 45 Gothenburg, Sweden. E-mail: jana.ekberg@vgregion.se

[4]JE and SBA contributed equally to this work.

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reduce the side effects of steroids, including PTDM. The systematic Cochrane review and meta-analysis in 2016[10] which included 48 studies with 7803 randomized participants, using different immunosuppressive protocols (either cyclosporine or standard-dose tacrolimus, MMF, or sirolimus), evaluated the risks and benefits of steroid-sparing strategies and concluded that these regimens are associated with an increased rate of acute rejection, but not increased graft loss in adult kidney transplant recipients. Clear beneficial effects, such as reduction in mortality or PTDM within 5 years after transplantation, have not been found. Nevertheless, meaningful conclusions could not be drawn owing to the low number of events observed in rather small studies, lack of a uniform definition of PTDM across studies, and short follow-up periods. Therefore, although the steroid-sparing regimen is a desirable goal after kidney transplantation, it is still not widely accepted because of the perceived increased risk of acute and chronic rejection.

At present, based on findings from the ELITE-Symphony study, the standard-of-care immunosuppressive regimen in kidney transplant recipients worldwide consists of induction with monoclonal interleukin-2 receptor antibody and maintenance with low-dose tacrolimus/MMF/steroids.[11] Although this regimen had lower rejection rate, better kidney function, and higher survival rate, compared with 2 cyclosporine and 1 sirolimus arm, the 1-year incidence of PTDM was highest (10.6%) in the low tacrolimus/MMF/steroid arm, despite the unclear diagnostic criteria for PTDM in this study. To better reduce the risk of PTDM, the optimal immunosuppressive protocol should ideally include avoidance of steroids and minimization of tacrolimus.

A few recent RCTs have evaluated the safety and efficacy of steroid-sparing protocols with the current tacrolimus/MMF-based regimen and using predefined American Diabetes Association criteria for PTDM.[12,13] The multicenter HARMONY study compared the following 3 arms: arm A: basiliximab-induction/tacrolimus/MMF/steroid maintenance therapy; arm B: basiliximab-induction/tacrolimus/MMF/rapid steroid withdrawal (at 1 week); and arm C: ATG induction/tacrolimus/MMF/rapid steroid withdrawal. The incidence of biopsy-proven acute rejection (the primary end point) was similar in the 3 arms, with a significant reduction in the 1-year incidence of PTDM (secondary end point) in both arms (B and C) with rapid steroid withdrawal (24% and 23%, respectively, vs. 39% in steroid maintenance-arm A, $P = 0.0004$). This study clearly revealed that ATG was not superior to basiliximab-induction for the prevention of acute rejection.[12] Nevertheless, 2 other recent RCTs using steroid-sparing protocols primarily evaluating PTDM revealed conflicting results.[13,14] In the trial that studied steroid withdrawal versus steroid minimization within 6 months on tacrolimus/MMF in recipients at a high risk for diabetes, the incidence of PTDM after 1 year was surprisingly higher in the tacrolimus/steroid withdrawal arm than in the tacrolimus/steroid minimization arm (38% vs. 26%, $P = 0.01$).[13] The authors speculated that this finding could be partly explained by the associated slight increase in biopsy-proven acute rejection in the steroid withdrawal arm (11.4% vs. 4.8%) with concomitant use of high corticosteroid doses. In the ADVANCE study that compared steroid withdrawal and steroid avoidance together with tacrolimus/MMF, but no control arm with steroid maintenance, the incidence of PTDM 24 weeks after kidney transplantation was similar and low in both arms (17.4% vs. 16.6%).[14]

The SAILOR study was conducted to evaluate whether a steroid avoidance protocol with tacrolimus/MMF/ATG induction in a population without diabetes with low immunologic risk reduces the incidence of PTDM with good efficacy and safety in 2 years, as compared with the standard steroid maintenance regimen. Because the SAILOR study was designed and initiated 3 years before the results of the HARMONY study were published, ATG was chosen as an induction therapy over basiliximab as it was then considered to be more effective for the prevention of acute rejection.[15,16] This was an effort to compensate probably less potent maintenance steroid avoidance immunosuppression with supposedly more potent induction to minimize the risk for rejection while reducing the risk of PTDM.

METHODS

Study Design and Patient Population

The SAILOR study was an investigator-initiated, randomized, controlled, multicenter, open-label trial, with a 2-year follow-up duration, conducted at 3 Scandinavian transplant centers (Gothenburg, Malmoe, Sweden; Aarhus, Denmark). Recipients aged >18 years with low immunologic risk who were to receive a first or second single-organ kidney transplant from a living/deceased donor were eligible for participation. Recipients with the following conditions were excluded: history or diagnosis of diabetes mellitus, plasma glucose at admission ≥11.1 mmol/l, panel-reactive antibodies >25% or those considered to be at high risk for rejection, treated with steroids at admission or likely to need steroids after transplantation, receiving ABO-incompatible or HLA-identical sibling transplant, and those unlikely to comply with study requirements or unable to give informed consent. The complete SAILOR protocol has been published previously.[17]

The study was approved by the Regional Ethical Board of Gothenburg (Dnr. 357-12) and Aarhus (Dnr. 1-10-72-211-13) and adhered to the ethical principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and the International Council for Harmonization guidelines. All study participants provided informed written consent and could withdraw from the study at any time. Clinical Trial Notification: EudraCT number: 2012-000451-13.

