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RESEARCH ARTICLE

Comparative Study of OD (Tacrolimus Extended-Release Capsules) Versus Conventional Tacrolimus in Renal Transplant Patients

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Abstract

Background: One of the common causes of chronic allograft nephropathy is non adherence to medications contributing to 30% of graft loss in developed world. The non-adherence is attributed to pill burden. Once-daily dosing of tacrolimus instead of conventional twice-daily dosing may enhance adherence to medication and improve long-term outcomes. The present study is a retrospective analysis comparing the safety and effectiveness of De Novo use of OD Tac (tacrolimus extended-release capsules) to conventional BD tacrolimus in renal transplant patients at our hospital.

Material and methods: Records of 24 De novo OD Tac transplant patients were analyzed and compared retrospectively to 24 De Novo conventional BD Tac transplant patients on regular follow up and who had completed 2 yrs. of follow up post-transplant at our center.

Results: Various parameters were recorded at last follow-up and were analyzed and compared. Average weight of the cohort (64.6 kg vs. 66.6 kg), average tacrolimus dose (2.7 mg vs. 2.15 mg), average Tac dose/kg body weight (0.04 mg vs. 0.03 mg), average Sr. Creatinine at Last Follow up (1.2 mg/dl vs. 1.32 mg/dl) were comparable in both groups and were statistically insignificant ($p > 0.05$). There was higher incidence of post-transplant diabetes mellitus (PTDM) noted in conventional tacrolimus group (37.5%) compared to OD Tac group (25%) andwas statistically significant (P 0.041). Infection rate (41.67%) in conventional tacrolimus group was much higher compared to OD Tac group (4.17%) and was statistically significant (P0.01). There was 100% patient and graft survival at the end of two years in both the groups. Over 2 yrs there were 3 mortalities in the conventional tacrolimus group due to infection, 2 UTI and 1 Pneumonia), 1 death was observed in OD Tac group. Tac dose for OD and Conventional Tac were similar.

Conclusion: OD Tac is comparable to conventional Tac in its safety and efficacy however scores over conventional tacrolimus in terms of post-transplant infections and post-transplant diabetes mellitus (PTDM) and stable trough levels of the drug.

Keywords

OD tacrolimus, Post-renal transplant, Immunosuppressant

Introduction

Tacrolimus, a calcineurin inhibitor, is derived from soil fungus Streptomyces tsukubaensi, found in Japan [1]. 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 long term graft survival [2].

Tacrolimus use is associated with a number of adverse effects like nephrotoxicity, neurotoxicity, new onset diabetes, hyperkalemia, hypertension, hyperlipidemia, hypomagnesemia and hyperuricemia [3]. A new formulation of tacrolimus i.e., tacrolimus extended release can be dosed once daily (OD) [4] and may have the ability to simplify immunosuppressive regimens and improve medication compliance translating to better long term allograft survival [5]. OD Tac (tacrolimus extended release capsules) is indicated for prophylaxis of organ rejection in adult patients receiving allogeneic kidney and liver transplants.

Once-daily dosing of tacrolimus instead of twice-

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daily dosing may enhance adherence to medication and improve long-term outcomes [6]. The present study is to compare the safety and efficacy of de novo OD Tac (tacrolimus extended-release capsules) to de novoconventional tacrolimus among renal transplant recipients transplanted at our hospital with at least 2 yrs. post-transplant follow-up.

Material and Methods

This is a single center retrospective analysis of data obtained from 24 consecutive patients started on de novo OD Tac vs. 24 consecutive patients on de novo Conventional Tac followed up for at least 2 yrs. post-transplant, in the department of nephrology, at Suguna Hospital, Rajajinagar, Bangalore, India. Study was approved by institutional ethical committee. Data was obtained from case records of patients who underwent kidney transplantation, and were on regular follow up at our center for at least 2 yrs. Patients, less than 18 years of age, on irregular follow up, Patients with previous renal or non-renal transplants, switch over patients to OD Tac from conventional Tac were excluded from study.

