



Original Research

A Comparative Analysis of Once-daily and Twice-daily Formulation of Tacrolimus in De Novo Kidney Transplant Recipients

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Abstract

Objectives: We aimed to compare the once-daily and twice-daily formulation of tacrolimus concerning the efficiency and effects on graft function in de novo kidney transplant patients.

Methods: Twenty once-daily (TAC-OD) and twenty twice-daily (TAC-BID) tacrolimus administrated de novo kidney recipients who had received initial immunosuppressive therapy according to protocols at our institution (0.2 mg/kg of tacrolimus combined with 1000 milligrams of steroid taper plus 720 mg of mycophenolate and with 2.5mg/kg anti-thymocyte globulin) assessed concerning demographics, drug doses and blood concentration, and graft function.

Results: The mean tacrolimus blood concentration measurements were higher in the TAC-OD group in the first sixty days after transplantation, and the TAC-OD group showed more blood concentration overshoots/fluctuations in the first 30 days of the treatment. The initial drug dose was significantly higher in the TAC-OD group than the TAC-BID group ($p=0.04$). There was no meaningful difference among groups according to graft function (creatinine measurements) ($p>0.05$).

Conclusion: Between de novo kidney recipients, the new TAC-OD formulation presents a similar short-term efficacy profile as TAC-BID. However, a higher daily dosage of TAC-OD is needed to achieve similar blood concentrations in the early postoperative period.

Keywords: Kidney transplantation; immunosuppression; tacrolimus, prolonged-release tacrolimus

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Tacrolimus is a milestone immunosuppressive drug in the field of organ transplantation, as proved by the outcomes of many studies.^[1-3] Tacrolimus has presented a notable decrease in the frequency and severity of acute allograft rejection episodes in solid organ (kidney, liver, and heart) transplants with enhanced graft survival in the long term.^[1,4]

The absence of new immunosuppressant medications in solid organ transplantation has inspired scientists to move

forward by altering known immunosuppressive therapies for advancing long term results. A prolonged-release new formulation (FK506E) was recently delivered (TAC OD, Advagraf, Astellas PharmaUS, Inc., Deerfield, Ill, United States), which allows for once-daily treatment of tacrolimus while keeping a safe and efficient blood concentration similar to twice-daily dosing. However, the data on this issue are scarce in the literature.^[5,6]

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Many authorities believe that non-adherence to immunosuppressant medication is the most significant problem on preventable graft loss after solid organ transplantation. [7,8] Once-daily dosing of tacrolimus instead of twice-daily dosing may enhance adherence to medication and improve long-term outcomes. Nevertheless, to date, an insufficient number of studies have analyzed the difference in blood-concentration and dosing profile of once-daily and twice-daily dosing tacrolimus at de novo kidney transplant patients. [3,7,9]

The once-daily dosing of tacrolimus was initiated in 2019 in our clinic, and we questioned in which recipient groups (once-daily tacrolimus vs. twice-daily tacrolimus) it was simpler to reach and sustain the target/ therapeutic blood concentration of tacrolimus (8-12 ng/ml) in the early postoperative period. We also compared once-daily and twice-daily formulation of tacrolimus concerning the efficiency and effects on graft function in de novo kidney transplant patients.

Methods

Inclusion criteria: We reviewed the medicinal data of de novo kidney recipients who received initial immunosuppressant therapy with once-daily tacrolimus (TAC-OD), conducted between January 2019 and February 2020 at our institution. We compared them with a group of 20 kidney transplants, who were randomly selected, using equivalent immunosuppression with twice-daily tacrolimus (TAC-BID), and performed between January 2019 and December 2019.

Preoperative management: The liver and kidney chemistry, complete blood count, coagulation profile, T- and B- cell cross matches, ABO blood group, serum for tissue typing tests, serology for CMV, EBV, VZV, toxoplasma, hepatitis B and C, HIV, pregnancy test if appropriate, urine culture (unless anuric), chest x-ray, electrocardiogram, pelvic duplex ultrasonography for the evaluation of iliac vessels were completed.