Randomization and Masking

Eligible patients were randomized using a central web-based computerized system to 1 of the 2 arms in a 1:1 ratio and stratified by study site and donor status (living/deceased). Subjects, investigators, and study site staff were not blinded to the study group assignments. Nevertheless, patients' identity and treatment assignment were concealed to the Primary Endpoint Committee, 2 independent nephrologists, who assessed the accuracy of the PTDM diagnosis, and to 2 pathologists, who centrally evaluated all transplant biopsies.

Procedures

Patients were randomized before kidney transplantation to 1 of the following treatment arms:

1. Steroid avoidance arm: induction with ATG 2.5 mg/kg perioperatively before perfusion at day 0 and day 1; methylprednisolone bolus 250 mg before the first and 50 mg before the second ATG dose, and maintenance treatment based on prolonged-release tacrolimus, starting dose at 0.2 mg/kg once daily with target trough levels of 5 to 10 μg/l within the first 3 months and thereafter 4 to 7 μg/l, and MMF 1 g twice a day controlled by a single mycophenolate acid area under the curve (MPA-AUC) measurement on days 10 ± 5 with target AUC of 40 to 60 mg × h/l.[18]
2. Steroid maintenance arm: induction with basiliximab 20 mg on days 0 and 4; methylprednisolone 250 to 500 mg on day 0 before reperfusion, according to the local center practice, and maintenance treatment as in steroid avoidance arm plus prednisolone in doses by local center practice, but final daily dose not <5 mg.

The following events were defined as treatment protocol deviations: addition of oral prednisolone for >30 consecutive days or >3 i.v. methylprednisolone boluses (500 mg) in the steroid avoidance arm, discontinuation of any study drug for >30 days, or addition of any other immunosuppressive agent in either arm.

The diagnosis of PTDM was based on American Diabetes Association criteria for type 2 diabetes mellitus adapted to population of patients after kidney transplantation[7,8] and determined, if one of the following was present: fasting plasma glucose ≥7.0 mmol/l ≥30 days apart; 2-hour plasma glucose ≥11.1 mmol/l in the oral glucose tolerance test; oral hypoglycemic agent or insulin given ≥30 consecutive days. The fasting plasma glucose was measured at each study visit (baseline, day 10 ± 5 days, 3 months, 6 months, 12 months, and 24 months); oral glucose tolerance test was scheduled at 3 and 12 months in all patients except those with clinically obvious PTDM.

In all patients with suspected acute rejection, a biopsy was performed to confirm the diagnosis, unless contraindicated. A protocol biopsy was scheduled at 1-year post-transplant for all patients. The biopsy samples were primarily evaluated locally at each center using the Banff 2009 classification to determine the eventual clinical action. Biopsy-proven acute rejections were treated with i.v. methylprednisolone (3 boluses of 500 mg/d). In case of acute rejection in the steroid avoidance arm, the decision regarding the addition of oral prednisolone was based on clinical considerations.

The second-look biopsy evaluation was performed *post hoc* centrally by 2 pathologists according to the revised Banff 2017 classification.[19] Borderline changes in the biopsy were not designated as rejection.

All patients at risk for primary cytomegalovirus infection (donor IgG+, recipient IgG−) received prophylaxis with valganciclovir for 6 months; cytomegalovirus IgG+ recipients were treated for 3 months at Gothenburg and Malmoe. All patients received *Pneumocystis jirovecii* pneumonia prophylaxis with trimethoprim-sulfamethoxazole or pentamidin for 6 months.

Major CV events were defined as acute coronary syndrome, myocardial infarction, and stroke. Safety was evaluated clinically by monitoring vital signs, laboratory analyses, drug dosage at each study visit, and evaluation of adverse events at the time of appearance.

End Points

The primary efficacy end point was the incidence of PTDM within the first post-transplant year. Secondary end points were as follows: (i) incidence of PTDM and use of antidiabetic agents at 2 years; (ii) incidence of biopsy-proven rejection at 1 year; (iii) composite measure of freedom from acute rejection, graft loss, and death at 1 and 2 years; (iv) kidney function measured by either iohexol- or chrominum-labeled–ethylenediamine tetra acetic acid clearance at 1 and 2 years; (v) occurrence of infections, major CV events, and

malignancies during 2 years; (vi) mean doses, mean AUC of doses, trough levels, and AUCs for immunosuppressants at defined time points and time periods; and (vii) use of antihypertensive and lipid-lowering agents in 2 years.

Statistical Analysis

All analyses were performed using the intention-to-treat population. The intention-to-treat population consisted of all randomized patients who received a kidney transplant, at least 1 study treatment, and 1 recorded follow-up. Patients who received treatment according to the protocol without major protocol deviations and completed the study for 2 years represent the per-protocol population.

For the sample size calculation, we based our assumption on the 36% incidence of PTDM, defined according to the American Diabetes Association criteria, reported at 1 year after transplant with a steroid-containing immunosuppressive protocol[7] and an estimated reduction to 18% with steroid avoidance. The sample size of 222 subjects was calculated using Fisher exact test to achieve 80% power for superiority of steroid avoidance arm over the control steroid maintenance arm, with a 2-sided type 1 error of 5% and allowing 5% dropout. For comparison between the groups, the following tests were used: Fisher exact test for dichotomous variables, Mantel-Haenszel χ^2 test for categorical variables, Fisher nonparametric permutation test for continuous variables, and t test for continuous variables. The time to reach PTDM, acute rejection, graft loss, or death will be analyzed using the Kaplan–Meier method, including the log-rank test. Statistical significance was set at a 2-sided $P < 0.05$. The statistical software SAS 9.4 was used for statistical analyses.

