A STUDY OF EFFICACY AND SAFETY OF TACROLIMUS COMPARED WITH CYCLOSPORIN A MICROEMULSION IN RENAL TRANSPLANTATION

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ABSTRACT

BACKGROUND

The aim of this retrospective study was to compare therapeutic efficacy and safety profile of Cyclosporin and Tacrolimus in post-transplant patients with respect to graft function and metabolic disorders.

MATERIALS AND METHODS

Data of patients who underwent renal transplant in Calicut Medical College during July 2014 to December 2015 was collected and baseline parameters like BP, Blood glucose, cholesterol, RFT and LFT levels were assessed at 2 weeks, 1 month, 6 months and at 1 year in one year completed subgroup. Incidence of delayed graft function and acute rejection were also included.

RESULTS

Clinical data of 60 patients (32 in Cyclosporin group and 28 in Tacrolimus group) were collected. Among the 60 patients, 32 patients (16 in Cyclosporin group and 16 in Tacrolimus group) completed one year. The incidence of acute rejection with Cyclosporin group and with Tacrolimus group was 14.7% and 13.6% and 31.2% and 25% at 6 months and 1 year respectively. At one year in the subgroup for 32 patients, serum creatinine was <1.2 mg/dL in 75% Cyclosporin group and 80.5% in Tacrolimus group. After 1 year, Hb>17 was seen in 6.25% (1/16) in Cyclosporin group and none in Tacrolimus group. Dyslipidaemia was observed in 56.3% (9/16) in Cyclosporin group and 32.5% (6/16) in Tacrolimus group. At one year, hirsutism was 18.7% with Cyclosporin group and 0% with Tacrolimus group.

CONCLUSION

No statistically significant difference in graft function & incidence of acute rejection between the two treatment groups at 6 months & 1 year.

KEYWORDS

Tacrolimus, Cyclosporin, Creatinine, Graft Rejection.

HOW TO CITE THIS ARTICLE: Krishnan JE, Puthiyottil NT, Melemadathil S. A study of efficacy and safety of tacrolimus compared with cyclosporin A microemulsion in renal transplantation. J. Evid. Based Med. Healthc. 2016; 3(95), 5225-5229. DOI: 10.18410/jebmh/2016/1090

BACKGROUND

Kidney transplant is the treatment of choice for most patients with End Stage Renal Disease. Standard protocols in use typically involve three drug groups [calcineurin inhibitors (e.g. Cyclosporin and Tacrolimus), anti-proliferative agents (e.g. Azathioprine or MMF) and steroids] each directed to a site in the T-cell activation or proliferation cascade which are central to rejection process.

AIM

A retrospective study was conducted to compare therapeutic efficacy and safety profile of Cyclosporin and Tacrolimus in post-transplant patients with respect to graft function and metabolic disorders.

Financial or Other, Competing Interest: None.
Submission 24-10-2016, Peer Review 01-11-2016,
Acceptance 21-11-2016, Published 26-11-2016.
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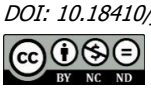
DOI: 10.18410/jebmh/2016/1090



MATERIALS AND METHODS

Data of patients who underwent renal transplant in Calicut Medical College during July 2014 to December 2015 were collected from the transplant registry. After obtaining consent, the patients were interviewed and their medical records data verified. The baseline parameters like age, sex, blood pressure, serum cholesterol, plasma glucose, renal function tests (RFT), Liver Function Test (LFT) were recorded. We collected the values of blood sugar, serum cholesterol, RFT and LFT at 2 weeks, 1 month, 6 months and at one year in the subgroup who completed one year. Incidence of Delayed Graft Function and acute rejection were also included for analysis. The study results were analysed by using statistical method of student's t-test.

Inclusion Criteria

Patients of both sexes who underwent renal transplant in Calicut Medical College from July 2014 to December 2015 were included.

Exclusion Criteria

Patients

a. Who were unwilling to give informed consent.
b. Who did not complete 6 months of post-transplant period and completed >2 years of transplant period.
c. Who were on Sirolimus/Azathioprine.
d. Patients with diabetic nephropathy.

OBSERVATIONS

Clinical data of 60 patients (32 in Cyclosporin group and 28 in Tacrolimus group) were collected. Among the 60 patients, 32 patients (16 in Cyclosporin group and 16 in Tacrolimus group) completed one year and their subgroup data was also analysed. Refer Table 1, 2, 3, and 4.

