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A randomized controlled trial on safety of steroid avoidance in immunologically low-risk kidney transplant recipients

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Running headline: Steroid avoidance in kidney transplant recipients
ABSTRACT

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 non-diabetic kidney recipients on the current standard of care maintenance regimen with tacrolimus/mycophenolate mofetil (MMF).

Methods. In this 2-year multicenter open-label trial, 222 patients were randomized to receive either steroid avoidance protocol: tacrolimus/MMF/antithymocyte globulin 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 endpoint (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 endpoint of freedom from acute rejection, graft loss, and death (81% vs. 85%, respectively, P=0.4), kidney function, or adverse events were comparable between the two arms. Moreover, 63.9% of patients in the steroid avoidance arm remained free from steroids at 2 years.

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

KEYWORDS: kidney transplantation, steroid avoidance, posttransplantation diabetes mellitus, biopsy-proven rejection
INTRODUCTION
Kidney transplantation remains the best possible option for eligible patients with kidney failure, as it offers better quality of life and longer survival compared to 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 disease (CVD) remains one of the major causes of graft loss in the long-term.¹

Posttransplant diabetes mellitus (PTDM) is associated with an unfavorable CV risk profile,² and is an independent predictor of CVD,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 two randomized controlled trials (RCTs) in kidney transplant recipients using a composite definition of PTDM based on the American Diabetes Association (ADA) criteria, the 1-year incidence of PTDM reached 30%–37% with standard-dose tacrolimus/mycophenolate mofetil [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 two decades, several RCTs with steroid-sparing protocols, including steroid avoidance and steroid withdrawal have been conducted worldwide to reduce the side effects of steroids, including PTDM. The systematic Cochrane review and meta-analysis in 2016¹⁰ 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 five years after transplantation, have not been demonstrated. However, meaningful conclusions could not be drawn due 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.\textsuperscript{11} While this regimen showed lower rejection rate, better kidney function, and higher survival rate, compared to two cyclosporine and one sirolimus arm, the 1-year incidence of PTDM was highest (10.6%) in the low-tacrolimus/MMF/steroid arm, in spite of 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 ADA criteria for PTDM.\textsuperscript{12,13} The multicenter HARMONY study compared the following
three arms: arm-A: basiliximab-induction/tacrolimus/MMF/steroid maintenance therapy; arm-B: basiliximab-induction/tacrolimus/MMF/rapid steroid withdrawal (at one week); and arm-C: ATG induction/tacrolimus/MMF/rapid steroid withdrawal. The incidence of biopsy-proven acute rejection (the primary endpoint) was similar in the three arms, with a significant reduction in the 1-year incidence of PTDM (secondary endpoint) in both arms (B and C) with rapid steroid withdrawal (24% and 23%, respectively, versus 39% in steroid maintenance-arm-A, P=0.0004). This study clearly showed that ATG was not superior to basiliximab induction for the prevention of acute rejection. However, two other recent RCTs using steroid-sparing protocols primarily evaluating PTDM showed conflicting results. In the trial that studied steroid withdrawal vs. steroid minimization within 6 months on tacrolimus/MMF in recipients at a high risk for diabetes, the incidence of PTDM after one year was surprisingly higher in the tacrolimus/steroid withdrawal arm than in the tacrolimus/steroid minimization arm (38% vs. 26%, P=0.01). 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%. The SAILOR study was conducted to assess whether a steroid avoidance protocol with tacrolimus/MMF/ATG induction in a non-diabetic population with low immunologic risk reduces the incidence of PTDM with good efficacy and safety over two years, as compared to the standard steroid maintenance regimen. Since SAILOR
study was designed and initiated three 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.\textsuperscript{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 two-year follow-up duration, conducted at three Scandinavian transplant centers (Gothenburg, Malmoe, Sweden; Aarhus, Denmark). Recipients >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 $\geq 11.1$ mmol/l, HLA antibodies, CDC-PRA $>25\%$ 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.\textsuperscript{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 one of the two 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. However, patients’ identity and treatment assignment was concealed to the Primary Endpoint Committee, two independent nephrologists, who assessed the accuracy of the PTDM diagnosis, and to two pathologists, who centrally evaluated all transplant biopsies.

