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ORIGINAL ARTICLE

Improvement of medication adherence with simplified once-daily immunosuppressive regimen in stable kidney transplant recipients: A prospective cohort study

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Summary *Background:* Many immunosuppressive drugs are prescribed as twice-daily dosing. A simplified once-daily dosing of immunosuppressive drug regimen may improve medication adherence. We investigated medication adherence of simplified once-daily immunosuppressive regimen consisting of extended-release tacrolimus, sirolimus, and corticosteroids along with the efficacy and safety of this regimen.
Methods: This study was a prospective, multicenter, controlled and cohort trial. Stable kidney transplant recipients who had received transplantation at least 3 months before the study enrollment were eligible for the study. Participants were required to fill-out the self-reported immunosuppressant therapy barrier scale (ITBS) questionnaire before and after the conversion. Other clinical laboratory parameters and adverse events were evaluated until 6 months post-conversion.

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Results: A total of 160 kidney recipients comprised the intention-to-treat population. The mean total ITBS score was 19.5 ± 4.0 at pre-conversion and 6 months after converting, the mean total ITBS score was 16.6 ± 3.6 ($p < 0.001$). Particularly, the ITBS scores of 4 questions related to the frequency of medication dosing were significantly different between pre-conversion and post-conversion. Only 1 patient (0.62%) was diagnosed as biopsy-confirmed acute rejection in the study period. There was no significant change in the mean estimated glomerular filtration rate after the conversion. Overall 95 patients (59.4%) had an adverse event and 28 patients (17.5%) had a serious adverse event. No graft loss and 1 death were reported.

Conclusion: Medication adherence after the conversion to the once-daily immunosuppressive regimen was significantly improved with no additional risks of efficacy failure or adverse events.

1. Introduction

In kidney transplantation, a considerable number of recipients fail to follow their prescribed immunosuppressive regimen. This non-compliance or non-adherence could range from accidental or occasional to permanent cessation of part or the entire immunosuppressive regimen. Post-transplantation non-compliance has been a critical risk factor associated with increased rates of graft dysfunction and loss.[1,2] In 10 cohort studies, a median of 36.4% kidney allograft losses was associated with prior non-adherence and a meta-analysis of the impact of non-adherence on graft survival demonstrated that the odds of graft failure were seven-fold greater in non-adherent subjects than in adherent subjects.[3]

Among many factors affecting compliance or adherence, the complexity (*i.e.*, doses per day) of the immunosuppressant medication regimen directly affects adherence rates.[4] The more times per day that a medication needs to be taken, the more likely patients are to miss doses. A previous review of quantitative medication adherence demonstrated that, on average, a single daily dose yielded the highest adherence rate at 79%. More frequent doses resulted in less adherence: twice-daily dosing yielded a 69% adherence rate, 3 doses per day yielded 65%, and four doses per day resulted in decrease to 51%.[5]

Extended-release tacrolimus (Advagraf®; Astellas Pharma, Tokyo, Japan) has been hypothesized to improve adherence to immunosuppressive regimens among kidney transplant recipients.[6–9] If patients take once-daily prescribed drugs for other medical condition, the conversion from twice-daily to once-daily immunosuppressive regimen can be beneficial for the patients. Among the other immunosuppressive agents, sirolimus and glucocorticosteroids can be used as part of a once-daily regimen. Simplified once-daily regimen can effectively remove the need to take drugs during socioeconomic activities. Such a regimen might improve treatment convenience correlated with medication adherence.[10] In terms of efficacy and safety, Oh et al previously reported a randomized prospective study demonstrating that conversion to once-daily tacrolimus was non-inferior in terms of efficacy and safety to twice-daily tacrolimus.[11]

This study aimed to investigate the improvement of medication adherence through the use of a simplified once-daily immunosuppressive regimen, and to evaluate the efficacy and safety of the regimen throughout the 6 months study period after the conversion of the immunosuppressive regimen.

2. Methods

2.1. Study design and participants

We performed a prospective, controlled and cohort trial study in eight transplant centers in Korea. A simplified immunosuppressive regimen was defined as immunosuppressive drug prescribed as a once-daily preparation. Measurements of medication adherence were performed immediately at pre-conversion and 6 months post-conversion.

