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TRANSPLANTOLOGY

# Clinical experience with once–daily tacrolimus in *de novo* kidney transplant recipients from living donors in Japan: 1–year follow up

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**Introduction.** We assessed our clinical experience with *de novo* kidney transplant recipients from living donors who received once–daily tacrolimus (OD TAC). In addition, we investigated tacrolimus pharmacokinetics and compared the dose of tacrolimus in *de novo* kidney transplant patients treated with OD TAC or twice–daily tacrolimus (BD TAC).

**Material and methods.** Ten patients (3 ABO incompatible, 2 preemptive), who had received a living donor kidney transplant at our hospital since February, 2009, received OD TAC with mycophenolate mofetil, methylprednisolone, and basiliximab. OD TAC doses were adjusted to maintain tacrolimus trough levels in the range of 9–12 ng/mL. We assessed clinical and pharmacokinetic profiles. We compared average total daily dose of tacrolimus between the OD TAC and BD TAC groups.

**Results.** Patient survival and graft survival rates were 100% at 15.7 months. Acute rejection was not found clinically. The protocol biopsies (week 3 and month 3) did not reveal biopsy–proven acute rejection, either. No calcineurin inhibitor toxicity occurred. Doses in the OD TAC and BD TAC groups at week 3 posttransplant were 0.308 mg/kg/day and 0.149 mg/kg/day, respectively.

**Conclusions.** OD TAC appears to have efficacy and safety equivalent to that of BD TAC. However, a larger dose of OD TAC compared to that of BD TAC may be required during the early period after kidney transplantation.

Key Words: kidney transplantation ‹› once–daily tacrolimus ‹› twice–daily tacrolimus

## INTRODUCTION

Tacrolimus is a macrolide family immunosuppressive drug that was found in and developed from a metabolite of an actinomycete, *Streptomyces tsukubaensis*, separated from Japanese soil in Tsukuba City in 1984. This drug is now used in 84 countries around the world because of its high efficacy in organ transplantation. Tacrolimus was approved in Japan in 1993 under the trade name Prograf® (Astellas Pharma Inc., Tokyo, Japan) for its effect and efficacy for suppressing immunologic rejection after liver transplantation and is taken twice daily (BD TAC). Tacrolimus is also an effective immunosuppressive drug for renal transplantation and was approved for this use in Japan in 1996.

The current protocol of renal transplantation requires patients to take immunosuppressants throughout their lives after engraftment. Failure to comply with this protocol leads to increased acute immunologic rejection, reduction in graft survival rate, and decreased overall survival rate [1, 3]. Graceptor® (Astellas Pharma Inc.), an extended–release formulation of tacrolimus, was launched in 2008. It is also known as Advagraf ® in Europe and the USA. This drug, which needs to be taken only once daily (OD TAC), has the same active ingredient (tacrolimus) as BD TAC, which must be taken twice daily. OD TAC has shown the equivalent pharmacokinetics of BD TAC, indicating the possibility of increased patient compliance and renal graft survival rate with-

out an increase in the complication rate [4, 5]. In the present study we assessed the clinical profile of OD TAC and evaluated efficacy and safety at 1–year follow–up in Japan. Additionally, although oral intake of the same dose of OD TAC once in the morning is reported to have the same efficacy as that of BD TAC taken twice daily [6], there have been few case reports of OD TAC administration in *de novo* kidney transplant patients from living donors in Japan. Therefore, we compared clinical data of the OD TAC group with those of the BD TAC group in setting the target trough of both drugs at the same level.

## MATERIALS AND METHODS

We retrospectively reviewed data on ten patients receiving *de novo* renal grafts from living donors after February, 2009, who were administered OD TAC and 35 patients receiving *de novo* renal grafts from living donors before February, 2009, in the Department of Urology, Graduate School of Medicine, Gifu University. The 35 patients undergoing transplantation immediately before this study began were considered as the controls. All patients were Japanese, and their posttransplantation follow–up period reached 1 year at the time of the study. We excluded patients treated with cyclosporine and those whose follow–up did not reach 1 year posttransplantation at the time of the study. Exclusion criteria included significant liver disease; previous organ transplantation; severe diarrhea, vomiting, an active peptic ulcer or a gastrointestinal disorder that may have affected the absorption of tacrolimus; malignancy or history of malignancy within the previous 5 years. Patients and donors were also excluded if they were known to be positive for hepatitis B virus, hepatitis C virus, or human immunodeficiency virus.