Procedures

Patients were randomized before kidney transplantation to one of 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 0.2 mg/kg once daily with target trough levels 5-10 ug/L within first three months and thereafter 4-7 ug/L, and MMF 1 g twice a day controlled by a single mycophenolate acid area under the curve (MPA-AUC) measurement on day 10±5 with target AUC 40-60 mg*h/L.
2) Steroid maintenance-arm: induction with basiliximab 20 mg on days 0 and 4; methylprednisolone 250-500 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 intravenous 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 ADA criteria for type 2 diabetes mellitus adapted to population of patients after kidney transplantation, and determined, if one of following was present: fasting plasma glucose (FPG) ≥7.0 mmol/L ≥30 days apart; 2-h plasma glucose ≥11.1 mmol/L in the oral glucose tolerance test (OGTT); oral hypoglycemic agent or insulin given ≥30 consecutive days. The FPG was measured at each study visit (baseline, day 10±5 days, 3, 6, 12, and 24 months); OGTT 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 one-year posttransplant for all patients. The biopsies were primarily assessed locally at each center using the Banff 2009 classification to determine the eventual clinical action. Biopsy-proven acute rejections were treated with intravenous methylprednisolone (three boluses of 500 mg/day). 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 assessment was performed post-hoc centrally by two pathologists according to the revised Banff 2017 classification. Borderline changes in the biopsy were not designated as rejection.

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

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

Endpoints

The primary efficacy endpoint was the incidence of PTDM within the first posttransplant year. Secondary endpoints were: 1) incidence of PTDM and use of antidiabetic agents at two years, 2) incidence of biopsy-proven rejection at one year, 3) composite measure of freedom from acute rejection, graft loss, and death at one and two years, 4) kidney function measured by either iohexol- or Cr-EDTA clearance at one and two years, 5) occurrence of infections, MACEs, and malignancies during
two years, 6) mean doses, mean AUC of doses, trough levels, and AUCs for
immunosuppressants at defined time-points and time-periods 7) use of
antihypertensive and lipid-lowering agents over two years.

Statistical analysis

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

For the sample size calculation, we based our assumption on the 36% incidence of
PTDM, defined according to the ADA criteria, reported at one-year after transplant
with a steroid-containing immunosuppressive protocol7 and an estimated reduction to
18% with steroid avoidance. The sample size of 222 subjects was calculated using
Fischer’s exact test to achieve 80% power for superiority of steroid avoidance-arm
over the control steroid maintenance-arm, with a two-sided type 1 error of 5% and
allowing 5% dropout. For comparison between groups, the following tests were
used: Fisher’s exact test for dichotomous variables, Mantel-Haenszel chi-squared
test for categorical variables, Fisher’s 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 two-sided p-value of
<0.05. The statistical software SAS 9.4 was used for statistical analyses.
RESULTS

Study patients (Figure 1)

In total, 224 patients were enrolled and randomized between February 2013-March 2017. Of these, 222 patients underwent kidney transplantation, received at least one study medication, and one follow-up. One hundred and thirteen patients received ATG-induction/tacrolimus/MMF (steroid avoidance-arm) and 109 received basiliximab-induction/tacrolimus/MMF/prednisolone (steroid maintenance-arm). Four patients in the steroid avoidance-arm and nine in the steroid maintenance-arm terminated the study prematurely due 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% (41/108) compared to 3.0% (3/100) in the steroid maintenance-arm (p<0.001), mainly because of the addition of oral prednisolone in the steroid avoidance-arm 36.1% (39/108). At two years, 63.9% (69/108) of patients in the steroid avoidance-arm remained free of oral steroids. Baseline characteristics were comparable between the two arms (Table 1).

Posttransplantation diabetes mellitus (PTDM)

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

Biopsy-proven rejections

In total, 302 biopsies were performed in 184/222 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. Thirty-three patients experienced rejection, 32 were biopsy-proven, and one clinical rejection (biopsy could not be performed because of the risk of excessive bleeding). Seven patients experienced >one rejection episode. None of the grafts was lost due to rejection during the study follow-up.

