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Original Article

A Comparative Study of Once Daily versus Twice Daily Tacrolimus in Liver Transplantation

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ABSTRACT

Background: Once daily (OD) tacrolimus, recently launched for post liver transplant immunosuppression might offer better compliance and efficacy compared to standard twice daily (BID) tacrolimus. Data from India, however is sparse. **Aim:** The aim of our study was to compare the efficacy and adverse effects of OD versus BID tacrolimus formulation in liver transplant recipients. **Methods:** This was a retrospective, observational, comparative study of 115 patients who were on tacrolimus based regimens (tacrolimus BID: 92; M: F-75:17 and tacrolimus OD: 23; M: F-22:1). Total daily dose and trough levels of tacrolimus were recorded at 1, 3, 6, 12 and 24 months after transplantation. **Results:** Median age in tacrolimus BID and OD groups were 45 years (6-64 years) and 50 years (1-70 years), respectively. The median tacrolimus dose was significantly lower in the tacrolimus OD arm at all the time points studied. Tacrolimus trough levels were significantly lower in the tacrolimus OD group at 3 and 6 months. The biopsy proven rejection rate was 15.2% and 0% in the tacrolimus BID and OD groups, respectively. Two year patient and graft survival rate was 89.4% in the tacrolimus BID and 87.5% in the tacrolimus OD group. The incidence of new onset diabetes, renal dysfunction, dyslipidemia, neurotoxicity, hyperkalemia and weight gain were comparable between the two arms. **Conclusion:** Tacrolimus OD has a lower rejection rate compared to its BID formulation. However, this does not translate into better patient or graft survival. Both the formulations appear to be comparable with respect to the adverse effect and tolerability profile.

Key words: Biopsy Proven Acute Rejection, Graft Survival, Patient Survival, Liver Transplantation, Tacrolimus Once Daily, Tacrolimus Twice Daily.

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INTRODUCTION

Liver transplantation is currently the sole choice for patients with end stage decompensated liver disease of chronic and acute aetiology.[1,2] Being an allogeneic graft, lifelong immunosuppression is essential to avoid liver graft rejection. However, long term immunosuppression is associated with a number of adverse effects such as infections, malignancy and other drug specific issues, which are often dose dependent.[3] As the window between under and over immunosuppression is narrow, therapeutic drug monitoring of immunosuppressant level is routinely performed to facilitate appropriate dosing. Nevertheless, maintaining optimal immunosuppression is often difficult and considered to be an art.[4]

Tacrolimus, a calcineurin-inhibitor is an important component of the immunosuppressive regimens employed following liver transplantation. It is usually used in combination with antiproliferative agents with or without corticosteroids. Tacrolimus has a narrow therapeutic window and the optimal drug level following liver transplantation is 5-15 ng/ml. The standard preparation of tacrolimus is administered twice daily (BID).[5] Lifelong consumption, day in day out, every 12 hours requires stringent discipline and could be demanding particularly in adolescent population. In fact, non-adherence with regular tacrolimus consumption has been a problem in western countries.[6] Furthermore, tacrolimus use is associated with a number of adverse effects including nephrotoxicity, neurotoxicity, new onset diabetes, hyperkalemia, hypertension, hyperlipidemia, hypomagnesemia and hyperuricemia. A new formulation of tacrolimus i.e., tacrolimus extended release can be dosed once daily (OD)[7] and may have the ability to simplify immunosuppressive regimens, improve medication compliance and long term allograft survival.[8] Twice daily tacrolimus results in two peaks in the drug level immediately after consumption followed by tapering over the next 12 hours. However, tacrolimus OD produces lower peak yet a sustained concentration. The pharmacokinetics of tacrolimus BID varies considerably between patients and even within one individual depending on food intake and other medications. It is claimed that pharmacokinetics of tacrolimus OD allows for a more uniform drug level throughout its action of 24 hours thereby producing better efficacy and diminished adverse effects.[9]

Although there are studies comparing the effectiveness and safety of the different tacrolimus formulations,[10-12] data from India is sparse. The present study has been designed to compare the safety and effectiveness of tacrolimus BID and OD formulations following liver transplantation at our hospital.