We collected demographic and clinical data from these patients, such as age and gender of the donors; age, gender, because of ESRD (end–stage renal disease), duration of dialysis, body weight, of the recipients; ABO blood type, HLA mismatch, type of donor, kidney procured from donor.

Induction of immunosuppressive therapy included the concomitant use of 4 types of drugs: tacrolimus(OD TAC or BD TAC), mycophenolate mofetil (MMF), methylprednisolone (MPSL), and basiliximab (BXM). OD TAC was taken once daily in the morning (2 hours after breakfast) and BD TAC was taken twice daily in the morning and evening.

In patients with a compatible ABO blood type, administration of tacrolimus 0.15–0.2 mg/kg/day and MMF 20–30 mg/kg/day was started seven days prior to transplantation, and oral intake of MPSL 20 mg/day was started three days before transplantation. BXM 20 mg was administered twice: on day 0 (day of kidney transplantation) and day 4 after kidney transplantation. On day 0, MPSL 250 mg/day was administered intravenously. The dose was tapered gradually to 4 mg daily by month 3. Three types of maintenance immunosuppressants were used concomitantly: tacrolimus, MMF, and MPSL. Therapeutic drug monitoring of tacrolimus was frequently conducted for tacrolimus to control the blood concentration of the drug strictly in accordance with the target trough level of 9–12 ng/ml during the first month, 6–8 ng/ml between first and third months, and 5–7 ng/ml thereafter.

In patients with an incompatible ABO blood type, oral administration of tacrolimus 0.15–0.2 mg/kg/day, MMF 20 mg/kg/day, and MPSL 8 mg/day was started 14 days prior to transplantation. Double–filtration plasmapheresis was carried out five and three days before the kidney transplantation, and plasma exchange was conducted on the day before kidney transplantation. The transplantation was performed after the titers of anti–A and anti–B antibodies had decreased to 1:16. In addition, 200 mg/kg of rituximab, an anti–CD20 monoclonal antibody, was administered 14 days before and the day before kidney transplantation. Splenectomy was not performed in any patient.

Biopsy of the renal graft was performed at week 3 or 4 and month 3 after transplantation to check acute rejection or CNI toxicity. Results to August 2010 (patient overall survival and renal graft survival), presence or absence of acute rejection, major complications after transplantation, and onset of infectious diseases were investigated.

A pharmacokinetic study of OD TAC was performed in the 10 patients before kidney transplantation and at weeks 2 and 3 after kidney transplantation. The blood concentration of the drug was taken at seven time points: immediately before administration and at 1, 2 ($C_2$), 4 ($C_4$), 8, 12, and 24 hours ($C_{min}$ [minimum concentration]) after administration. The $AUC_{0–24}$ was obtained by the moment–analysis method.

Daily drug dosage and $C_{min}$ were compared between the group administered OD TAC and the group administered BD TAC, with the target trough at week 3 or 4 after kidney transplantation adjusted to 9–12 ng/mL. The same immunosuppressive therapy was conducted for both the OD TAC and BD TAC administration groups.

Statistical analysis was carried out with the Statistics Program for Social Science for Windows (SPSS II, ver. 11; SPSS Inc., Chicago, IL, USA). We performed descriptive statistical analysis on each of the variables, and we used Student's *t*–test and Fischer's exact test for bivariate analysis. Values of $P < 0.05$