Adult kidney transplant recipients (age 20—65 years) were eligible for enrollment in this study if they received transplantation more than 3 months before study enrollment, and were taking tacrolimus. The key exclusion criteria were as follows: serum creatinine higher than 2.0 mg/dL; 24-h urinary protein excretion more than 750 mg/day; any recent rejection or infection within 1 month before enrollment; leukocyte count <2500/μL, or neutrophils <1500/μL, or platelets <75,000/μL; evidence of psychiatric or mental illness; and severe liver disease.

The Participants visited to clinic at the day before conversion (baseline) and at 1, 2, 4, and 6 months post-conversion. The physical examination and laboratory tests (kidney function, liver function, lipid metabolism, hematology, proteinuria and trough levels of immunosuppression) were checked and data were collected at all visit. We assessed renal function according to the serum creatinine level and estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) formula.[12] Medication adherence was measured with the self-reported immunosuppressant therapy barrier

scale (ITBS).[13] This validated questionnaire is a generic tool for the measurement of medication adherence in immunosuppression therapy and includes a 13-item scale consisting of 5-point Likert responses that rate self-reported agreement with 8 "uncontrollable" factors and 5 "controllable" factors. The scores range from 13 to 65, with a higher score corresponding to more barriers to adherence. The questionnaire was translated to Korean and completed by the patients before conversion of the immunosuppressive regimen and at 6 months post-conversion.

This study was conducted in accordance with the Declaration of Helsinki and in compliance of Good Clinical Practice guidelines. The institutional review board of each center approved this study protocol. This study was registered with ClinicalTrials.gov (registration identifier = NCT01964014).

2.2. Immunosuppression

We converted twice-daily tacrolimus to once-daily tacrolimus on a 1:1 mg proportion basis for the total daily dose. Also, mycophenolate mofetil or enteric-coated mycophenolate sodium were converted to once-daily sirolimus 2 mg as starting dose. All the prescribed medicine was scheduled to be taken in the morning. The tacrolimus trough levels were measured, and the dose was adjusted to keep the trough level within the target range (3–8 ng/dL). In the same way, the sirolimus dose was adjusted to keep within the target range (3–8 ng/dL). All other drugs, including corticosteroids were changed to once-daily prescription or slow-release preparations if indicated. The drug levels were monitored by immunoassay methods in all centers.

2.3. Study assessments

The primary assessment was medication adherence, which was measured by ITBS scores, to the twice-daily regimen at baseline, and to the simplified once-daily regimen at 6 months after conversion. Secondary assessment included the incidence of biopsy-confirmed acute rejection (BCAR), graft loss, patient death and loss to follow-up until 6 months post-conversion. The transplanted kidney biopsy was operated if patients showed clinical findings suggestive of acute rejection. The biopsy was completed at least 48 h before the initiation of anti-rejection therapy. The Banff criteria were used to grade the biopsy specimens.[14] Rejection was treated using corticosteroids with or without anti-thymocyte globulin, depending on the histological grade and clinical course. Other prospectively defined assessments included the renal graft function and 24 h urinary protein excretion. Safety assessments included incidences of adverse events (AEs) and serious AEs (SAEs). An AE is defined as any untoward medical occurrence, including exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product.[15] The event did not necessarily have a causal relationship with this treatment. The severity grades of AEs were defined as follows: 1) mild, usually transient in nature and generally not interfering with normal activities; 2) moderate, sufficiently discomforting to interfere with normal activities; and 3) severe, prevents normal activities.[15] SAE was defined as any AE undesirable signs, symptoms, or medical conditions that met any one of the following criteria: 1) was fatal or life-threatening; 2) resulted in persistent or significant disability/incapacity; 3) required hospitalization or prolonged the existing hospitalization; 4) was a congenital anomaly/birth defect; and 5) was an important medical event that may jeopardize the patient and might require medical or surgical intervention to prevent any of the above-listed outcomes.[11]

2.4. Sample size and statistical analysis

A sample size of 160 was determined on the basis of a power of 0.8, a type I error probability of 0.025, a non-inferiority margin of 15%, and a 10% drop out rate with reference to a previous study.[16,17] Categorical variables were analyzed using Pearson's chi-square test. Continuous variables were analyzed using a t-test or analysis of variance, and expressed as mean ± standard deviation. P value of 0.05 was considered to indicate significance. All analyses were operated by SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Study characteristics

