Original Article / Özgün Makale

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1145373

J Med Palliat Care 2022; 3(3): 175-181

# Outcomes of de novo extended-release tacrolimus use (Advagraf®) in kidney transplantation: 1-year, single-center experience

## Böbrek naklinde de novo uzamış salınımlı takrolimus kullanımı sonuçları: tek merkez, 1 yıllık sonuçlar

Gülcin Turkmen Sarıyıldız[1], Mehmet Emin Demir[2], Siren Sezer[2], Ulas Sozener[1], Zafer Ercan[3], Merter Gulen[1], Canan Çiçek Demir[4], Aykut İlker Arslan[5], Fatma Necla Özşeker[6]

[1]Medicana International Ankara Hospital, Department of General Surgery and Organ Transplantation, Ankara, Turkey
[2]Atılım University, Medicana International Ankara Hospital, Department of Nephrology and Organ Transplantation Unit, Ankara, Turkey
[3]Sakarya Education and Training Hospital, Departmentof Nephrology, Sakarya, Turkey
[4]Atılım University, Medicana International Ankara Hospital, Department of Endocrinology, Ankara, Turkey
[5]Atılım University, Vocational School of Health, Ankara, Turkey
[6]Medicana International Ankara Hospital, Department of Organ Transplantation, Ankara, Turkey

**Cite this article as/Bu makaleye atıf için:** Türkmen Sarıyıldız G, Demir ME, Sezer S, et al. Outcomes of de novo extended-release tacrolimus use (Advagraf®) iın kidney transplantation: 1-year, single-center experience. J Med Palliat Care 2022; 3(3): 175-181.

## ABSTRACT

**Aim:** Once daily extended-release tacrolimus (tac-ER) was introduced to support medication adherence in kidney transplant (KTx) recipients, with similar efficacy to immediate-release tacrolimus (tac-IR). However, most of the experiences regarding tac-ER efficacy were obtained from the switches from tac-IR to tac-ER in kidney transplant recipients (KTRs). In this study, we aimed to demonstrate 1-year outcomes of de novo use of tac-ER in KTRs.

**Material and Method:** This single-center retrospective study included 72 de novo KTRs between January 2020 and January 2021. KTRS were divided into two groups who received a tac-ER or tac-IR. 1-year allograft functions, allograft survival, daily doses of tacrolimus in milligram/day and milligram/kg/day, trough levels, and acute rejection episodes were compared between the two groups. The factors that might have an impact on allograft functions and acute rejection episodes also were investigated.

**Results:** A total of 69 de novo kidney allograft recipients (30 recipients in the tac-ER and 39 recipients in the tac-ER groups); were evaluated. Three KTRs were excluded due to the deaths within the early posttransplant period. Serum creatinine and tacrolimus trough levels were similar for 12 months after transplantation ($p>0.05$). More daily tacrolimus doses (in milligram/day and milligram/kg/day) were required to obtain a targeted trough level up to 3 months in the tac-ER group. Acute rejection rates also were found similar between the two groups ($p=0.281$). Univariate regression analysis demonstrated that higher total daily tacrolimus doses within a posttransplant month 1 may (milligram/kg/day) have an impact on lower acute rejection episode(s) independent of tacrolimus trough levels ($p=0.02$).

**Conclusion:** De novo use of extended-release tacrolimus Advagraf® is as effective as immediate-release tacrolimus in preventing acute rejection episode(s) and provides satisfactory 1-year allograft function and survival.

**Keywords:** Extended-release tacrolimus, acute rejection, kidney transplantation

## ÖZ

**Amaç:** Böbrek nakli alıcılarında günde tek doz uzamış salınımlı takrolimus (tac-ER) kullanımı, erken salınımlı takrolimus (tac-IR) kullanımına benzer etkinlik ve daha iyi ilaç uyumu sağlaması amacıyla geliştirilmiştir. Ancak uzamış salınımlı takrolimus ile ilgili deneyimler daha çok nakil sonrası dönemde yapılan "switch" protokollerine dayanmaktadır. Bu çalışmada böbrek alıcılarında de novo tac-ER kullanımı ile ilgili deneyimlerimizi ve 1 yıllık sonuçları sunmayı amaçladık.

**Gereç ve Yöntem:** Bu tek merkezli retrospektif çalışmaya Ocak 2022-Ocak 2021 arasında yapılan 72 de novo böbrek nakli hastası dahil edilmiştir. Hastalar tac-ER ve tac-IR alan iki gruba ayrıldı. Bir yıllık allogreft fonksiyonları ve sağ kalımları, hastaların günlük ilaç dozları ve bunların akut rejeksiyon atakları ile ilişkileri karşılaştırıldı. Allogreft fonksiyonları ve akut rejeksiyon atakları üzerine etki eden faktörler incelendi.

