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Original Article

Safety and efficacy of early corticosteroid withdrawal in liver transplant recipients: A randomized controlled trial

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Backgrounds/Aims: Prolonged use of steroids after liver transplantation (LT) significantly increases the risk of diabetes or cardiovascular disease, which can adversely affect patient outcomes. Our study evaluated the effectiveness and safety of early steroid withdrawal within the first year following LT.
Methods: This study was conducted as an open-label, multicenter, randomized controlled trial. Liver transplant recipients were randomly assigned to one of the following two groups: Group 1, in which steroids were withdrawn two weeks posttransplantation, and Group 2, in which steroids were withdrawn three months posttransplantation. This study included participants aged 20 to 70 years who were scheduled to undergo a single-organ liver transplant from a living or deceased donor at one of the four participating centers.
Results: Between November 2012 and August 2020, 115 patients were selected and randomized into two groups, with 60 in Group 1 and 55 in Group 2. The incidence of new-onset diabetes after transplantation (NODAT) was notably higher in Group 1 (32.4%) than in Group 2 (10.0%) in the per-protocol set. Although biopsy-proven acute rejection, graft failure, and mortality did not occur, the median tacrolimus trough level/dose/weight in Group 1 exceeded that in Group 2. No significant differences in safety parameters, such as infection and recurrence of hepatocellular carcinoma, were observed between the two groups.
Conclusions: The present study did not find a significant reduction in the incidence of NODAT in the early steroid withdrawal group. Our study suggests that steroid withdrawal three months posttransplantation is a standard and safe immunosuppressive strategy for LT patients.

Key Words: Tacrolimus; Treatment outcome; Immunosuppression; Diabetes mellitus; Safety

INTRODUCTION

Steroids have played a pivotal role in the immunosuppressive protocols after solid organ transplantation since its inception [1,2]. They are routinely administered as high-dose boluses during and following transplant procedures to manage acute cellular rejection. However, extended usage can lead to serious side effects, including hypertension, hyperlipidemia, obesity, diabetes mellitus, osteoporosis, and increased susceptibility to infections [2,3]. Despite these challenges, most liver transplantation (LT) centers maintain the practice of gradual steroid withdrawal over a period of 3 to 6 months posttransplantation.

New-onset diabetes after transplantation (NODAT) is currently the most common metabolic complication following LT, with reported incidence rates ranging from 9% to 63.3% [4-6]. NODAT is characterized by a sustained elevated blood glucose level posttransplantation in individuals who were not diabetic before the procedure and who postoperatively met the diagnos-

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tic criteria for diabetes, as defined by the World Health Organization. The development of NODAT is closely linked to several factors, including recipient age, hepatitis C virus infection, advanced liver cirrhosis, deceased donor grafts, use of tacrolimus (TAC), alcoholic liver disease, steroid administration, high body mass index, hypomagnesemia, biopsy-proven acute rejection (BPAR), infections, chronic cardiovascular diseases, and renal dysfunction. These factors are major contributory factors to mortality rates among LT recipients [4,5,7-15]. Furthermore, patients who develop NODAT experience higher rates of acute rejection, increased susceptibility to infections, reduced long-term survival, and heightened healthcare costs [5,7,16].

The duration of steroid usage within TAC-based immunosuppressive regimens for LT patients remains a contentious topic, prompting the initiation of a randomized, multicenter study. This study aimed to determine which of the two options, defined by the duration of steroid usage, is more effective in facilitating early steroid withdrawal within the combination of TAC and mycophenolate mofetil (MMF) immunosuppressive therapy during the first year post-LT.

MATERIALS AND METHODS

Study design and participants

This prospective, open-label, investigator-initiated, intention-to-treat randomized controlled trial was conducted across four centers in Korea from November 2012 to August 2020. This study included patients who received at least one dose of a study drug or underwent LT. The study population consisted of the following two groups: the safety population and the intention-to-treat population. Additionally, a more stringent per-protocol set (PPS) population was established that included patients who adhered strictly to the study protocol throughout the entire research duration and completed the final follow-up after 12 months. Enrollment was limited to participants aged between 20 and 70 years slated to undergo their first LT from a living or deceased donor.

Eligible patients willingly volunteered and met specific criteria, such as white blood cell (WBC) count ≥ 3,000/μL and women testing negative for urine human chorionic gonadotropin while practicing contraception, during the clinical trial. Exclusion criteria were pretransplantation diabetes, prior multi-organ transplants, liver donation after cardiac death, ABO-incompatible living donor liver transplants, use of any other investigational drug within four weeks prior to screening, ongoing or recent corticosteroid therapy, intolerance to study medications, cold ischemia time exceeding 12 hours, hemoglobin level < 6.5 g/dL, WBC count < 1,500/μL, and platelet count < 30,000/μL at the time of screening. Other exclusion criteria included a history of malignancy, other than hepatocellular carcinoma (HCC) or skin cancer, liver graft with positive hepatitis B surface antigen, positive human immunodeficiency virus status in either the donor or recipient, previous use of a liver support system, symptoms of somatic or psychiatric illnesses that hindered comprehension and participation in the trial, inability to communicate effectively, inability to follow study guidelines or provide informed consent, unstable concurrent medical conditions, significant gastrointestinal complications, such as severe diarrhea or peptic ulcer disease at the time of screening, bowel diseases causing malabsorption, clinically significant infections, women of childbearing potential who refused to use effective contraception throughout the study, pregnant or lactating women, and individuals who could not communicate due to psychological issues.

