RESEARCH ARTICLE / *Araştırma Makalesi*

De novo extended-release Tacrolimus in Kidney Transplant Patients; Is it safe?

Böbrek Nakli Hastalarında De novo uzatılmış salımlı Takrolimus; Güvenli mi?

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Geliş Tarihi / Received : **20.07.2022** Kabul Tarihi / Accepted: **04.09.2023** Çevrimiçi / Online: **30.09.2023**

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Cite this article/Atıf:
Islam M, Fırat N, Pınar M, Öztop KE, Çakırsoy Çakar G, Sarıgedik E, Ercan Z, Dheir H. De novo extended-release Tacrolimus in Kidney Transplant Patients; Is it safe?, Sakarya Tıp Dergisi 2023;13(3): 478-483 DOI: 10.31832/smj.1326320

Abstract

Introduction	This study aimed to investigate whether de novo extended-release tacrolimus therapy is safe in kidney recipients.
Materials and Methods	The study was single-center, retrospective, and included a total of 57 patients, including 30 patients in the extended-release tacrolimus group (Group 1) and 27 patients in the immediate-release tacrolimus group (Group 2). Demographic and laboratory characteristics of the patients were recorded. Complications such as acute drug toxicity, acute rejection, new-onset diabetes mellitus after transplantation, and development of hypertension, opportunistic infection, and hospitalization data were recorded.
Results	The mean age of the patients was 46.23±14.2 years in group 1 and 47.04±14.6 years in group 2. There were 21 (70%) males in group 1, while 20 (74%) patients in group 2 had a male gender (P=0.73). The rate of improved serum creatinine values in the first week postoperatively was similar in both groups. While the mean tacrolimus levels on postoperative day 1 were significantly lower in group- 1 (P<0.05), there was no significant difference between tacrolimus levels on postoperative days 2-7. There was no significant difference between the groups regarding opportunistic infections, diabetes mellitus, and the need for hospitalization in the first six months of follow-up.
Conclusion	Initiation of de novo extended-release tacrolimus therapy in kidney recipients is safe in the long term and preserves graft function.
Keywords	Kidney transplantation, extended-release tacrolimus, immediate-release tacrolimus, graft function.

Öz

Amaç	*Bu çalışmada, böbrek alıcılarında de novo uzatılmış salımlı takrolimus tedavisinin güvenli olup olmadığını araştırmayı amaçlandı.*
Yöntem ve Gereçler	*Çalışma tek merkezli, retrospektif olup, uzatılmış salınımlı takrolimus grubunda 30 hasta (Grup 1) ve hızlı salınımlı takrolimus grubunda 27 hasta (Grup 2) olmak üzere toplam 57 hastayı içermektedir. Hastaların demografik ve laboratuvar özellikleri kaydedildi. Akut ilaç toksisitesi, akut rejeksiyon, nakil sonrası yeni başlayan diyabet, hipertansiyon gelişimi, fırsatçı enfeksiyon gibi komplikasyonlar ile hastaneye yatış verileri kaydedildi.*
Bulgular	*Hastaların yaş ortalaması grup 1'de 46,23±14,2 yıl, grup 2'de 47,04±14,6 yıl idi. Grup 1'de 21 (%70) erkek hasta bulunurken, grup 2'de 20 (%74) hasta erkek idi (P=0.73). Ameliyat sonrası ilk haftada serum kreatinin değerlerinde iyileşme oranı her iki grupta da benzerdi. Ameliyat sonrası 1. gün ortalama takrolimus düzeyleri grup 1'de anlamlı derecede düşük iken (P<0.05), ameliyat sonrası 2-7. günler arasındaki takrolimus düzeyleri arasında anlamlı fark yoktu. İlk altı aylık takipte fırsatçı enfeksiyon, diyabet ve hastaneye yatış ihtiyacı açısından gruplar arasında anlamlı fark yoktu.*
Sonuç	*Böbrek alıcılarında de novo uzatılmış salımlı takrolimus tedavisine başlanması uzun vadede güvenlidir ve greft fonksiyonunu yönünden güvenli bir seçenektir..*
Anahtar Kelimeler	*Böbrek nakli, uzatılmış salınımlı takrolimus, hızlı salınımlı takrolimus, greft fonksiyonu.*