All patients were on standard immunosuppressive regimen consisting of tacrolimus, mycophenolate mofetil, and steroids. Induction therapy was given with two doses of Basiliximab. Our transplant protocol includes use of Induction in unmatched emotionally related and cadaveric transplant. Tacrolimus is initiated day-5 at a dose of 0.5 mg/kg twice daily to obtain Tac level on day 0 of transplant and adjust the dose to avoid vast variations in levels in immediate post-transplant period. Tac dose were titrated to achieve target T0 level of 5-9 ng/ml during the first 3 months and maintenance level of 3 to 5 ng/ml beyond 3 months post-transplant. MMF is initiated day -1 at a dose of 0.5 g twice daily. Prednisolone is initiated at a dose of 30 mg previous night of transplant, IV Methylprednisolone 1 g is used at time of clamp release, followed by, 500 mg and 250 mg on day 1 and 2 post-transplant respectively. Prednisolone is started at 20 mg OD on POD3 and is tapered 2.5 mg every 15 days to achieve dose of 7.5 mg OD daily by 10 weeks.

Patients were divided in two groups, patients receiving De novo OD Tac (tacrolimus extended-release capsules, one/day) and those on conventional tacrolimus (two times/day). Patients from the two groups were matched in a group matching fashion. The primary objective of the study was to compare, initial tacrolimus dose and T0 Trough levels on Day 0 transplant, Creatinine at discharge, Creatinine at last visit, average Tac dose/kg body weight, between these 2 groups. Data was also collected to compare side effect profile, incidence of post-transplant diabetes mellitus (PTDM), infections and rejection episodes.

Collected data was compiled using Microsoft Excel, and analyzed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi-square test or Fisher exact test as applicable. P-value less than 0.5 was considered as statistically significant.

Results

In present study, general parameters such as age, gender, body weight, type of donor and time since treatment were comparable among both groups and difference was not statistically significant ($p > 0.05$) (Table 1).

Basic Renal Disease causing ESRD has been recorded for each group in Table 2.

Parameters at the time of last follow-up were compared for each of the group and are recorded in Table 3.

Average weight (64.6 kg vs. 66.6 kg), average tacrolimus dose (2.7 mg vs. 2.15 mg), average dose/kg body weight (0.04 mg/kg vs. 0.03 mg/kg), tacrolimus dose at last visit (3 mg vs. 2.6 mg), average Sr. Creatinine at last visit (1.2 mg/dl vs. 1.32 mg/dl), were comparable among both OD tacrolimus and conventional tacrolimus

Table 1: General parameters.

Parameter	OD Tacrolimus (n = 24)	Convention Tacrolimus (n = 24)	P value
Average age	41.1 years	43.7 years	0.72
Gender			0.86
Male	19 (79.17%)	20 (83.33%)	
Female	5 (20.83%)	4 (16.67%)	
Average weight	57.9 kg	61.5 kg	0.67
Type of donor			0.59
Related	13 (54.17%)	11 (45.83%)	
Un-related	6 (25%)	13 (54.17%)	
Cadaveric	5 (20.83%)	0	
Time since treatment (mean)	42.2 months	46.6 months	0.83

Table 2: Basic renal disease distribution for each group.

	OD Tacrolimus (n = 24)	Convention Tacrolimus (n = 24)
Diabetic Nephropathy	8 (33.33%)	8 (33.33%)
IgA Nephropathy	5 (20.83%)	4 (16.67%)
Nephrotic Syndrome	4 (16.67%)	1 (4.17%)
Chronic Interstitial Nephritis	3 (12.5%)	4 (16.67%)
Hypertensive Nephropathy	2 (8.33%)	4 (16.67%)
Chronic Glomerular Nephritis	1 (4.17%)	1 (4.17%)
Chronic Pyelonephritis	1 (4.17%)	1 (4.17%)
Congenital Disease	0	1 (4.17%)

Table 3: Parameters at last follow-up.