**Table 1.** *Recipient characteristics of OD TAC and BD TAC groups*

| | OD TAC (n = 10) | BD TAC (n = 35) |
|---|---|---|
| Recipient age (years; mean, range) | 37.8 (17–62) | 47.0 (19–67) |
| Recipient gender (%) | | |
| Male | 7 (70.0%) | 28 (80.0%) |
| Female | 3 (30.0%) | 7 (20.0%) |
| Cause of ESRD | | |
| Diabetic nephropathy | 1 | 2 |
| Chronic glomerulonephritis | 4 | 9 |
| IgA nephropathy | 2 | 6 |
| Mesangial proliferative glomerulonephritis | 1 | 2 |
| Hypoplastic kidney | 1 | 0 |
| Bartter's syndrome | 1 | 0 |
| polycystic kidney | 0 | 1 |
| nephrosclerosis | 0 | 1 |
| reflux nephropathy | 0 | 1 |
| other cause | 0 | 13 |
| Duration of dialysis (months; mean, range) | 7.6 (0–109) | 23.2 (0–294) |
| PET (%) | 2 (20.0%) | 4 (11.4%) |
| ABO blood type (%) | | |
| Compatible | 7 (70.0%) | 21 (60.0%) |
| Incompatible | 3 (30.0%) | 14 (40.0%) |
| HLA mismatch (mean, range) | 2.50 (1–5) | 2.94 (0–6) |
| Body weight (kg; mean ±SD) | 53.2 ±11.3 | 56.5 ±10.0 |
| Type of donor (%) | | |
| Living related | 9 (90.0%) | 21 (60.0%) |
| Living unrelated | 1 (10.0%) | 14 (40.0%) |
| Donor age (years; mean, range) | 60.5 (24–69) | 58.0 (33–84) |
| Donor gender (%) | | |
| Male | 3 (30.0%) | 8 (22.8%) |
| Female | 7 (70.0%) | 27 (77.2%) |
| Kidney procured from donor (%) | | |
| Left side | 7 (70.0%) | 30 (85.7%) |
| Right side | 3 (30.0%) | 5 (14.3%) |

OD TAC, once–daily tacrolimus; BD TAC, twice–daily tacrolimus; ESRD, end–stage renal disease; PET, pre–emptive transplantation; HLA, human leukocyte antigen.

were considered to be statistically significant. The study protocol was approved by an institutional review board (IRB) at our institution to ensure that study procedures were performed in accordance with the Helsinki Declaration.

## RESULTS

Characteristics of the patients who received OD TAC and BD TAC are shown in Table 1.

The mean follow–up period was 15.7 months (range, 12.9–18.5 months). Overall patient survival and renal graft survival rates were both 100%. Acute rejection was not found clinically, and protocol biopsies performed at week 3 and month 3 did not reveal biopsy–proven acute rejection. No calcineurin inhibitor toxicity, including imbalance of electrolytes, was seen. Noteworthy perioperative complications did not occur.

Infection after transplantation, as evidenced by positive results of cytomegalovirus antigenemia (CMV–Ag) assay, occurred in three patients (OD TAC group), 15 patients (BD TAC group). Reduction in MMF dose and administration of ganciclovir

**Table 2.** *Pharmacokinetic parameters of OD TAC and BD TAC groups at week 3*

| OD TAC (n = 10) | BD TAC (n = 35) | P–Value |
|---|---|---|
| 0.308 ±0.16 | 0.149 ±0.09 | 0.015 |
| 11.2 ±2.25 | 10.8 ±1.94 | 0.643 |

OD TAC, once–daily tacrolimus; BD TAC, twice–daily tacrolimus; Cmin, trough value.

