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Steroid Use in ABO-Incompatible Kidney Transplants: Withdrawal vs Maintenance

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Background: The incidence of ABO-incompatible (ABO-i) kidney transplantation (KT) is increasing. Furthermore, it has a higher early mortality rate than ABO-compatible (ABO-c) KT, which is largely attributed to the extensive use of immunosuppressive agents. While steroid use in patients with ABO-c KT is being reduced, this effort is less prevalent in patients with ABO-i KT. Therefore, our study investigated the specific impact of steroid withdrawal on graft survival in patients with ABO-i KT.

Material/Methods: This study evaluated 33 patients who underwent ABO-i KT. The primary outcome was biopsy-proven acute rejection. The secondary outcomes were graft function, infection, new-onset diabetes mellitus after transplantation (NODAT), and delayed graft function.

Results: In an average follow-up period of 57.0±23.7 months, the cumulative probabilities of biopsy-proven rejection at 3 years post-transplantation were 30.8% in the steroid maintenance group and 40.0% in the steroid withdrawal group, with no significant difference (hazard ratio, 1.11; 95% confidence interval 0.32-3.9; *P*=0.648). Graft function was similar between the 2 groups. Steroid withdrawal did not affect the rates of infection, NODAT, osteoporosis, cardiovascular disease, BK virus viremia, or cytomegalovirus viremia.

Conclusions: Steroid withdrawal did not differ from steroid maintenance in the rate of rejection or graft function due to any cause.

Keywords: **Graft Rejection • Graft Survival • Kidney Transplantation**

Abbreviations: **BKVN** – BK virus nephropathy; **BMI** – body mass index; **CIT** – cold ischemic time; **CMV** – cytomegalovirus; **CVD** – cardiovascular disease; **DC** – discharge; **DM** – diabetes mellitus; **ESKD** – end-stage kidney disease; **HLA** – human leukocyte antigens; **HTN** – hypertension; **KT** – kidney transplant; **MMF** – mycophenolate mofetil; **NODAT** – new-onset diabetes after transplantation; **PCKD** – polycystic kidney disease; **TAC** – tacrolimus

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Introduction

Kidney transplantation is a crucial treatment offering survival opportunities for patients with end-stage kidney disease [1-3]. However, the organ donor shortage has compelled the exploration of various methods to increase transplantation rates. ABO-incompatible kidney transplantation (ABO-i KT) has been increasingly used as an alternative in various countries and transplant centers where ABO-compatible kidney transplantation (ABO-c KT) is not possible [4,5].

Recent systematic reviews and meta-analyses have highlighted higher early mortality rates in ABO-i KT, which are largely attributed to intensive immunosuppressive therapies [6]. In transplant patients on long-term steroid use, the well-known adverse effects include cardiovascular disease (CVD) and infections [7-9]. Steroid use can also exacerbate pre-existing diabetes preoperatively and increase the incidence of new-onset diabetes after transplantation (NODAT) [10]. Recent studies on patients with ABO-c KT that explored various strategies for reducing steroid use have reported that steroid withdrawal does not adversely affect graft function [11-13].

Although steroid withdrawal has been successfully implemented in patients undergoing ABO-c KT [11-13], evidence regarding its safety and efficacy in ABO-i KT remains limited. A few studies have reported favorable outcomes following steroid withdrawal in ABO-i KT [14-17], but these were mostly constrained by small sample sizes and delayed timing of withdrawal. Thus, the impact of steroid withdrawal on graft outcomes in ABO-i KT patients is still unclear. Given this clinical uncertainty, we aimed to investigate the effects of steroid withdrawal on graft survival in patients receiving ABO-i KT.

Material and Methods

Ethics Approval

This study adhered to the principles of the Declaration of Helsinki and the Declaration of Istanbul. The study protocol was approved by Yonsei University Wonju College of Medicine (CR320194), which waived the requirement of informed consent because of the retrospective nature of the study.

Study Population

This retrospective observational study included 33 patients who underwent ABO-i KT at Wonju Severance Christian Hospital from January 2014 to December 2021.

ABO-i Protocols

At our institution, we implement a preconditioning protocol for patients undergoing ABO-i KT, which includes rituximab to deplete B cells, and perform procedures, such as plasmapheresis or intravenous immunoglobulin, to remove ABO antibodies from the plasma. For induction therapy, we use interleukin (IL)-2 receptor blockade or anti-thymocyte globulin [18,19]. Furthermore, all patients receive sulfamethoxazole/trimethoprim for prophylaxis. CMV prophylaxis is administered only to high-risk patients, specifically those with donor-positive/recipient-negative (D+/R-) serostatus, in accordance with our institutional ABO-i KT protocols. This approach reflects established evidence that targeted CMV prophylaxis in patients with high-risk serostatus combinations improves graft outcomes, as demonstrated in large-scale studies [20].

Subgroup Analyses

The interval between transplantation and steroid withdrawal significantly affects outcomes; thus, additional subgroups were defined as follows: 1) rapid steroid withdrawal: Steroid withdrawal within 1 month after transplantation; and 2) delayed steroid withdrawal: Steroid withdrawal at any time from 1 month after transplantation.