MATERIALS AND METHODS

This study was conducted at the Gastrointestinal Surgery department of Amrita Institute of Medical Sciences. Patients of either sex who had undergone liver transplantation between January 2012 and July 2015 and who were started on either tacrolimus BID or OD were included in the study. The selection between OD or BID tacrolimus was a personal preference, often dictated by the patients' fiscal capability. The cost of 0.5 mg of tacrolimus BID is Rs 21 while the cost of equivalent dosage of tacrolimus OD is Rs 59.5. Along with tacrolimus, our protocol included

mycophenolate and steroids. Steroids would be normally tapered and stopped within 3 months. Mycophenolate is maintained for 3 months after which its dose is reduced and finally withdrawn by 6 to 9 months. Any alteration in liver function test with suspicion of rejection would be biopsied for confirmation. If there was, delay in resolution of liver function following standard acute cellular rejection (pulsed methyl prednisolone), additional immunosuppression, either mycophenolate or steroid would be continued for longer periods. Patients who died within 1 month of transplantation were excluded. This was an observational study and patient data relevant to the study was collected retrospectively from patient files and hospital health information system. The study was approved by the Institutional Research Committee.

The baseline demographics, aetiology, co-morbidities, body mass index (BMI) and model for end stage liver disease (MELD) scores of the recipients were recorded. Donor details like gender, living/deceased, ABO compatibility and relationship to recipient were also recorded. Total daily dose and trough levels of tacrolimus were recorded at 1, 3, 6, 12 and 24 months following liver transplantation. In addition, incidence of biopsy proven acute rejection (BPAR), new onset diabetes mellitus, dyslipidemia, neurotoxicity, increase in serum creatinine, hyperkalemia and weight gain were also recorded. Rejection was defined according to the Banff criteria on liver biopsy.[13] The number of immunosuppressive therapies received by the patient at discharge, 1, 3, 6, 12 and 24 months was also recorded.

Continuous variables were described with mean, median, standard deviation or ranges. Categorical variables were tabulated and expressed as percentage. Continuous variables were compared using Mann Whitney U test while for categorical variables Chi square test was used. P<0.05 was considered significant. All statistical analyses were carried out with Graph Pad Prism software.

RESULTS

In the present study, 115 patients who received tacrolimus formulations following liver transplantation were analysed. Out of this population, 92 patients received tacrolimus BID based regimens whilst 23 patients received tacrolimus OD based regimens. The median age in tacrolimus BID and OD groups were 45 years (6-64 years) and 50 years (1-70 years), respectively. Recipient demographics of BID and OD tacrolimus are given in Table 1. In both the treatment groups, majority of the patients were in the age group of 41-60 years (65.2% and 52.2% in the tacrolimus BID and OD groups, respectively). However, the tacrolimus OD group had a significantly higher proportion of patients aged >60 years (30.4%) compared to tacrolimus BID group (3.3%) [P<0.0001]. A significantly higher proportion of patients (30.4%) in the tacrolimus OD group suffered from hepatocellular carcinoma compared to the tacrolimus BID group (5.4%) [P=0.0005]. The two treatment groups were comparable with respect to BMI, MELD scores and co-morbidities.

With respect to the donor demographics, the details are shown in Table 2. Majority of the patients in both the treatment groups underwent ABO compatible transplantation. ABO incompatible transplantation was performed in 3 patients in the tacrolimus BID group. In addition to the standard immunosuppressive regimen, these patients received rituximab and plasmapheresis. Majority of the patients received a right hepatic lobe graft (88% and 78.3% in the tacrolimus BID and OD groups, respectively).

At different time points during the course of the study, both the groups were comparable with respect to the number of immunosuppressive therapies received by the patients. A trend towards a decrease in the number of immunosuppressive therapies was observed as the time from transplantation increased (Table 3). At the time of discharge, majority of the patients in the tacrolimus BID group (93.5%) and all the patients in the tacrolimus OD group were on triple drug therapy. At the end of 12 months following transplantation, 60% and 80% patients in the tacrolimus BID and tacrolimus OD groups, respectively were on monotherapy. Similarly, at the end of 24 months following transplantation, majority of the patients in both the treatment groups (72.9% and 66.7% in the tacrolimus BID and OD groups, respectively) were on monotherapy.

The median daily tacrolimus dose at 1 month was 3 mg in the tacrolimus BID group and 2 mg in the tacrolimus OD group. At 24 months after transplantation, the median daily tacrolimus dose was 3 mg in the tacrolimus BID group and 1.5 mg in the tacrolimus OD group. Median daily tacrolimus dose was significantly lower in the tacrolimus OD group compared to the tacrolimus BID group at all the time point studied (Table 4).