The study was conducted with strict adherence to the Declaration of Helsinki and Good Clinical Practice guidelines. Institutional review boards at all participating institutions approved this study (SMC-2012-11-071, SNUH-H-1312-098-544, AJIRB-MED-CT4-14-010, and CR-14-060-L). The trial was registered with ClinicalTrials.gov under the identifier NCT02095418. All patients provided written informed consent and retained the option to withdraw from the study at any point.

Randomization

The participants were centrally randomized into two groups using a 1:1 allocation ratio. The randomization list was generated using SAS software (version 8.1; SAS Institute) and stratified according to the individual centers involved in the study. Each participating center was provided consecutively numbered sealed envelopes. After obtaining informed consent from the participants, the trial coordinator opened the envelopes on the day of the LT procedure.

Study intervention

Basiliximab was administered at a dose of 20 mg intravenously within 12 hours after reperfusion and on postoperative day 4, adhering to the protocols of each participating institution. All study participants were prescribed a triple immunosuppressant regimen comprising TAC, steroids, and/or MMF as part of their maintenance therapy. Additionally, a single intraoperative corticosteroid dose of 500 mg methylprednisolone (MPD) was administered to both groups.

Group 1 underwent steroid treatments for 14 ± 3 days after LT, while Group 2 received steroids for 3 months ± 2 weeks after LT. In Group 1, a tapering regimen of MPD was administered for 14 ± 3 days. Group 2 received a tapering dose of intravenous MPD for seven days, followed by oral MPD. Oral MPD was gradually tapered and discontinued within three months. For both groups, oral TAC was initiated at a dose of 0.5 mg twice daily within 24 hours after LT, with subsequent adjustments to achieve a target trough level of 5–12 ng/mL for a period of 12 months. The commencement of MMF was synchronized with TAC administration, contingent upon the total WBC count exceeding 3,000/μL. MMF usage was discontinued based on the investigator's judgment or patient intolerance. Additionally, all patients received antifungal agents and trimetho-

prim-sulfamethoxazole for Pneumocystis jirovecii prophylaxis for at least six months.

The treatment team retained the discretion to withhold or continue any immunosuppressant if it was deemed clinically necessary. Patients were excluded from the analysis if, in the opinion of the treatment team, steroid maintenance was deemed essential in the steroid-free group for reasons other than rejection. Any suspected rejection, as indicated by an unexplained elevation of transaminases, underwent confirmation through biopsy and was graded according to Banff criteria. Data pertaining to the occurrence of and time to the first BPAR episode, necessitating treatment within 12 months post-transplantation, were documented. Whenever feasible, anti-rejection therapy was postponed until a histological diagnosis of rejection was established.

Outcomes

The primary endpoint of this study was the incidence of NODAT up to one year following LT. NODAT was defined as the presence of symptoms indicative of diabetes, such as random plasma glucose level ≥ 200 mg/dL, two consecutive fasting plasma glucose measurements ≥ 126 mg/dL more than 30 days after LT, 2-hour plasma glucose level ≥ 200 mg/dL on an oral glucose tolerance test, or need for treatment with anti-diabetic medications or insulin [5].

Secondary endpoints included the incidence of BPAR, the time taken to experience the first BPAR episode, the rate of treatment failure, the occurrence of chronic kidney disease (CKD), graft failure, and/or patient mortality.

BPAR was categorized as mild, moderate, or severe by the pathologists in accordance with the Banff protocol, considering biopsies conducted from the day of transplantation (Visit 2) up to the finial visit (Visit 10). BPAR was specifically defined as a rejection activity index ≥ 4 points recorded at least once. Treatment failure was characterized by two cumulative instances of BPAR, additional use of immunosuppressants other than the study drug, discontinuation of immunosuppressant administration for > 14 days, discontinuation of cumulative immunosuppressant administration for > 30 days, graft loss, or patient mortality. Graft failure was determined if a patient required retransplantation. Chronic renal failure (CRF) was defined as an estimated glomerular filtration rate (eGFR) < 15 mL/min, and CKD was defined as an eGFR < 60 mL/min.