Data Collection

Data on the demographics of the recipients and donors were retrieved from the hospital database. We separately collected donor characteristics, such as age, sex, body mass index (BMI), history of hypertension and diabetes mellitus, and serum creatinine level at the time of donation. The cold ischemic time for all donors was also recorded.

According to the data collection intervals of the hospital, data on serum creatinine, immunosuppressant regimens, steroid use, and mycophenolate mofetil (MMF) were collected at discharge and at 6 months, 12 months, and annually thereafter. Tacrolimus (TAC) trough levels were also collected at discharge and at 6 months, 12 months, and annually thereafter. Graft function was evaluated using the estimated glomerular filtration rate (eGFR), which was calculated using the Modification of Diet in Renal Disease equation [21].

Outcomes

The primary outcome was biopsy-proven rejection. The secondary outcomes were graft function, infection, new-onset diabetes mellitus after transplantation (NODAT), osteoporosis, and CVD. Infection was defined as confirmation of pathogens during admission.

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Statistical Analysis

For the comparison of numerical variables, the *t* test or Mann-Whitney U test was used. Results are expressed as mean±standard deviation or median, based on the normality of distribution. The chi-square test was used for categorical variables. Kaplan-Meier analysis was performed to compare the cumulative probability of post-transplant events, and statistical significance was confirmed using the log-rank test. All analyses were performed using standard software (IBM SPSS version 25.0; IBM Corp., Armonk, NY, USA). *P* values <0.05 were considered significant.

Results

Baseline Characteristics

In total, 33 patients were included in the study. Their baseline characteristics are presented in **Table 1**. Thirteen patients were included in the steroid maintenance group, and 20 patients were in the steroid withdrawal group. The mean age of patients in the steroid maintenance group was 46.9±15.8 years, while that in the steroid withdrawal group was 49.9±10.0 years, with no significant difference between the groups (*P*=0.519). No significant differences were observed between the groups in sex, BMI, and cause of end-stage kidney disease. Furthermore, no significant differences were found in dialysis duration and presence of diabetes mellitus or CVD between the groups. Comparison of the donors revealed no significant differences in donor type, age, sex, BMI, and pre-transplant donor creatinine levels between the 2 groups. The cold ischemic time was 72.1±18.4 minutes in the steroid maintenance group and 76.4±19.0 minutes in the steroid withdrawal group, with no significant difference (*P*=0.522). The human leukocyte antigen mismatch was 4.0±1.2 in the steroid maintenance group and 3.9±1.2 in the steroid withdrawal group, with no significant difference. Furthermore, no differences were found in the induction agents used or in the prescription of valganciclovir at discharge between the 2 groups.

The baseline characteristics of the steroid maintenance group and steroid withdrawal group for the subgroup analysis are presented in **Table 2**. The steroid maintenance group had more prescriptions of valganciclovir at discharge than in the rapid steroid withdrawal group (*P*=0.012). No significant differences in other baseline characteristics were found between the 2 groups. The baseline characteristics of the 2 groups are provided in **Table 3**. A significant difference in induction agents was found between the 2 groups. In the delayed steroid withdrawal group, anti-thymocyte globulin was administered in 11 patients (78.6%), whereas in the rapid steroid withdrawal group, IL-2 receptor antibody was administered in 6 patients (100.0%; *P*=0.001). At discharge, valganciclovir was prescribed to 7 patients (50.0%) in the delayed steroid withdrawal group and to none in the rapid steroid withdrawal group (*P*=0.032). No significant differences in other baseline characteristics were found between the 2 groups.

Maintenance Immunosuppression

The use of maintenance immunosuppressants was compared between the steroid maintenance and withdrawal groups (**Figure 1**). Most patients were on TAC and MMF at discharge, with no significant differences between the groups (*P*=0.413). At 6 months, the frequency of TAC and MMF use decreased in the steroid maintenance group, but the difference between the groups remained statistically insignificant (*P*=0.149). This trend was consistent at 12, 24, and 36 months (**Figure 2A**). In the steroid withdrawal group, 14 patients (70%) were prescribed steroids at discharge. This decreased to 12 patients (60%) at 6 months, 9 patients (45%) at 12 months, 6 patients (31.6%) at 24 months, and 5 patients (26.3%) at 36 months (**Figure 2B**). In the steroid withdrawal group, the average time to steroid cessation was 11±12.6 months. Six patients restarted steroids after cessation. The average duration of steroid discontinuation was 13.2±12.4 months. Steroids were restarted due to rejection in 1 case, proteinuria in 1 case, elevated creatinine in 2 cases, fatigue in 1 case, and rheumatologic disease in 1 case. The TAC trough levels at discharge were 6.0±2.0 ng/mL in the steroid maintenance group and 7.2±4.4 ng/mL in the steroid withdrawal group, with no significant difference (*P*=0.353). This absence of a significant difference persisted at 6, 12, 24, and 36 months (**Figure 2C**). The MMF dose at discharge in the steroid maintenance group was 1192±389 mg, while it was 1047±264 mg in the steroid withdrawal group, with no significant difference (*P*=0.219). No significant differences in MMF dose were observed between the groups at 6, 12, and 24, months. At 36 months, the MMF dose was 1157±545 mg in the steroid maintenance group, while it was 817±203 mg in the steroid withdrawal group, which differed significantly (*P*=0.034; **Figure 2D**).