Patients were enrolled from April 2012 to March 2015. A total 160 kidney transplant recipients provided at least one dose of the study drug after enrollment comprised the intention-to-treat (ITT) population. Among the patients, 140 patients completed the study follow-up and completed the trial, and comprised the per-protocol (PP) population. The patient enrollment flow chart is in Fig. 1. The major reasons for premature discontinuation of study participation were as follows: lost to follow-ups (nine patients), rejection or unable to maintain regimen (four patient), withdrawal of consent (three patients), protocol violations (two patients), patient death (one patients), and other (one patients). The basic characteristics of recipients and donors are presented in Table 1.

3.2. Tacrolimus and sirolimus exposure

The mean doses and trough levels of tacrolimus and sirolimus at 1, 2, 4, and 6 months post-conversion are presented in Table 2. The mean doses and trough levels of tacrolimus did not change over the study period ($p > 0.05$). The mean doses of sirolimus were significantly reduced to 1.5 ± 0.5 mg/day at 6 months post-conversion ($p < 0.001$) to keep the target blood level at 3–8 ng/mL. The mean blood trough levels of sirolimus were maintained within the target range throughout the study period. The mean doses of corticosteroids were not changed.

3.3. Medication adherence

The results of ITBS score was listed in Table 3. The mean total ITBS score before the conversion was 19.5 ± 4.0. Six months after converting to the simplified immunosuppressive

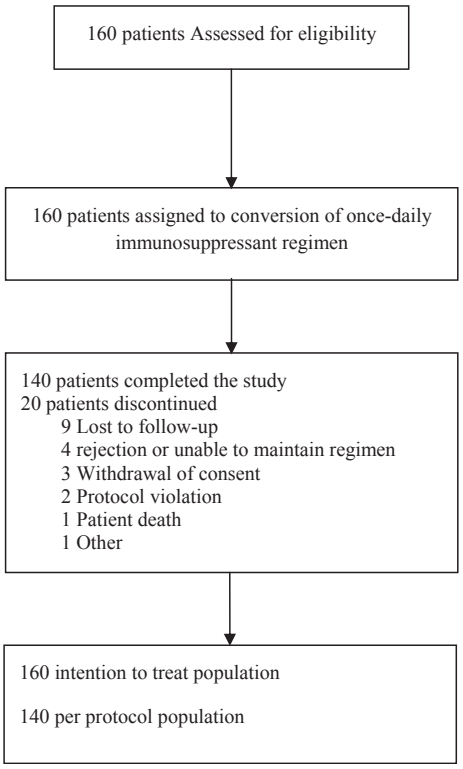

Figure 1 Patients enrollment flow chart.

regimen, the mean total ITBS score was 16.6 ± 3.6 ($p < 0.001$). In particular, the ITBS scores of four questions related to the frequency of medication dosing were significantly decreased from pre-conversion to post-conversion. The questionnaire items included the following: "Q1: I have to take the immunosuppressant medication(s) too many times per day" (2.49 ± 1.13 *vs* 1.39 ± 0.6, $p < 0.001$); "Q2: I have to take too many capsules (or tablets) of my immunosuppressant medication(s) at one time" (2.60 ± 1.19 *vs* 1.98 ± 1.10, $p < 0.001$); "Q4: I skip doses of my immunosuppressant medication(s) when I go out of town" (1.46 ± 1.01 *vs* 1.19 ± 0.52, $p = 0.004$); and "Q9: It is hard for me to remember to take my immunosuppressant medication(s)" (1.98 ± 1.23 *vs* 1.54 ± 0.93, $p = 0.001$). Among mentioned questions above, question number 1, 2, 4 were belonging to "uncontrollable" factors and question number 9 was one of the "controllable" factor questions. In contrast, the ITBS scores of two questions associated with "controllable" factor significantly increased after the conversion (questions 11 and 13).

Table 1 Baseline demographics and clinical characteristics of ITT & PP population.

