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Research

Novel Once-daily Extended-release Tacrolimus Versus Twice-daily Tacrolimus in *De Novo* Kidney Transplant Recipients During the Early Posttransplant Period

Erken Posttransplant Dönemde Hızlı Salınımlı Takrolimus ve Uzun Salınımlı Takrolimusun *De Novo* Kullanımı

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ABSTRACT

Objective: Tacrolimus is used in more than 80% of kidney transplant recipients due to its ability to avoid rejection. Irregularities in tacrolimus level may affect clinical outcomes by subjecting patients to adverse events associated with graft rejection or immunosuppressive therapy. There are two forms of tacrolimus; immediate-release (IR-T) and prolonged release (PR-T). This study is designed to compare the clinical follow-up of kidney transplant patients who are receiving prolonged-release (PR-T; Advagraf) and immediate-release (IR-T; Prograf) tacrolimus in the posttransplant first week.

Methods: This study included 78 *de novo*, adult kidney transplant patients to prolonged-release tacrolimus 0.15 mg/kg/day (group 1, n=39) and immediate-release tacrolimus 0.15 mg/kg/day (group 2, n=39) for the first week in the posttransplant period. Demographic features, whole blood tacrolimus levels and kidney function were compared between the two groups. The presence of acute rejection and adverse events, antihypertensive drug use and arterial blood pressure of all patients were considered. Drug doses were determined according to the previously targeted tacrolimus level. SPSS 22 for Windows was used for statistical analysis.

Results: Acute rejection was not seen in any patient and there were no adverse events in the posttransplant first week. However, group 2 patients were found to have higher tacrolimus levels on the posttransplant 1st, 4th and 7th days (p=0.02, p=0.009 and p=0.013 respectively). Serum creatinine levels were significantly increased in group 2 patients on the posttransplant 7th day (p=0.02). Systolic, diastolic or mean arterial blood pressure were not different between the groups.

Conclusion: Prolonged-release tacrolimus is effective in preventing acute rejection when adequate blood levels are maintained, and appears promising as it makes it possible to avoid interindividual variation in absorption and early calcineurin inhibitor toxicity.

Keywords: Immediate-release tacrolimus, kidney transplantation, prolonged-release tacrolimus

ÖZ

Amaç: Takrolimus, rejeksiyonu önleme yeteneği nedeniyle böbrek nakli alıcılarının %80'inden fazlasında kullanılmaktadır. Takrolimusun hem düşük hem de aşırı dozu, hastaları greft reddi veya immünosüpresif tedaviyle ilişkili advers olaylara maruz bırakarak klinik sonuçları etkileyebilir. Takrolimus, hızlı salınımlı (IR-T) ve yavaş salınımlı (PR-T) olmak üzere iki formda bulunmaktadır. Bu çalışma, posttransplant birinci haftada, yavaş salınımlı (PR-T; Advagraf) ve hızlı salınımlı (IR-T; Prograf) takrolimus alan böbrek nakli alıcılarımızın klinik takibini karşılaştırmak için tasarlanmıştır.

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Gereç ve Yöntem: Bu çalışma, nakil sonrası yedi gün boyunca yavaş salınımlı takrolimus 0,15 mg/kg/gün (grup 1, n=39) ve hızlı salınımlı takrolimus 0,15 mg/kg/gün (grup 2, n=39) alan 78 *de novo*, yetişkin böbrek nakli alıcılarını içermektedir. Takrolimus düzeyi ve böbrek fonksiyonu, demografik özellikler ve klinik parametreler iki grup arasında karşılaştırıldı. Tüm hastalarda akut rejeksiyon ve advers olay varlığı, antihipertansif ilaç kullanımı ve arteriyel kan basıncı araştırıldı. Önceden hedeflenen takrolimus düzeyine göre ilaç dozları belirlendi. İstatistiksel analiz için Windows için SPSS 22 kullanıldı.