We also performed a subgroup analysis comparing the maintenance immunosuppressants between the steroid maintenance group and rapid steroid withdrawal group. During the follow-up period, a significant difference in TAC trough levels was found between the 2 groups. The TAC trough level at discharge in the steroid maintenance group was 6.0±2.0 ng/mL, while in the steroid withdrawal group it was 12.1±3.6 ng/mL (*P*=0.000193). No differences were observed during the other timepoints. Furthermore, we compared the use of maintenance immunosuppressants between the delayed and rapid steroid withdrawal groups. A significant difference in TAC trough level was observed between the 2 groups. At discharge, the delayed steroid withdrawal group had a TAC trough level of

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Table 1. Baseline characteristics.

Variable	Steroid maintenance (n=13)	Steroid withdrawal (n=20)	*P* value
Age (years)	46.9±15.8	49.9±10.0	0.519
Sex, male	9 (69.2)	9 (45.0)	0.172
BMI (kg/m^2)	24.8±5.1	23.5±2.8	0.363
Year of KT			0.900
2014-2017	3 (23.1)	5 (25.0)	
2018-2021	10 (76.9)	15 (75.0)	
Re-transplantation	0 (0.0)	1 (5.0)	0.413
Cause of ESKD			0.867
DM	5 (38.5)	8 (40.0)	
Hypertension	1 (7.7)	3 (15.0)	
Glomerular disease	5 (38.5)	5 (25.0)	
PCKD	1 (7.7)	1 (5.0)	
Unknown	1 (7.7)	3 (15.0)	
Dialysis duration (months)	7.7±12.3	15.8±27.6	0.333
DM	5 (38.5)	10 (50.0)	0.515
CVD	0 (0.0)	1 (5.0)	0.413
Donor type			0.297
Parent	3 (23.1)	3 (15.0)	
Offspring	3 (23.1)	5 (25.0)	
Sibling	0 (0.0)	2 (10.0)	
Spouse	5 (38.5)	10 (50.0)	
Other unrelated	2 (15.4)	0 (0.0)	
Donor age (years)	48.6±13.2	47.7±14.4	0.855
Donor sex, male	9 (69.2)	11 (55.0)	0.414
Donor BMI (kg/m^2)	26.7±4.4	25.6±2.9	0.364
Donor creatinine at donation (mg/dL)	0.98±0.30	0.86±0.15	0.116
Donor HTN	2 (15.4)	7 (35.0)	0.216
Donor DM	1 (7.7)	1 (5.0)	0.751
CIT (min)	72.1±18.4	76.4±19.0	0.522
HLA mismatch	4.0±1.2	3.9±1.2	0.753
Induction agent			0.353
IL-2 receptor antibody	8 (61.5)	9 (45.0)	
Anti-thymocyte globulin	5 (38.5)	11 (55.0)	
Prescription of valganciclovir at discharge	8 (61.5)	7 (35.0)	0.169

Data are expressed as mean±standard deviation or number (%). BMI – body mass index; CIT – cold ischemic time; CVD – cardiovascular disease; DM – diabetes mellitus; ESKD – end-stage kidney disease; HLA – human leukocyte antigens; HTN – hypertension; KT – kidney transplant; PCKD – polycystic kidney disease.

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Table 2. Baseline characteristics.

Variable	Steroid maintain (n=13)	Rapid steroid withdrawal (n=6)	*P* value
Age (years)	46.9±15.8	48.2±13.5	0.870
Sex, male	9 (69.2)	2 (33.3)	0.141
BMI (kg/m^2)	24.8±5.1	22.1±3.5	0.263
Year of KT			0.200
2014-2017	3 (23.1)	0 (0.0)	
2018-2021	10 (76.9)	6 (100)	
Re-transplantation	0 (0.0)	0 (0.0)	
Cause of ESKD			0.811
DM	5 (38.5)	2 (33.3)	
Hypertension	1 (7.7)	1 (16.7)	
Glomerular disease	5 (38.5)	1 (16.7)	
PCKD	1 (7.7)	1 (16.7)	
Unknown	1 (7.7)	1 (16.7)	
Dialysis duration (months)	7.7±12.3	30.8±46.7	0.106
DM	5 (38.5)	2 (33.3)	0.829
CVD	0 (0.0)	0 (0.0)	
Donor type			0.499
Parent	3 (23.1)	2 (33.3)	
Offspring	3 (23.1)	1 (16.7)	
Sibling	0 (0.0)	1 (16.7)	
Spouse	5 (38.5)	2 (28.6)	
Other unrelated	2 (15.4)	0 (0.0)	
Donor age (years)	48.6±13.2	53.5±12.9	0.460
Donor sex, male	9 (69.2)	5 (83.3)	0.516
Donor BMI (kg/m^2)	26.7±4.4	26.2±3.0	0.788
Donor creatinine at donation (mg/dL)	0.98±0.30	0.90±0.21	0.555
Donor HTN	2 (15.4)	2 (33.3)	0.372
Donor DM	1 (7.7)	1 (16.7)	0.554
CIT (min)	72.1±18.4	73.3±15.4	0.886
HLA mismatch	4.0±1.2	3.3±0.8	0.244
Induction agent			0.077
IL-2 receptor antibody	8 (61.5)	6 (100)	
Anti-thymocyte globulin	5 (38.5)	0 (0.0)	
Prescription of valganciclovir at discharge	8 (61.5)	0 (0.0)	0.012