Parameter	OD Tacrolimus	Conventional Tacrolimus	P value
Average weight (kg)	64.6	66.6	0.78
Average Tacrolimus dose (mg)	2.7 mg	2.15	0.82
Average Dose mg/kg body weight	0.04	0.03	
Last Dose of tacrolimus	3	2.6	0.69
Average Sr. Creatinine (mg/dl)	1.2	1.32	0.73

Table 4: Incidence of post-transplant diabetes mellitus.

Duration to develop PTDM	OD Tacrolimus (n = 24)	Convention Tacrolimus (n = 24)
1-week post-transplant	3 (12.5%)	2 (8.33%)
2-weeks post-transplant	0	1 (4.17%)
3-weeks post-transplant	2 (8.33%)	0
1-month post-transplant	0	1 (4.17%)
2-months post-transplant	1 (4.17%)	0
1-year post-transplant	0	3 (12.5%)
2-years post-transplant	0	1 (4.17%)
3.8-years post-transplant	0	1 (4.17%)

Table 5: Infections observed.

Type of Infection	OD group (n = 24)	Convention Tacrolimus group (n = 24)
UTI	0	7 (29.17%)
Pneumonia	0	1 (4.17%)
Mucor	0	1 (4.17%)
TB Effusion	0	1 (4.17%)
Millary TB	1 (4.17%)	0

respectively which was statistically insignificant ($p > 0.05$).

In present study higher incidence of post-transplant diabetes mellitus was noted in convention tacrolimus group (37.5%) as compared to OD tacrolimus group (25%). The difference was statistically significant (P - 0.041) (Table 4).

We noted a very low incidence of infections in OD tacrolimus group (4.17%) as compared to Conventional Tac group (41.67%) & difference was statistically very significant (p - 0.01) (Table 5).

We have observed that there was 100% patient and graft survival at the end of two years in OD Tac group, however. At the end of two years, 3 deaths were recorded in conventional tacrolimus group due to infection. 2 diabetics died of Pneumonia & UTI, 1 PTDM patient died following complicated UTI.

Scatter plot of Initial 0-day tacrolimus trough level for both groups recorded with 0.1 mg/kg/day of tacrolimus dose showed a more concentrated cluster around the acceptable range for OD tacrolimus group unlike with the conventional tacrolimus. Scatter with conventional tacrolimus was much more diffuse and out layered. This probably suggests the stable and sustained levels achieved with OD tacrolimus dosing (Figure 1).

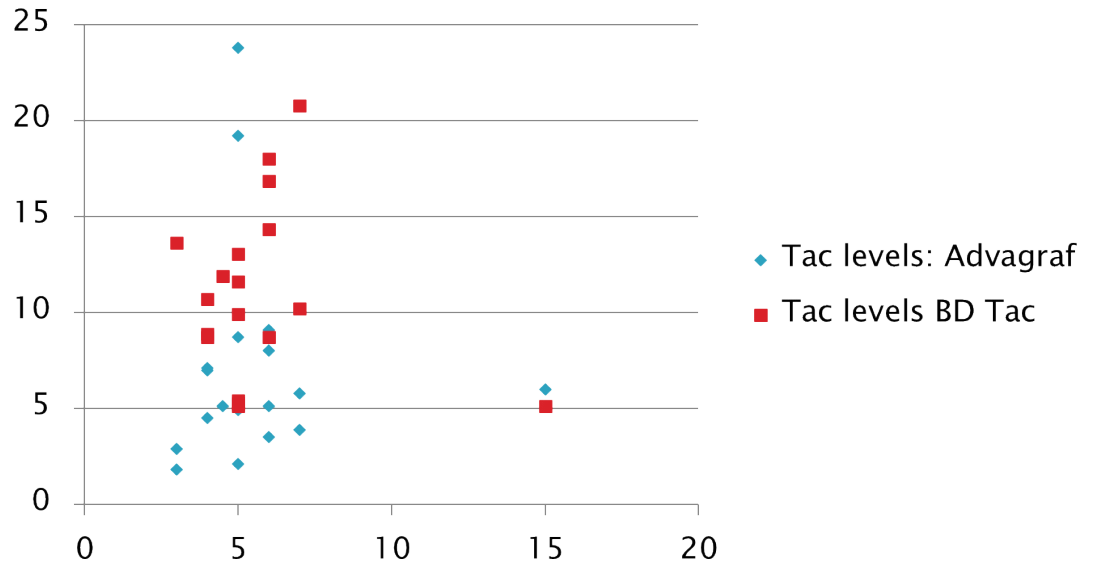

Figure 1: Scatter plot of Tac trough levels for OD tacrolimus and conventional tacrolimus.