**Bulgular:** Toplam 69 hastanın (uzamış salınımlı grupta 30 hasta ve erken salınımlı grupta 39 hasta) verileri incelendi. Üç hasta posttransplant erken dönemde öldüğü için analize dahil edilmedi. Nakil sonrası 12 aylık izlem boyunca her iki grup arasında serum kreatinin ve takrolimus çukur değerler bencer bulundu ($p>0,05$). İlk 3 ay içinde hedef takrolimus değerlere ulaşmak için, tac-ER grubunda daha yüksek günlük dozlar (milligra/gün ve milligram/gün/kg) gerekti ($p<0,05$). Nakil sonrası ilk 12 ay içinde her iki grupta da rejeksiyon oranları benzerdi ($p=0,281$). Tek değişkenli analizde posttransplant 1. aydaki takrolimus dozu (milligram/kg/gün) takrolimus çukur değerinin aksine rejeksiyon gelişimi üzerinde etkili görüldü ($p=0,02$).

**Sonuç:** Böbrek naklinde uzamış salınımlı takrolimusun (Advagraf®) de novo kullanımı, erken salınımlı takrolimus kullanımına benzer etkinlik, allogreft sağ kalımı ve fonksiyonu sağlar.

**Anahtar Kelimeler:** Uzamış salınımlı takrolimus, akut rejeksiyon, böbrek nakli

**Corresponding Author/Sorumlu Yazar**: Mehmet Emin Demir, Medicana International Ankara Hospital, Nephrology Department, Ankara, Turkey
**E-mail/E-posta:** demirmehmetemin@hotmail.com
**Received/Geliş:** 19.07.2022 **Accepted/Kabul:** 22.08.2022

## INTRODUCTION

Kidney transplantation (KTx) is the preferred choice for the treatment of end-stage renal disease (ESRD). A proper immunosuppressive treatment is a key point to the success of KTx, and the success substantially depends on strict adherence to the medications. Many studies have shown that adherence to the single-dose drug is better than to the multiple-dose drug (1,2).

Tacrolimus, a calcineurin inhibitor, has been the pivotal point of immunosuppression in preventing acute rejection episodes after allograft transplantation since its first introduction (3). Tacrolimus is both a powerful anti-rejection drug and also has important side effects such as nephrotoxicity (4). It has been demonstrated that most acute toxic effects of the drug are associated with peak serum levels occurring within 2 hours of drug ingestion (4). The drug is traditionally given in two equal doses every 12 hours and mostly the doses are adjusted according to trough levels. Morning and evening drug doses may be different due to day and night gastrointestinal motility differences.

Once-daily extended-release tacrolimus (tac-ER) (Advagraf®) is an novel formulation of tacrolimus that might facilitate kidney transplant recipients' compliance to medicines lifelong (5). The tac-ER formulation consists of the drug which is layered onto sugar spheres and an ethylcellulose polymer coating to retard the release of the drug (6). Immediate release tacrolimus (tac-IR) reaches its peak activity 2 hours after taking the drug and 100% of the drug is absorbed in the proximal gastrointestinal system (GİS) (7). Contrastly, tac-ER due to its unique formulation is absorbed along the entire GİS without reaching a peak plasma level of tacrolimus as high as tac-IR (7,8). The extended-release formulation of tacrolimus is used in both two ways, which first is switching from tac-IR to tac-ER in allograft recipients with stable kidney function and the second is de novo use. Literature has reported plausible outcomes of the switching protocols, rather than the outcomes of the de novo use. Additionally, the de novo use of tac-ER is still not the preferred first approach compared to tac-IR in many transplant centers regarding tacrolimus use, probably due to scarce evidence related to the posttransplant 1-year outcomes with de novo tac-ER use (9,10).

Here, we present our 1-year experiences on the de novo tac-ER use compared to tac-IR.

## MATERIAL AND METHOD

The study was carried out with the permission of Medicana Hospital, Noninvasive Clinical Researches Ethics Committee (Date: 28.01.2022, Decision No: 2022/01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective single-center study was conducted between January 2020 and January 2021 in a university affiliated-private hospital. All domestic ESRD patients who underwent a KTx in our hospital were included in the study (since the follow-up protocols varied in patients coming from outside of Turkey they were excluded). All recipients have received center-specific induction and immunosuppression protocols in preventing acute allograft rejection (**Table 1**). All de novo KTx recipients received the center-specific standard immunosuppression protocol involving either an (tac-ER) or tac-IR as a calcineurin inhibitor. Clinical and laboratory features of recipients were noted. Recipients' age, gender, primary kidney disease, comorbidities, tacrolimus doses, and tacrolimus serum trough and creatinine levels, urea, and electrolyte levels and drug-related side effects were documented. Acute rejection episodes, mortality, and hospitalization required infection rates were also noted.