Data are expressed as mean±standard deviation or number (%). BMI – body mass index; CIT – cold ischemic time; CVD – cardiovascular disease; DM – diabetes mellitus; ESKD – end-stage kidney disease; HLA – human leukocyte antigens; HTN – hypertension – KT – kidney transplant; PCKD – polycystic kidney disease.

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Table 3. Baseline characteristics.

Variable	Delayed steroid withdrawal (n=14)	Rapid steroid withdrawal (n=6)	*P* value
Age (years)	50.6±8.6	48.2±13.5	0.636
Sex, male	7 (50.0)	2 (33.3)	0.492
BMI (kg/m^2)	24.1±2.4	22.1±3.5	0.154
Year of KT			0.091
2014-2017	5 (35.7)	0 (0.0)	
2018-2021	9 (64.3)	6 (100)	
Re-transplantation	1 (7.1)	0 (0.0)	0.502
Cause of ESKD			0.609
DM	6 (42.9)	2 (33.3)	
Hypertension	2 (14.3)	1 (16.7)	
Glomerular disease	4 (28.6)	1 (16.7)	
PCKD	0 (0.0)	1 (16.7)	
Unknown	2 (14.3)	1 (16.7)	
Dialysis duration (months)	9.6±11.3	30.8±46.7	0.113
DM	8 (57.1)	2 (33.3)	0.329
CVD	1 (7.1)	0 (0.0)	0.502
Donor type			0.389
Parent	1 (7.1)	2 (33.3)	
Offspring	4 (28.6)	1 (16.7)	
Sibling	1 (7.1)	1 (16.7)	
Spouse	8 (57.1)	2 (28.6)	
Other unrelated	0 (0.0)	0 (0.0)	
Donor age (years)	45.2±14.7	53.5±12.9	0.249
Donor sex, male	6 (42.9)	5 (83.3)	0.095
Donor BMI (kg/m^2)	25.3±3.0	26.2±3.0	0.546
Donor creatinine at donation (mg/dL)	0.84±0.12	0.90±0.21	0.405
Donor HTN	5 (35.7)	2 (33.3)	0.919
Donor DM	0 (0.0)	1 (16.7)	0.117
CIT (min)	77.7±20.7	73.3±15.4	0.649
HLA mismatch	4.1±1.5	3.3±0.8	0.287
Induction agent			0.001
IL-2 receptor antibody	3 (21.4)	6 (100)	
Anti-thymocyte globulin	11 (78.6)	0 (0.0)	
Prescription of valganciclovir at discharge	7 (50.0)	0 (0.0)	0.032

Data are expressed as mean±standard deviation or number (%). BMI – body mass index; CIT – cold ischemic time; CVD – cardiovascular disease; DM – diabetes mellitus; ESKD – end-stage kidney disease; HLA – human leukocyte antigens; HTN – hypertension; KT – kidney transplant; PCKD – polycystic kidney disease.