Population	ITT (n = 160)	PP (n = 140)
Recipient variables		
Age (year)	45.4 ± 10.5	44.7 ± 10.5
Male recipient (%)	79 (49.4%)	74 (52.9%)
Weight (kg)	60.8 ± 9.5	61.0 ± 9.6
Height (cm)	163.9 ± 8.8	164.5 ± 8.7
Body mass index (kg/m^2)	22.6 ± 3.1	22.5 ± 3.0
Post-transplant months	29.9 ± 35.3	28.1 ± 34.1
Kidney disease (%)		
Hypertension	16 (10.0%)	12 (8.6%)
Glomerulonephritis	37 (23.1%)	32 (22.9%)
Diabetes	13 (8.1%)	11 (7.9%)
Polycystic kidney disease	6 (3.8%)	4 (2.9%)
Others	4 (2.5%)	4 (2.9%)
Unknown	84 (52.5%)	77 (55.0%)
Types of dialysis (%)		
Hemodialysis	125 (78.1%)	109 (77.9%)
Continuous ambulatory peritoneal dialysis	26 (16.3%)	23 (16.4%)
Pre-emptive	9 (5.6%)	8 (5.7%)
Donor variables		
Age (year)	44.4 ± 13.9	44.7 ± 15.6
Male donor (%)	95 (59.4%)	81 (57.9%)
Weight (kg)	64.3 ± 11.9	64.1 ± 11.2
Height (cm)	165.7 ± 10.4	166.0 ± 8.9
Body mass index (kg/m^2)	23.3 ± 3.5	23.2 ± 3.5
Type of donation (%)		
Living related	50 (31.3%)	45 (32.1%)
Living unrelated	25 (15.6%)	21 (15.0%)
Deceased	85 (53.1%)	74 (52.9%)
Degree of HLA-A mismatch		
0	38 (23.8%)	31 (22.1%)
1	83 (51.9%)	76 (54.3%)
2	39 (24.3%)	33 (23.6%)
Degree of HLA-B mismatch		
0	21 (13.1%)	18 (12.8%)
1	61 (38.1%)	54 (38.6%)
2	78 (48.8%)	68 (48.6%)
Degree of HLA-DR mismatch		
0	39 (24.4%)	35 (25.0%)
1	82 (51.2%)	74 (52.9%)
2	39 (24.4%)	31 (22.1%)

Continuous variables are expressed as the mean ± standard deviation and categorical variables are expressed as number (%).
ITT = intention-to-treat; PP = per-protocol.

3.4. Efficacy and graft renal function

The overall incidence of BCAR within 6 months post-conversion in the ITT population was 0.62% (1 of 160 subjects). The patient enrolled in this study at 7 month after the transplantation and the BCAR of this patient (chronic allograft rejection, grade 1, mild type) was developed at 5 month after the conversion. The patient received a steroid pulse therapy and graft function was resolved without complication. No graft loss and one patient death were reported. In the ITT population, the mean eGFR at pre-conversion was 64.6 ± 16.2 mL·min^{-1}·1.73 m^{-2}. At 1, 2, 4, and 6 months post-conversion, the mean eGFR was 64.6 ± 17.4, 62.7 ± 16.6, 64.0 ± 18.8, and 62.4 ± 18.7 mL·min^{-1}·1.73 m^{-2}, respectively ($p = 0.728$). The 24 h urinary protein excretion at pre-conversion was significantly lower than at 6 months post-conversion (100.3 ± 150.4 mg/day *vs* 206.5 ± 433.5 mg/day, $p < 0.001$).

In the PP population, the mean eGFR at pre-conversion was 63.8 ± 15.6 mL·min^{-1}·1.73 m^{-2}. At 1, 2, 4, and 6 months post-conversion, the mean eGFR was 64.1 ± 17.2,

Table 2 Tacrolimus & sirolimus doses and blood levels (PP population).

Group	Tacrolimus	Sirolimus	Steroid
Dose (mg/day) & their p-values[a]	**0.999**	**<0.001**	**0.997**
Month 0	4.3 ± 2.6	2.0 ± 0.1	6.5 ± 4.0
Month 1	4.3 ± 2.6	1.8 ± 0.4	6.7 ± 3.9
Month 2	4.4 ± 2.5	1.7 ± 0.5	6.6 ± 3.9
Month 4	4.3 ± 2.5	1.6 ± 0.5	6.7 ± 3.9
Month 6	4.4 ± 2.6	1.5 ± 0.5	6.6 ± 3.9
Blood trough level (ng/mL) & their p-values[a]	**0.136**	**0.155**	
Month 1	4.5 ± 1.8	6.5 ± 2.9	
Month 2	4.8 ± 1.9	6.2 ± 2.6	
Month 4	4.6 ± 1.6	5.8 ± 2.6	
Month 6	4.9 ± 2.3	5.9 ± 2.5	

PP = per-protocol.
[a] Continuous variables are expressed as the mean ± standard deviation and their p-values are calculated with analysis of variance.