### Risk Definition

The recipients addressed in protocol 1 were described as with low immunological risk. Other recipients were labeled to receive one option of protocols 2, 3, 4, and 5 and were considered to have moderate to high immunological risk. Re-transplantation recipients were treated similarly to other recipients according to established protocols as mentioned.

Target trough levels for tacrolimus in our center;

- 8-10 ug/L (within posttransplant month 1)
- 7-10 ug/L (between posttransplant months 1-3)
- 5-8 ug/L after posttransplant month 3

In low immunological risk patients, the lower level of the range and in moderate-high patients higher levels of the range were targeted.

### Statistical Analysis

Statistical analyses were performed using SPSS (IBM Corp. Released 2012. IBM SPSS [Statistical Package for Social Science] Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). The Kolmogorov Smirnow test and a histogram evaluation test were used to demonstrate the normality of the continuous variables. Continuous variables were expressed as mean ± standard deviation or median (interquartile range) depending on the distribution of the variable. Categorical variables were reported as numbers and percentages. Parametric and nonparametric continuous variables were compared by using independent samples t-test and Mann-Whitney U test, respectively. Chi-squared test and Fisher's Exact Test were used in comparison of the categorical variables. Univariate and multivariate regression tests were used to investigate the factors that had an impact on rejection

**Table 1.** Immunosuppression protocols given to recipients in our cohort

| | Protocol 1* | Protocol 2 | Protocol 3 | Protocol 4 | Protocol 5 |
|---|---|---|---|---|---|
| | LCM (-) + PRA (-) + FULL MATCH | LCM (-) + PRA (-) + FULL MISMATCH | LCM (-) + PRA (+) + Variable HLA compliance | LCM (-) + PRA (+) + DSA MFI < 2000 | LCM (-) + PRA (+) + DSA MFI > 2000 |
| Induction | -ATG: Single dose; 1,5 mg/kg + -3 consecutive doses of MP (500 mg/day) | -3 ATG doses + -3 consecutive doses of MP (500 mg/day) | | | Rituximab* + IVIG** Protocol 3 |
| Maintenance | Prednisolon 40 mg/day, tapered to 5 mg/day in 2 months + Tacrolimus 0,10 mg/kg + MMF 2 gr/day | Prednisolon 40 mg/day, tapered to 5 mg/day in 2 months + Tacrolimus 0,10 mg/kg + MMF 2 gr/day | 5-7 sessions pretransplant PE therapy + Protocol 2 | Protocol 3 | *375mg/1.73 m², two doses, -14 and -7 days ** 2 gr/kg (total dose) |

Note: LCM positive recipient candidates received a center-specific desensitization protocol as established in protocol 5 including rituximab + IVIG + PE therapy. After LCM becomes negative Protocol 2 is given (but 5-7 ATG doses were given instead of 3 doses) to recipients. Flow-cytometry is interpreted with other clinical data. MFI >2000 individuals were investigated with C1q in a single-beaded antigen test to detect the potency of the antibodies to activate the complement system.
Abbreviations: LCM; lymphocyte cross-match, PRA; panel reactive antibody, HLA; human leukocyte antigen, DSA; donor-specific antigen, MFI; mean flow intensity, ATG; anti-thymocyte globülin, MP; methylprednisolone, MMF; mycophenolate mofetil, PE; plasma exchange, IVIG; intravenous immunoglobulin
* Variable HLA compliance was assessed along with DR allele existence. Recipients without HLA DR compliance also received additional dose(s) of ATG, however, if they are not full mismatch was assigned to Protocol 1. Note: Tac-IR or Tac-ER were administered on the operation day after observing a satisfactory urine output (> 1-2 ml/kg/hour).

episode(s). $p<0.05$ was accepted statistically significant with a 95% confidence interval (CI).

## RESULTS

A total of 125 KTx was performed in our center between January 2020 and January 2021. 72 (57.6%) recipients were citizen of the Republic of Turkey and the remaining 63 (42.4%) recipients were from other countries, most of them from Arabic geography. All recipients from Turkey were evaluated. Three recipients (%2,4) died within the early posttransplant interval; one due to COVID-19 posttransplant month 3, one within the first week of the operation, and one due to a cardiac event within posttransplant month 1. Clinical and laboratory features of the study cohort are given in **Table 2**. Cytomegalovirus and polyoma BK virus DNA were detected positive in only two recipients, by using a polymerase chain reaction kit, however, were in low titers, and those recipients did not require the immunosuppressive dose reduction. Hyperglycemia (62.8%), elevated blood pressure (45.2%), diarrhea (28.6%), tremor (20.5%), and orthostatic hypotension (8.2%) were the most common adverse reaction noted in the hospital health software system regarding tacrolimus use. Two formulations of tacrolimus were found similar for adverse reaction rates ($p>0.05$).