The study also conducted a comprehensive safety assessment involving clinical evaluations, monitoring vital signs, and conducting laboratory analyses to identify and record all adverse events (AEs), serious adverse events (SAEs), incidents of infection, malignancies, and instances of mortality during the study. Serial laboratory results and the proportion of patients exhibiting clinically significant abnormalities were documented and reported.

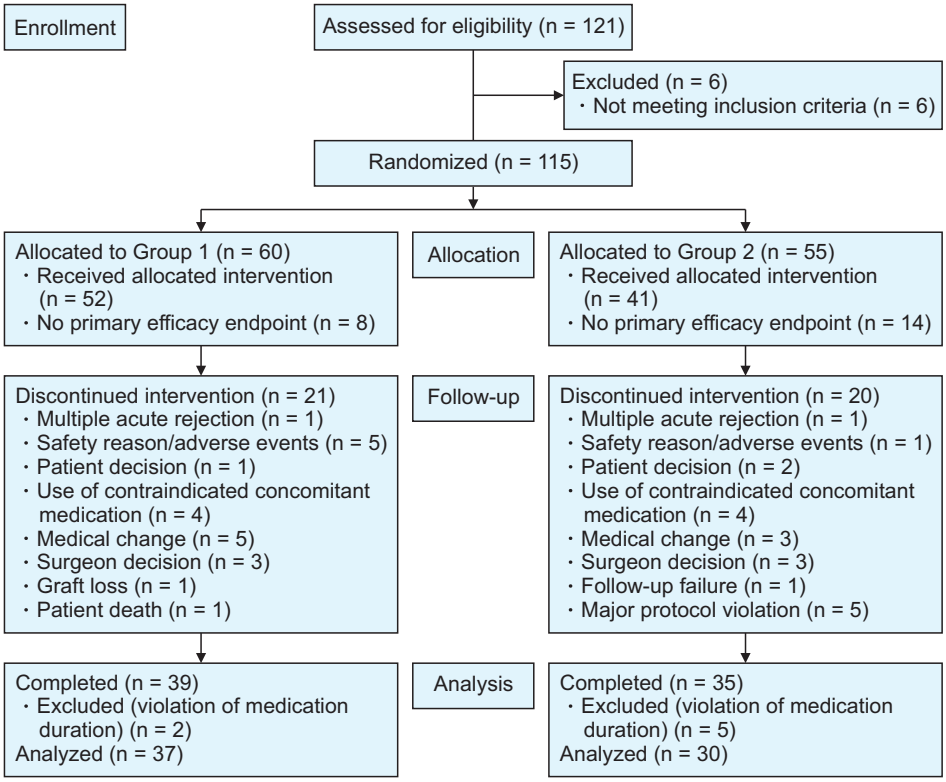

Fig. 1. Patient distribution and study population.

Assessment

Patients underwent a series of assessments at several time points throughout the study, including screening (pretransplant), baseline (day 0), and posttransplantation weeks 1, 2, 4, 8, 12, 24, 36, and 52, with the aim to analyze the study endpoints. During each of these scheduled visits, a comprehensive evaluation was conducted, which included a physical examination, laboratory values, hematologic parameters, trough level of TAC, and documentation of problems. Renal function was closely examined by assessing the serum creatinine level and calculating eGFR using the Modification of Diet in Renal Disease formula. These assessments provided valuable insights into the kidney function and helped monitor any potential kidney-related complications over the course of the study [17]. The data collected during the study were recorded, entered into an electronic database, and subjected to a rigorous evaluation process by external monitors. The monitors were responsible for overseeing the progress of the study and ensuring the accuracy and integrity of the data.

Statistical analysis

This trial was initiated as a prospective randomized controlled study involving 115 patients. Over 12 months, the incidence of NODAT was 18.8% in the control group and 10.2% in the study group [18]. The sample size for this study was determined based on the following parameters: a one-sided significance level (α) of 2.5%, a 95% confidence interval, 80% power, and a 10% dropout rate. The calculated minimum sample size required in each group to effectively assess the primary endpoint was 50 patients.

Statistical analyses were performed using SPSS software (version 22.0; SPSS Inc.). Data are presented as medians with ranges or as frequencies with percentages. For categorical variables, the chi-square test or Fisher's exact test was used, while continuous variables were analyzed using the Mann–Whitney U test. The differences in the cumulative incidence of NODAT between the two groups were assessed using the Kaplan–Meier survival method. A p-value less than 0.05 was considered statistically significant. Follow-up for data collection was con-