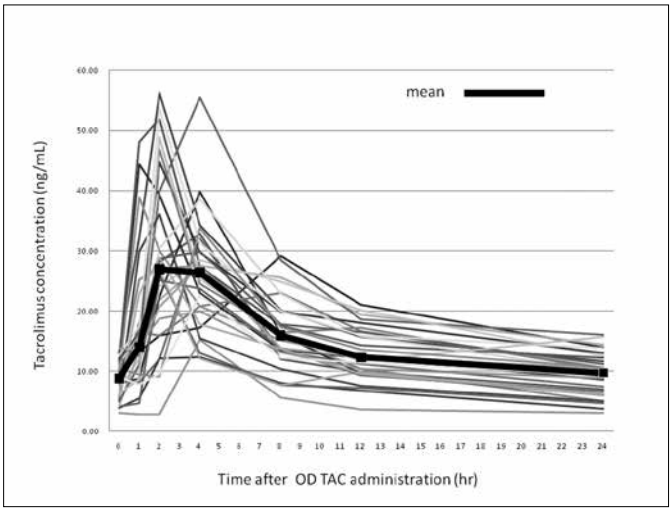


**Figure 1.** *Time course of observed whole blood concentrations of once–daily tacrolimus (OD TAC) at week 3.*

or valganciclovir hydrochloride (VGCV) cured these patients, preventing serious infection. Herpes zoster occurred in two patients and was mitigated by a reduction in MMF dose and administration of vidarabine or valacyclovir hydrochloride. Although 1 patient developed adenovirus cystitis 30 days after kidney transplantation, reduction in MMF dose improved the inflammation, and all symptoms disappeared within 14 days.

Pharmacokinetic study yielded 210 values for tacrolimus blood concentration and 30 values for the AUC (Figure 1). The plot was scattered because the pharmacokinetic studies of OD TAC were performed at different times: before kidney transplantation and at weeks 2 and 3 after kidney transplantation. The pharmacokinetic parameters of tacrolimus observed were $C_0$ 8.77 ±3.22 ng/mL (mean ±SD), $C_2$ 26.96 ±14.16 ng/mL, $C_4$ 26.38 ±9.37 ng/mL, $C_8$ 15.96 ±6.04 ng/mL, $C_{12}$ 12.29 ±4.36 ng/mL, $C_{min}$ 9.71 ±3.62 ng/mL, and $AUC_{0–24}$ 368.74 ±109.53 ng·h/mL. The median value of $C_{min}$ was 9.71 ng/mL and was close to the target value, whereas the value of $C_{max}$ (maximum concentration) exceeded 50 ng/mL in some patients.

The pharmacokinetic parameters of the 10 patients in the OD TAC group were compared to those of the 35 control patients in the BD TAC group (Table 2). Though there were no significant differences in patient demographics between the two groups, the mean dose at week 3 after kidney transplantation was 0.308 ±0.16 mg/kg/day in the OD TAC group and was 0.149 ±0.09 mg/kg/day in the BD TAC group (P = 0.015). Most patients required a dose higher than the initial dose of 0.15–0.2 mg/kg/day. Biopsy–proven acute rejection occurred in 0% and 2.8%, and CNI toxicity occurred in 0% and 11.4% of patients, respectively, at week 3.

## DISCUSSION

In the multicenter non–blind study performed by the United States Multicenter FK506 Kidney Transplant Group, 120 *de novo* renal transplant patients were divided into three groups according to the whole blood trough level of tacrolimus (low: 5–14 ng/mL, medium: 15–25 ng/mL, high: 26–40 ng/mL) and examined. The incidence of acute rejection and adverse events were 21.2%, 10.0%, and 10.3% (P = 0.29) and 33.3%, 50.0%, and 62.1% (P = 0.03) in the low, medium, and high groups, respectively. Although the incidence of acute rejection was higher in the low group, no statistically significant difference was found among the groups. The incidence of adverse events was significantly higher in the high trough level group [7]. High $C_{max}$ may possibly induce adverse effects. In this respect, OD TAC is a sustained–release drug equivalent to BD TAC, and its $C_{max}$ is lower than that of BD TAC [8]. Surprisingly, in the present study, we experienced a patient with $C_{max}$ exceeding 50 ng/mL, though the median value of $C_{min}$ was close to the target value. Although protocol biopsy did not reveal CNI toxicity, large doses of tacrolimus might lead to renal toxicity. The cause of the high $C_{max}$ in our study remains unclear. Because the absorption mechanism of OD TAC is different between individuals, blood concentration needs to be measured and the dose adjusted depending on the patient's condition.

In our institution, the 10 patients who underwent *de novo* living kidney transplantation from living donors after February, 2009, were administered OD TAC. Although the mean follow–up period was only 15.7 months, no rejection was observed, and the grafts survived in all the patients. Therefore, we believe there are no major concerns regarding the efficacy of OD TAC. Other reports [9] concluded that the efficacy and safety of OD TAC are equivalent to those of BD TAC and that the pharmacokinetics of OD TAC and BD TAC are also equivalent for renal and liver transplantation. Krämer et al. [10] reported a multicenter, randomized, parallel–group, noninferiority study between OD TAC and BD TAC. There was no

relation between tacrolimus trough levels and viral infection rates, and opportunistic or severe infections were rare and balanced between the groups. The incidence and nature of other adverse events and serious adverse events were generally comparable between the two groups.