The tac-ER and tac-IR groups were compared for allograft functions, rejection episode(s), trough levels, daily total dose (mg/kg), and recipients' demographic features (**Table 3** and **Table 4**). The two groups were found similar for age, body mass index (BMI) serum creatinine and tacrolimus trough levels at discharge, posttransplant months 1, 3, 6, and 12 ($p>0.05$) (**Table 3** and **Table 4**). Tacrolimus daily total doses (milligram/day and milligram/kg/day) at discharge, posttransplant months 1, and 3 were higher in the tac-ER group; p=0.015 and p=0.014, p=0.016 and p=0.013, and p=0.009 and p=0.004, respectively (**Table 4**). Multivariable logistic regression analysis indicated that the higher daily total doses of tacrolimus at discharge, posttransplant months 1, and 3 did not impact individually on serum creatinine levels; p=0.511 (milligram/day) and p=0.622 (milligram/kg/day). Rate of rejection episode(s), allograft loss, and total ATG doses were similar between the two groups, p=0.281, p=0.127, and p=0.253, respectively (**Table 3**).

The clinical and laboratory features of individuals with rejection episodes were compared with rejection-free individuals. (**Table 5**). As expected, serum creatinine levels were higher in the rejection group and serum creatinine levels remained at higher levels at month 12. Since the number of the sample was small, we did not evaluate the outcomes of the rejection episode(s)' according to classification as early or late rejection. However, according to our clinical observations, most of the early rejections did not recover to a satisfactory level of serum creatinine as can be assumed from **Table 4**. Linear regression analysis test demonstrated retransplantation had no impact on rejection episodes, p=0.414. Also, death-censored including all-cause allograft loss rate was similar between the two groups (p=0.508) (**Table 5**).

Tacrolimus dose in milligram/kilogram/day was similar in the rejection and rejection-free groups (**Table 6**) within post-transplant 12 months. Seven acute rejection episodes occurred within the posttransplant month 6. Recipient age, RRT duration, immunological risk status, tacrolimus dosing at 1, 3, and 6 months, and tacrolimus trough levels at 1, 3, and month 6 also were investigated whether they had an impact on acute rejection by univariate analysis (**Table 7**). A univariate regression analysis revealed only month 1 daily dosage significantly may impact acute rejection episode(s) (p=0.02).

| **Table 2.** Clinical and laboratory features of RTX recipients | |
|---|---|
| Age, years | 43.90 ± 12,35 |
| Gender; male/female, N, % | 46 / 26 (63,9% / 36.1%) |
| BMI, kg/m2 | 23.89 ± 4.49 |
| Weight, kilogram | 68.01 ± 14.94 |
| Immunological risk, N, %<br>Low<br>Moderate to severe | <br>42 (58.3%)<br>30 (41.7%) |
| rATG; number of doses (every dose 100 mg/day) | 2.68 (Mean dose 260 mg for each RTx case) |
| Rejection episode(s) (Yes/No); N, %<br>BPAR, n=<br><br><br>ABMR, n=<br>TCMR, n= | 9 / 60 (13% / 84.1%) 3 exitus not included<br>8 (8 of 9 cases were BPAR and 1/9 was diagnosed on clinical suspicion and rapid response to the antirejection therapy) 7 of 8 acute rejection developed within posttransplant month 6<br>7<br>1 |
| Renal replacement duration, month, median | 6.5 (0-132) |
| Preemptive yes/no, N, % | 24 / 48 (33.3 % / 66.7%) |
| Allograft source | All from living donor |
| Re-transplantation, n=(%) | 9 (12.5%) |
| Exitus | 3 (4.2%) all deaths within posttransplant 3 months (one death due to COVID-19 at posttransplant month 3, one within the first week of the operation, and one due to cardiac event within posttransplant month 1) |
| Allograft loss, N, %<br>Death-censored graft loss<br>Allograft loss (except death)<br>Primary nonfunction | 7 (9.7%)<br>3 (4.2%)<br>4 (5.5%) (1/2 primary nonfunction allograft)<br>2 (%2.7) |
| Primary disease, N, %<br>HT<br>DM<br>GN<br>PCKD<br>OTHERS<br>Unknown | <br>9 (12.5%)<br>19 (26.4%)<br>12 (16.7%) (41.7% IgA, 25.0% FSGS and 33.3% FMF)<br>2 (2.8%)<br>10 (13.9%)<br>20 (27.7%) |
| Follow-up, months mean | 11.6 |
| Creatinine, mg/dl (preoperative) | 6.85±2.12 |
| Creatinine, mg/dl (at discharge, approx. day 5) | 1.40±0.94 |
| Creatinine, mg/dl (month 1) | 1.27±0.70 |
| Creatinine, mg/dl (month 3) | 1.27±0.40 |
| Creatinine, mg/dl (month 6) | 1.27±0.36 |
| Creatinine, mg/dl (month 12) | 1.28±0.40 |
| Tacrolimus ER & IR, N, % | 30 (43.5%) & 39 (56.5%) |
| Tacrolimus discharge (approximately day 5)<br>Trough, mg/dl<br>At target, %<br>Dose mg/day | <br>8.47±3.03<br>61.5%<br>7.01±2.39 |
| Tacrolimus month 1<br>Trough, mg/dl<br>At target, %<br>Dose mg/day | <br>8.40±2.97<br>86.8%<br>6.47±3.70 |
| Tacrolimus month 3<br>Trough, mg/dl<br>At target, %<br>Dose mg/day | <br>7.41±2.16<br>80.4%<br>5.28±2.58 |
| Tacrolimus month 6<br>Trough, mg/dl<br>At target, %<br>Dose mg/day | <br>6.61±1.81<br>80%<br>4.70±2.54 |
| Tacrolimus month 12<br>Trough, mg/dl<br>At target, %<br>Dose mg/day | <br>7.95±1.93<br>82.4%<br>3.61±1.52 |