62.6 ± 16.8, 63.9 ± 18.8, and 62.4 ± 18.7 mL·min^{-1}·1.73 m^{-2}, respectively (p = 0.896). The 24 h urinary protein excretion at pre-conversion was significantly lower than at 6 months post-conversion (87.1 ± 140.9 mg/day *vs* 206.5 ± 433.5 mg/day, p < 0.001).

3.5. Safety assessments

In the ITT population, a total of 95 (59.4%) had an AE. Twenty-eight patients (17.5%) had a SAE, five patients (3.1%) had a severe AE, and four patients (2.5%) discontinued study drug due to AE. Among a total of 228 reported AEs, the most frequent AEs according to organ systems were as followed; skin and subcutaneous tissue disorders (21.5%), infections and infestations (18.4%), gastrointestinal disorders (14.1%), renal and urinary disorders (13.2%), metabolism and nutrition disorders (6.1%), musculoskeletal and connective tissue disorders (6.1%), and nervous system disorders (5.7%) (Table 4). The most frequent AEs according to specific disease were upper respiratory tract infection (13.2%), urinary tract infection (8.3%), oral ulcer (5.7%), and diarrhea (5.3%) as shown in Table 5. Laboratory values were compared between pre-conversion and 6 months post-conversion (Table 6). The mean triglyceride level at 6 months post-conversion was significantly higher than at pre-conversion (185.9 ± 141.1 mg/dL *vs* 129.1 ± 76.8 mg/dL, p = 0.008).

4. Discussion

This multicenter conversion trial involving 160 kidney transplant recipients, evaluating the improvement of medication adherence to simplified once-daily regimen, resulted in that conversion of regimen statistically

Table 3 Results of ITBS (Immunosuppressant Therapy Barrier Scale[a]) score.

ITBS Questions	Before	6 months after	P-value
"Uncontrollable" factor			
1. I have to take the immunosuppressant medication(s) too many times per day.	2.49 ± 1.13	1.39 ± 0.66	<0.001
2. I have to take too many capsules (or tablets) of my immunosuppressant medication(s) at one time.	2.60 ± 1.19	1.98 ± 1.10	<0.001
3. I cannot tell if my immunosuppressant medication(s) is (are) helping me.	2.21 ± 1.42	1.94 ± 1.25	0.091
4. I skip doses of my immunosuppressant medication(s) when I go out of town.	1.46 ± 1.01	1.19 ± 0.52	0.004
5. I miss doses of my immunosuppressant medication(s) when I feel depressed.	1.04 ± 0.28	1.05 ± 0.22	0.619
6. I get confused about how to take my immunosuppressant medication.	1.16 ± 0.50	1.07 ± 0.29	0.084
7. I do not understand when to take my immunosuppressant medication(s).	1.04 ± 0.36	1.02 ± 0.15	0.521
8. I often run out (or do not have enough) of immunosuppressant medication(s).	1.21 ± 0.68	1.09 ± 0.31	0.060
"Controllable" factor			
9. It is hard for me to remember to take my immunosuppressant medication(s).	1.98 ± 1.23	1.54 ± 0.93	0.001
10. I miss a dose of my immunosuppressant medication(s) when I think there may be side effects.	1.09 ± 0.43	1.08 ± 0.40	0.793
11. I sometimes skip doses of my immunosuppressant medication(s) when I feel good (or better).	1.00 ± 0.00	1.03 ± 0.17	0.043
12. I miss doses of my immunosuppressant medication(s) when I get out of my daily routine.	1.21 ± 0.69	1.19 ± 0.60	0.810
13. I skip doses of my immunosuppressant medication(s) when I am short of money.	1.01 ± 0.85	1.06 ± 0.26	0.031
Total	**19.50 ± 4.00**	**16.62 ± 3.62**	**<0.001**

[a] Scale grades: 1 'strongly disagree'; 2 'disagree'; 3 'neutral'; 4 'agree'; 5 'strongly agree'. The scores range from 13 to 65, with a higher score corresponding to more barriers to adherence.