RESULTS

Study Patients

In total, 224 patients were enrolled and randomized between February 2013 and March 2017. Of these, 222 patients underwent kidney transplantation, received at least 1 study medication, and had 1 follow-up. There were 113 patients who received ATG induction/tacrolimus/MMF (steroid avoidance arm) and 109 who received basiliximab-induction/tacrolimus/MMF/prednisolone (steroid maintenance arm). Furthermore, 4 patients in the steroid avoidance arm and 9 in the steroid maintenance arm terminated the study prematurely owing to death, graft loss, or consent withdrawal. In patients who completed the study, protocol deviation was significantly more frequent in the steroid avoidance arm at 37.9% (41 of 108) compared with 3.0% (3 of 100) in the steroid maintenance arm ($P < 0.001$), mainly because of the addition of oral prednisolone in the steroid avoidance arm at 36.1% (39 of 108). At 2 years, 63.9% (69 of 108) of the patients in the steroid avoidance arm remained free of oral steroids. Baseline characteristics were comparable between the 2 arms (Figure 1 and Table 1).

Post-Transplantation Diabetes Mellitus

The incidence of PTDM within the first post-transplant year was similar in the 2 study arms, 12.4% in the steroid avoidance arm versus 18.3% in the steroid maintenance arm ($P = 0.3$, CI: 16.3–4.4), as found in Supplementary Figure S1, which also describes the criteria for PTDM diagnosis. The Kaplan–Meier curve indicates that most PTDM events occurred early, within the first 6 months post-transplant, and PTDM-free survival estimate at 2 years did not differ significantly between the steroid avoidance and steroid maintenance arms (Figure 2). At 2 years, the cumulative incidence of PTDM also did not differ significantly between the 2 arms (13.3% vs. 19.3%, $P = 0.3$, CI: 16.6–4.6); PTDM was resolved in 40.0% of the patients in the steroid avoidance arm versus 28.5% in the steroid maintenance arm ($P = 0.72$) (Table 2).

Biopsy-Proven Rejections

In total, 302 biopsies were performed in 184 of 222 patients (83%), 92 in each arm. The for-cause/protocol biopsy ratio was 82/75 in the steroid avoidance arm and 70/75 in the steroid maintenance arm. Furthermore, 33 patients experienced rejection, 32 were biopsy proven, and 1 clinical rejection (biopsy could not be performed because of the risk of excessive bleeding). There were 7 patients who experienced >1 rejection episode. None of the grafts were lost owing to rejection during the study follow-up.

The incidence of overall biopsy-proven rejections at 1 year was not significantly different between the arms, 15% (or 15.9% if 1 clinical rejection was included) in steroid avoidance arm versus 13.8% in steroid maintenance arm ($P = 0.85$ and $P = 0.71$, respectively).

A detailed central blinded *post hoc* histopathologic assessment according to the Banff 2017 classification revealed 22 rejections (T cell-mediated rejection [TCMR] and/or antibody-mediated rejection [ABMR]) to be acute and 10 chronic. Acute rejections were diagnosed mainly within the first 6 months by for-cause biopsies and chronic mainly at 1 year by protocol biopsy (Figure 3a).

The incidence of acute TCMR was significantly higher in the steroid avoidance arm than in the steroid maintenance arm (11.5% vs. 3.7%, $P = 0.04$). These resolved with i.v. methylprednisolone. Nevertheless, the incidence of active ABMR, observed only in the steroid

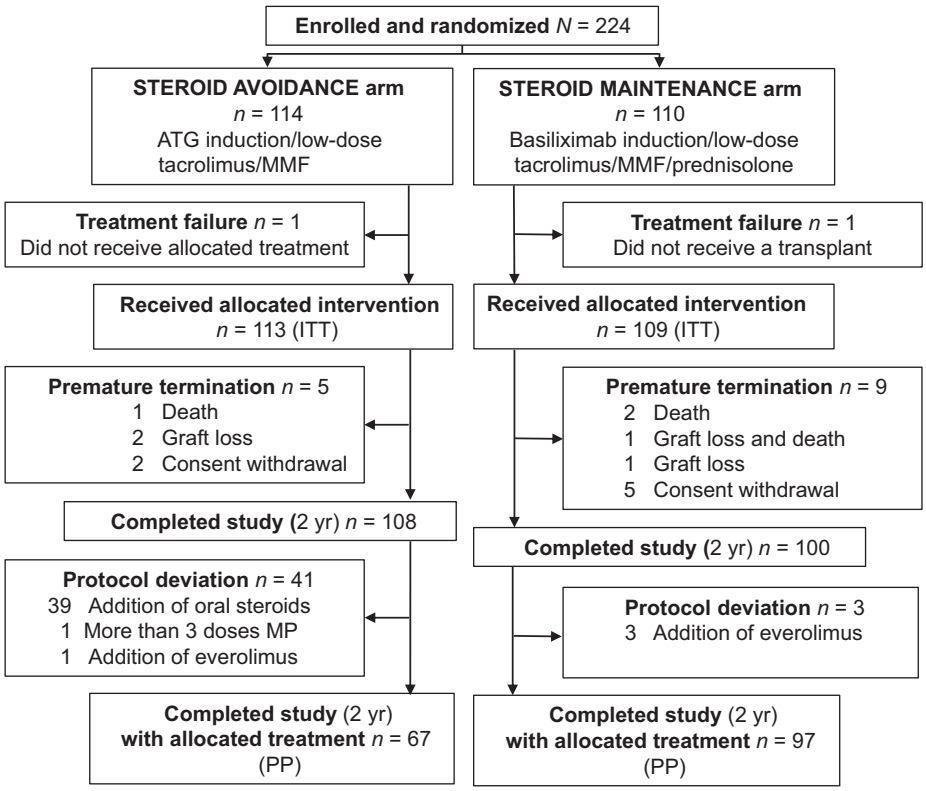

Figure 1. Study flowchart, patient disposition. ATG, antithymocyte globulin; ITT, intention-to-treat population; MMF, mycophenolate mofetil; MP, methylprednisolone; PP, per-protocol population.

maintenance arm, was significantly higher than that in the steroid avoidance arm (4.6% vs. 0%, $P = 0.03$). Of these rejections, 2 were accompanied by TCMR and both resolved partially with methylprednisolone boluses, rituximab, i.v. immunoglobulin with/without plasma exchange, and ATG.