Table 1. Baseline characteristics

	Group 1 (n = 60)	Group 2 (n = 55)	p-value
Donor			
Age (yr)	28 (19–65)	29 (12–64)	0.859
Sex (male)	33 (55.0)	33 (60.0)	0.588
HBsAg (positive)	3 (5.0)	2 (3.6)	0.720
Anti-HCV (positive)	1 (1.7)	1 (1.8)	0.950
Recipient			
Age (yr)	54 (29–70)	54 (21–67)	0.797
BMI (kg/m^2)	24.1 (15.7–35.5)	23.7 (15.4–35.2)	0.834
Sex (male)	45 (75.0)	38 (69.1)	0.480
HBsAg (positive)	33 (55.0)	28 (50.9)	0.742
Anti-HCV (positive)	4 (6.7)	4 (7.3)	0.898
White blood cells (/uL)	7,000 (1,000–9,090)	6,300 (2,470–16,960)	0.529
Hemoglobin (g/dL)	9.4 (6.4–15.7)	10.0 (6.8–14.4)	0.484
Platelet (/uL)	85,500 (33,000–123,000)	91,000 (32,000–119,000)	0.795
Creatinine (mg/dL)	0.82 (0.50–2.19)	0.75 (0.31–4.49)	0.080
eGFR (mL/min/1.73 m^2)	98.0 (33.8–191.1)	108.5 (14.9–249.7)	0.052
Total bilirubin (mg/dL)	3.1 (0.5–26.2)	2.4 (0.4–30.0)	0.408
AST (U/L)	197 (18–1,709)	68 (19–1,340)	0.162
ALT (U/L)	141 (8–578)	189 (6–1,397)	0.105
ALP (U/L)	50 (13–316)	45 (19–284)	0.213
Cholesterol (mg/dL)	71 (23–180)	71 (24–200)	0.751
Triglyceride (mg/dL)	42 (8–185)	42 (9–115)	0.851
HDL (mg/dL)	22 (3–82)	24 (3–66)	0.650
LDL (mg/dL)	38 (4–130)	48 (11–135)	0.449
HbA1c (%)	5.1 (3.0–6.9)	5.1 (3.3–6.6)	0.832

Values are presented as mean (range) or number (%).
Group 1, steroid withdrawal at 2 weeks after transplantation; Group 2, steroid withdrawal at 3 months after transplantation.
HBsAg, hepatitis B surface antigen; Anti-HCV, anti-hepatitis C virus; BMI, body mass index; eGFR, estimated glomerular filtration rate; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; HDL, high density lipoprotein; LDL, low density lipoprotein; HbA1c, hemoglobin A1c.

ducted whenever possible with patients who were prematurely removed from the study. The study design did not include an interim assessment.

RESULTS

Baseline characteristics

In this study, 115 patients were enrolled across four participating centers. The patients were randomly assigned to the following two groups: Group 1 consisted of 60 patients who underwent early steroid withdrawal at two weeks after LT, while Group 2 included 55 patients who underwent steroid withdrawal at three months posttransplantation (Fig. 1).

The baseline characteristics of the groups were well balanced (Table 1). There were no statistically significant differences in terms of age, sex, or viral status between the recipients or donors in the two groups. Additionally, comprehensive assessments, including complete blood counts, renal function tests, liver function tests, and lipid profiles, revealed no notable differences between Groups 1 and 2 (Table 1).

The distribution of deceased donor LT was similar in the groups, with 25.0% (n = 15) in Group 1 and 23.6% (n = 13) in Group 2. Alcoholism, hepatitis B virus infection, and HCC were the primary etiologies leading to LT. Furthermore, there were no statistically significant differences observed in cold ischemia time, graft-to-recipient weight ratio, or use of basiliximab between the two groups (Table 2).

Table 2. Perioperative characteristics

	Group 1 (n = 60)	Group 2 (n = 55)	*p*-value
Type of liver transplantation (DDLT)	15 (25.0)	13 (23.6)	0.865
Liver graft			0.888
Left	2 (3.3)	3 (5.5)	
Right	43 (71.7)	39 (70.9)	
Whole	15 (25.0)	13 (23.6)	
Etiology for liver transplantation			0.452
Acute liver failure	0 (0)	3 (5.5)	
Alcoholic cirrhosis	20 (33.3)	14 (25.5)	
HBV	15 (25.0)	17 (30.9)	
HCV	2 (3.3)	2 (3.6)	
HCC	29 (48.3)	14 (25.5)	
Metabolic disease	0 (0)	1 (1.8)	
Others	3 (5.0)	3 (5.5)	
Unknown	0 (0)	1 (1.8)	
Cold ischemic time (min)	90 (13–441)	97 (18–383)	0.234
GRWR	1.15 (0.59–1.37)	1.17 (0.73–1.52)	0.570
Basiliximab use	55 (91.7)	53 (96.4)	0.442

Values are presented as number (%) or mean (range).
Group 1, steroid withdrawal at 2 weeks after transplantation; Group 2, steroid withdrawal at 3 months after transplantation.
DDLT, deceased donor liver transplantation; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; GRWR, graft to recipient weight ratio.

Tacrolimus and mycophenolate mofetil

The study included an analysis of several key parameters related to the administration of TAC (Supplementary Table 1). The TAC trough level (C0), TAC dose, the ratio of C0 to TAC dose, and the ratio of C0 to TAC dose adjusted for the recipient body weight were evaluated at each visit.