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

A detailed central blinded post-hoc histopathological assessment according to the Banff 2017 classification revealed 22 rejections (TCMR and/or ABMR) to be acute and 10 chronic. Acute rejections were diagnosed mainly within the first six months by for-cause biopsies and chronic mainly at one 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 intravenous methylprednisolone. On the other hand, the incidence of active ABMR,
observed only in the steroid maintenance-arm, was significantly higher than that in
the steroid avoidance-arm (4.6% vs. 0%, P=0.03). Two of these rejections were
accompanied by TCMR, and both resolved partially with methylprednisolone boluses,
rituximab, IVIG 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 histological phenotypes of rejection and incidences
are shown in Figure 3b and Table 2.

Analysis of DSA at one year was performed in 193 patients. Twelve patients (six in
each arm) developed de novo DSAs: three associated with chronic TCMR in the
steroid avoidance-arm and three with active ABMR in the steroid maintenance-arm.
The remaining six patients with DSAs did not show any clinical or histological signs of
rejection.

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

**Other outcomes** (Table 2)

Kidney function in patients with functioning grafts assessed by mGFR (mean) in
functioning grafts at one year was 53.6 ml/min/1.73 m$^2$ in steroid avoidance-arm vs.
55.0 ml/min/1.73 m$^2$ in steroid maintenance-arm (P=0.55) without any significant
deterioration at two years (53.0 ml/min vs. 54.5 ml/min, respectively, P=0.58). There were no significant differences in kidney function between the two arms even when stratified according to different GFR stages (≥60, 45-59, 30-44, <29 ml/min/1.73 m²).

The incidence of infections, MACE, and malignancies, graft and patient survival at two years were comparable between the two arms. One patient died in the steroid avoidance-arm because of pancreatic cancer, and three patients died in the steroid maintenance-arm due to uremia (refused dialysis), encephalitis, and lung cancer. In total, four graft losses were observed, two in each arm; the causes were primary non-function, thrombosis, uremia, and recurrence of glomerulonephritis in the graft.

**Immunosuppression, other medication** (Table 3)

The mean tacrolimus daily dose at all defined time-intervals and the mean AUC of total tacrolimus dose over the entire study period were similar between the two 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 where the level was significantly higher in the steroid avoidance-arm vs. steroid maintenance-arm (11.8 vs. 9.9 ug/L, P=0.003). The mean MMF daily dose during all time periods and the mean AUC of the total MMF dose over the entire study period were similar between the two arms. However, the mean single MPA-AUC (day 10±5) was lower in steroid avoidance-arm vs. steroid maintenance-arm (51.9 vs. 61.4 mg/L*H, P=0.002).

Prednisolone was added (>30 days) in 39/108 patients in steroid avoidance-arm, due to suspected or proven rejection (N=21) or when MMF was reduced due to
leucopenia/CMV infection/side effects (N=15) or other reasons (N=3), mainly during the first six months (Supplemental Figure S2).

The antihypertensive treatment was more intense during first three months in steroid maintenance-arm with higher mean number of medications, being 2.02 vs. 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 vs. 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 endpoint) did not differ significantly between the two arms, the steroid avoidance protocol was not associated with an increased risk of biopsy-proven rejections for up to two years. In addition, composite measure of acute rejection/graft loss/death-free survival, kidney function, and incidence of complications such as infections, malignancies, or MACEs at two years were similar between the two arms. At two years, the majority of 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 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 prior to transplantation were excluded from the SAILOR study. Thus, our cohort of participants had stricter inclusion criteria and were
probably at low risk for PTDM.\textsuperscript{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, \( P=\text{NS} \)).\textsuperscript{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 endpoint of biopsy-proven rejections was of major concern initially due 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 two groups, even when including the findings of protocol biopsies at one year. Moreover, graft and kidney survival were also similar in the two 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 showed no increased risk of acute rejection after steroid withdrawal with a tacrolimus/MMF-based regimen.\textsuperscript{12,20} Of note, our RCT has demonstrated no increased risk of overall rejection with complete steroid avoidance for up to two 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.\textsuperscript{21} Although the mean tacrolimus trough levels in the first
six months in our patients were slightly higher than those in the Symphony study\textsuperscript{11},

they were comparable with those in the Harmony study.\textsuperscript{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.\textsuperscript{22}

Our study has several strengths, including a follow-up duration of two years, protocol
biopsies at one year, the measured GFR, stricter selection of patients without
diabetes, and the use of adapted ADA 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 two 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 avoidance-arm. OGTT was not
performed at baseline (before inclusion) or at two years, but pretransplant OGTT is
not feasible in a deceased-donor setting. HbA1c was also not included in the analysis
at any time-point; however, this was due to the well-recognized limitation of HbA1c in
renal anemia, which might persist even months after kidney transplantation.