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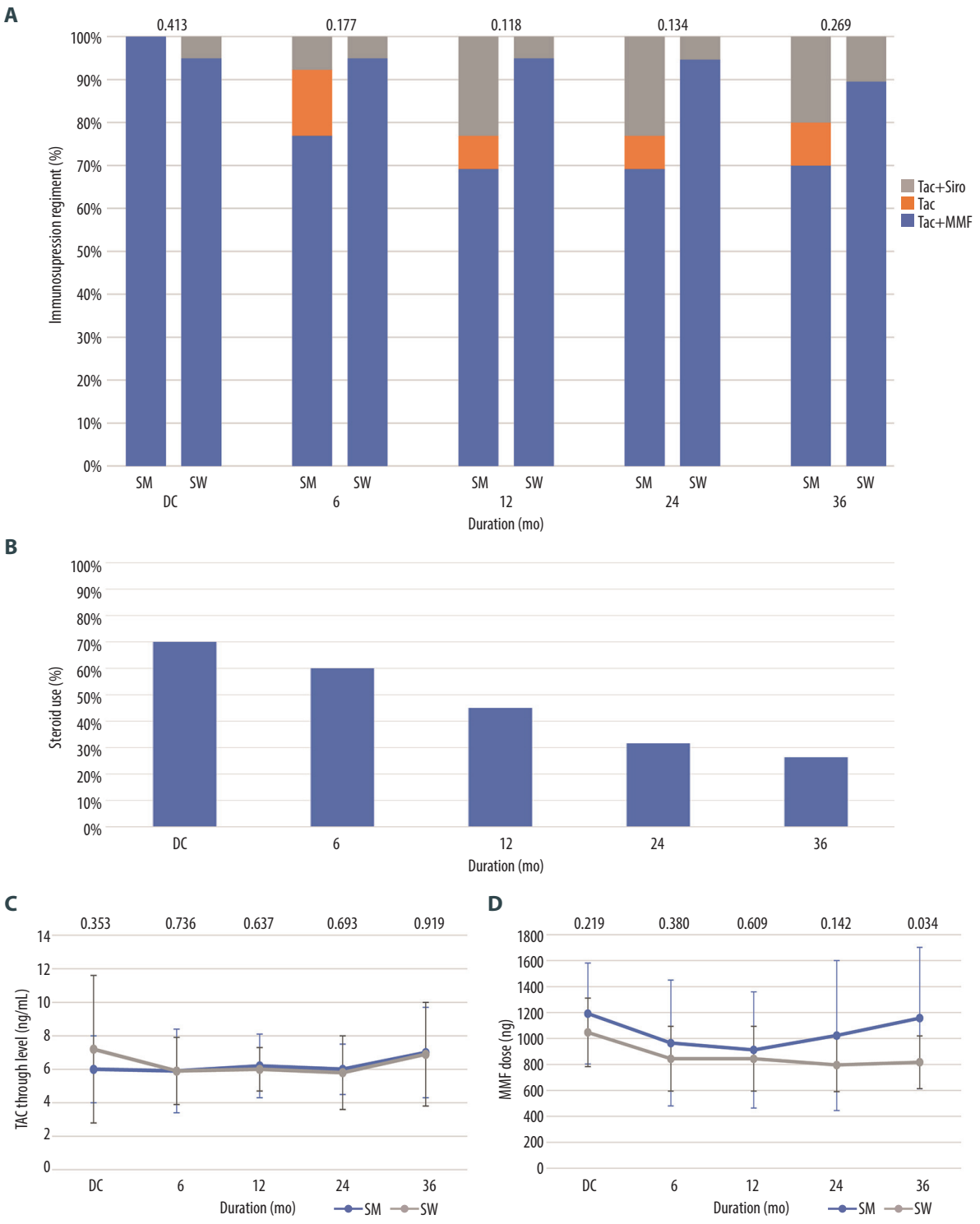

Figure 1. Comparison of maintenance immunosuppression regimen between the steroid maintenance and steroid withdrawal groups. (**A**) Immunosuppression regimens; (**B**) Steroid use in steroid withdrawal group; (**C**) TAC dose, and (**D**) MMF dose. * The numerical value in italics represents the *P* value. DC – discharge; MMF – mycophenolate mofetil; Siro – sirolimus; SM – steroid maintenance; SW – steroid withdrawal; TAC – tacrolimus. *Created using Microsoft Excel 2019 (version 16.0.10416.20073; Microsoft Corp., Redmond, WA, USA).*

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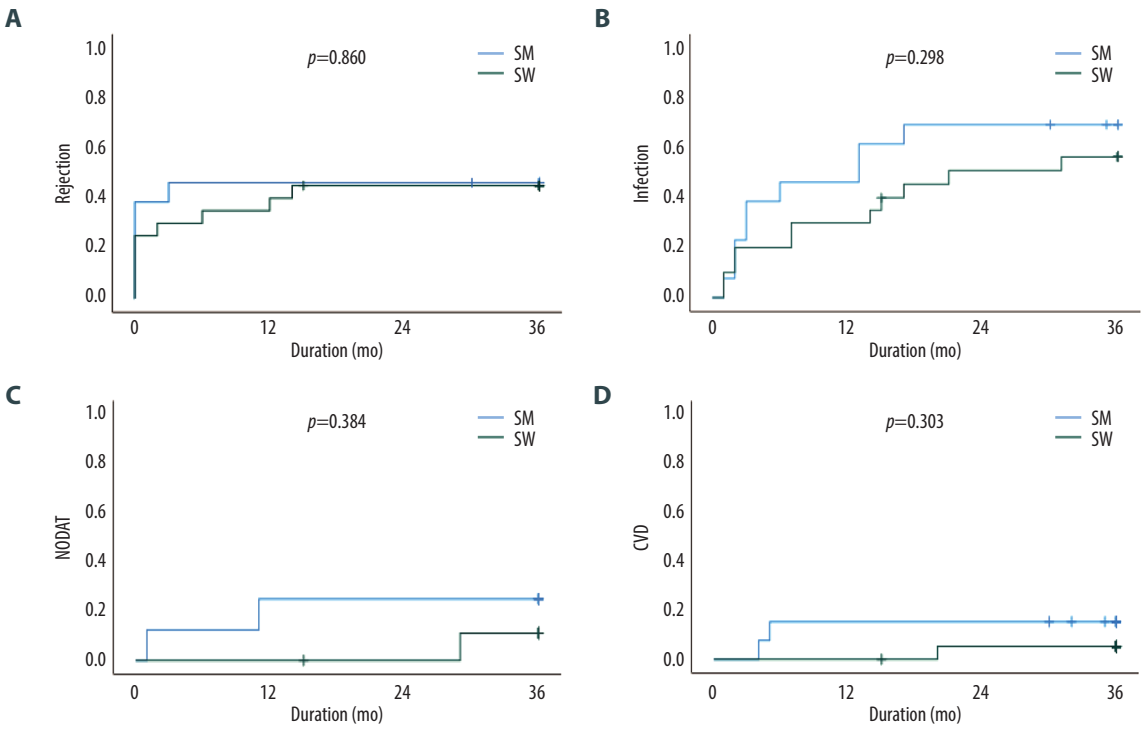