Taking acute TCMR and active ABMR together, the overall incidence of biopsy-proven acute/active rejection was similar in both arms (11.5% in steroid avoidance arm, 8.3% in steroid maintenance arm, $P = 0.50$). The incidence of chronic TCMR was similar in both arms. The different histologic phenotypes of rejection and incidences are found in Figure 3b and Table 2.

Analysis of donor-specific antibodies at 1 year was performed in 193 patients. There were 12 patients (6 in each arm) who developed *de novo* donor-specific antibodies: 3 associated with chronic TCMR in the steroid avoidance arm and 3 with active ABMR in the steroid maintenance arm. The remaining 6 patients with donor-specific antibodies did not have any clinical or histologic signs of rejection.

The composite measure of freedom from acute rejection, graft loss, and death at 2 years was similar in the 2 arms (81% in the steroid avoidance arm and 85% in the steroid maintenance arm ($P = 0.4$) (Figure 4).

Table 1. Baseline characteristics between the 2 arms

Characteristics	Steroid avoidance arm ($n = 113$)	Steroid maintenance arm ($n = 109$)
Age, yr, mean (SD)	52.1 (13.9)	49.2 (14.5)
Age >60, *n* (%)	33 (29.2)	28 (25.7)
Females, *n* (%)	30 (26.5)	31 (28.4)
BMI, kg/m^2, mean (SD)	25.9 (3.9)	26.2 (4.0)
Waist-hip ratio, mean (SD)	0.98 (0.1)	0.98 (0.1)
Plasma glucose baseline (mmol/l)	5.4 (0.7)	5.4 (0.8)
Blood pressure systolic, mm Hg, mean (SD)	143.8 (18.3)	143.5 (18.9)
Blood pressure diastolic, mm Hg, mean (SD)	85.1 (10.4)	84.9 (11.0)
Cause of ESKD, *n* (%)		
Polycystic kidney disease	38 (33.6)	32 (29.4)
Glomerulonephritis	34 (30.1)	32 (29.4)
Other defined causes	28 (24.7)	26 (23.9)
Undefined cause	13 (11.5)	19 (17.4)
Second transplant, *n* (%)	3 (2.7)	0
Deceased donor, *n* (%)	63 (55.8)	68 (62.4)
HLA antigen mismatch A; B; DR (mean)	1.1; 1.3; 1.2	1.1; 1.4; 1.1

BMI, body mass index; ESKD, end-stage kidney disease.
Between-group differences for demographic and clinical characteristics were not statistically significant, calculated with Fisher exact test. Data are *n* (%) or mean (SD).

Other Outcomes

Kidney function in patients with functioning grafts evaluated by measured glomerular filtration rate (mean) in functioning grafts at 1 year was 53.6 ml/min per 1.73 m^2 in steroid avoidance arm versus 55.0 ml/min

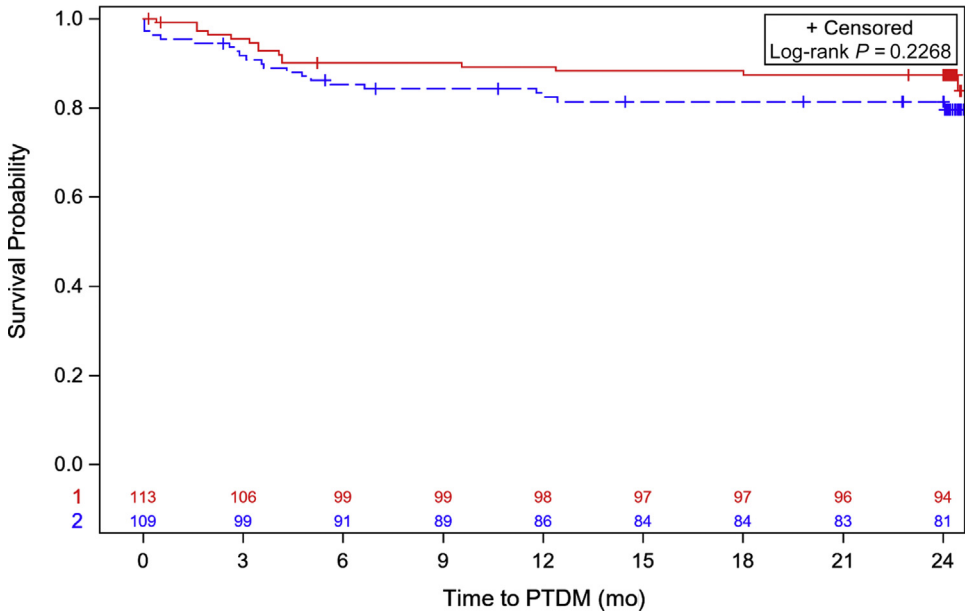

Figure 2. Kaplan–Meier of PTDM-free survival at 2 years according to study arm. Intention-to-treat analysis. Steroid avoidance arm ——; steroid maintenance arm – – –; PTDM, post-transplantation diabetes mellitus.

per 1.73 m^2 in steroid maintenance arm ($P = 0.55$) without any significant deterioration at 2 years (53.0 ml/min vs. 54.5 ml/min, respectively, $P = 0.58$). There were no significant differences in kidney function between the 2 arms even when stratified according to different glomerular filtration rate stages (≥60, 45–59, 30–44, <29 ml/min per 1.73 m^2) (Table 2).