The incidence of acute rejection was 14.7% with Cyclosporin group and 13.6% with Tacrolimus group at 6 months. At one year in the subgroup of 32 patients, incidence of acute rejection was 31.2% (5/16) with Cyclosporin group and 25% (4/16) with Tacrolimus group.

At two weeks, Serum creatinine was less than 1.2 mg/dL in 73.5% in Cyclosporin group and 82.5% in Tacrolimus group. At the end of 6 months, serum creatinine was less than 1.2 mg/dL in 72.3% in Cyclosporin group and 76.3% in Tacrolimus group.

At one year in the subgroup of 32 patients, serum creatinine was less than 1.2 mg/dL in 75% Cyclosporin group and 80.5% in Tacrolimus group.

Haemoglobin (Hb) >17 was not observed at two weeks or 1 month in any group. At 6 months, Hb>17 was seen in 11.6% in Cyclosporin group and none in Tacrolimus group. At one year in the subgroup of 32 patients, Hb>17 was seen in 6.25% (1/16) in Cyclosporin group and none in Tacrolimus group.

Dyslipidaemia was observed in 16.7% in Cyclosporin group and 11 % in Tacrolimus group at two weeks. They were put on stains and excluded. Among the rest at six months, Dyslipidaemia was observed in 36. 8% in Cyclosporin group and in 32.3% in Tacrolimus group. At one year in the subgroup of 32 patients, Dyslipidaemia was observed in 56.3% (9/16) in Cyclosporin group and 32.5% (6/16) in Tacrolimus group.

Post-Transplant Diabetes Mellitus (PTDM) was observed in 2.6% in Cyclosporin group and 3.8% in Tacrolimus group at 2 weeks. At six months, PTDM was observed in 12.2% of Cyclosporin group and 16.7% of Tacrolimus group. At one year in the subgroup of 32 patients, PTDM was observed in 12.5% of Cyclosporin group and 25% of Tacrolimus group.

Delayed graft function was observed in 6.3% in Cyclosporin group and 7.1% in Tacrolimus group at less than 2 weeks.

Tremors were complained by 3.1% in Cyclosporin group and 28.4% in Tacrolimus group at six months. At one year in the subgroup of 32 patients, tremors were complained by none in Cyclosporin group and 32.5% in Tacrolimus group seizures were not seen in any.

Incidence of hirsutism was 24.5% with Cyclosporin group and 0% with Tacrolimus group at six months. At one year in the subgroup of 32 patients, incidence of hirsutism was 18.7% with Cyclosporin group and 0% with Tacrolimus group.

	Cyclosporin group	Tacrolimus group	P value
S. creatinine	1.21	1.10	.201
Hb	8.7	10.1	0261
FBS	94.3	99.7	.327
PPBS	126.0	124.9	.90
Total cholesterol	178.5	179.9	.825
LDL–chol	126.4	124.3	.184
HDL C	32.45	34.6	.243
VLDL C	22.76	25.7	.555
TAG	146.56	148.678	.433
SGPT	32.8	27.4	.536

Table 1. Results of Laboratory Parameters at Two Weeks

	Cyclosporin group	Tacrolimus group	P value
S. creatinine	1.06	1.08	.54
Hb	10.7	10.1	.457
FBS	102.4	103.9	.673
PPBS	133.2	123.4	.906
Total cholesterol	190.7	183.6	.534
LDL chol	132.45	134.4	.134
HDL C	35.5	33.43	.245
CLDL C	25.5	27.87	.567
TAG	146.675	148.57	.122
SGPT	39.54	29.675	.564

Table 2. Results of Laboratory Parameters at 1 Month

	Cyclosporin group	Tacrolimus group	P value
S. creatinine	1.13	1.32	.345
HB	12.9	9.9	.896
FBS	101.4	103.5	.164
PPBS	142.9	148.9	.575
Total cholesterol	203.6	189.4	.673
LDL–chol	139.3	133.7	.744
HDL C	31.6	36.87	.098
VLDL C	24.4	26.8	.432
TAG	143.6	148.8	.455
SGPT	32.1	39.1	.367

Table 3. Results of Laboratory Parameters at Six Months

	Cyclosporin group	Tacrolimus group	P value
S. creatinine	1.13	1.32	.425
Hb	12.9	9.9	.367
FBS	101.4	103.5	.004
PPBS	142.9	148.9	.025
Total cholesterol	203.6	189.4	.006
LDL chol	145.07	136.345	.004
HDL C	32.43	34.5	.875
VLDL C	23.64	24.657	.344
TAG	156.674	152.87	.095
SGPT	32.1	39.1	.453

Table 4. Results of Laboratory Parameters at 1 Year

DISCUSSION

We conducted this study in our 3500 bedded hospital which has a patient population which extends from Central to North end of Kerala. This was a retrospective study of medical records evaluation and patient followup.