Immunosuppressant therapy protocol: According to protocols at our institution, 0.2 mg/kg of tacrolimus, a calcineurin inhibitor, was started as an induction agent the night before the surgery. In the TAC-OD group, the daily amount of tacrolimus was administered as a single dose. In the TAC-BID group, the daily amount of tacrolimus was divided into two equal doses. Furthermore, 500 milligrams of steroid taper, methylprednisolone, with 720 mg of mycophenolate mofetil was administered during the operation morning. Lastly, 500 mg additional dose of steroid taper, methylprednisone, with 2.5 mg/kg anti-thymocyte globulin was also applied during operation. Tacrolimus blood

concentrations of the individuals were first analyzed on the 3rd postoperative day, and dose adjustment was made according to these results. Afterward, blood tacrolimus concentrations were measured every day during hospitalization. The expected therapeutic range of tacrolimus level was 8-12 ng/ml in our clinic.

Slow graft function: Serum creatinine >3 mg/dL on postoperative day five but not requiring dialysis. [10]

Warm ischemia time: The time in seconds from clamping of the renal artery until obtaining clear efflux from the renal vein on the bench. [11]

Cold ischemia time: Time interval between cold solution perfusion and revascularization was incomplete. [12]

Compared variables: Demographics, Human leukocyte antigen mismatch, co-morbid conditions, serum creatinine levels, warm and cold ischemia times were analyzed. Also, serum creatinine levels, tacrolimus doses and blood concentrations at 7th, 30th, 60th, and 180th days after operation were evaluated.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Also, the ethics committee of Istanbul Okan University approved the study protocol (21.10.2020/56665618-204.01.07).

Statistical Analysis

We practiced the Number Cruncher Statistical System-2007® (USA) computer application for statistical evaluation of the study data. We used descriptive statistical techniques (mean, standard deviation, median, first quadrant, third quadrant, frequency, percentage and minimum, maximum) to evaluate data. Fisher's Exact test was applied to analyze the qualitative data. Statistical significance was taken as $p < 0.05$.

Results

Overall, 40 kidney recipients enrolled in the study protocol. No significant differences between recipients using TAC-OD and TAC-BID were observed according to demographics and clinical data demonstrated in Table 1. There was one acute rejection observed in either TAC-OD and TAC-BID groups. The mean tacrolimus blood concentration measurements were higher in the TAC-OD group in the first sixty days after transplantation (Table 2). Five patients' tacrolimus blood concentration was higher than the target concentration; however, the level curves in both groups were similar between day-60 and day-180 after transplantation (Fig. 1). The initial tacrolimus blood concentration

Table 1. Demographics and clinical data of kidney transplant recipients on once-daily and twice-daily tacrolimus

	Once-daily tacrolimus (n=20)	Twice-daily tacrolimus (n=20)
Recipient age (years), Mean±SD (min-max)	37±6.3 (23-61)	42.8±14.4 (26-64)
Recipient gender, n (%)	13 (65) male/7 (35) female	10 (50) male/10 (50) female
Recipient BMI* (kg/m ²), Mean±SD (min-max)	27.5±5.3 (18-35.2)	27.5±4.9 (16.6-32.1)
Donor age (years), Mean±SD (min-max)	29±9.8 (26-68)	48.5±14 (30-65)
Donor gender, n (%)	12 (60) female/8 (40) male	11 (55) male/9 (45) female
Donor type, n (%)	19 (95) living/1 (5) deceased	18 (90) living/2 (10) deceased
Comorbidities, n (%)		
Diabetes mellitus	9 (45)	7 (35)
Hypertension	11 (55)	10 (50)
Coronary artery disease	2 (10)	5 (25)
Chronic kidney disease etiology, n (%)		
Diabetes mellitus	9 (45)	7 (35)
Hypertension	2 (10)	3 (15)
Kidney stone disease	1 (5)	1 (5)
Polycystic kidney disease	1 (5)	1 (5)
Focal segmental glomerulosclerosis	1 (5)	0 (0)
Amyloidosis	0 (0)	1 (5)
Membranoproliferative glomerulonephritis	1 (5)	1 (5)
Unknown	4 (20)	6 (30)
HLA* type mismatch, Mean		
Type A	1.12	0.88
Type B	0.54	0.5
Type DR-B1	0.62	0.57
Type DQ-B1	0.56	0.56
PRA* grade, n (%)		
0-50	20 (100)	1 (5)
>50	0 (0)	1 (5)
Warm ischemia time (minutes), Mean±SD (min-max)	2.09±0.45 (1.5-3)	1.87±0.55 (1.5-3)
Cold ischemia time (minutes), Mean±SD (min-max)	58±10.99 (41-76)	61.54±44.7 (42-77)
Acute rejection, n (%)	1 (5)	1 (5)
Graft loss, n (%)	0 (0)	0 (0)
CMV infection, n (%)	1 (5)	2 (10)