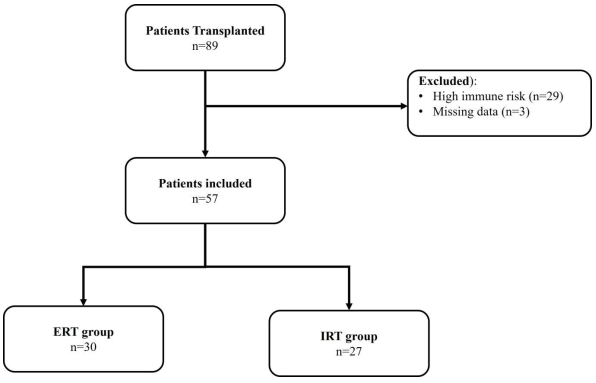
INTRODUCTION

Kidney transplantation is still the best renal replacement therapy option that significantly improves patient survival and quality of life.[1] After transplantation, patients have to take regular immunosuppressive drugs to prevent graft loss in the long term. Calcineurin inhibitors are indispensable drugs used in solid organ transplants.[2] Immediate-release tacrolimus (IRT) has been shown to significantly reduce acute rejection rates, resulting in successful kidney transplantation in the short term and, thus, considerably improving graft and patient survival.[3] In recent years, long-release tacrolimus (ERT) therapy, which allows once-daily use, is safe with pharmacokinetic and efficacy studies.[4] Noncompliance is one of the more critical risk factors for kidney graft loss over the long term. A meta-analysis that investigated nonadherence in kidney transplant recipients showed that the odds of graft failure increased sevenfold (95% confidence interval, 4%–12%) in non-adherent patients compared with adherent patients.[5] In addition, using de novo ERT in renal recipients may reduce non-adherence events, especially in the long term. This study aimed to investigate the efficacy of de novo extended-release tacrolimus versus immediate-release tacrolimus therapy in kidney recipients.

MATERIAL and METHODS

Patients who underwent kidney transplants between May 2019 and March 2022 were evaluated retrospectively. Ethical approval of the study was obtained from the Sakarya University Ethics Committee (no: E-71522473-050.01.04.146272-192). All patients received steroid and anti-thymocyte globulin (ATG) as induction therapy, followed by a maintenance immunosuppressive therapy consisting of prednisone, tacrolimus, and mycophenolate mofetil. We included 57 patients, 30 in the ERT (Group 1) and 27 in the IRT (Group 2) group as shown in figure 1. Demographic and laboratory characteristics of the patients were recorded. Both types of tacrolimus drugs were started at a dose of 0.15 mg/kg/day on the day of the operation, and necessary dose changes were made so that the target serum level for both drugs was between 8-10 ng/mL. Cadaveric transplants, patients under 18 years of age, patients who underwent different immunosuppressive therapy protocols, patients with high immune risk, patients with active malignancies, and patients using drugs interacting with tacrolimus were not included in the study. Patients' information on dialysis duration, primary disease, presence of comorbid disease, hospitalization time, graft functions, tacrolimus blood levels, acute drug toxicity, acute rejection, new-onset diabetes mellitus after transplantation (NODAT), development of hypertension, opportunistic infection, and hospitalization was recorded. All results were evaluated in the first 6 months.

Figure1: Flowchart of the study population



Abbreviations: ERT: extended-release tacrolimus, IRT: intermittent-release tacrolimu

Statistical analysis

SPSS version 26.0 software was used for statistical analysis (SPSS Inc., Chicago, IL, USA). Mean, standard deviation, number, and percentage values were used for descriptive variables, and median and interquartile range values were used for data showing non-parametric distribution. Whether the numerical variables showed normal distribution or not was evaluated with the Kolmogorov-Smirnov test. Independent samples t-test was used for independent groups in comparing two normally distributed groups, and the Mann-Whitney U test was used in comparing the two groups in terms of normally distributed numerical variables. Statistical significance was accepted as $p < 0.05$.

RESULTS

The mean age of patients in was 46.23±14.2 years and 47.04±14.6 years in ERT and IRT groups, respectively. 70% (n=21) of the ERT group were male versus 74 % (n=20) in the IRT group (P=0.73). The number of preemptive transplants was similar (n=18) in both groups (Table 1).