The incidence of infections, major CV event, malignancies, graft, and patient survival at 2 years was comparable between the 2 arms. One patient died in the steroid avoidance arm because of pancreatic cancer, and 3 patients died in the steroid maintenance arm owing to uremia (refused dialysis), encephalitis, and lung cancer. In total, 4 graft losses were observed, 2 in each arm; the causes were primary nonfunction, thrombosis, uremia, and recurrence of glomerulonephritis in the graft.

Immunosuppression, Other Medication

The mean tacrolimus daily dose at all defined time intervals and the mean AUC of total tacrolimus dose in the entire study period were similar between the 2 arms. The whole blood tacrolimus trough levels were comparable at all time points (1, 3, 6, 12, 24 months), except at 1-week post-transplant in which the level was significantly higher in the steroid avoidance arm versus steroid maintenance arm (11.8 vs. 9.9 μg/l, $P = 0.003$). The mean MMF daily dose during all time periods and the mean AUC of the total MMF dose in the entire study period were similar between the 2 arms. Nevertheless, the mean single MPA-AUC (days 10 ± 5) was lower in steroid avoidance arm versus steroid maintenance arm (51.9 vs. 61.4 mg/l × h, $P = 0.002$) (Table 3).

Prednisolone was added (>30 days) in 39 of 108 patients in the steroid avoidance arm, owing to suspected or proven rejection ($n = 21$) or when MMF was reduced owing to leucopenia/cytomegalovirus infection/side effects ($n = 15$) or other reasons ($n = 3$), mainly during the first 6 months (Supplementary Figure S2).

The antihypertensive treatment was more intense during the first 3 months in steroid maintenance arm with higher mean number of medications, being 2.02 versus 1.66 in steroid avoidance arm ($P = 0.02$). Moreover, during the same period, a higher number of patients in the steroid maintenance arm required ≥3 antihypertensive drugs, 36 versus 22 in the steroid avoidance arm ($P = 0.03$). The lipid-lowering treatment did not differ statistically between the groups.

DISCUSSION

In our SAILOR study, although the incidence of PTDM (the primary end point) did not differ significantly between the 2 arms, the steroid avoidance protocol was not associated with an increased risk of biopsy-proven rejections for up to 2 years. In addition, composite measure of acute rejection/graft loss/death-free survival, kidney function, and incidence of complications, such as infections, malignancies, or major CV events, at 2 years were similar between the 2 arms. At 2 years, most patients in the steroid avoidance arm (63.9%) remained free of oral steroids. The 18.3% incidence of PTDM in the steroid maintenance arm was found to be

Table 2. Secondary end points

End point	Steroid avoidance arm ($n = 113$)	Steroid maintenance arm ($n = 109$)	P
Patient survival at 2 yr	112 (99)	106 (97)	0.68
Graft survival at 2 yr	111 (98)	107 (98)	1.00
Graft loss at 2 yr	2 (1.77)	2 (1.83)	1.00
FPG (mmol/l) at 2 yr	5.93 (1.28) $n = 38$	5.5 (0.67) $n = 28$	0.09
PTDM incidence (%) at 2 yr	15 (13.3)	21 (19.3)	0.28
PTDM persistent at 2 yr or ET (%)	9/15 (60.0)	15/21 (71.4)	0.72
Any antidiabetic treatment (%)	3/9 (33.3)	11/15 (73.3)	0.09
FPG (mmol/l) in treated	7.1 (1.13)	6.84 (0.64)	0.66
No antidiabetic treatment	6/9 (66.7)	4/15 (26.7)	0.09
FPG (mmol/l) in not treated	8.38 (2.27)	9.47 (1.12)	0.48
PTDM resolved at 2 yr (%)	6/15 (40.0)	6/21 (28.6)	0.72
FPG (mmol/l) in resolved	6.22 (0.34)	5.92 (0.91)	0.47
All rejections, cumulative incidence at 1 yr	18 (15.9)	15 (13.8)	0.71
Biopsy-proven rejections, cumulative incidence at 1 yr	17 (15.0)	15 (13.8)	0.85
Acute TCMR	13 (11.5)	4 (3.7)	0.04
Chronic TCMR	4 (3.5)	6 (5.5)	0.53
Active ABMR	0	5 (4.6)	0.03
Acute TCMR + active ABMR	13 (11.5)	9 (8.3)	0.50
Mean mGFR (ml/min per 1.73 m^2) at 1 yr	53.6 (17.0) $n = 104$	55 (16.6) $n = 94$	0.55
Mean mGFR (ml/min per 1.73 m^2) at 2 yr	53.0 (18.0) $n = 97$	54.5 (17.9) $n = 89$	0.58
mGFR >60, n (%)	32 (33.3)	31 (34.8)	1.00
mGFR 45–59	34 (35.4)	28 (31.5)	0.55
mGFR 30–44	21 (21.9)	22 (24.7)	0.87
mGFR 15–29	7 (7.3)	7 (7.9)	1.00
mGFR <15	2 (2.1)	1 (1.1)	1.00
Subject with AE at 2 yr	101 (89.1)	97 (89.0)	1.00
Infection	73 (64.6)	84 (77.1)	0.06
MACE	7 (6.2)	5 (4.6)	0.80
Malignancy	7 (6.2)	10 (9.2)	0.46
Subjects with SAE at 2 yr	73 (64.6)	69 (63.3)	0.89