*BMI: Body mass index; HLA: Human leukocyte antigen; PRA: Panel reactive antibody.

was higher in the TAC-OD group (Fig. 1), and the TAC-OD group showed more blood concentration overshoots in the first 30 days of the treatment (Fig. 2). Additionally, more patients were under target concentration in the first month of the treatment in the TAC-BID group (Fig. 3), but two recipients in either group were under target concentration after six-months of therapy. The blood concentration curves were smoother (less fluctuating) in recipients receiving twice-daily tacrolimus (Fig. 3).

The initial drug dose was significantly higher in the TAC-OD group than the TAC-BID group ($p=0.04$). The dose adjustments needed for optimal blood concentration were higher in the TAC-OD group, but the difference was non-significant ($p>0.05$) (Fig. 4).

There was no meaningful difference among groups according to graft function (creatinine measurements) ($p>0.05$). One graft from the TAC-OD group and two grafts from the TAC-BID group showed slow graft function, but these three grafts were obtained from deceased donors. Also, none of the recipients suffered severe liver dysfunction.

Discussion

The presented study showed that recipients using de novo TAC-OD needed higher drug doses to achieve the target blood concentration even if the baseline demographics of the recipients were identical. However, the sixth-month graft function in patients using TAC-OD and TAC-BID was similar.

Table 2. Creatinine measurements and immunosuppressive therapy of the recipients once-daily and twice-daily tacrolimus

	Once-daily tacrolimus (n=20)	Twice-daily tacrolimus (n=20)
Creatinine (mg/dl), Mean±SD (min-max)		
Day 7	1.34±0.37 (0.69-5.19)	1.58±0.69 (0.7-4.12)
Day 30	1.14±0.25 (0.6-3.25)	1.2±0.39 (0.81-2.32)
Day 60	1.23±0.21 (0.8-2)	1.39±0.58 (0.74-1.9)
Day 180	1.21±0.37 (0.77-2.1)	1.34±0.56 (0.84-2.26)
Steroid dose (gr/kg), Mean±SD (min-max)		
Day 7	0.26±0.04 (0.18-0.48)	0.31±0.08 (0.20-0.44)
Day 30	0.15±0.05 (0.09-0.18)	0.16±0.05 (0.11-0.26)
Day 60	0.10±0.04 (0.07-0.16)	0.10±0.05 (0.07-0.09)
Day 180	0.05±0.04 (0.03-0.06)	0.06±0.04 (0.02-0.10)
Mycophenolic acid dose (gr/kg), Mean±SD (min-max)		
Day 7	1.89±0.35(1.3-3.5)	2.04±0.63 (1.5-3.6)
Day 30	1.44±0.62 (1.1-2.6)	1.88±0.69 (1.6-2.7)
Day 60	1±0.34 (0.9-1.6)	1.21±0.46 (1.1-1.9)
Day 180	0.81±0.15 (0.62-1.34)	1.07±0.16 (0.8-1.4)
Tacrolimus dose (mg/kg), Mean±SD (min-max)		
Day 7	0.27±0.04 (0.23-0.28)	0.24±0.04 (0.2-0.25)
Day 30	0.23±0.03 (0.22-0.25)	0.17±0.03 (0.14-0.2)
Day 60	0.18±0.03 (0.15-0.19)	0.12±0.01 (0.11-0.13)
Day 180	0.13±0.01 (0.12-0.13)	0.1±0.01 (0.09-0.1)
Tacrolimus blood concentration (ng/ml), Mean±SD (min-max)		
Day 7	10.4±0.02 (9.9-10.5)	10.2±0.01 (10.1-10.3)
Day 30	11.3±0.02 (10.8-11.4)	10.5±0.01 (10.2-10.8)
Day 60	10.7±0.01 (10.1-10.8)	10.8±0.02 (10.4-11.1)
Day 180	9.3±0.02 (8.9-9.4)	9.4±0.01 (9.2-9.5)