Table 1: Demographic characteristics of patients

Characteristics	ERT Group, no=30	IRT Group, no=27	P
Age (year)*	46.23±14.2	47.04±14.6	0.917
Sex M/F, No (%)	21(9%)	20 (7%)	0.733
BMI, kg/m2*	23.9±4.7	24.2±6.4	0.786
Type of transplantation, no, %			0.460
Preemptive	18 (60)	18 (66.7)	
After Dialysis	12 (40)	9 (33,30)	
Pre-transplant dialysis duration, month, %	9.0 (20.7)	10.8 (34.8)	0.870
Primary Disease, no, %			0.107
Diabetes Mellitus	8 (26.7)	2 (7.4)	
Hypertension	4 (13.3)	4 (14.8)	
Chronic glomerulonephritis	9 (30)	8 (29.6)	
Polycystic kidney Disease	2 (6.7)	5 (18.5	
Other	7 (23.3)	8 (29.6)	
Pretransplant residual urine, ml/day*	1437±1217	1555±1072	0.785
HLA mismatch (median)	3 (1-5)	3 (1-6)	0.5
Cumulative total ATG dose, mg*	391.7±194.3	534.5±350.9	0.262

Abbreviations: ATG: Anti-thymocyte globulin, ERT: Extended-release tacrolimus, IRT: immediate release tacrolimus, M: male, F: female, BMI: body mass index, HLA: human leucocyte antigen,
* Shown as mean±SD

The difference between the two groups in terms of primary disease, HLA miss-match, and cumulative ATG induction treatment was not significant (P>0.05) (Table 1). Both groups had similar rates of improvement in serum creatinine values in the first week after transplantation. Tacrolimus levels were significantly lower in the ERT group on the first postoperative day, but there was no difference between the two groups on the subsequent days. Additionally, there were no appreciable differences between the groups in terms of opportunistic infections, NODAT, or the requirement for hospitalization in the initial six months of follow-up. Although the ERT group experienced a greater rate (1.8 times) of acute rejection than the IRT group (26.6% vs. 14.8%). This difference was not statistically significant (p=0.273) (Table 2).

Table 2: Laboratory outcomes of patients in both study groups

Characteristics	ERT Group, no=30	IRT Group, no=27	P
Basal serum Creatinine, mg/dl	6.48±1.61	6.39±1.52	0.773
1st day Creatinine, mg/dl	3.21±1.98	2.83±1.26	0.492
2nd day Creatinine, mg/dl	2.11±2.23	1.71±1.41	0.329
3rd day Creatinine, mg/dl	1.85±2.02	1.39±0.97	0.306
5th day Creatinine, mg/dl	1.58±1.39	1.19±0.59	0.125
7th day Creatinine, mg/dl	1.41±0.78	1.35±1.03	0.357
1st month Creatinine, mg/dl	1.24±0.23	1.21±0.37	0.517
3rd month Creatinine, mg/dl	1.22±0.24	1.18±0.38	0.370
6th month serum Creatinine, mg/dl	1.24±0.33	1.14±0.27	0.447
1st day Tacrolimus ng/mL	5.5 (1.4-30)	7.3 (4.1-36)	0.040
3rd day Tacrolimus ng/mL	8.6 (2.4-21)	8.4(4.3-21)	0.672
5th day Tacrolimus ng/mL	8 (3.2-19)	8.5 (4.6-15)	0.362
7th day Tacrolimus ng/mL	7.9 (2.7-16.7)	8.5 (1.8-14)	0.299
BK nephropathy, no, %	1 (3.33)	2 (7.40)	0.492
CMV infection, n, %	1 (3.33)	0 (0)	0.339
NODAT, n, %	0 (0)	1 (3.7)	0.288
Re-hospitalization, n, %	12 (40)	13 (48.1)	0.536
Biopsy proven acute rejection, n, %	8 (26.6)	4 (14.8)	0.273

Abbreviations: CMV: Cytomegalovirus, ERT: Extended-release tacrolimus, IRT: immediate release tacrolimus NODAT: New onset diabetes mellitus after transplantation