The median C0 to TAC dose ratios at Visits 5, 6, 9, and 10 were significantly higher in Group 1 than in Group 2. Consequently, the median C0 to TAC dose ratios adjusted for the recipient body weight at Visits 5 and 9 were also significantly greater in Group 1 than in Group 2 (Fig. 2). In both study groups, the median daily dose of MMF was consistently 1,000 mg, with a range spanning from 500 mg to 1,500 mg, at each visit throughout the study period.

Efficacy

In the full-analysis set (FAS) population, the incidence of

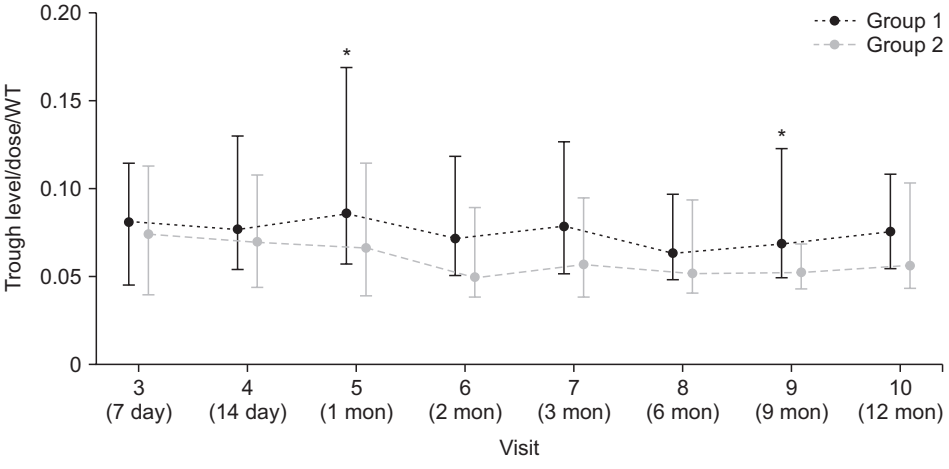

Fig. 2. Median tacrolimus trough level/dose/WT at each visit. Group 1, steroid withdrawal at 2 weeks after transplantation; Group 2, steroid withdrawal at 3 months after transplantation. WT, weight. *$p < 0.05$.

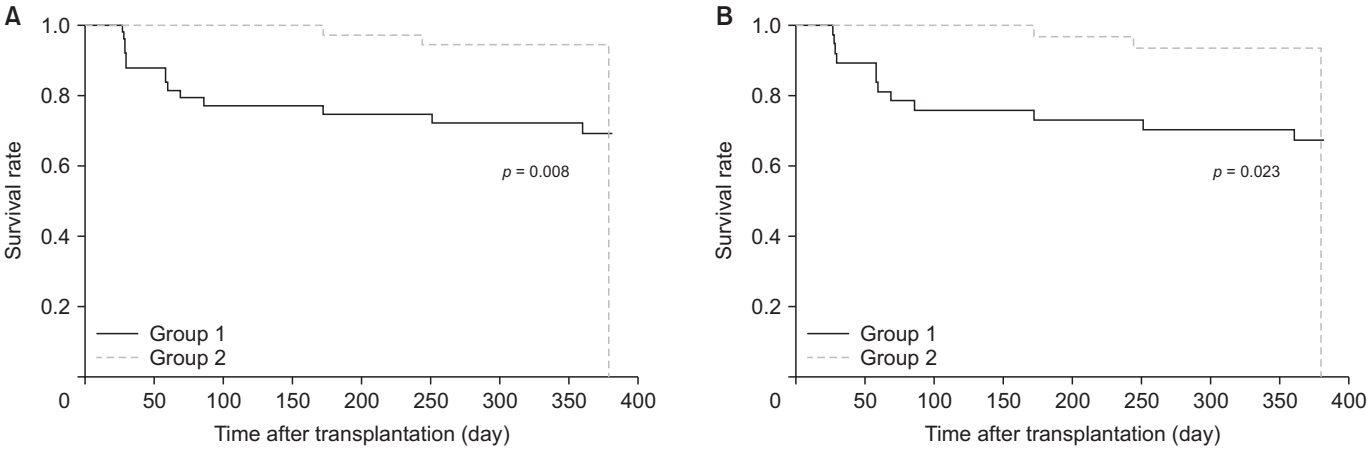

Fig. 3. New-onset diabetes after transplantation development after liver transplantation. (A) Full-analysis set. (B) Per-protocol set. Group 1, steroid withdrawal at 2 weeks after transplantation; Group 2, steroid withdrawal at 3 months after transplantation.