Figure 2. Comparison of post-transplant events between steroid maintenance and withdrawal groups. (**A**) Rejection; (**B**) Infection; (**C**) NODAT; (**D**) CVD. * The numerical value in italics represents the *P* value. CVD – cardiovascular disease; NODAT – new-onset diabetes after transplantation. *Created using IBM SPSS (version 25.0; IBM Corp., Armonk, NY, USA).*

Table 4. Infectious complications within 1 year after kidney transplant.

Variable	Steroid maintenance (n=13)	Steroid withdrawal (n=20)	*P* value
Urinary tract infection	2 (15.4)	3 (15.0)	0.976
Gastrointestinal infection	2 (15.4)	0 (0.0)	0.070
Bacteremia	1 (7.7)	0 (0.0)	0.208
Viral infection	1 (7.7)	2 (10.0)	0.822
Soft-tissue infection	0 (0.0)	1 (5.0)	0.413

Data are expressed as mean±standard deviation or number (%).

5.2±2.9 ng/mL, while the rapid steroid withdrawal group had 12.1±3.6 ng/mL (*P*=0.000236). No differences were observed for the other periods.

Outcomes

The mean follow-up period was 57.0±23.7 months. Four patients (12.1%) were lost to follow-up due to transfer to other hospitals. No deaths or death-censored graft failures occurred during the follow-up period. The cumulative probability of rejection was 23.1% at 1 year and 30.8% at 3 years of follow-up in the steroid maintenance group compared with 30.0% at 1 year and 40.0% at 3 years in the steroid withdrawal group (hazard ratio [HR] 1.113, 95% confidence interval [CI] 0.315-3.925; *P*=0.648; **Figure 2A**). The cumulative probability of infection was 46.2% at 1 year and 69.2% at 3 years of follow-up in the steroid maintenance group, compared with 30.0% at 1 year and 56.4% at 3 years of follow-up in the steroid withdrawal group (HR 0.547, 95% CI 0.214-1.398; *P*=0.298; **Figure 2B**). The cumulative probability of infection did not differ significantly between the 2 groups. No significant differences were observed in the rates of urinary tract infection, gastrointestinal infection, bacteremia, viral infection, and soft-tissue infection (**Table 4**). Among patients without pre-transplant

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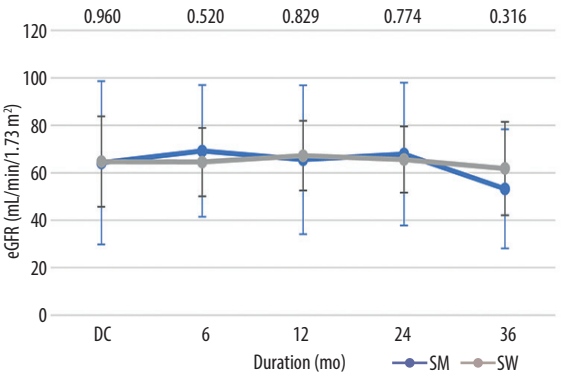

Figure 3. Comparison of post-transplant graft function between steroid maintenance and steroid withdrawal groups. * The numerical value in italics represents the *P* value. SM – steroid maintenance; SW – steroid withdrawal. *Created using Microsoft Excel 2019 (version 16.0.10416.20073; Microsoft Corp., Redmond, WA, USA).*

diabetes, the cumulative probability of NODAT was 25.0% at 1 year and 25.0% at 3 years of follow-up in the steroid maintenance group, compared with 0.0% at 1 year and 11.1% at 3 years of follow-up in the steroid withdrawal group (*P*=0.384; **Figure 2C**). The cumulative probability of CVD was 15.4% at 1 year and 15.4% at 3 years of follow-up in the steroid maintenance group, compared with 0.0% at 1 year and 5.3% at 3 years of follow-up in the steroid withdrawal group (*P*=0.303; **Figure 2D**). The cumulative probability of osteoporosis was 7.7% at 1 year and 15.4% at 3 years of follow-up in the steroid use group, compared with 0.0% at both 1 and 3 years of follow-up in the steroid withdrawal group (*P*=0.099). No cases of biopsy-confirmed BK virus (BKV) nephropathy were found during the study. The cumulative probability of BKV viremia was 7.7% at 1 year and 7.7% at 3 years of follow-up in the steroid maintenance group, compared with 5.0% at both 1 and 5.0 3 years of follow-up in the steroid withdrawal group (*P*=0.773) The cumulative probability of cytomegalovirus (CMV) viremia was 46.2% at 1 month and 69.2% at 3 years of follow-up in the steroid maintenance group, compared with 25.0% at 1 month and 40.0% at 3 years of follow-up in the steroid withdrawal group (*P*=0.105). Furthermore, at 4.2 months, 1 case of CMV infection was reported in the steroid maintenance group.