ABMR, antibody-mediated rejection; ET, early termination; AE, adverse event; FPG, fasting plasma glucose; mGFR, measured glomerular filtration rate; MACE, major adverse cardiac event; PTDM, post-transplantation diabetes mellitus; SAE, serious adverse event; TCMR, T cell-mediated rejection.
Intention-to-treat analysis. Data are presented as n (%) or mean (SD). Differences between arms were calculated using Fisher exact test for dichotomous variables and Fisher nonparametric permutation test for continuous variables.

much lower than our initial assumption of 36%[7] and lower than the incidence of 39% in the control arm of the HARMONY study, although the treatment regimen and PTDM diagnostic criteria were very similar. A possible explanation could be the presence of differences in the study populations. Unlike the HARMONY study, patients with a history of diabetes or elevated plasma glucose before transplantation were excluded from the SAILOR study. Thus, our cohort of participants had stricter inclusion criteria and was probably at low risk for PTDM.[12] Similar to our findings, even the ADVANCE study reported a lower incidence of PTDM at 24 weeks in both early steroid withdrawal and steroid avoidance arms (17.4% and 16.6%, respectively, P = not significant).[14] The low incidence of PTDM in both arms in our study may have been the reason why steroid avoidance was not significantly superior to steroid maintenance.

The secondary end point of biopsy-proven rejections was of major concern initially owing to the absence of steroids in the steroid avoidance arm. Although an increased incidence of early acute TCMR in the steroid avoidance arm and active ABMR in the steroid maintenance arm were observed, the overall incidence of biopsy-proven rejections did not differ between the 2 groups, even when including the findings of protocol biopsies at 1 year. Moreover, graft and kidney survival were also similar in the 2 arms.

We chose the newer Banff 2017 classification for *post hoc* biopsy assessment to distinguish TCMR more accurately and ABMR in terms of acute/chronic/active features. Our findings are in line with the HARMONY study that revealed no increased risk of acute rejection after steroid withdrawal with a tacrolimus/MMF-based regimen.[12,20] Of note, our RCT has revealed no increased risk of overall rejection with complete steroid avoidance for up to 2 years.

The mean tacrolimus trough levels in the current study were lower in the steroid maintenance arm at 7 days. This difference, which was not observed at later time points, might be due to the well-known drug interaction of steroids reducing tacrolimus concentrations.[21] Although the mean tacrolimus trough levels in the first 6 months in our patients were slightly higher than those in the Symphony study,[11] they were comparable with those in the HARMONY study.[12] Moreover, the early single MPA-AUC level was found to be significantly higher in the steroid maintenance-arm; however, this effect was small and not maintained during follow-up. This effect could not be explained by any known interaction of MMF with steroids or tacrolimus. In fact, steroid tapering has been associated with increased MPA-AUC levels, and tacrolimus has little effect on MMF pharmacokinetics.[22]

Our study has several strengths, including a follow-up duration of 2 years, protocol biopsies at 1 year, the measured glomerular filtration rate, stricter selection of patients without diabetes, and the use of adapted American Diabetes Association criteria for defining PTDM.

This study also has some limitations. The power calculation was performed with the assumption of a PTDM incidence of 36% in a control arm, based on previous studies. Therefore, a significant difference between the 2 arms could not be achieved with a real PTDM incidence of 18.3% in the steroid maintenance arm. The open-label study design may have created a possible bias for clinicians involved in patient care, such as introduction of prednisolone in steroid