Table 1: Patient demographic and clinical characteristics.

Characteristics	Tacrolimus BID (N=92)	Tacrolimus OD (N=23)	P-value
Gender			
Male	75 (81.5)	22 (95.7)	0.0953
Age (Years)			
<18	8 (8.7)	1 (4.3)	0.4874
18-40	21 (22.8)	3 (13)	0.3018
41-60	60 (65.2)	12 (52.2)	0.2475
>60	3 (3.3)	7 (30.4)	<0.0001
Mean (SD)	42.9 (13.27)	48.6 (16.62)	0.0326
Body mass index			
Mean (SD)	24.3 (5.32)	23.9 (3.59)	0.8802
Aetiology			
Alcoholic cirrhosis	37 (40.2)	9 (39.1)	0.9242
Cryptogenic	23 (25)	4 (17.4)	0.4413
Fulminant hepatic failure	12 (13)	2 (8.7)	0.5684
Autoimmune	1 (1.1)	0	0.6155
Hepatocellular carcinoma	5 (5.4)	7 (30.4)	0.0005
Wilson's disease	2 (2.2)	0	0.4756
HBV related cirrhosis	9 (9.8)	0	0.1182
HCV related cirrhosis	2 (2.2)	0	0.4756
Biliary atresia	1 (1.1)	1 (4.3)	0.2846
Byler's disease	1 (1.1)	0	0.6155
Cholestatic disease; Vanishing bile duct syndrome	1 (1.1)	0	0.6155
Primary sclerosing cholangitis	1 (1.1)	0	0.6155
MELD Scores			
Mean (SD)	22 (5.8)	22.4 (8.2)	0.5630
Co-morbid conditions			
Diabetes mellitus	44 (47.8)	11 (47.8)	1.0
Hypertension	12 (13)	6 (26.1)	0.1236
Dyslipidemia	1 (1.1)	0	0.6155
Others	3 (3.3)	2 (8.7)	0.2530

BID=twice daily, HBV=hepatitis B virus, HCV=hepatitis C virus, MELD=model for end stage liver disease, N=number of patients, OD=once daily, SD=standard deviation.

Table 2: Donor characteristics.

Characteristics	Tacrolimus BID (N=92)	Tacrolimus OD (N=23)	P-value
Gender			
Female	66 (71.7)	20 (86.9)	0.1328
Donor type			
Living	88 (95.7)	21 (91.3)	0.4017
ABO compatibility			
Compatible	86 (93.5)	22 (95.7)	0.6631
Incompatible	3 (3.3)	0	
Unknown	3 (3.3)	1 (4.3)	
Relationship to recipient			
Spouse	37 (40.2)	9 (39.1)	0.0841
Sibling	21 (22.8)	2 (8.7)	
Parent	12 (13)	2 (8.7)	
Child	10 (10.9)	1 (4.3)	
Others	6 (6.5)	6 (26.1)	
Unknown	5 (5.4)	2 (8.7)	
Grandparent	1 (1.1)	1 (4.3)	

BID=twice daily, N=number of patients, OD=once daily. The values represent number of patients (%)

Table 3: Number of immunosuppressive therapies

	N	Tacrolimus BID	N	Tacrolimus OD	P-value
Discharge	92	3 (2-4)	23	3 (3-3)	0.4089
1 Month	92	3 (2-4)	23	3 (2-3)	0.4479
3 Months	89	2 (1-4)	22	2 (1-3)	0.1442
6 Months	86	2 (1-4)	22	2 (1-3)	0.9967
12 Months	80	1 (1-4)	10	1 (1-2)	0.1900
24 Months	59	1 (1-3)	6	1 (1-2)	0.7818

BID=twice daily, N=number of patients, OD=once daily. The values represent median (range)

Table 4: Daily tacrolimus dose (mg).