rATG; rabbit anti-thymocyte globülin, HT; hypertension, DM; diabetes mellitus, GN; glomerulonephritis, PCKD; polycystic kidney disease, FMF; familial Mediterranean fever, ER; extended-release, IR; immediate release

**Table 3.** Comparison of tac-IR & tac-ER for clinical and laboratory features.

| | Tac-ER, N=30 | Tac-IR, N=39 | P-value |
|---|---|---|---|
| Age, year | 44.96±10.75 | 41.92±13.01 | 0.309 |
| BMI, kg/m2 | 24.52±4,35 | 23.28±4.54 | 0.271 |
| Weight, kilogram | 68.57±13,46 | 67.65±16.29 | 0.810 |
| RRT duration, month | 6.5 (0-72) | 7 (0-132) | 0.675 |
| Rejection episode(s) | 2/30 (6.7%) | 7/39 (17.9%) | 0.281 |
| Allograft loss | 0/30 (0%) | 4/39 (10.3%) | 0.127 |
| Immun risk low/moderate-high | 18/21 | 11/19 | 0.469 |
| Re-transplantation yes/no, N | 4/26 | 5/34 | 1.000 |
| rATG dose (every dose 100 mg/day) | 2.75±1.18 | 2.62±1.45 | 0.253 |
| Serum creatinine; | | | |
| At discharge* | 1.28±1.03 | 1.59±1.02 | 0.242 |
| Month 1 | 1.16±0,43 | 1.49±1.16 | 0.141 |
| Month 3 | 1.21±0.44 | 1.51±1.06 | 0.215 |
| Month 6 | 1.15±0.25 | 1.59±1.52 | 0.132 |
| Month 12 | 1.10±0.29 | 1.40±0.43 | 0.107 |

BMI; body mass index, RRT; renal replacement therapy, rATG; rabbit anti-thymocyte globulin

**Table 4.** Comparison of tac-ER and tac-IR for tacrolimus trough levels, milligram/day and milligram/kilogram/day within posttransplant 12 months.

| | Tac-ER, N=30 | Tac-IR, N=39 | P value |
|---|---|---|---|
| Tacrolimus trough level; | | | |
| At discharge* | 8.19±2.32 | 8.57±3.50 | 0.614 |
| Month 1 | 8.85±3.16 | 7.95±2.72 | 0.223 |
| Month 3 | 7.62±1.72 | 7.28±2.43 | 0.578 |
| Month 6 | 6.58±1.52 | 6.67±2.00 | 0.879 |
| Month 12 | 8.37±2.07 | 7.53±1.82 | 0.403 |
| Tacrolimus doses; milligram/day | | | |
| At discharge* | 7.89±2.59 | 6.31±1.96 | **0.015** |
| Month 1 | 7.72±4.46 | 5.29±2.25 | **0.016** |
| Month 3 | 6.41±2.93 | 4.30±1.79 | **0.009** |
| Month 6 | 5.53±3.07 | 3.92±1.68 | 0.101 |
| Month 12 | 3.80±1.78 | 3.37±1.18 | 0.571 |
| Tacrolimus doses; milligram/kg/day | | | |
| At discharge* | 0.12±0.06 | 0.09±0.02 | **0.014** |
| Month 1 | 0.12±0.08 | 0.08±0.03 | **0.013** |
| Month 3 | 0.10±0.05 | 0.06±0.02 | **0.004** |
| Month 6 | 0.91±0.05 | 0.59±0.02 | 0.057 |
| Month 12 | 0.06±0.04 | 0.50±0.21 | 0.372 |

*Approximately at posttransplant day 5.