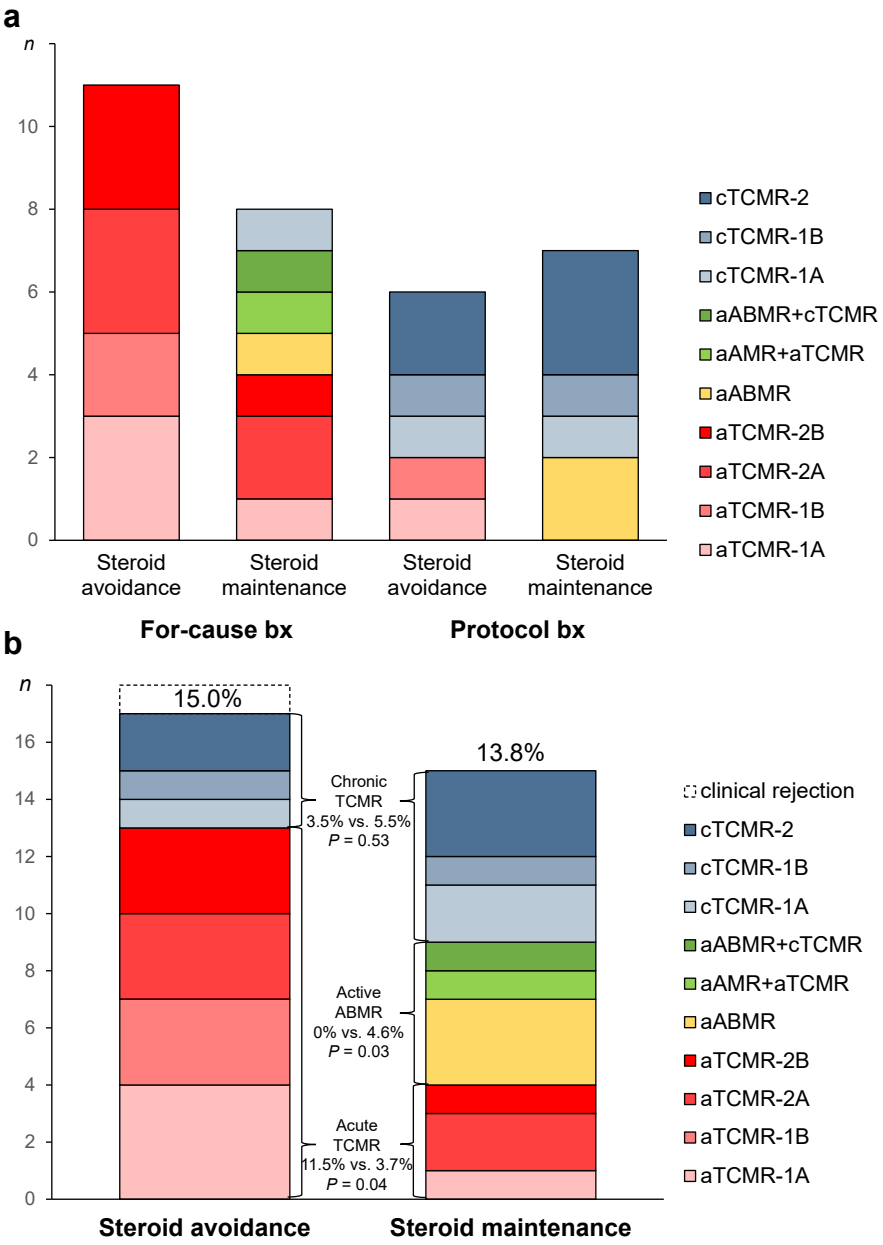

Figure 3. (a) Biopsy-proven rejections at 1 year according to type of bx, study arm, and histologic phenotypes of rejection (Banff 2017 classification). Intention-to-treat analysis. (b) Incidence (%) of biopsy-proven rejection at 1 year according to study arm and histologic phenotypes of rejection (Banff 2017 classification). Intention-to-treat analysis. Incidence of biopsy-proven rejections in steroid avoidance arm versus steroid maintenance arm at 15% versus 13.8% ($P = 0.85$). ABMR, antibody-mediated rejection; a, acute/active; bx, biopsy, c, chronic; *n*, number of patients; TCMR, T cell-mediated rejection.

avoidance arm. Oral glucose tolerance test was not performed at baseline (before inclusion) or at 2 years, but pretransplant oral glucose tolerance test is not feasible in a deceased-donor setting. Furthermore, hemoglobin A1c was not included in the analysis at any time point; however, this was due to the well-recognized limitation of hemoglobin A1c in renal anemia, which might persist even months after kidney transplantation. Furthermore, the 2 study arms had different induction therapies with either ATG or basiliximab, including different early tacrolimus and MPA-AUCs. The use of ATG may have affected the rate of acute rejection and graft function in the steroid avoidance arm. Nonetheless, this concern was found to be unfounded in the recent randomized controlled HARMONY study in which ATG did not have superiority over basiliximab in the prevention of acute rejection. Moreover, the higher early tacrolimus levels may have compensated for lower MPA-AUC in the steroid avoidance arm, thus rendering equipotent oral immunosuppression in both arms. Therefore, we do not believe that the differences in the induction or early

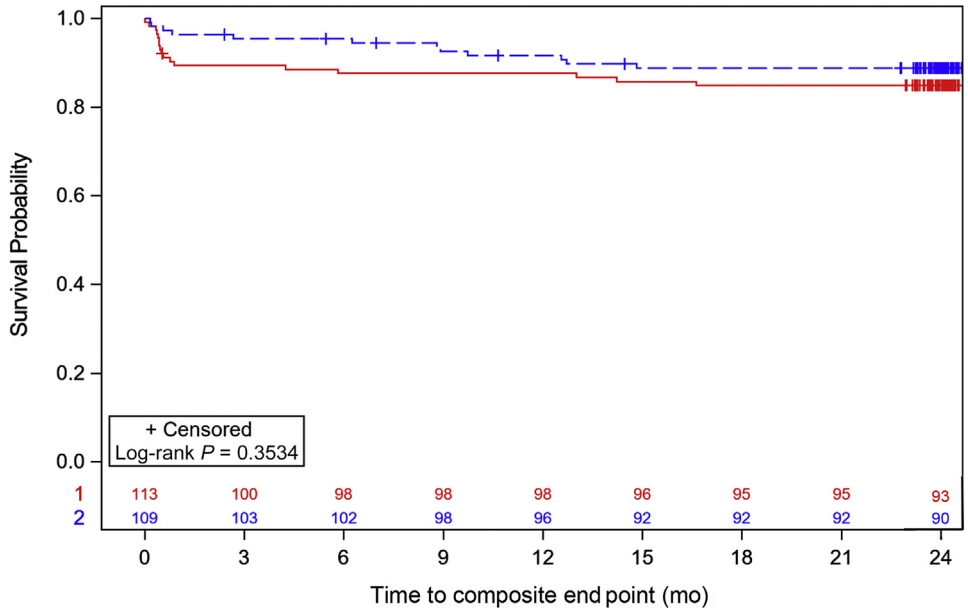

Figure 4. Kaplan–Meier of composite end point (acute rejection, graft loss, and death) according to study arm. Intention-to-treat analysis. Steroid avoidance arm ——; Steroid maintenance arm – – –.

maintenance therapy affected the rate of biopsy-proven rejections or graft function in this study. Another limitation could be that a significant proportion of patients in the steroid avoidance arm (36.1%) started oral steroids during the course of the study; nonetheless, most could remain free of oral steroids at 2 years.