Wlodarczyk et al. [11] compared the pharmacokinetics in patients administered OD TAC or BD TAC. Among the 66 patients receiving *de novo* renal transplantation (age, 18–65 years), 34 patients were administered OD TAC orally, whereas 32 patients were administered BD TAC orally in the fasting state. The mean daily doses of the drugs were almost the same, but the mean $AUC_{0-24}$ was approximately 30% lower for OD TAC than for BD TAC at comparable doses (232 and 361 ng·h/mL, respectively) on day 1 after transplantation. However, the mean $AUC_{0-24}$ for the OD TAC group was comparable to that of the BD TAC group on day 14 (364 and 344 ng·h/mL, respectively) and week 6 (331 and 383 ng·h/mL, respectively). Furthermore, trough levels were similar for both formulations by day 4. Mean $C_{min}$ levels for OD TAC and BD TAC were within target levels at every measurement. Namely, when the doses for OD TAC and BD TAC are the same, the AUC becomes lower in the OD TAC group immediately after transplantation but returns to the same level as that in the BD TAC group after patient condition stabilizes between day 14 and week 6. In the present study, in contrast to that of Wlodarczyk et al. [11], a larger dose of OD TAC was required compared to that of BD TAC on week 3 after the kidney transplantation to maintain the same target trough concentration. This means that the $C_{min}$ would become lower in the OD TAC group when the same dose was administered. We believe that patients with diabetic gastroparesis have poorer absorption of OD TAC; however, in diabetic patients, PK–PD data suggested that OD TAC was absorbed normally. Compared with the Wlodarczyk et al. [11] study, no significant difference was found in $C_{min}$ between the OD TAC and BD TAC groups in the present study, but the dose of OD TAC was higher. Generally, several factors, such as the absorption mechanism of the digestive tract, intestinal P–glycoprotein, CYP3A4 expression, and CYP3A5 genotype, have been suggested to be associated with the bioavailability and clearance of tacrolimus [12, 13]. This difference could be due to either incomplete absorption across the gut wall or to a higher degree of metabolism on the first pass through the liver due to a slower rate of absorption [14]. Imanishi et al. [15] reported that blood trough concentration correlated with $AUC_{0-24}$ in both OD TAC and BD TAC. Therefore, we adjusted the dose of tacrolimus in our study according to the blood trough concentration. Although protocol biopsy did not reveal toxicity, large doses of tacrolimus might lead to renal toxicity, especially in patients with low eGFR. The cause of the high $C_{max}$ in our patients remains unclear. However, we need to modify the estimation of the blood trough concentration in a future study.

Crespo et al. [16] reported that among *de novo* renal transplantation patients, OD TAC offered a short–term efficacy profile similar to that of BD TAC. However, it was necessary to use up to a 50% higher dose of OD TAC than BD TAC to achieve similar trough levels during the first 6 months of treatment. Their conclusion is similar to our conclusion.

It is generally considered that a daily dose of OD TAC that is the same as that of BD TAC can maintain the target trough concentration in stable renal transplant patients when BD TAC is switched to OD TAC [17]. However, this seems not to apply to patients in the early period after kidney transplantation.

There are some limitations to our study. First, the sample size is small, and all patients were Japanese. Second, we analyzed data from a single center, and the follow–up period extends only to 1 year. Third, we do not have enough pharmacokinetic BD TAC data to compare with that of OD TAC. Finally, our subjects were not chosen in a randomized fashion. Despite these limitations, we consider that our results will contribute to a better understanding of such patients with poorer absorption of OD TAC.

## CONCLUSIONS

OD TAC appears to have efficacy and safety equivalent to that of BD TAC. However, a larger dose of OD TAC compared to that of BD TAC may be required during the early period after kidney transplantation.

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