NODAT was 23.3% (n = 14) in Group 1 and 5.5% (n = 3) in Group 2, with a significant difference between groups (p = 0.008). The cumulative NODAT-free survival rate was also significantly higher in Group 2 than in Group 1 (p = 0.008). In the PPS population, the incidence of NODAT remained significantly higher in Group 1 than in Group 2, with rates of 32.4% and 10.0%, respectively (p = 0.029). Similarly, the cumulative NODAT-free survival rates favored Group 2 over Group 1 (p = 0.023) (Fig. 3).

Despite these differences in the NODAT incidence, there was no significant variation between the two groups in terms of BPAR, treatment failure, graft failure, patient mortality, CRF, CKD, or infection rate in the FAS and PPS populations (Table 3). Neither group exhibited cases of steroid-resistant rejection.

Among the HCC patients in Groups 1 and 2, 10.0% (2/20) and 7.1% (1/14) experienced HCC recurrence after LT, respectively. However, this difference in HCC recurrence rates between the two groups was not statistically significant.

Safety

The study groups exhibited a similar incidence of AEs, SAEs, AEs related to MMF, and adverse drug reactions (Table 4, Fig. 4). Steroid insufficiency-induced AEs did not occur in Group 1. In Group 1, 279 AEs occurred in 47 patients, while in Group 2, there were 316 AEs in 45 patients. Statistical analysis did not reveal a significant difference in the total number of AEs between the two groups (p = 0.641). Group 1 had a total of 33

Table 3. Efficacy

	Group 1	Group 2	*p*-value
FAS	60	55	
NODAT	14 (23.3)	3 (5.5)	0.015
BPAR	2 (3.3)	2 (3.6)	0.929
Treatment failure	20 (33.3)	17 (30.9)	0.781
Graft failure	2 (3.3)	1 (1.8)	0.611
Death	1 (1.7)	0 (0)	0.336
CRF	0 (0)	2 (3.6)	0.227
CKD	25 (41.7)	17 (30.9)	0.234
Infection	17 (28.3)	20 (36.4)	0.426
HCC (n = 34)	2/20 (10.0)	1/14 (7.1)	0.773
PPS	37	30	
NODAT	12 (32.4)	3 (10.0)	0.029
BPAR	0 (0)	0 (0)	
Treatment failure	6 (16.2)	7 (23.3)	0.464
Graft failure	0 (0)	0 (0)	
Death	0 (0)	0 (0)	
CRF	0 (0)	1 (3.3)	0.478
CKD	17 (46.0)	11 (36.7)	0.444

Values are presented as number only or number (%).
Group 1, steroid withdrawal at 2 weeks after transplantation; Group 2, steroid withdrawal at 3 months after transplantation.
FAS, full-analysis set; NODAT, new-onset diabetes after transplantation; BPAR, biopsy-proven acute rejection; CRF, chronic renal failure; CKD, chronic kidney disease; HCC, hepatocellular carcinoma; PPS, per-protocol set.

Table 4. Adverse events

	Group 1 (n = 60)	Group 2 (n = 55)	*p*-value
Adverse events	279 (n = 47, 78.3%)	316 (n = 45, 81.8%)	0.641
Severe adverse events	33 (n = 21, 35.0%)	36 (n = 23, 41.8%)	0.452
Mycophenolate mofetil-related adverse events	40 (n = 25, 41.7%)	39 (n = 20, 36.4%)	0.561
Adverse drug reaction	20 (n = 10, 16.7%)	21 (n = 13, 23.6%)	0.351

Group 1, steroid withdrawal at 2 weeks after transplantation; Group 2, steroid withdrawal at 3 months after transplantation.

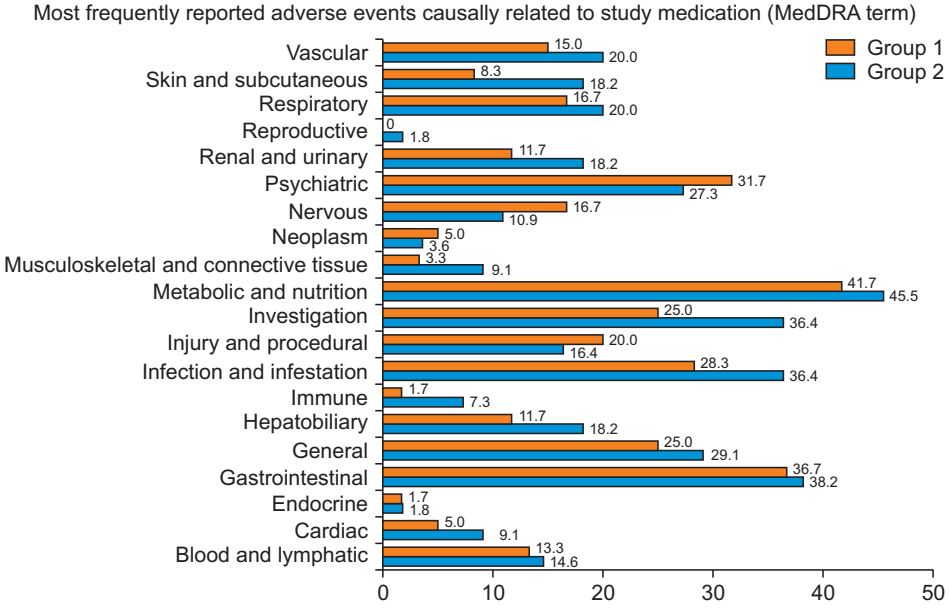

Fig. 4. Adverse events. Group 1, steroid withdrawal at 2 weeks after transplantation; Group 2, steroid withdrawal at 3 months after transplantation.