	N	Tacrolimus BID		N	Tacrolimus OD		P-value
		Mean (SD)	Median (Range)		Mean (SD)	Median (Range)	
1 Month	91	2.9 (1.22)	3 (1-6.5)	23	2.1 (1.05)	2 (0.5-4)	0.0076
3 Months	89	3.8 (1.56)	4 (1-7)	22	2.8 (1.41)	2.75 (0.5-5)	0.0084
6 Months	86	3.8 (1.61)	4 (1-7)	22	2.8 (1.57)	3 (0.5-6)	0.0092
12 Months	80	3.7 (1.50)	3.5 (1-7)	10	2.4 (1.32)	3 (0.5-4)	0.0273
24 Months	59	3.4 (1.47)	3 (1-6.5)	6	1.8 (0.99)	1.5 (0.5-3.5)	0.0065

BID=twice daily, N=number of patients, OD=once daily, SD = standard deviation.

Table 5: Tacrolimus level (ng/ml)

	N	Tacrolimus BID		N	Tacrolimus OD		P-value
		Mean (SD)	Median (Range)		Mean (SD)	Median (Range)	
1 Month	92	3.6 (2.35)	3 (0.3-11)	23	2.7 (1.63)	1.9 (0.7-7)	0.0822
3 Months	87	6.4 (3.7)	6 (1.3-28.5)	22	4.4 (3.58)	3.7 (0.2-15)	0.0028
6 Months	83	6.6 (2.54)	6.3 (1-13.7)	19	5 (2.75)	4.9 (0.2-9.7)	0.0254
12 Months	77	6.5 (2.81)	6.2 (0.5-13.5)	9	5 (3.18)	4 (1.5-11.8)	0.0625
24 Months	55	6.8 (3.54)	6.1 (0.8-16.7)	5	5.6 (3.28)	5.2 (2.1-10.5)	0.5383

BID=twice daily, N=number of patients, OD=once daily, SD = standard deviation.

Table 6: Adverse events.

Adverse event	Tacrolimus BID (N=92)	Tacrolimus OD (N=23)	P-value
New onset diabetes	22 (23.9)	5 (21.7)	0.8259
Increase in creatinine	24 (26.1)	5 (21.7)	0.6676
Dyslipidemia	37 (40.2)	9 (39.1)	0.9242
Neurotoxicity	32 (34.8)	6 (26.1)	0.4278
Hyperkalemia	28 (30.4)	8 (34.8)	0.6876
Weight gain	22 (23.9)	4 (17.4)	0.5036

BID=twice daily, N=number of patients, OD=once daily. The values represent number of patients (%)

Table 7: Patient and graft survival rates

	N	Tacrolimus BID	N	Tacrolimus OD
3 Months	92	89 (96.7)	23	22 (95.6)
6 Months	91	86 (94.5)	23	22 (95.6)
12 Months	86	80 (93)	11	10 (90.9)
24 Months	66	59 (89.4)	8	7 (87.5)

BID=twice daily, N=number of patients, OD=once daily.

Mean tacrolimus trough levels in the tacrolimus OD group were not significantly different from tacrolimus BID group at 1 month after transplantation. However, at 3 and 6 months after transplantation, the tacrolimus trough levels were significantly lower in the tacrolimus OD group compared to the BID group (P=0.0028 and 0.0254, respectively) [Table 5].

In the present study, biopsy proven rejection was observed in 14 (15.2%) patients in the tacrolimus BID group and none of the patients in the tacrolimus OD group. Eleven patients had a single episode while in 3 patients there were multiple episodes. The average time (in days) to the first, second and third rejection episode was 134.5 (range: 16-421), 253.3 (99-397) and 305 (197-413) days, respectively. Both tacrolimus BID and OD were well tolerated and the incidence of adverse events was comparable between the arms (Table 6).

In the present study, the patient and graft survival rates for tacrolimus BID and OD were comparable at 12 and 24 months (Table 7). In our study, all patients who lost the graft died since none of the patient under-

went retransplantation. This was due to the extreme difficulty in obtaining deceased donor grafts.

DISCUSSION

The primary aim of the study was to analyse the incidence of BPAR and long term adverse events between the two formulations of tacrolimus. In our study, the incidence of BPAR was significantly lower in the tacrolimus OD group. Our results are in contrast to those of Trunecka *et al* [10] who had reported comparable event rates of BPAR at 6 and 12 months with the tacrolimus BID and OD formulations. Our results are interesting since this lower rate of rejection in the tacrolimus OD group was despite the lower tacrolimus dose in the OD arm as compared to the BID arm. The tacrolimus trough levels in the OD arm were also significantly lower at 3 and 6 months after transplantation due to the lower dose of tacrolimus OD. Sanko-Resmer *et al*[14] have reported similar adequate immunosuppression of patients despite low exposure to tacrolimus, with no cases of acute rejection even though individual's minimum trough levels were below 2 ng/ml on isolated occasions.