In our study, the incidence of AR was 14.7% in Cyclosporin group or 13.6% in Tacrolimus group with no significant difference between both the drugs at 6 months. At one year in the subgroup of 32 patients, incidence of acute rejection was 31.2% (5/16) with Cyclosporin group and 25% (4/16) with Tacrolimus group which was not different statistically, though numerically it was more with Cyclosporin.

Johnson et al in 2000 compared Cyclosporin microemulsion vs. Tacrolimus in a multicentre trial.[1] The incidence of AR was 05-20% in both the two groups. Two single centre trials.[2,3] compared Cyclosporin microemulsion versus Tacrolimus with MMF and steroids. They also found no superiority of Tacrolimus over Cyclosporin microemulsion in preventing acute rejection. Incidence in both these groups was 13-17%.

Another study.[4] concluded that odds ratio for graft loss with Tacrolimus compared to Cyclosporin was 0.95. A study.[5] in 2005 concluded that odds ratio for graft loss at 6 months was significantly reduced in Tacrolimus recipient (RR 0.5695% CI) and this benefit persisted up to 3 years.

Tacrolimus was directly compared with Cyclosporin A in a large prospective trial.[6] that evaluated as primary endpoint the proportion of patients with biopsy-proven rejection at 6 months.

Mean Tacrolimus and Cyclosporin A, blood concentrations at 1 month were roughly 12 and 250 mg/mL, thus corresponding to standard guidelines. Concomitant immunosuppression consisted of AZA for 3 months and steroids. While patient and graft survival were similar, the rate of biopsy-proven rejection was significantly less with Tacrolimus than with Cyclosporin A (20 versus 37 percent, P<0.0001), as was the rate of corticosteroid–resistant rejection episodes (9 percent with Tacrolimus versus 21% with Cyclosporin A, P<0.0001) when combined with MMF, there is no convincing evidence for the superiority of Tacrolimus over Cyclosporin A in the prevention of acute or cortico-resistant rejection episodes.

At two weeks, serum creatinine was less than 1.2 mg/dL in 73.5% in Cyclosporin group and 82.5% in Tacrolimus group. At the end of 6 months, S. creatinine was less than 1.2 mg/dL in 72.3% in Cyclosporin group and 76.3% in Tacrolimus group. At one year in the subgroup of 32 patients, serum creatinine was less than 1.2 mg/dL in 75% Cyclosporin group and 80.5% in Tacrolimus group.

Multicentre clinical trials.[7] compared the efficacy and safety of Cyclosporin with Tacrolimus and demonstrated comparable long-term patient survival and graft survival in renal transplant recipients. But treatment with Tacrolimus was associated with reductions in the incidence and severity of acute rejection episodes. The overall efficacy of the two agents was similar. The availability of these two immunosuppressants allows the clinician improved options when choosing an immunosuppressive regimen in solid organ transplantation.

In report of the European Tacrolimus Multicentre Renal Study Group,[8] 1 year graft survival rate (82.5% vs. 86.2%; P=0.380) did not differ significantly between the two treatment groups. Overall, the safety profiles of the Tacrolimus and Cyclosporin based regimens were quite comparable. Higher incidences of elevated serum creatinine, tremor, diarrhoea, hyperglycaemia, diabetes mellitus, and angina pectoris were reported in the Tacrolimus treatment group, whereas acne, arrhythmia, gingival hyperplasia, and hirsutism were more frequent with Cyclosporin treatment. Intent-to-treat analysis revealed equivalent patient and graft survival between treatment arms at 5 years of follow-up (79.1% vs. 81.4%; P=0.472 and 64.3% vs. 61.6%; P=0.558) among Tacrolimus and Cyclosporin A treated patients, respectively. However, the rate of crossover was significantly higher among patients randomised to receive Cyclosporin A-based therapy (27.5% vs. 9.3%; P<0.001).

In our study, the incidence in Dyslipidaemia at 6 months was 36.8% in Cyclosporin group and 32.3% in Tacrolimus group which was not different statistically, though numerically it was more with Cyclosporin. At one year in the subgroup of 32 patients, Dyslipidaemia was observed in 56.3% (9/16) in cyclosporin group and 32.5% (6/16) in Tacrolimus group which was significant.