SAEs in 21 patients, while Group 2 had 36 SAEs in 23 patients; there was no statistically significant difference in the total number of SAEs between the two groups (p = 0.452). These findings suggest that the study groups had a similar safety profile in terms of AEs and SAEs, as well as in terms of the events related to MMF and adverse drug reactions.

DISCUSSION

This randomized controlled trial was initially designed based on the hypothesis that early steroid withdrawal would prevent the development of NODAT. However, the study findings did not support this hypothesis, as steroid withdrawal did not lead to a significant reduction in the incidence of NODAT following LT. In fact, early steroid withdrawal was associated with an increased risk of NODAT, which was attributed to high exposure to the immunosuppressive drug TAC.

Previous studies have suggested that reducing or eliminating steroids shortly after LT could be beneficial by mitigating the typical side effects associated with steroids, such as NODAT, abnormal lipid metabolism, recurrence of viral hepatitis, and relapse of liver malignancy [2]. However, these potential benefits are often counterbalanced by a higher risk of acute rejection, steroid-resistant rejection, and elevated serum creatinine level compared with immunosuppressive regimens that include steroids [1,3]. The varying durations and dosing regimens for steroids in the previous studies contributed to the uncertainty regarding the overall advantages and disadvantages of steroid avoidance or withdrawal in LT patients [1,3].

In this study, early steroid withdrawal at two weeks posttransplantation did not result in increased mortality, reduced survival rates, poor graft outcomes, or death-censored graft failure. Importantly, there were no significant associations between early steroid withdrawal and outcomes, such as BPAR, graft failure, or patient mortality, as no graft failures or deaths were reported in the study population. Furthermore, cardiovascular events and infections were not linked to early steroid withdrawal. These findings suggest that rapid steroid withdrawal at two weeks posttransplantation is a safe approach for LT patients and it does not lead to an increased incidence of acute rejection episodes.

The onset of NODAT following LT has been found to be linked to several factors, including administration of high doses of steroids, immunosuppressive medications, and physical inactivity. Almost all LT patients experience postoperative hyperglycemia due to the stress of the surgical procedure and the administration of high-dose steroids [4,5,9,11,14,15,19,20]. Furthermore, posttransplantation patients may encounter a variety of challenges during the first year after LT, including surgical complications, infections, and other comorbid conditions. These factors can contribute to elevated stress levels in patients during this critical period [21,22]. A recent study has highlighted the association between the use of TAC and steroids at the time of discharge and an increased risk of NODAT in LT recipients. Our results were very disconcerting. Previous studies have reported that the incidence of NODAT might decrease with steroid withdrawal [23], but our randomized controlled trial revealed the opposite in comparison with previous studies, which were retrospective in nature. No randomized controlled trial for assessing the incidence of NODAT after LT had been performed prior to our study. Our results differ from the results of preexisting studies and indicate that early steroid withdrawal at 2 weeks after LT does not have a benefit in preventing NODAT. Conversely, basiliximab induction therapy

and the use of antimetabolites at discharge were associated with a decreased risk of NODAT [24]. In our study, the incidence of basiliximab usage was 91.7% in Group 1 and 96.4% in Group 2. Most of the patients were infused with basiliximab, and there was no difference in the incidence of NODAT between patients who did and did not receive basiliximab. Given the severity of the adverse effects associated with steroid use, it is common to gradually taper the steroid dose to zero within the first three to six months following LT.

TAC has been associated with adverse effects on glucose metabolism following LT. These medications can impair insulin secretion and sensitivity, inhibit the transcription of insulin genes, and even directly damage pancreatic islet cells [25]. As a result, patients treated with TAC are at a significantly higher risk of developing NODAT compared to those treated with other immunosuppressive agents, such as cyclosporine [5]. Although the exact reasons for this difference between TAC and cyclosporine in terms of NODAT risk are not entirely clear, TAC use is often associated with a greater incidence of NODAT in LT patients. One possible explanation for this disparity is that TAC may have a more pronounced negative impact on glucose metabolism [16,26]. Recent studies have suggested that a minimal TAC regimen, with lower doses of TAC, may help reduce the long-term risk of NODAT following LT [11,19]. Furthermore, research has indicated that maintaining a TAC trough level > 8 ng/mL at the three-month posttransplantation mark is associated with an increased likelihood of NODAT [11,19]. This suggests that higher TAC concentrations can significantly contribute to the development of NODAT in LT patients. Our study also demonstrates that high exposure to TAC contributes to NODAT development after LT.