Discussion

Tacrolimus is drug with narrow therapeutic range and demonstrates inter- and intra-patient pharmacokinetic (PK) variability [7]. Tacrolimus trough levels are monitored to guide dose adjustment, as it is highly correlated with tacrolimus AUC and subsequently clinical outcomes [4,8].

Conventional tacrolimus is formulated for immediate release and is available for absorption till proximal small bowel, while once daily tacrolimus is a prolonged release formulation of tacrolimus, available for absorption even at distal small bowel and ascending colon. Since the expression of CYP3A4 and PgP reduce in the distal bowel, the pre-systemic metabolism is avoided and absorption continues [9].

There is a clear relationship between the complexity of the overall drug regimen and patient adherence. The more drugs and doses a patient had to remember, the greater the likelihood that some would be forgotten. Overall, they reported, “the best predictor of medication compliance seems to be simplicity”. The simpler the prescription, the better the compliance [10].

Denhaerynck, et al. [11] found a weighted mean prevalence of nonadherence at 27.7% (range, 2% to 67%) in 10 studies that measured adherence by self-report. The prevalence of nonadherence in 2 studies that employed electronic event monitoring was 26% and 20%. Non-adherence was associated with poor clinical outcomes, contributing to a weighted mean of 19.9% of late AR episodes in 3 studies and 16.3% of graft losses in 8 studies. Distress over cosmetic and other side effects of immunosuppressive drugs also may trigger nonadherence, as noted by De Geest and Moons [12].

In order to reduce non-adherence, concept of once daily tacrolimus was introduced. It potentially improves inter- and intra-subject variability in exposure and improves compliance. OD tacrolimus therapeutically is equivalent to twice daily tacrolimus with same therapeutic monitoring as noted in earlier studies [2,3,5].

Bakr MA, et al. [13] noted that renal function and rejection episodes showed no statistical significance among recipients of both groups. Despite slightly higher unit doses, there was no statistical difference regarding the tacrolimus trough levels, between the two groups.

Our single center experience revealed that at almost similar dose, OD tacrolimus had similar outcome to conventional tacrolimus on rejection episodes and graft survival at 2 yrs post-transplant. The difference from previous studies being that the dose for OD tacrolimus was same as conventional tacrolimus.

Helen F, et al. [14], in their study with OD Tac (N106) and standard-release Tac (N 95) recorded comparable eGFR at 12 months (58.8 ± 17 vs. 59.2 ± 18 mL/min, P 0.307), New-onset diabetes (17 vs. 20%, P 0.581), BK viremia (10 vs. 7%, P0.450), acute rejection (7 vs. 16%, P0.067) or graft survival (97 vs. 95%, P0.301). In this study OD Tac patients required fewer adjustments of doses suggesting stable levels. These findings were similar to results recorded in our study.

Our study showed a lesser incidence of PTDM and significantly lower incidence of post-transplant infections in OD tacrolimus groups compared to conventional tacrolimus attributed probably to a steady state of levels with OD Tac unlike with conventional Tac which would provide 2 surges per day. This difference has been recorded for the first time and probably needs to be evaluated in a large randomized controlled trial, as it would translate to better post-transplant outcomes and lesser post-transplant infections.

Our study has certain limitations, such as retrospective design, non- randomized study, absence of pharmacokinetic characteristics and a small sample size.

Conclusion

OD tacrolimus is comparable to conventional tacrolimus in their efficacy and safety. OD Tac however provides a more stable and steady state blood levels which probably translate to lower incidence of PTDM and Post-transplant infections. This however needs to be corroborated in large RCT.

Conflict of Interest

None to declare.

Source of Funding

Nil.

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