Table 4 Summary of adverse events over 6 months of treatment (ITT population).

No. of patients with Any AE	95 (59.4%)
No. of patients with SAEs	28 (17.5%)
No. of patients with Severe AEs	5 (3.1%)
AEs leading to study drug discontinuation	4 (2.5%)
No. of AEs reported by system organ class	228 (100%)
Skin and subcutaneous tissue disorders	49 (21.5%)
Infections and infestations	42 (18.4%)
Gastrointestinal disorders	32 (14.1%)
Renal and urinary disorders	30 (13.2%)
Metabolism and nutrition disorders	14 (6.1%)
Musculoskeletal and connective tissue disorders	14 (6.1%)
Nervous system disorders	13 (5.7%)
Respiratory. thoracic and mediastinal disorders	13 (5.7%)
Reproductive system and breast disorders	5 (2.2%)
Eye disorders	4 (1.8%)
Injury. poisoning and procedural complications	3 (1.3%)
Psychiatric disorders	3 (1.3%)
Endocrine disorders	2 (0.9%)
Blood and lymphatic system disorders	2 (0.9%)
Hepatobiliary disorders	1 (0.4%)
Cardiac disorders	1 (0.4%)

Categorical variables are expressed as number (%).
ITT = intention-to-treat; AE = adverse event; SAE = serious adverse event.

improved the medication adherence at 6 months post-conversion without any additional risk of AEs.

In general, there are several available methods for evaluating compliance or drug adherence to an immunosuppressive regimen. Direct methods include observation and drug monitoring through assays, and indirect methods include self-reports, collateral reports, pill counts, prescription refills, clinical outcomes, and electronic event monitoring.[18] A major methodological obstacle in transplant compliance research is the lack of a valid and reliable measurement of compliance with the immunosuppressive regimen. Patients' interviews or self-reports concerning immunosuppressive regimen compliance are easy, cheap and feasible in virtually all care settings.[13] According to medication adherence through the ITBS used in this study, this simplified once-daily regimen can improve medication adherence for kidney transplant recipients and this result may enable to improve the long-term outcome in kidney transplantation. In this study, several ITBS subscales including "uncontrollable" factors showed decreased scores after conversion to the simplified once-daily regimen. This suggests that the simplified once-daily regimen may help reduce the barrier to medication adherence.

Table 5 Most frequently reported adverse events over 6 months of treatment (ITT population).

Upper respiratory infection	30 (13.2%)
Urinary tract infection	19 (8.3%)
Oral ulcer	13 (5.7%)
Diarrhea	12 (5.3%)
Graft dysfunction	10 (4.4%)
Headache	9 (3.9%)
Edema	9 (3.9%)
Hyperlipidemia	7 (3.1%)
Abdominal pain	5 (2.2%)
Glucose intolerance	5 (2.2%)
Dental problem	5 (2.2%)
Cough	5 (2.2%)
Others	99 (43.4%)
All AEs	228 (100%)

Categorical variables are expressed as number (%).
ITT = intention-to-treat; AE = adverse event.

In contrast, responses to the two questions of the ITBS showed that patients were less adherent to medication after the conversion of regimen. Because those questions were about "controllable" factors, there was a possibility that the patients' tendency to misreport could have influenced the result. As self-reports tend to overestimate medication adherence, patient dishonesty could possibly interfere with the validity of the ITBS, in particular the "controllable" factor scales. Furthermore, patients tend to be dishonest and ashamed to admit their non-adherence since it is not socially accepted. Moreover, the patients' desire to avoid being reprimanded for non-adherence to the immunosuppressant therapy could result in response bias in the self-reports.[19] Thus, it can be assumed that the non-adherent result from the two "controllable" questions may not have a strong influence on the actual medication adherence resulting from the regimen conversion. This assumption is supported by the concept that "controllable" factors are less correlated with the frequency of medication doses.[13]

In aspect of individual question of ITBS, it seemed to be less consistency because not all the questionnaire score was indicating towards improved medication adherence. However, total score of ITBS is more important than each questionnaire's score which means that ITBS can be used as a tool for improvement of barrier to adherence in comparative study such as the study of changing regimen and circumstances of patients, and of cost-effective generic medication. Also, every questionnaire score could be affected by individual conditions and a complexity of interpretation has existed in using ITBS, including socio-economic status, ages, and numbers of family protector. In recent cohort study of New Zealand and Australia, the risk of graft loss from noncompliance was significantly increased from 16 to 24 years, peaking at 19–21 years.[20] Therefore, a comprehensive understanding of the complexity of compliance should be followed by customized and detailed management of patients with immunosuppressive therapy.