**Table 5.** Comparison of individuals with and without rejection episodes.

| | Rejection-Yes, N=9 | Rejection-No, N=60 | P value |
|---|---|---|---|
| Age, year | 40.66±8.93 | 43.61±12.64 | 0.501 |
| BMI, kg/m2 | 23.46±3.39 | 23.88±4.68 | 0.650 |
| Weight, kilogram | 70.27±8.92 | 67.60±16.02 | 0.500 |
| Serum creatinine; | | | |
| At discharge* | 2.36±1.43 | 1.31±0.88 | **0.003** |
| Month 1 | 2.17±1.64 | 1.21±0.68 | **0.003** |
| Month 3 | 2.22±1.79 | 1.22±0.40 | **0.001** |
| Month 6 | 2.45±1.76 | 1.18±0.27 | **<0.001** |
| Month 12 | 2.13±0.23 | 1.18±0.29 | **<0.001** |
| Tacrolimus trough **level**; | | | |
| At discharge* | 8.45±2.93 | 8.39±3.07 | 0.962 |
| Month 1 | 7.70±1.24 | 8.46±3.16 | 0.473 |
| Month 3 | 7.06±2.33 | 7.50±2.05 | 0.591 |
| Month 6 | 5.98±1.40 | 6.75±1.84 | 0.339 |
| Month 12 | 8.20±2.68 | 7.91±1.94 | 0.855 |
| Tacrolimus daily total doses; mg | | | |
| At discharge* | 7.00±2.64 | 6.96±2.38 | 0.948 |
| Month 1 | 5.81±2.22 | 6.57±3.88 | 0.591 |
| Month 3 | 5.16±2.33 | 5.30±2.61 | 0.907 |
| Month 6 | 3.16±1.25 | 4.89±2.61 | 0.275 |
| Month 12 | 2.25±0.35 | 3.78±1.52 | 0.187 |
| Allograft loss, n(%) | 1 (11.1%) | 1 (1.6%) | 0.252 |
| Death-censored including allograft loss | 1(11.1%) | 4 (6.6%) | 0.508 |
| Immun risk low/moderate-high | 3/6 | 37/23 | 0.152 |
| Re-transplantation, yes | 2/9 | 7/60 | 0.333 |
| ATG dose (every dose 100 mg/day) | 3.22±1.71 | 2.59±1.26 | 0.194 |
| RRT duration, month | 0 (0-72) | 7 (0-132) | 0.402 |

BMI; body mass index, ATG; anti-thymocyte globulin, RRT; renal replacement therapy

**Table 6.** Daily total dosing (milligram per kilogram) of tacrolimus in rejection and rejection free groups, and in tac-Er and tac-IR groups

| | Rejection-Yes | Rejection-No | P-value |
|---|---|---|---|
| Tacrolimus dosage; (daily milligram/kg) | | | |
| At discharge* | 0.09±0.027 | 0.11±0.541 | 0.532 |
| Month 1 | 0.08±0.025 | 0.10±0.072 | 0.351 |
| Month 3 | 0.07±0.027 | 0.08±0.049 | 0.555 |
| Month 6 | 0.05±0.027 | 0.07±0.044 | 0.343 |
| Month 12 | 0.03±0.002 | 0.06±0.032 | 0.176 |

**Table 7.** The impact of the factors on the acute rejection rate

| | P value | 95% CI |
|---|---|---|
| Recipient age, year | 0.481 | -0,860 (-0.09-0.004) |
| RRT duration | 0.315 | -0.126 (-0.04-0.315) |
| Immunological risk | 0.102 | 0.197 (-0.27-0.295) |
| Tacrolimus dosing month 1 | 0.022 | -0.123 (-2.187-0.857) |
| Tacrolimus dosing month 3 | 0.555 | -0.099 (-3.479-1.898) |
| Tacrolimus dosing month 6 | 0.343 | -0.194 (-4.529-1.639) |
| Tacrolimus trough month 1 | 0.452 | -0.094 (-0.040-0.018) |
| Tacrolimus trough month 3 | 0.595 | -0.074 (-0.060-0.035) |
| Tacrolimus trough month 6 | 0.339 | -0.159 (-0.102-0.036) |

## DISCUSSION

Calcineurin inhibitors are the key point of immunosuppression in kidney transplant recipients. Tacrolimus is commonly used as a two-divided daily dose. Daily single-dose formulation of tacrolimus (tac-Er) may contribute to the recipient's life-long immunosuppressive adherence and thus to have a good functioning allograft. This study adds new contributions to the effectiveness of tac-ER in KTx recipients.