A previous multicenter study conducted over one year compared the effectiveness and safety of an immunosuppressive regimen that involved steroid withdrawal at day 14 following transplantation. The study found a higher incidence of acute rejection in the group in which steroids were withdrawn early [27]. However, the higher rejection rate was somewhat balanced by a trend towards a reduced need for anti-diabetic treatment, indicating a potential benefit in terms of preventing NODAT. Importantly, early withdrawal of steroids did not lead to a significant increase in the incidence of BPAR compared with the group that continued steroid therapy. The rejection rate was similar in the two groups, with a 3.3% incidence in the early steroid withdrawal group and a 3.6% incidence in the continued steroid therapy group.

In the FAS population, BPAR occurred in two participants in each group, with incidence rates of 3.3% and 3.6% in Groups 1 and 2, respectively. However, BPAR did not occur in both groups in the PPS population. These rejection rates were lower than those reported in previous randomized controlled trials [21,22]. High-dose steroid pulses were sometimes administered during the maintenance phase to manage rejection episodes, which could potentially contribute to the development of diabetes. However, in the PPS population, in which BPAR did not occur and steroid pulse therapy was not used, there was a significant difference in the incidence of NODAT between the groups. Specifically, the incidence of NODAT was much higher in the early steroid withdrawal group (Group 1) compared with the group that continued steroids for three months (Group 2). High-dose steroid pulses were also administered during the maintenance phase to treat rejection episodes, which could precipitate the onset of diabetes. However, the incidence of NODAT in the PPS population was 32.4% in Group 1 and 10.0% in Group 2, even though BPAR did not occur and steroid pulse therapy was not received. This suggests that while early steroid withdrawal may not increase the risk of rejection, it may have a notable impact on glucose metabolism, increasing the risk of NODAT in LT patients. Therefore, the timing of steroid withdrawal in immunosuppressive regimens needs to be carefully considered to balance the risks and benefits for patients.

The incidence of CKD, defined as an eGFR < 60 mL/min, was similar between the two groups over the 12 months. This finding suggests that the early steroid withdrawal group (Group 1) and the group that continued steroid therapy for three months (Group 2) had comparable rates of CKD development, indicating that early steroid withdrawal did not have a significant advantage in preserving renal function in this study. Additionally, the infection rate was lower in Group 1 than in Group 2 (28.3% vs. 36.4%). This suggests that early steroid withdrawal might be associated with a reduced risk of infection compared with continued steroid therapy for a longer duration. However, detailed information could not be provided about the types or severity of infections; thus, further investigation is needed to better understand the clinical significance of this finding.

Our study has some limitations. First, the study is underpowered because the premature discontinuation in a significant proportion of patients (approximately one-third) and the unexpected absence of BPAR occurrences may have affected the statistical power of the study. This underpowered nature may have limited the ability to draw definitive conclusions, and larger sample sizes could have provided more robust findings. Second, the follow-up period was limited to one year after LT. Given that some outcomes, such as cardiovascular events, graft loss, or mortality, may take longer to manifest, the short duration of observation could not provide insights into the long-term effects of early steroid withdrawal. Third, the number of patients who completed the study as per protocol (the PPS population) was smaller than expected. This reduced the statistical power of the PPS population analysis and could have limited the generalizability of the findings. Fourth, LT populations in Korea and Western countries differ significantly in terms of race, diet, genetic background, and primary liver disease etiology. This raises questions about the generalizability of the study findings to other populations. Fifth, our study lacked some detailed information, such as the type and severity of infections.

In conclusion, this randomized controlled trial did not find a significant reduction in the incidence of NODAT when comparing early steroid withdrawal, two weeks after LT, with steroid use for three months after LT. Furthermore, there were no significant differences in outcomes related to acute rejection, CKD, infection rate, graft failure, or death between the two groups. These results indicate that steroid withdrawal three months posttransplantation within the combination of TAC and MMF regimen is a standard and safe immunosuppressive strategy for LT patients. This approach may help mitigate the risks associated with prolonged steroid use, such as the development of NODAT. Further research and longer-term follow-up studies may help to refine and validate these findings.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.14701/ahbps.23-129.

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CONFLICT OF INTEREST

The trial was designed and run by Jongman Kim (JK) and Jae-Won Joh (JWJ) who received financial support from Roche Pharma AG. The funders had no role in data collection, data analysis, data interpretation, or writing of the manuscript. An independent contract research organization (A-CRO, Seoul, Korea) was responsible for data collection, monitoring, and statistical analyses. JK and JWJ had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Conceptualization: JK, JWJ. Data curation: All authors. Methodology: JK, JWJ. Writing - original draft: JK. Writing - review & editing: All authors.

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