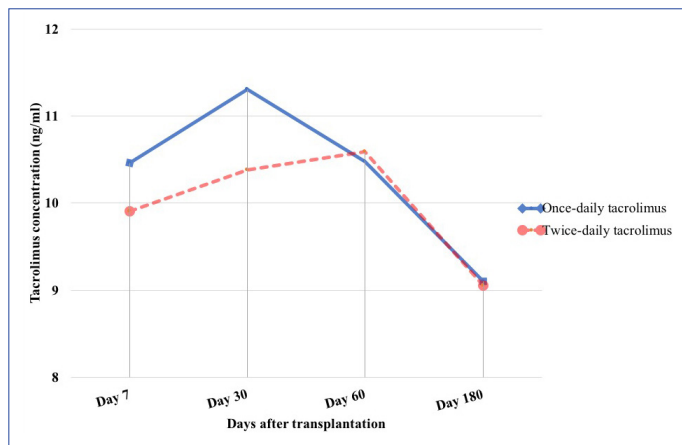


Figure 1. Tacrolimus levels among kidney recipients using once-daily and twice-daily tacrolimus.

Several studies revealed that TAC-OD required higher daily doses up to six months after transplantation than those on TAC-BID.^[2,13,14] Kitada H. et al. showed that recipients on TAC-OD therapy have lower tacrolimus blood concentration and necessitate being administered higher doses than those receiving TAC-BID in the early posttransplant phase.^[15] Our outcomes on daily dosage were consistent with pre-

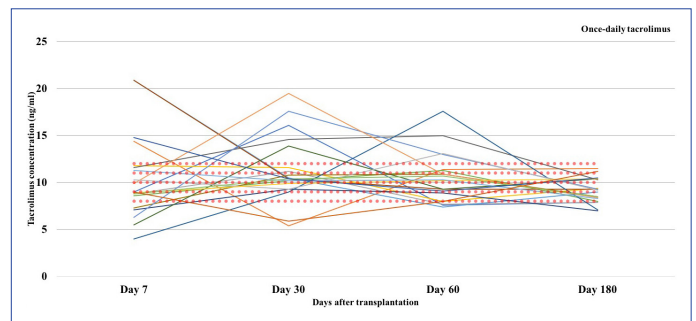


Figure 2. Therapeutic blood concentration monitoring of once-daily tacrolimus (Red dots indicates the expected therapeutic range of tacrolimus level (8-12 ng/ml) in our clinic).

vious studies; recipients having TAC-OD immunosuppressive therapy needed higher doses than those receiving TAC-BID. Tacrolimus is principally absorbed from the intestines. The inactive components inserted into the capsule covering the active drug form create disparity among once-daily and twice-daily forms.^[14,15] This prolonged-release period may be linked with problems in optimizing the blood concentration in the target concentration through the initial post-transplant period. Several determinants (polymor-