Bulgular: Hiçbir hastada akut rejeksiyon olmadı ve nakil sonrası ilk haftada herhangi bir yan etki görülmedi. Ancak, grup 2 hastalarında nakil sonrası 1., 4. ve 7. günlerde tam kan takrolimus düzeyleri daha yüksek bulundu (sırasıyla p=0,02, p=0,009 ve p=0,013). Ayrıca grup 2 hastalarında transplantasyon sonrası 7. günde serum kreatinin seviyeleri anlamlı olarak arttı (p=0,02). Sistolik, diyastolik veya ortalama arteriyel kan basıncı gruplar arasında farklı değildi.

Sonuç: Yavaş salınımlı takrolimus, yeterli kan seviyeleri sağlandığında akut rejeksiyonu önlemede etkilidir, ayrıca emilim ve erken kalsinörin inhibitörü toksisitesinde bireyler arası varyasyondan kaçınmayı mümkün kılması nedeni ile de umut verici görünmektedir.

Anahtar Kelimeler: Hızlı salınımlı takrolimus, böbrek nakli, yavaş salınımlı takrolimus

INTRODUCTION

Tacrolimus (TAC) is a macrolide immunosuppressive isolated from *Streptomyces tsukubaensis* in 1984 (1). It is used in over 80% of kidney transplant patients due to its ability to prevent rejection. Metabolism of TAC exists in the liver by cytochrome p450 3A4 and cytochrome p3A5 and 1% of TAC is excreted in urine (2). Oral bioavailability of TAC exhibits large variability, ranging 5% to 90%. Drugs that induce or inhibit CYP3A enzymes interact with TAC blood level. Also, gut motility affects absorption and high blood levels of TAC can be seen in diarrhea because of decreased p-glycoprotein activity. TAC binds to FK-binding protein and TAC- FK-binding protein complex interferes with calcineurin. After the inhibition of calcineurin, dephosphorylation of nuclear factor of activated T cells does not occur and T cell proliferation is stopped. TAC has a narrow therapeutic index so the drug concentration must be monitored. After the transplant, blood TAC level is kept between 5 and 15 ng/mL (3). Irregularities in TAC level may affect clinical outcomes by subjecting patients to adverse events associated with graft rejection or immunosuppressive therapy. Acute and chronic nephrotoxicity, hypertension, hyperlipidemia, electrolyte imbalance, diarrhea, posttransplant diabetes mellitus (PTDM) and neurotoxicity are common advers events of TAC (4).

There are two forms of TAC; immediate-release (IR-T) and prolonged release (PR-T). While the excipient of IR-T is croscarmellose, excipient of PR-T is ethylcellulose and this slows down the diffusion of the drug. While IR-T is taken twice a day, PR-T is taken once a day. After oral administration IR-T reaches a maximum plasma concentration in about 174 min, PR-T reaches in about 300 min. Conversion from IR-T to PR-T in the early period of posttransplant or using *de novo* PR-T in kidney transplantation has been studied in many studies. In Osaka Trial, PR-T regimen showed similar efficacy to IR-T regimen (5). The effectiveness and safety of both TAC preparation is well known and similar, but PR-T has an advantage of single daily dose. Nonadherence to immunosuppressive drugs in renal transplant patients is a immense problem. Nonadherence to immunosuppressive drugs is a serious cause of rejection. A study that compares adherence to IR-T and PR-T in renal transplant patients found that adherence was higher in the IR-T group than the PR-T group (6). The other problem about TAC is to reach steady-state trough levels. Intra and interpatient variability of TAC level is reported to be higher in IR-T than PR-T. High intra- and interpatient variability is related to graft loss, kidney dysfunction and acute rejection (7). Due to pharmacokinetic characteristics of PR-T, it reduces intra- and interpatient instability.