Whether the lower level of rejection in the tacrolimus OD group is entirely due to the improved efficacy is open to debate since we did not perform pharmacokinetic and pharmacodynamic profile of the two drugs. Nevertheless, in studies, tacrolimus OD has been reported to produce lower peak concentrations and a more uniform drug level throughout its action of 24 hours compared to tacrolimus BID.[9] The steady maintenance of drug concentration with OD formulation compared to the BID dosage is claimed to be the logic behind the better efficacy seen in the tacrolimus OD group. Moreover, we have analysed only BPAR rates. It is possible that there were instances of biochemical abnormalities suggestive of clinical rejection which we have not included in our definition of rejection. Often such biochemical rejection may be treated empirically by augmented immunosuppressive therapy without resorting to a liver biopsy. This may explain the reduced rejection rate in the tacrolimus OD group. Perhaps with a larger sample size and longer follow up, the difference in rejection between the groups may become less significant.

Both tacrolimus BID and OD were well tolerated and the incidence of new onset diabetes, increase in creatinine level, dyslipidemia, neurotoxicity, hyperkalemia and weight gain were comparable between the arms. Our results are consistent with those of Trunecka *et al* [10] who had also reported comparable safety profile for both tacrolimus formulations. The incidence of diabetes (21.8% and 21.9% in the tacrolimus BID and OD groups, respectively) and nervous system disorders like tremor and headache (31.6% and 27% in the tacrolimus BID and OD groups, respectively) reported in their study is comparable to our results. However, the incidence of hyperkalemia and increase in blood creatinine was comparatively lower in their study (nearly 5% and 10%, respectively). The DIAMOND (A**D**VAGRAF stud**I**ed in combin**A**tion with **M**yc**O**-phenolate mofetil a**ND** basiliximab in liver transplantation) study had reported low incidence of diabetes mellitus which may be due to the corticosteroid free maintenance protocol employed.[15]

In the present study, the patient and graft survival rates for tacrolimus BID and OD were comparable at 12 and 24 months. Our results are consistent with those of Trunecka *et al* [10] who have reported 90.8% and 89.2% patient survival rates for tacrolimus BID versus OD at 12 months. The graft survival rates in their study at 12 months were 85.6% and 85.3% in the tacrolimus BID and OD groups, respectively.

In our study, 7 patients (4 males and 3 females) in the tacrolimus BID group and 1 male patient in the tacrolimus OD group had expired. An increased mortality rate in female liver transplant recipients with tacrolimus OD has been reported in a post hoc analysis.[10] This was not observed in our study. In our study, however, the numbers were too small to derive any concrete conclusions on this aspect.

The report of the European Liver Transplant Registry has shown a significant graft survival advantage in the tacrolimus OD compared to the BID group at 3 years.[16] Although, this registry suggested a trend towards improved patient survival, this was not statistically significant. It has to be mentioned that we had only 23 patients in the tacrolimus OD arm of which only 8 patients had a follow up data at 2 years. Perhaps it is too early to notice a discernible difference between the two groups in our study. Thus, it would be however interesting to follow up our patients over longer periods to investigate the long term outcomes with tacrolimus OD in the Indian set up.

Our study has several drawbacks. Firstly, it is not a randomized study, so it is possible that OD tacrolimus being a new drug, was prescribed preferentially in stable patients. Nevertheless, the pre-operative demographics and operative variables were similar in the 2 groups. Secondly, we did not perform pharmacokinetic study. Such data would have been interesting in our Indian population. Thirdly, our sample size is small, particularly in the OD tacrolimus group.

CONCLUSION

Once daily tacrolimus has a lower rate of rejection compared to twice daily formulation. This however does not translate to better long term patient or graft survival. Both the formulations when consumed for more than 3 months appear to be comparable with respect to the adverse effect and tolerability profile.

CONFLICT OF INTEREST

None

ABBREVIATION USED

BPAR: biopsy proven acute rejection, BMI: body mass index, MELD: model for end stage liver disease, OD: once daily, TD: twice daily

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