According to large-scale data, a regimen of mycophenolate mofetil, and corticosteroids in combination with low-dose tacrolimus may be advantageous for renal function, allograft survival, and acute rejection rates.[21] Tacrolimus is now a keystone immunosuppressive agent used in the prevention of kidney rejection after transplantation. Since the extended-release formulation of

Table 6 Laboratory values at pre-conversion and 6 months after conversion (ITT population).

	Pre-conversion	6 months	p-value*
White blood cell count (x1000/mm^3)	7.06 ± 2.45	7.32 ± 2.14	0.581
Hemoglobin (g/dl)	13.7 ± 1.6	14.0 ± 2.03	0.084
Platelet count (x1000/mm^3)	218.4 ± 55.2	224.8 ± 62.6	0.158
Cholesterol (mg/dl)	187.1 ± 43.4	208.3 ± 43.8	0.086
Tri-glyceride (mg/dl)	129.1 ± 76.8	185.9 ± 141.1	0.008
LDL-cholesterol (mg/dl)	112.9 ± 95.3	117.2 ± 35.9	0.771
HDL-cholesterol (mg/dl)	58.8 ± 17.8	60.9 ± 19.2	0.721

Continuous variables are expressed as the mean ± standard deviation.
* P-values are calculated with t-test.
ITT = intention-to-treat; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

tacrolimus was introduced into clinical practice to improve the compliance and effectiveness of the post-transplantation immunosuppressive regimen, several studies on its efficacy and safety have been reported.[22–25] Additionally, as part of a once-daily immunosuppression regimen, medications such as sirolimus and corticosteroids can be used.[26,27] In this study, a simplified immunosuppressive regimen was defined as a regimen in which every immunosuppressive drug was prescribed in a once-daily preparation. The only immunosuppressive combination of the simplified regimen consisted of extended-release tacrolimus, sirolimus, and corticosteroids, which can be prescribed on a once-daily basis.

In this study, mean triglyceride level was much higher after conversion of once-daily regimen which includes sirolimus. Previous study reported that the association between sirolimus and dyslipidemia was particularly strong and low density lipoprotein (LDL) levels were higher in the sirolimus arm of this previous study.[28] In our results, however, LDL levels were not significantly different between pre- and post-conversion. Also there has been concern about sirolimus induced proteinuria in kidney transplant recipients. A previous study reported that sirolimus induced proteinuria may be a dose-dependent effect of the drug on key podocyte structures.[29] In our study, 24 h urinary protein excretion at post-conversion is higher than at pre-conversion and this result may be caused by sirolimus effect. There is a necessity that physician have to consider the balance between benefit and side effect of using sirolimus.

Our study has several limitations. First, we could use only one study instrument for evaluating medication adherence. The ITBS conducted in this study is very useful method for evaluating a barrier to adherence but more detailed result would be drawn if we added other measurement methods for medication adherence and treatment satisfaction. Second, because only patients willing to change their medication schedule could participate, the participants might have had a positive bias towards the simplified regimen. Additionally, there was a possibility that some participants did not disclose their true medicine-taking behavior. Therefore, our data on self-reported medication adherence might overestimate the effect on treatment convenience of the once-daily immunosuppressive regimen.[13] However, the assessment period of our study was 6 months, proper period for establishing patients' daily pattern of taking medication. Consequently, we thought that a relatively long assessment period could balance the overestimation of medication adherence. Third, this study had a weakness of study population because this study was conducted by single-group cohort study. To achieve more concrete result, we thought that comparative study including more than two study groups should be considered.

In conclusion, a once-daily immunosuppressive regimen consisting of extended-release tacrolimus, sirolimus, and corticosteroids can improve medication adherence in adult kidney transplant patients with stable renal function without the additional risks of adverse effects from the regimen.

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Conflict of interest

None.

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