Furthermore, the two study arms had different induction therapies with either ATG or
basiliximab, as well as 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 shown to be unfounded in the recent randomized controlled HARMONY study in which ATG did not show 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 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, the majority could remain free of oral steroids at two years. The present conclusions are limited only to a low immunologic risk kidney transplant population mainly of Caucasian race and cannot be extrapolated to those with high immunologic risk or other races. Lastly, 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. However, we believe that because of the randomized design of the study, these missing confounding factors were most likely balanced in the two 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 over the first two-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 high-risk for PTDM or are fragile with multiple comorbidities.
1 DISCLOSURES

2 Jana Ekberg – research stipendium from The Foundation for kidney patients, Sweden, Seema Baid-Agrawal - none, Bente Jespersen - none, Ragnar Källen - none, Ehab Rafael- none, Karin Skov - none, Per Lindné - unconditional grant from Astellas Pharma

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18 SUPPLEMENTARY MATERIAL

19 Two supplementary figures, S1 and S2 and the CONSORT checklist (PDF) are available at KI Report’s website.
REFERENCES


FIGURE LEGENDS

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

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, posttransplantation diabetes mellitus.

FIGURE 3a. Biopsy-proven rejections at 1 year according to type of biopsy (bx), study arm and histological phenotypes of rejection (Banff 2017 classification). Intention-to-treat analysis. ABMR, antibody mediated rejection; a, acute/active; c, chronic; N, number of patients; TCMR, T-cells mediated rejection.

FIGURE 3b. Incidence (%) of biopsy-proven rejection at 1 year according to study arm and histological phenotypes of rejection (Banff 2017 classification). Intention-to-treat analysis. Incidence of biopsy-proven rejections in steroid avoidance-arm vs. steroid maintenance-arm 15% vs. 13.8% (P=0.85). ABMR, antibody mediated rejection; a, acute/active; c, chronic; N, number of patients; TCMR; T-cells mediated rejection.

FIGURE 4. Kaplan-Meier of composite endpoint (acute rejection, graft loss and death) according to study arm. Intention-to-treat analysis. Steroid avoidance-arm ——; Steroid maintenance-arm – – – –.
Table 1.

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<td>Waist-hip ratio (mean (SD))</td>
<td>0.98 (0.1)</td>
<td>0.98 (0.1)</td>
</tr>
<tr>
<td>Plasma glucose baseline (mmol/L)</td>
<td>5.4 (0.7)</td>
<td>5.4 (0.8)</td>
</tr>
<tr>
<td>Blood pressure systolic, mm Hg (mean (SD))</td>
<td>143.8 (18.3)</td>
<td>143.5 (18.9)</td>
</tr>
<tr>
<td>Blood pressure diastolic, mm Hg (mean (SD))</td>
<td>85.1 (10.4)</td>
<td>84.9 (11.0)</td>
</tr>
<tr>
<td>Cause of ESKD (n (%))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>polycystic kidney disease</td>
<td>38 (33.6)</td>
<td>32 (29.4)</td>
</tr>
<tr>
<td>glomerulonephritis</td>
<td>34 (30.1)</td>
<td>32 (29.4)</td>
</tr>
<tr>
<td>other defined causes</td>
<td>28 (24.7)</td>
<td>26 (23.9)</td>
</tr>
<tr>
<td>undefined cause</td>
<td>13 (11.5)</td>
<td>19 (17.4)</td>
</tr>
<tr>
<td>Second transplant (n (%))</td>
<td>3 (2.7)</td>
<td>0</td>
</tr>
<tr>
<td>Deceased donor (n (%))</td>
<td>63 (55.8)</td>
<td>68 (62.4)</td>
</tr>
<tr>
<td>HLA antigen mismatch A; B; DR (mean)</td>
<td>1.1; 1.3; 1.2</td>
<td>1.1; 1.4; 1.1</td>
</tr>
</tbody>
</table>