Kidney transplant recipients are forced to have lifelong strict medical adherence, which involves many daily pills. This rationale depends on that nonadherence to immunosuppressive regimens has a negative impact on allograft functions and survival (11-14). Nonadherence also is associated with de novo donor-specific antibody development and acute rejection. Each acute rejection episode needs more intensive immunosuppression and additional approaches which result in more daily pills. This vicious cycle complicates recipients' therapy adherence and consequently allograft survival.

Nonadherence is associated with either reluctance to take medicine due to drug burden or missed or delayed doses of tacrolimus. On the other hand symptom experience (tremor, headache, diarrhea, high blood pressure levels) may impact recipient drug-tacrolimus- adherence (15). It is well known most acute tacrolimus toxicity is related to the peak serum levels of the drug which is achieved within the 2 hours after ingestion (4,7,15). Recipients under minimal immunosuppression are likely more vulnerable to nonadherence. Only one missed a dose of tacrolimus has resulted in a reduction of 49% in trough serum levels of tacrolimus (15).

Extended-release tacrolimus (Advagraf®) promised more medication adherence and comparable outcomes at its commercial introduction. The ensuing pieces of evidence of tac-ER have revealed improved compliance and satisfaction as well as comparable allograft function and similar adverse reaction compared to tac-IR (16,17). Additionally, at least theoretically it could be expected, a relatively less serum peak levels of tacrolimus with Advagraf® may contribute to achieving a less acute toxicity rate.

In this study, we substantially focused on assessing the effectiveness of 1- year de novo tac-ER compared to tac-IR (16-18). Wakasugi et al. (8) reported the 5-year outcomes of 250 de novo kidney transplants who were addressed to receive tac-ER in their study, however, the study was not in a comparative design to compare the effectiveness of tac-ER and tac-IR. They emphasized that 5-year outcomes and adverse reaction rates did not indicate any safety signals. Andres et al. (9) reported the outcomes of 79 kidney allograft recipients with mean 4 months follow-up and demonstrated a similar safety and efficacy rate in the de novo tac-ER group compared to tac-IR. Our study demonstrates similar 1-year allograft functions with tac-ER use compared to tac-IR. In previous studies rejection rates in de novo tac-ER use have been found lower, however, the difference was not at statistically significant levels (9,19). A similar result was obtained in our study. Biopsy proven acute rejection rate was lower in tac-ER (6.7% vs 17.9), however, it was not at a statistically significant level. Given all, it is known that tac-ER is not inferior to prevent acute rejection in solid organ transplantation including KTx (19-21).

Dosing tac-Er is commercially suggested similar to tac-IR; 0.10 mg/kg/day. However, at a rate of 1:1, 1:1.1, and 1:1.2 dosages in the switches protocols, and in the de novo use of Advagraf may be also utilized (1; tac-IR, the reference point). This may be due to recent, but weak, evidence that suggests using up to a 50% higher dose of tac-ER than tac-IR to achieve similar trough levels during the first 6 months. Crespo et al. (22) reported that de novo kidney transplant recipients need higher doses of Advagraf compared with Prograf to get therapeutic levels, and our study demonstrated a similar result. In our cohort, daily tac-ER dosage was higher at 25% at discharge, 46% at month 1, 49% at month 3, 41% at month 6, and 12% than tac-IR at month 12 posttransplant. Surprisingly, a higher dosage of tac-ER at month 1 (despite statistically similar trough levels between the two groups), likely has had an impact on acute rejection episode(s). ATG doses, immunological risk assessment, RRT duration, and age were similar between the two groups and regression analysis revealed no impact of those parameters on rejection development.

Our study has some limitations; some rejections were pre-diagnosis and anti-rejection therapies were established on clinical view rather than biopsy-proven rejection. Also, since we do have not a routine allograft biopsy protocol we are not able to compare the two groups for CNI nephrotoxicity. Additionally, we did not examine the adverse reactions or symptom-based drug usage behaviors of the recipient. However, we think the study will encourage many clinicians to use de novo extended-release tacrolimus formulation.

## CONCLUSION

A lifelong strict adherence to immunosuppressive medications to prevent acute rejection episodes is mandatory in KTx recipients. In this regard, a daily dose instead of multiple doses of immunosuppressive drugs may enhance the patients' compliance to therapy and that is one of the crucial points of the success in KTx. One-daily doses of tacrolimus; extended-release tacrolimus (Advagraf®), may provide more adherence to therapy and similar 1-year allograft function and rejection rates with tac-IR.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Medicana Hospital, Noninvasive Clinical Researches Ethics Committee (Date: 28.01.2022, Decision No: 2022/01).