Result from the phase 3 US multicentre trial confirmed that Tacrolimus-treated patients experienced lower total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels compared with Cyclosporin A treated patients, demonstrated hereby the significantly lower use of lipid-reducing drugs over time. Patients treated with Cyclosporin A experienced an increase in both total cholesterol and triglycerides of approximately 30 mg/dL, and increase LDL cholesterol of approximately 20 mg/dL.[9] Unlike Cyclosporin A, Tacrolimus does not influence lipid metabolism. Thus, total cholesterol was approximately 30 mg/dL higher among Cyclosporin A patients as compared to those receiving Tacrolimus in several large scale randomised comparative trials.[2,6] Switching patients from Cyclosporin A to Tacrolimus results in significant reductions in total

cholesterol, LDL cholesterol, and triglycerides, with no change in HDL cholesterol.[10]

Incidence of de novo hypercholesterolaemia was significantly higher in the Cyclosporin A group (28 vs. 8%) whereas incidence of hypertriglyceridaemia was similar in both groups. Prevalence of LDL–C was significantly higher in the Cyclosporin A group (65% vs. 31%; P<.001), whereas there was no difference in high density lipoprotein (HDL)-C levels. Mean serum lipid levels and incidence and prevalence of hyper TC, especially LDL-C was significantly higher in patients receiving Cyclosporin A when compared with Tacrolimus. TG and HDL-C levels were similar. Although the study was retrospective, our results confirm that Cyclosporin A increase lipid levels, whereas Tacrolimus does not. Lipid disorders are frequently observed in renal transplant recipients. Cyclosporin A, but not Tacrolimus, significantly increases incidence and prevalence of high TC and LDL-C.

In our study, incidence of PTDM was 12.2% in Cyclosporin group and 16.7% in Tacrolimus group. Incidence of PTDM was numerically more with Tacrolimus though not statistically significant. At one year in the subgroup of 32 patients, PTDM was observed in 12.5% of Cyclosporin group and 25% of Tacrolimus group. The relative risk of PTDM was 1.86 with Tacrolimus, compared to Cyclosporin in a study.[11]

In early studies, the incidence of de novo PTDM, which was defined as the requirement of insulin administration for at least 1 month, was higher with Tacrolimus (10-20 percent) than with CsA (2-5 percent).[2,3] The risk factors for developing PTDM include older age, family history of diabetes, black race, and high doses of Tacrolimus or steroids. Although a reduction in Tacrolimus and steroid doses frequently makes it possible to stop insulin therapy, up to 50 percent of patients with de novo diabetes require insulin indefinitely, suggesting that this complication is sometimes irreversible. With the use of lower Tacrolimus concentrations (10-15 mg/mL), the incidence of PTDM has been reduced to around 5 percent, which is numerically, but not significantly, above the figures reported for Cyclosporin A.[6]

First and colleagues.[12] compared TAC-based and Cyclosporin A-based immunosuppression and found no significant difference in the incidence of PTDM (5.7% Tacrolimus vs. 3.3% Cyclosporin; P=0.453) when TAC trough levels were within the ranges specified by modern treatment guidelines.

In a Korean study.,[13] the cumulative incidence of PTDM according to ADA criteria was 57.1% at 6 months of post-renal transplantation, which was considerably high compared with the incidence of PTDM from previous studies. Considering that the prevalence of diabetes in the group of 30-64 years in Korea is 7.2% (28), and the 1-year prevalence of PTDM associated with Cyclosporin A-based immunosuppression is 23.7%, the incidence of PTDM in that study is very high. Several factors might explain this unexpectedly high incidence of PTDM. First, we can consider the ethnic difference. In general, non-Caucasian patients experienced a twofold increase in the risk of PTDM compared with Caucasian.

The incidence of tremors was statistically greater with Tacrolimus (28.4%) than Cyclosporin (3.1%) at 6 months and 1 year (32.5% vs. 0). Neurological side effects such as tremor and paraesthesia are distinctly more common under Tacrolimus.[2,3] The incidence of hirsutism was 24.5% in Cyclosporin group and 0% in Tacrolimus group. Delayed graft function was observed in 6.3% in Cyclosporin group and 7.1% in Tacrolimus group at less than 2 weeks.

CONCLUSIONS

It was concluded that there was no statistically significant difference in graft function & incidence of acute rejection between the two treatment groups at 6 months & 1 year. A higher incidence of tremor was seen in Tacrolimus group, but hirsutism was observed more with Cyclosporin group. At 6 months, there was no significant difference in the incidence of NODM, but at 1 year it was observed significantly more in Tacrolimus group. At 6 months, there was no significant difference in the incidence of Dyslipidaemia but at 1 year it was observed significantly more in Cyclosporin group.

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