Between-group differences for demographic and clinical characteristics were not statistically significant, calculated with Fisher’s exact test. BMI, body mass index; SD, standard deviation. Data are n (%) or mean (SD).
### Table 2. Secondary endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Steroid avoidance- arm (n=113)</th>
<th>Steroid maintenance- arm (n=109)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient survival at 2 years</td>
<td>112 (99)</td>
<td>106 (97)</td>
<td>0.68</td>
</tr>
<tr>
<td>Graft survival at 2 years</td>
<td>111 (98)</td>
<td>107 (98)</td>
<td>1.00</td>
</tr>
<tr>
<td>Graft loss at 2 years</td>
<td>2 (1.77)</td>
<td>2 (1.83)</td>
<td>1.00</td>
</tr>
<tr>
<td>FPG (mmol/l) at 2 years</td>
<td>5.93 (1.28)</td>
<td>5.5 (0.67)</td>
<td>0.09</td>
</tr>
<tr>
<td>Patient survival at 2 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTDM incidence (%) at 2 years</td>
<td>15 (13.3)</td>
<td>21 (19.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>PTDM persistent at 2 years or ET (%)</td>
<td>9/15 (60.0)</td>
<td>15/21 (71.4)</td>
<td>0.72</td>
</tr>
<tr>
<td>Any antidiabetic treatment (%)</td>
<td>3/9 (33.3)</td>
<td>11/15 (73.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>FPG (mmol/L) in treated</td>
<td>7.1 (1.13)</td>
<td>6.84 (0.64)</td>
<td>0.66</td>
</tr>
<tr>
<td>No antidiabetic treatment</td>
<td>6/9 (66.7)</td>
<td>4/15 (26.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>FPG (mmol/L) in not treated</td>
<td>8.38 (2.27)</td>
<td>9.47 (1.12)</td>
<td>0.48</td>
</tr>
<tr>
<td>PTDM resolved at 2 years (%)</td>
<td>6/15 (40.0)</td>
<td>6/21 (28.6)</td>
<td>0.72</td>
</tr>
<tr>
<td>FPG (mmol/l) in resolved</td>
<td>6.22 (0.34)</td>
<td>5.92 (0.91)</td>
<td>0.47</td>
</tr>
<tr>
<td>All rejections, cumulative incidence at 1 year</td>
<td>18 (15.9)</td>
<td>15 (13.8)</td>
<td>0.71</td>
</tr>
<tr>
<td>biopsy-proven rejections, cumulative incidence at 1 year</td>
<td>17 (15.0)</td>
<td>15 (13.8)</td>
<td>0.85</td>
</tr>
<tr>
<td>acute TCMR</td>
<td>13 (11.5)</td>
<td>4 (3.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>chronic TCMR</td>
<td>4 (3.5)</td>
<td>6 (5.5)</td>
<td>0.53</td>
</tr>
<tr>
<td>active ABMR</td>
<td>0</td>
<td>5 (4.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>acute TCMR + active ABMR</td>
<td>13 (11.5)</td>
<td>9 (8.3)</td>
<td>0.50</td>
</tr>
<tr>
<td>Mean mGFR (ml/min/1.73m²) at 1 year</td>
<td>53.6 (17.0)</td>
<td>55 (16.6)</td>
<td>0.55</td>
</tr>
<tr>
<td>N=104</td>
<td>N=94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean mGFR (ml/min/1.73m²) at 2 years</td>
<td>53.0 (18.0)</td>
<td>54.5 (17.9)</td>
<td>0.58</td>
</tr>
<tr>
<td>N=97</td>
<td>N=89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGFR &gt;60 (n (%))</td>
<td>32 (33.3)</td>
<td>31 (34.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>mGFR 45-59</td>
<td>34 (35.4)</td>
<td>28 (31.5)</td>
<td>0.55</td>
</tr>
<tr>
<td>mGFR 30-44</td>
<td>21 (21.9)</td>
<td>22 (24.7)</td>
<td>0.87</td>
</tr>
<tr>
<td>mGFR 15-29</td>
<td>7 (7.3)</td>
<td>7 (7.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>mGFR &lt; 15</td>
<td>2 (2.1)</td>
<td>1 (1.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Subject with AE at 2 years</td>
<td>101 (89.1)</td>
<td>97 (89.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Infection</td>
<td>73 (64.6)</td>
<td>84 (77.1)</td>
<td>0.06</td>
</tr>
<tr>
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<td></td>
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<td>----------------------</td>
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<td>------</td>
</tr>
<tr>
<td></td>
<td>7 (6.2)</td>
<td>5 (4.6)</td>
<td>0.80</td>
</tr>
<tr>
<td>MACE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>7 (6.2)</td>
<td>10 (9.2)</td>
<td>0.46</td>
</tr>
<tr>
<td>Subjects with SAE at 2 years</td>
<td>73 (64.6)</td>
<td>69 (63.3)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Intention-to-treat analysis. Data are presented as n (%) or mean (SD). Differences between arms were calculated using Fisher’s exact test for dichotomous variables and Fisher’s non-parametric permutation test for continuous variables.