PR-T has been used safely in kidney transplantation for less than a decade. Our experience with switching form IR-T to PR-T goes along with the successful results reported in the literature. However since we were not so sure about using *de novo* PR-T in kidney transplant patients we designed a prospective randomized study to compare the clinical follow-up of kidney transplant patients who are receiving PR-T and IR-T in the first week of posttransplant period.

METHODS

This study included 78 *de novo* adult kidney transplant patients (38 male, 30 female; age ranging from 14 to 66 years) receiving PR-T 0.15 mg/kg/day (group 1, n=39) and IR-T 0.15 mg/kg/day (group 2, n=39) in the posttransplant first week. Both forms of TAC were started on the day before the operation. All the patients had low immunological risk and all the patients received anti-thymocyte globulin 2.5 mg/kg/day for 3 days according to our treatment protocol for kidney transplant patients. Demographic features, whole blood TAC levels and kidney function were compared between the groups. Adverse events, acute rejection, antihypertensive drug use and arterial blood pressure of all patients were considered. Drug doses were determined according to the previously targeted TAC level. The demographic and clinical data were obtained from the files of the patients. Written informed consent was obtained

from all patients. The study protocol was approved by the Ethics Committee of Acıbadem University on 02.09.2021 with approval number 2021-16/01.

Statistical Analysis

The results were analyzed by use of the Statistical Package for the Social Sciences, version 22 (SPSS, Chicago, Ill, United States). Values displaying a normal distribution are defined as mean ± standard deviation. Differences between numeric variables were tested with the use of independent-samples Student t-test or Mann-Whitney U test, that was appropriate. Chi-square tests were used to compare categorical variables. The degree of relation between two parametric values was analyzed with Pearson correlation test while Spearman correlation test was preferred for nonparametric values. A value was considered statistically significant at $p<0.05$.

RESULTS

Data regarding demographic and clinical aspects such as age, gender, diagnosis of diabetes mellitus, hypertension and presence of acute rejection episodes were described.

This study included 78 *de novo* adult kidney transplant patients (38 male, 30 female; age ranging from 14 to 66 years) receiving PR-T 0.15 mg/kg/day (group 1, n=39) and IR-T 0.15 mg/kg/day (group 2, n=39) in the posttransplant first week. Mean age of group 1 was 44±13.6 and mean age of group 2 was 43.9±13.7. No age difference was seen between the two groups (p=0.980), but male predominance was present in group 1 (p=0.02) (Table 1). Creatinine levels on the postoperative first 6 days were comparable in both groups, but serum creatinine levels of the postoperative 7th day were lower in group 1 (p=0.025) (Table 2). Diabetic or hypertensive nephropathy prevalence as the etiology of chronic kidney disease in each group was comparable. Also, none of these diseases were seen in the early posttransplant period. Regarding TAC levels, target trough values (8-12 ng/mL) were achieved in two groups, however mean TAC levels on days 1, 4, 5, and 7 were higher in group 2 (p=0.020 p=0.009 p=0.013 p=0.013 respectively) (Table 3). Neither acute rejection episodes nor graft loss was seen in both groups. There was no statistically significant difference between the two groups in terms of systolic, diastolic or mean arterial blood pressure (Table 4).

DISCUSSION

Since TAC is the cornerstone of the immunosuppressive therapy, its appropriate use in kidney transplant patients plays an imperative role in determining graft and patient survival. Adjustment of the optimal TAC dose for not only preventing acute rejection, but also avoiding the adverse effects is an important parameter leading to reach high survival rates.