DISCUSSION

In this study, we found that de novo ERT can be used safely and effectively in living donor kidney recipients without considerable immunological risk. Similar cumulative steroid and ATG doses were administered to both groups. In the postoperative follow-up, the rates of graft function improvement and hospital stay were comparable betwe-

en the two groups. ERT's excellent benefits for transplant recipients' quality of life and facilitate treatment adherence. In the systemic review, de novo ERT compared to IRT showed similar posttransplant 6-month graft survival rates in deceased and living kidney transplant recipients.[6] In Our study conducted only on living kidney recipients, we found similar 6-month graft function results. ERT generally requires higher daily dosages than IRT to achieve the target through blood levels, at least in de novo use from the first day of kidney transplantation. However, similar blood concentrations are achieved in ERT and IRT 3 days after starting treatment.[7] In our study, however, we used the same dose per kilogram (0.15 mg/kg/day) from baseline for both drug forms and tacrolimus levels measured every other day for one week post-transplant were similar in both groups except day one only. Regarding pharmacokinetic properties, tacrolimus blood level shows high intra- and inter-patient variability. The balance between effective tacrolimus concentrations and toxicity is difficult to find, and close monitoring is required in the first days after transplantation to adjust the level of the drug therapeutically.[8] The patients who received ERT had a broader range of tacrolimus level values on their first day than the patients who received IRT. The results were noticeably different between the two groups. However, both groups' tacrolimus blood levels in the following days were comparable. We made the necessary dose modifications to reach the targeted drug level in both patient groups. The similarity between the two groups may be because we made fewer dose adjustments, and the drug levels were evaluated every other day rather than daily. In addition, this may have reduced the frequency of drug variability. The advantages of switching to ERT in adherence to an immunosuppressed regimen in liver transplant patients have been demonstrated.[9] The immunosuppressive regimen in kidney transplant patients requires multiple drugs, A Swedish study evaluating compliance with ERT and ERT regimens reported no significant difference between the two groups in the 12-month evaluation[10]. Fluctuations in tacrolimus drug concentrations can occur due to delayed or missed doses, which can lead to rejection.[11] Most patients prefer to eliminate evening doses of immunosuppressive therapy, with ERT being associated with improved quality of life compared to ERT and adherence to immunosuppressive therapy.[12] The meta-analysis showed that the studies performed mostly had short-term results of 6 and 12 months and that there was no significant difference between the two groups.13 Beyond our expectations, patients receiving ERT had a higher rejection rate than patients receiving IRT, but the results were not statistically significant. This should not be misinterpreted and should not be generalized to all transplanted patients.. Tacrolimus causes glucose metabolism disorder as a side effect and thus may cause diabetes[6]. During the specified follow-up period, diabetes mellitus was observed in 1 patient in the ERT group. There was no statistical difference between the two groups regarding drug-induced diabetes mellitus. Post-transplant infections can impact graft and patient survival, and infectious complications can cause significant morbidity and require hospitalization and follow-up of patients[7]. There was no significant difference between the two groups regarding post-discharge hospitalization, BK nephropathy, and CMV infection.

Our study has some limitations. First, it is retrospective and included a small number of matched patients in both arms. As a low-volume single renal transplant center, we had few eligible patients compliant with the inclusion criteria within the time frame of the study.

In conclusion, de novo ERT was found to be as safe and as effective as ERT in kidney transplant recipients. Nonadherence to medications has multiple reasons, but the increased frequency of administration of medications constitutes the most important one. Therefore, the improved convenience of less frequent administration would be expected to improve adherence and, consequently, increase graft survival. De novo ERT drug level monitoring every other day rather than daily may prevent rapid dose changes and variability of drug levels. Initiating de novo ERT therapy

in kidney recipients is safe in the long term and preserves graft function. Randomized prospective studies with higher numbers will contribute to a better clarification of this issue.

Acknowledgment

We thank Dr. Fehmi Çelebi, Dr. Fatih Altınparmak, and Dr. Emrah Akın for their logistic support and help in our study.

Declaration of Competing Interest:

All authors declare that they have no known competing financial interests or personal relationships related to any content in this manuscript.

Authorship contribution statement:

Coceptualization: HD, Mİ. Methodology: HD, Mİ, NF. Data collection: HD, Mİ, NF, ES, ZE, GÇÇ, MP. Data analysis and interpretation: Mİ, ES. Preparation of first draft: HD, Mİ. Review and editing: HD, Mİ, NF, ES, ZE, GÇÇ, MP, KEÖ. Supervision: HD.

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