ABMR, antibody-mediated rejection; AE, adverse event; FPG, fasting plasma glucose; mGFR, measured glomerular filtration rate; MACE, major adverse cardiac events; PTDM, post-transplantation diabetes mellitus; SAE, serious adverse event; TCMR, T-cell mediated rejection.
**Table 3. Immunosuppression and other medication**

<table>
<thead>
<tr>
<th>Timepoint /interval</th>
<th>Steroid avoidance-arm (mg)</th>
<th>Steroid maintenance-arm (mg)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus mean daily dose</td>
<td>(0–3) mo</td>
<td>7.89 (3.05) N=112</td>
<td>8.58 (3.64) N=108</td>
</tr>
<tr>
<td></td>
<td>(3–6) mo</td>
<td>5.96 (3.03) N=112</td>
<td>6.33 (3.42) N=105</td>
</tr>
<tr>
<td></td>
<td>(6–12) mo</td>
<td>5.03 (2.51) N=110</td>
<td>5.25 (2.69) N=106</td>
</tr>
<tr>
<td></td>
<td>(12–24) mo</td>
<td>4.23 (1.98) N=105</td>
<td>4.52 (2.00) N=98</td>
</tr>
<tr>
<td>Tacrolimus mean AUC of dose</td>
<td>(0–24) mo</td>
<td>5.27 (2.56) N=110</td>
<td>5.45 (2.55) N=108</td>
</tr>
<tr>
<td>Tacrolimus trough level (µg/L)</td>
<td>(7) d (±4)</td>
<td>11.8 (4.8) N=98</td>
<td>9.86 (4.03) N=90</td>
</tr>
<tr>
<td></td>
<td>(1) mo (±1w)</td>
<td>9.99 (2.79) N=57</td>
<td>9.98 (2.99) N=54</td>
</tr>
<tr>
<td></td>
<td>(3) mo (±1)</td>
<td>8.54 (2.66) N=74</td>
<td>9.26 (2.66) N=68</td>
</tr>
<tr>
<td></td>
<td>(6) mo (±1)</td>
<td>7.67 (2.77) N=41</td>
<td>7.79 (2.89) N=40</td>
</tr>
<tr>
<td></td>
<td>(12) mo (±1)</td>
<td>6.93 (1.75) N=20</td>
<td>6.51 (2.26) N=30</td>
</tr>
<tr>
<td></td>
<td>(24) mo (±1)</td>
<td>6.49 (1.80) N=20</td>
<td>5.99 (1.54) N=14</td>
</tr>
<tr>
<td>MMF mean daily dose (mg)</td>
<td>(0–3) mo</td>
<td>1714 (419) N=112</td>
<td>1728 (385) N=109</td>
</tr>
<tr>
<td></td>
<td>(3–6) mo</td>
<td>1310 (627) N=112</td>
<td>1449 (509) N=107</td>
</tr>
<tr>
<td></td>
<td>(6–12) mo</td>
<td>1196 (555) N=108</td>
<td>1321 (511) N=107</td>
</tr>
<tr>
<td></td>
<td>(12–24) mo</td>
<td>1180 (499) N=102</td>
<td>1274 (460) N=101</td>
</tr>
<tr>
<td>MMF mean AUC of dose (mg)</td>
<td>(0–24) mo</td>
<td>1252 (476) N=112</td>
<td>1361 (411) N=108</td>
</tr>
<tr>
<td>MPA-AUC (mg*h/l) at 10 d (±5)</td>
<td>51.9 (17.2) N=96</td>
<td>61.4 (21.9) N=89</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>0–3 mo</td>
<td>3–6 mo</td>
<td>6–12 mo</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>Prednisolone mean AUC of dose (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Intention-to-treat analysis. Differences between arms were calculated with Fisher’s exact test for dichotomous variables and Fisher’s non-parametric permutations test for continuous variables. Data are presented as n (%) or mean (SD).