Table 1. Demographic features

	Group 1	Group 2	p
Gender	19 males (48.7%)	29 males (48.7%)	0.020
	20 females (51.3%)	10 females (25.6%)	
Age (years)	44.0±13.6	43.9±13.7	0.980

Table 2. Creatinine levels on postoperative days 1-7

	Group 1		Group 2		
Serum creatinine (mg/dL)	**Mean ± SD**	**Min-max (median)**	**Mean ± SD**	**Min-max (median)**	**p**
Day 1	2.13±1.00	0.58-5.22 (1.99)	2.34±0.93	0.88-4.26 (2.12)	0.348
Day 2	1.17±0.57	0.46-2.85 (1.09)	1.28±0.52	0.59-2.53 (1.16)	0.259
Day 3	0.99±0.43	0.42-2.27 (0.89)	1.01±0.38	0.1-2.03 (0.91)	0.532
Day 4	1.01±0.45	0.41-2.88 (0.94)	1.06±0.33	0.59-2.08 (0.99)	0.296
Day 5	1.02±0.41	0.46-2.55 (0.98)	1.03±0.31	0.17-1.69 (0.98)	0.407
Day 6	1.03±0.42	0.46-2.56 (0.99)	1.10±0.33	0.6-2.01 (1.05)	0.407
Day 7	1.02±0.38	0.45-2.3 (0.99)	1.17±0.33	0.59-2.11 (1.12)	0.025

SD: Standard deviation, min: Minimum, max: Maximum

Conversion from IR-T to PR-T has been evaluated in many studies, but *de novo* use of PR-T and its effects are still unclear. In Osaka study, which compared *de novo* use of PR-T and IR-T outcomes in both groups were evaluated. Patient and graft survival was similar in all groups (4). Kolonko et al. (8) enrolled 72 kidney transplant patients and converted from IR-T to PR-T. They found that the conversion from IR-T to PR-T was followed by advancement in kidney graft function, but this improvement was not associated with TAC blood trough levels (8). In an overview of phase 3 and 4 studies in *de novo* patients, it was shown that PR-T and IR-T had a similar effect to avoid graft dysfunction and rejection (9).

Table 3. Tacrolimus levels on postoperative days 1-7

	Group 1		Group 2		
TAC (ng/mL)	Mean ± SD	Min-max (median)	Mean ± SD	Min-max (median)	p
Day 0	9.2±5.0	2-27.6 (8.6)	7.4±3.5	3.1-18.4 (6.6)	0.115
Day 1	11.3±5.4	2.6-29.3 (10.7)	18.2±14.1	4.5-56.4 (13)	0.020
Day 2	14.1±6.1	7.5-29.5 (12.8)	14.8±7.1	6.9-44.2 (12.8)	0.904
Day 3	11.4±4.1	7.1-20.5 (10.1)	12.5±4.5	0.2-21.1 (13.4)	0.377
Day 4	12.9±4.7	6.8-27.8 (11.8)	15.8±5.1	6.6-32.4 (14.2)	0.009
Day 5	11.6±3.7	6.2-19.8 (10.8)	14.5±4.1	9-27.5 (14)	0.013
Day 6	16.8±23.0	7-108 (11.9)	12.7±3.7	1.3-23.4 (12.1)	0.352
Day 7	11.3±4.3	6-23.5 (10.7)	13.4±4.5	8.3-27.4 (12)	0.013