Table 3. Immunosuppression and other medications

Drug related variable	Time point/interval	Steroid avoidance arm	Steroid maintenance arm	*P*
Tacrolimus mean daily dose (mg)	0–3 mo	7.89 (3.05) $n = 112$	8.58 (3.64) $n = 108$	0.13
	3–6 mo	5.96 (3.03) $n = 112$	6.33 (3.42) $n = 105$	0.41
	6–12 mo	5.03 (2.51) $n = 110$	5.25 (2.69) $n = 106$	0.52
	12–24 mo	4.23 (1.98) $n = 105$	4.52 (2.00) $n = 98$	0.31
Tacrolimus mean AUC of dose (mg)	0–24 mo	5.27 (2.56) $n = 110$	5.45 (2.55) $n = 108$	0.59
Tacrolimus trough level (μg/l)	7 d (±4)	11.8 (4.8) $n = 98$	9.86 (4.03) $n = 90$	0.003
	1 mo (±1 w)	9.99 (2.79) $n = 57$	9.98 (2.99) $n = 54$	0.98
	3 mo (±1)	8.54 (2.66) $n = 74$	9.26 (2.66) $n = 68$	0.10
	6 mo (±1)	7.67 (2.77) $n = 41$	7.79 (2.89) $n = 40$	0.87
	12 mo (±1)	6.93 (1.75) $n = 20$	6.51 (2.26) $n = 30$	0.48
	24 mo (±1)	6.49 (1.80) $n = 20$	5.99 (1.54) $n = 14$	0.42
MMF mean daily dose (mg)	0–3 mo	1714 (419) $n = 112$	1728 (385) $n = 109$	0.80
	3–6 mo	1310 (627) $n = 112$	1449 (509) $n = 107$	0.07
	6–12 mo	1196 (555) $n = 108$	1321 (511) $n = 107$	0.09
	12–24 mo	1180 (499) $n = 102$	1274 (460) $n = 101$	0.16
MMF mean AUC of dose (mg)	0–24 mo	1252 (476) $n = 112$	1361 (411) $n = 108$	0.07
MPA-AUC (mg*h/l) at	10 d (±5)	51.9 (17.2) $n = 96$	61.4 (21.9) $n = 89$	0.002
Prednisolone mean daily dose (mg)	0–3 mo	5.74 (6.04) $n = 44$	13.9 (2.8) $n = 108$	<0.0001
	3–6 mo	5.44 (4.17) $n = 42$	7.13 (1.7) $n = 107$	0.001
	6–12 mo	8.82 (3.49) $n = 38$	5.99 (3.27) $n = 104$	0.04
	12–24 mo	5.71 (3.82) $n = 34$	5.28 (2.21) $n = 98$	0.44
Prednisolone mean AUC of dose (mg)	0–24 mo	6.82 (6.87) $n = 48$	7.33 (2.55) $n = 106$	0.53
No. of antihypertensives	3 mo	1.66 (1.11) $n = 113$	2.02 (1.06) $n = 109$	0.02
No. of antihypertensives	24 mo	1.67 (1.04) $n = 113$	1.80 (1.21) $n = 109$	0.45
≥3 antihypertensives	3 mo	22 (19.5)	36 (33.0)	0.03
≥3 antihypertensives	24 mo	26 (23.0)	33 (30.3)	0.36
Any lipid-lowering drug	Baseline	96 (85.0)	82 (75.2)	0.10
Any lipid-lowering drug	24 mo	37 (32.7)	46 (42.2)	0.19

AUC, area under the curve; MMF, mycophenolate mofetil; MPA-AUC, mycophenolic acid AUC.
Intention-to-treat analysis. Differences between arms were calculated with Fisheŕs exact test for dichotomous variables and Fisheŕs nonparametric permutations test for continuous variables. Data are presented as n (%) or mean (SD).

The present conclusions are limited only to a low immunologic risk kidney transplant population mainly of White race and cannot be extrapolated to those with high immunologic risk or other races. Last, some baseline characteristics, such as donor age, cold ischemia time, and presence of delayed graft function, which could have an impact on clinical outcomes, were not captured in this study. Nevertheless, we believe that because of the randomized design of the study, these missing confounding factors were most likely balanced in the 2 arms, thus minimizing any potential bias on the results.

In conclusion, the SAILOR study provides further evidence for the feasibility, safety, and efficacy of early steroid-free treatment in immunologically low-risk kidney recipients in the first 2 years after transplantation. Although a significant reduction in the incidence of PTDM was not observed with the steroid avoidance regimen in this selected group at low risk for diabetes, it may be a preferred treatment option in recipients who are deemed at high risk for PTDM or are fragile with multiple comorbidities.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Incidence of PTDM at 1 year according to study arm. Intention-to treat analysis. Steroid avoidance (N = 113); steroid maintenance (N = 109). PTDM diagnostic criteria: 2× FPG ≥ 7.0 mmol/l ≥ 30 days apart; OGTT, 2-h plasma glucose ≥ 11.1 mmol/l; insulin treatment ≥ 30 consecutive days. FPG, fasting plasma glucose; N, number of patients; OGTT, oral glucose tolerance test; PTDM, post-transplantation diabetes mellitus.

Figure S2. Kaplan–Meier of start of prednisolone in steroid avoidance arm.

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