A subgroup analysis of the cumulative probabilities was conducted and compared the steroid maintenance and rapid steroid withdrawal groups. No significant differences were found in the cumulative probability of rejection, infection, NODAT, osteoporosis, CVD, and BKV viremia between the 2 groups. However, the cumulative probability of CMV viremia was 46.2% at 1 month and 69.2% at 3 years of follow-up in the steroid maintenance group, compared with 0.0% both at discharge and 3 years of follow-up in the steroid withdrawal group (*P*=0.029). The maintenance immunosuppressants administered in the delayed and rapid steroid withdrawal groups were compared. No differences were found in the cumulative probabilities of rejection, infection, NODAT, and CVD between the 2 groups. However, the cumulative probability of CMV viremia was 42.9% at 1 month and 57.1% at 3 years of follow-up in the delayed steroid withdrawal group, compared with 0.0% both at 1 month and 3 years of follow-up in the steroid withdrawal group (*P*=0.029). No osteoporosis events were observed in either group.

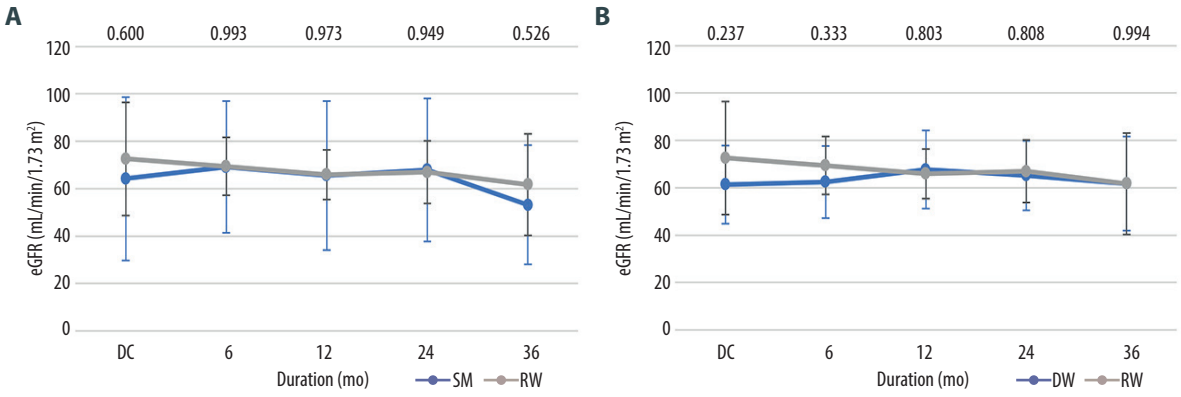

Figure 4. Comparison of post-transplant graft function between subgroups. (**A**) Comparison of post-transplant graft function between steroid maintenance and rapid steroid withdrawal groups. (**B**) Comparison of post-transplant graft function between delay and rapid steroid withdrawal groups. * The numerical value in italics represents the *P* value. DW – delay steroid withdrawal; SM – steroid maintenance; SW – steroid withdrawal. *Created using Microsoft Excel 2019 (version 16.0.10416.20073; Microsoft Corp., Redmond, WA, USA).*

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eGFR was compared between the steroid maintenance and withdrawal groups during the follow-up period. At 1 year, the eGFR was 65.5±31.4 in the steroid maintenance group and 67.2±14.7 in the steroid withdrawal group (P = 0.829). At 3 years, the eGFR was 53.2±25.1 in the steroid maintenance group and 61.8±19.7 in the steroid withdrawal group (P=0.316), with no significant difference between the 2 groups (**Figure 3**). A similar result was observed in the subgroup analysis (**Figure 4**). Steroid withdrawal did not affect the rates of rejection, infection, NODAT, osteoporosis, CVD, or BKV viremia. However, the incidence of CMV viremia was lower in the rapid steroid withdrawal group.

Discussion

Among patients who received ABO-i KT, we found no significant difference in rejection or graft function between those who underwent steroid withdrawal and those who maintained steroid therapy.

Steroid withdrawal has been attempted in patients undergoing ABO-c KT, with successful outcomes. For instance, a randomized controlled trial (RCT) conducted in the USA with 385 participants found no significant differences in mortality rate or death-censored graft function between the early steroid withdrawal group and the steroid maintenance group [13]. Another RCT in the USA categorized 337 kidney transplant recipients into steroid-free, steroid withdrawal, and standard steroid groups and found no differences in graft survival, renal function, mortality, or rejection rate among the groups [11]. Another study in the USA, which included 386 kidney transplant recipients, compared early steroid withdrawal and continued steroid use and found slightly higher rejection rates in the early withdrawal group. However, no significant differences were observed in graft survival, renal function, or mortality rates between the 2 groups [12]. These findings are consistent with the results obtained in our study on ABO-i KT, indicating that steroid withdrawal can be safely implemented in kidney transplantation.