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

## REFERENCES

1. Richter A, Anton SF, Koch P, Dennett SL. The impact of reducing dose frequency on health outcomes. Clin Ther 2003; 25: 2307-35.
2. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of the literature. J Behav Med 2008; 31: 213-24.
3. Shrestha BM. Two Decades of Tacrolimus in Renal Transplant: Basic Science and Clinical Evidences. Exp Clin Transplant 2017; 15: 1-9.
4. Yin J, Hsu T, Kerr JS, Steiner R, Awdishu L. Relationship between 2-Hour Tacrolimus Concentrations and Clinical Outcomes in Long Term Kidney Transplantation. Pharmacy (Basel) 2020; 8: 60.
5. Bakr MA, Nagib AM, Donia AF, et al. Comparative analysis for optimizing the modified release tacrolimus (Advagraf) after kidney transplantation: a prospective randomized trial. Saudi J Kidney Dis Transpl 2018; 29: 1267-73.
6. Shin TH, Ho MJ, Kim SR, et al. Formulation and in vivo pharmacokinetic evaluation of ethyl cellulose-coated sustained-release multiple-unit system of tacrolimus. Int J Biol Macromol 2018; 109: 544-50.
7. Staatz CE, Tett SE. Clinical pharmacokinetics of once-daily tacrolimus in solid-organ transplant patients. Clin Pharmacokinet 2015; 54: 993-1025.
8. Wakasugi N, Uchida H, Uno S. Safety and Effectiveness of Once-Daily, Prolonged-Release Tacrolimus in De Novo Kidney Transplant Recipients: 5-year, Multicenter Postmarketing Surveillance in Japan. Transplant Proc 2018; 50: 3296-305.
9. Andrés A, Delgado-Arranz M, Morales E, et al. Extended-release tacrolimus therapy in de novo kidney transplant recipients: single-center experience. Transplant Proc 2010; 42: 3034-7.
10. Rummo O, Carmellini M, Kamar N, et al. Long-term, prolonged-release tacrolimus-based immunosuppression in de novo kidney transplant recipients: 5-year prospective follow-up of the ADHERE study patients. Transpl Int 2020; 33: 161-73.
11. Lee SY, Chu SH, Oh EG, Huh KH. Low adherence to ımmunosuppressants ıs associated with symptom experience among kidney transplant recipients. Transplant Proc 2015; 47: 2707-11.
12. Sellarés J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. Am J Transplant 2012; 12: 388-99.
13. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Rates and determinants of progression to graft failure in kidney allograft recipients with de novo donor-specific antibody. Am J Transplant 2015; 15: 2921-30.
14. Ichimaru N, Kakuta Y, Abe T, et al. Treatment adherence in renal transplant recipients: a questionnaire survey on immunosuppressants. Transplant Proc 2008; 40: 1362-5.
15. Saint-Marcoux F, Woillard JB, Monchaud C, et al. How to handle missed or delayed doses of tacrolimus in renal transplant recipients? A pharmacokinetic investigation. Pharmacol Res 2015; 100: 281-7.
16. Lehner LJ, Reinke P, Hörstrup JH, et al. Evaluation of adherence and tolerability of prolonged-release tacrolimus (Advagraf™) in kidney transplant patients in Germany: A multicenter, noninterventional study. Clin Transplant 2018;32.
17. Bonani M, Balaphas A, Bedino G, et al. Adherence to, and patient convenience of, prolonged-release tacrolimus in stable kidney and liver transplant recipients after conversion from immediate-release tacrolimus in routine clinical practice in Switzerland. Swiss Med Wkly 2021; 151: w20453.
18. Tran D, Vallée M, Collette S, et al. Conversion from twice-daily to once-daily extended-release tacrolimus in renal transplant recipients: 2-year results and review of the literature. Exp Clin Transplant 2014; 12: 323-7.
19. Cross SA, Perry CM. Tacrolimus once-daily formulation: in the prophylaxis of transplant rejection in renal or liver allograft recipients. Drugs 2007; 67: 1931-43.
20. Saengram W, Vadcharavivad S, Poolsup N, Chancharoenthana W. Extended release versus immediate release tacrolimus in kidney transplant recipients: a systematic review and meta-analysis. Eur J Clin Pharmacol 2018; 74: 1249-60.
21. Vadcharavivad S, Saengram W, Phupradit A, Poolsup N, Chancharoenthana W. Once-daily versus twice-daily tacrolimus in kidney transplantation: a systematic review and meta-analysis of observational studies. Drugs 2019; 79: 1947-62.
22. Crespo M, Mir M, Marin M, et al. De novo kidney transplant recipients need higher doses of Advagraf compared with Prograf to get therapeutic levels. Transplant Proc 2009; 41: 2115-7