SD: Standard deviation, min: Minimum, max: Maximum, TAC: Tacrolimus

Table 4. Blood pressure levels in both groups

		Group 1		Group 2		
		Mean ± SD	Min-max (median)	Mean ± SD	Min-max (median)	p
Systolic blood pressure	Day 1	138.7±16.2	106-177 (140)	141.8±15.0	100-170 (140)	0.370
	Day 2	140.5±19.9	100-190 (140)	144.6±16.4	118-186 (149)	0.320
	Day 3	141.0±20.9	90-189 (140)	143.7±18.0	110-190 (140)	0.512
	Day 4	140.2±14.6	110-170 (140)	139.7±16.3	100-180 (140)	0.876
	Day 5	132.6±16.5	92-170 (132.5)	137.8±14.8	110-180 (140)	0.137
	Day 6	131.2±15.6	100-160 (130)	137.6±18.9	110-190 (135)	0.211
	Day 7	127.8±17.4	80-162 (130)	133.7±19.4	100-180 (130)	0.378
Diastolic blood pressure	Day 1	83.3±11.5	56-104 (80)	86.6±10.1	60-103 (90)	0.237
	Day 2	82.9±10.7	60-108 (80)	85.2±11.5	70-116 (80)	0.577
	Day 3	84.5±11.8	50-110 (85)	85.7±10.8	65-110 (90)	0.791
	Day 4	83.6±10.4	70-109 (80)	84.2±10.5	60-103 (80)	0.660
	Day 5	81.9±9.8	60-100 (80)	83.7±10.1	70-110 (80)	0.490
	Day 6	80.4±10.7	50-100 (80)	82.3±11.1	70-120 (80)	0.734
	Day 7	77.6±10.6	50-97 (80)	80.7±12.0	60-104 (80)	0.439
Mean arterial pressure	Day 1	101.8±11.3	72.7-123.3 (101.7)	105.0±10.1	80-120 (106.7)	0.198
	Day 2	102.1±12.0	73.3-123.3 (103.3)	105.0±11.8	86.7-139.3 (105)	0.286
	Day 3	103.3±13.5	63.3-130.3 (104.7)	105.0±11.8	80-136.7 (106.7)	0.652
	Day 4	102.5±10.7	84.7-125 (100)	102.7±11.2	73.3-120 (100)	0.729
	Day 5	96.3±19.3	0-119 (98.7)	101.8±9.8	83.3-126.7 (100.3)	0.205
	Day 6	94.8±19.0	0-116.7 (96.7)	100.7±12.8	83.3-140 (100)	0.364
	Day 7	84.6±31.2	0-116 (93.3)	78.2±42.1	0-126.7 (93.3)	0.976

SD: Standard deviation, min: Minimum, max: Maximum

Our study involved 78 *de novo*, adult kidney transplant patients receiving PR-T and IR-T in the posttransplant period. Target trough levels of TAC (8-12 ng/mL) were reached in both groups. Lower mean levels of TAC with lower serum creatinine levels on the postoperative 7th day were remarkable in patients with the PR-T groups immunosuppression is the main risk factor for PTDM. TAC decreases insulin release from pancreatic beta cells (10) and PTDM enhances the risk of cardiovascular disease, kidney graft loss and death. Regarding PTDM, Silva et al. (11) found that the incidence of PTDM was lower with PR-T than IR-T (11), however we did not observe any difference in the early posttransplant period.

As it is known 18%-30% of renal transplant patients die from cardiovascular diseases (12). Hypertension is one of the most important causes of cardiovascular diseases. Hypertension is seen with the prevalence of 80% in kidney transplant patients in the early posttransplant period and it reduces to 50% at the end of the first year. So, blood pressure control is critical for renal transplant patients. TAC use is one of the reasons for hypertension in renal transplant recipients. PR-T and IR-T were compared in many studies for developing hypertension. Guirado et al. (13) did not find any statistical significance when compared the two forms of TAC in developing uncontrolled hypertension and we also did not observe any difference between IR-T and PR-T groups in terms of arterial blood pressure.

CONCLUSION

Our results suggesting lower levels of TAC with lower serum creatinine levels in the PR-T group seem safe and effective in terms of preventing acute rejection when effective blood level is provided and it also protects from calcineurin inhibitor toxicity.

ETHICS

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Acıbadem University on 02.09.2021 with approval number 2021-16/01.

Informed Consent: Written informed consent was obtained from all patients.

Authorship Contributions

Surgical and Medical Practices: E.Ö., M.Y., İ.B., Concept: G.Y., İ.B., Ü.Ç., Design: G.Y., A.H.K., İ.B., Data Collection or Processing: E.Ö., M.Y., Analysis or Interpretation: E.Ö., M.Y., Ü.Ç., Literature Search: G.Y., A.H.K., Writing: G.Y., Ü.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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