AUC, area under the curve; MMF, mycophenolate mofetil; MPA AUC, mycophenolic acid AUC.
Completed study (2 years) N=108

- **Steroid Avoidance**- arm
  - N=114
  - ATG induction/low-dose tacrolimus/ MMF

- **Steroid Maintenance**- arm
  - N=110
  - Basiliximab induction/low-dose tacrolimus/MMF/prednisolone

- **Treatment failure** N=1
  - Did not receive allocated treatment

- **Received allocated intervention** N=113 (ITT)

- **Premature termination** N=5
  - 1 Death
  - 2 Graft loss
  - 2 Consent withdrawal

- **Completed study (2 years)** N=108

- **Protocol deviation** N=41
  - 39 Addition of oral steroids
  - 1 More than 3 doses MP
  - 1 Addition of everolimus

- **Completed study (2 years) with allocated treatment** N=67 (PP)

- **Completed study (2 years) with allocated treatment** N=97 (PP)

- **Treatment failure** N=1
  - Did not receive a transplant

- **Received allocated intervention** N=109 (ITT)

- **Premature termination** N=9
  - 2 Death
  - 1 Graft loss and death
  - 1 Graft loss
  - 5 Consent withdrawal

- **Completed study (2 years)** N=100

- **Protocol deviation** N=3
  - 3 Addition of everolimus

Figure 1.
Steroid avoidance
Steroid maintenance
Steroid avoidance
Steroid maintenance

CTCMR-2
CTCMR-1B
CTCMR-1A
aABMR+cTCMR
aAMR+aTCMR
aABMR
aTCMR-2B
aTCMR-2A
aTCMR-1B
aTCMR-1A

FIGURE 3a.
Steroid avoidance

Chronic TCMR
3.5% vs. 5.5%
P=0.53

Active ABMR
0% vs. 4.6%
P=0.03

Acute TCMR
11.5% vs. 3.7%
P=0.04

Steroid maintenance

Clinical rejection

CTCMR-2

CTCMR-1B

CTCMR-1A

aABMR+cTCMR

aAMR+aTCMR

aABMR

aTCMR-2B

aTCMR-2A

aTCMR-1B

aTCMR-1A

FIGURE 3b.
FIGURE 4.

Time to composite endpoint (months)
# A Randomized Controlled Trial on Safety of Steroid Avoidance in Immunologically Low-Risk Kidney Transplant Recipients

## Methods and cohort

**SAILOR Study**  
2-year multicenter open-label trial  
Immunologically low-risk non-diabetic kidney recipients  
N = 222  

**Steroid Avoidance (SA)**  
N = 113  

**Steroid Maintenance (SM)**  
N = 109  

## Results

<table>
<thead>
<tr>
<th>Follow up</th>
<th>Outcomes</th>
<th>SA*</th>
<th>SM*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>Incidence of PTDM*</td>
<td>12.4%</td>
<td>18.3%</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Biopsy-proven rejection</td>
<td>15.0%</td>
<td>13.8%</td>
<td>0.8</td>
</tr>
<tr>
<td>2 year</td>
<td>Composite outcome*</td>
<td>81%</td>
<td>85%</td>
<td>0.4</td>
</tr>
</tbody>
</table>
|           | Kidney Function  
Mean mgFR mL/min/1.73m² | 53.0 | 54.5 | 0.5 |
|           | Subjects with adverse events | 101 | 97 | 1.0 |

*SA, tacrolimus/MMF/antithymocyte globulin induction; SM, tacrolimus/MMF/prednisolone/basiliximab induction;  
PTDM, Posttransplant diabetes mellitus.  
*Freedom from acute rejection, graft loss, and death.  

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

*Shared first authorship