In a study in Denmark involving 50 recipients of ABO-i KT, steroids were administered for the first 3 months after transplantation before considering withdrawal. It reported a 3-year survival rate of 93% and a 3-year graft survival rate of 91%, with a rejection rate of 19%. However, the study focused solely on patients who underwent steroid withdrawal [16]. A study in Japan involving 15 ABO-i KT recipients compared outcomes between steroid withdrawal and maintenance. The steroid withdrawal group discontinued steroids 14 days postoperatively and were followed for 22±26 months. The study found no differences in survival, graft survival, or infection rates between the steroid withdrawal and maintenance groups [17], which is similar to our findings. However, they did not investigate complications such as CVD, NODAT, or osteoporosis. Guidelines on the exact timelines for discontinuing steroids have not been established. Our study clarifies the impact of steroid withdrawal in ABO-i KT cases, highlighting the need for further research to define optimal timing and conditions for safely reducing steroid use in this patient population.

Interestingly, although steroid withdrawal is generally associated with an increased risk of T cell-mediated rejection (TCMR) due to reduced suppression of cellular immunity, no cases of TCMR were observed in our cohort. Instead, all biopsy-proven rejections were antibody-mediated rejection (ABMR). This may reflect the dominant role of humoral immunity in ABO-incompatible kidney transplantation, as well as the sustained efficacy of our immunosuppression protocols in suppressing cellular responses, even after steroid withdrawal.

The adverse effects of steroid use in patients undergoing kidney transplant, such as hyperlipidemia, hypertension, and diabetes, are major causes of mortality [22]. A study in the Netherlands involving 364 transplant recipients reported lower incidences of hypertension, hyperlipidemia, and diabetes in the steroid withdrawal group [23]. Similarly, a study in the USA showed that early steroid withdrawal reduced the incidence of hyperlipidemia, diabetes, and weight gain [12]. A meta-analysis also confirmed significantly lower rates of hypertension, hypercholesterolemia, and new-onset diabetes in the steroid withdrawal group [24]. These studies indicate that steroid withdrawal in patients undergoing kidney transplant can reduce the risk of cardiovascular complications. Although our study did not find statistically significant differences in CVD, likely due to a smaller sample size, our findings agree with the findings of these previous studies.

A study conducted in Italy demonstrated that steroid use in patients undergoing kidney transplant can adversely affect vertebral bone density [25]. Furthermore, a study in the Netherlands showed that steroid use in patients undergoing kidney transplant increased body fat and decreased bone mineral density in the lumbar spine [26]. In contrast, our study did not find significant evidence of osteoporosis occurrence, which may be further verified by conducting future studies that focus solely on the occurrence of osteoporosis itself as the outcome.

The second leading cause of mortality in kidney transplant recipients is infection [22]. Patients undergoing ABO-i KT tend to be administered more immunosuppressive medications compared with patients undergoing ABO-c. Excessive induction of immunosuppression can increase the risk of severe bacterial or viral infections [27,28]. However, a study conducted in the USA that categorized 337 transplant recipients into steroid-free, steroid withdrawal, and standard steroid groups,

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found no significant difference in infection rates among these groups [11]. Similarly, an early steroid withdrawal study in 386 transplant recipients found no significant difference in infection rates [12]. A study in the Netherlands with 364 transplant recipients, focusing on steroid withdrawal, similarly found no differences in infection rates between the steroid withdrawal group and other subgroups [23]. Our study also yielded similar findings. However, we found that the steroid withdrawal group had a more significant reduction in CMV viremia than the steroid maintenance group.

This study adds to the limited evidence on steroid withdrawal in patients undergoing ABO-i KT, particularly in high immunologic risk settings. We observed no significant differences in graft function or rejection rates between the steroid maintenance and withdrawal groups, suggesting that steroid withdrawal can be safely used in selected ABO-i KT recipients.

The mean follow-up duration of 57.0±23.7 months was sufficient to assess rejection events, but was limited in evaluating long-term complications and mortality. This study is limited by its single-center, retrospective design and small sample size (n=33). In addition, all included patients received kidneys from living donors, which limits the generalizability of our findings to deceased donor kidney transplantation. Deceased donor KT is typically associated with longer cold ischemia times, a higher incidence of delayed graft function, and greater baseline immune activation, which can influence responses to immunosuppressive strategies.

Future prospective, multicenter studies involving larger and more diverse transplant populations are warranted to confirm the safety and efficacy of steroid withdrawal in ABO-incompatible and other high-risk transplant settings.

Conclusions

This study demonstrated that steroid withdrawal is safe in ABO-incompatible kidney transplantation, as it does not affect rejection rates or graft function compared with steroid maintenance.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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