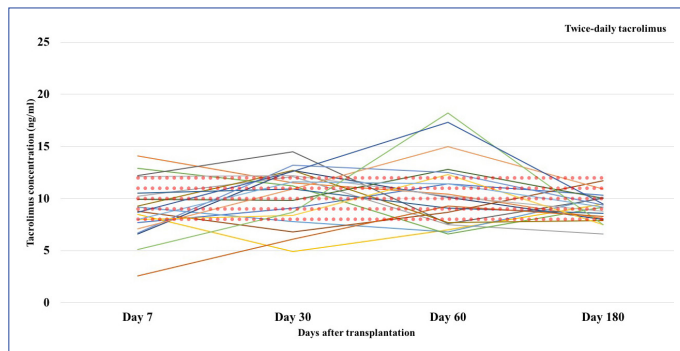


Figure 3. Therapeutic blood concentration monitoring of twice-daily tacrolimus (Red dots indicates the expected therapeutic range of tacrolimus level (8-12 ng/ml) in our clinic).

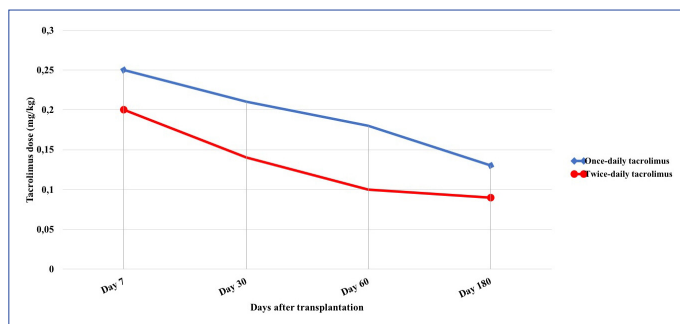


Figure 4. Tacrolimus doses among kidney recipients using once-daily and twice-daily tacrolimus.

phisms of the CYP3A enzyme,^[16,17] daily-diet,^[18] and intestinal motility^[19] have been associated with the absorption of tacrolimus.

Romina et al. observed that de novo TAC-OD administered kidney recipients had lower blood concentration than TAC-BID using patients. They also observed that TAC-OD using recipients and recipients who changed medication from TAC-BID to TAC-OD three months after transplantation had an excellent functioning graft and did not occur acute rejection.^[2] However, Morales et al. revealed that there was a significant reduction in tacrolimus blood concentration after switching to TAC-OD. They required increasing the daily dosage of tacrolimus to keep the blood concentration on the target level.^[20] We did not notice any trouble in the graft capacity of TAC-OD, or TAC-BID received patients after the six months in our study, and TAC-OD was effective in de novo as TAC-BID.

In the presented study, the creatinine levels were insignificantly higher in recipients who were using TAC-BID. This finding was also noticed in patients who were switched from TAC-BID to TAC-OD on long-term observation. The advance in graft function looked to be independent of fluctuations in tacrolimus blood concentration.^[15,21]

This study should be analyzed in light of some limitations.

Retrospective, single-institution conducted nature, and the limited number of individuals are among the limitations of our research. Multicenter conducted with larger sample size investigations are needed to ratify our findings. Secondly, several investigations have implied that non-adherence is a notable reason for graft failure. Non-adherence to medication is an essential determinant that should be discussed.^[6,7,15] We attempted to ascertain the incidence of non-adherence by utilizing a self-administered questionnaire. Although all of the TAC-OD and TAC-BID recipients were de novo cases, adherence to medication was sufficient in both groups. Nevertheless, we decided that the results were unreliable in our study groups. We think that medication adherence characteristics can be best evaluated in patients who have switched from TAC-BID to TAC-OD. Also, given that all individuals included in the present study had caucasian ethnicity, presented conclusions may not be generalizable to kidney recipients with different ethnicities.

Conclusion

De novo TAC-OD therapy after kidney transplantation is reliable, ensuring equal stability in drug blood concentrations than the TAC-BID form, and did not have any negative influence on graft function. However, recipients using de novo TAC-OD after kidney transplantation need higher daily medication doses than TAC-BID, but this dosage difference tends towards non-significance over time.

Disclosures

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Also, the ethics committee of Istanbul Okan University approved the study protocol (21.10.2020/56665618-204.01.07).

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