ORIGINAL ARTICLE

Dyslipidaemia among renal transplant recipients: cyclosporine versus tacrolimus

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Abstract

Objectives: To compare new onset dyslipidaemia in live-related renal transplant recipients taking cyclosporine versus tacrolimus after 3 months of therapy.

Methods: The randomised controlled trial was conducted at the Sindh Institute of Urology and Transplantation (SIUT) Karachi, from September 2010 to April 2011, and included 182 End Stage Renal Disease patients on maintenance haemodialysis with pre-transplant normal lipid profile. The patients, who had live-related renal transplant, were randomly allocated to two equal groups using lottery. Group A received cyclosporine (3mg/kg) and group B was treated with tacrolimus (0.1mg/kg).

All patients had pre-transplant fasting lipid profile checked when they were on maintenance haemodialysis and 3 months after renal transplantation. Serum fasting lipid profile was collected by taking 5ml blood by venipuncture after an overnight fast of 9-12 hours. SPSS 10 was used for statistical analyses.

Results: Of the 182 patients, 144(79.1%) were males and 38(20.9%) were females. The overall mean age was 30.18±9.57 years, and the mean weight was 54.41±11.144kg. Significant difference was not observed between the two groups regarding age and weight of the patients. Dyslipidaemia was found in 115(63.2%) subjects; 61(67%) in group A and 54(59.3%) in group B. There was no statistical difference (p=0.28) when comparison was done after 3 months of therapy.

Conclusions: The occurrence of new onset hyperlipidaemia is similar in renal transplant recipients receiving either cyclosporine or tacrolimus in first 3 months post-transplant, but there is room for more research in this field as dyslipidaemia following successful renal transplantation is a frequent and persistent complication.

Keywords: Dyslipidaemia, Cyclosporine, Tacrolimus, Renal transplant, Lipid. (JPMA 64: 496; 2014)

Introduction

The End Stage Renal Disease (ESRD) population requiring maintenance haemodialysis or renal transplantation is growing and the prevalent dialysis population almost doubles every decade and the transplant population grows by slightly more than double over the same time period.[1] Renal transplantation has become the therapy of choice for ESRD patients[2] and it not only improves quality of life, but also offers extended life expectancy compared with dialysis.[3]

Dyslipidaemia is common in patients with chronic kidney disease (CKD) and after kidney transplantation[4] and it may lead to increased cardiovascular morbidity and mortality. Statins significantly reduce hyperlipidaemia and cardiovascular events in kidney transplant recipients.[5] The use of immunosuppressants, including Calcineurin Inhibitors (cyclosporine and tacrolimus) and mammalian Target Of Rapamycin (mTOR) inhibitors (sirolimus, everolimus) is associated with dyslipidaemia.[6] Pronounced global differences in use of cyclosporine and tacrolimus exist. In 2009, in United States, 81% of new renal transplant recipients received tacrolimus, in combination with mycophenolic acid, for immunosuppression and after 1 year of transplantation, 72% patients were on tacrolimus compared with only 5.3% receiving cyclosporine.[7] In our institution, because of economic reasons, cyclosporine is still the major immunosuppressant and tacrolimus is used only when the match is poor.[8] Tacrolimus is considered more effective immunosuppressant than cyclosporine, and at currently recommended doses it shares many side effects with cyclosporine, although it causes less hypercholesterolaemia than cyclosporine.[9] In renal transplanted patients, the pattern of dyslipidaemia comprises elevated total cholesterol (TC), low density lipoprotein (LDL) cholesterol, very low density lipoprotein (VLDL) cholesterol, triglycerides (TG) and decreased high density lipoprotein (HDL) cholesterol.[10] Cardiovascular disease still is the prime cause of death among renal allograft recipients and lipid-lowering drugs (statins, ezitimibe) lower serum lipids after renal transplantation, but their effect on lowering the mortality is not established in renal transplant recipients.[11] A study from Iran has concluded that hyperlipidaemia among renal transplant recipients is an associated biochemical

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phenomenon secondary to the use of immunosuppressive drugs and does not have obvious role in cardiovascular atherogenesis.[12]

The current study compared the short-term side effect (dyslipidaemia) of two most commonly used immunosuppressive drugs in renal transplant patients after 3 months of receiving therapy. No such study has been conducted in South Asian region and knowledge regarding choice of immunosuppressive regime in our population is wanting. The study will help to make a choice between the two cacineurin inhibitors among renal transplant recipients.

Patients and Methods

The randomised controlled trial was conducted at the Sindh Institute of Urology and Transplantation (SIUT), Karachi, from September 2010 to April 2011 after approval by the institutional ethics review committee. Informed consent was obtained from all the subjects who had live-related renal transplant at the SIUT and had normal pre-transplant lipid levels. Patients who had body mass index (BMI) of more than 30, those already on lipid-lowering drugs, patients with diabetes mellitus, nephrotic syndrome, hypothyroidism or hyperthyroidism and those who were taking beta blockers were excluded from the study. Patients whose serum creatinine was more than 1.5 mg/100ml at 3 months post-transplant were also later excluded. Patients whose immunosuppression (cyclosporine or tacrolimus) was changed during the study either because of acute rejection, infection or due to side effects were further excluded.

The patients were randomly allocated to two equal groups. Group A was given cyclosporine (3mg/kg body weight) and group B was given tacrolimus (0.1mg/kg body weight). Both groups also received azathioprine (3mg/kg) and prednisolone (0.5mg/kg tapering to 0.1mg/kg in 3 months) as part of immunosuppressive regimen. Blood samples for serum cholesterol, TG, LDL and HDL were obtained by venesection after an overnight fast of at least 9-12 hours and sent to the laboratory in vacuum glass tubes. The first blood samples were drawn before renal transplant operation and the second samples three months after the transplantation.

Data was noted on predesigned proforma and it was analysed using SPSS 10.0. Mean ± Standard Deviation (SD) were calculated for weight and age of the patients. Frequency and percentages were calculated for gender and dyslipidaemia. Chi-square test was applied to compare dyslipidaemia in the two groups. P value of less than or equal to 0.05 was taken as significant.

Results

A total of 198 patients were initially registered, but 16 (8%) were later excluded because of serum creatinine more than 1.5mg/dl three months post-transplant. As such, the final study population was 182. Of them, 144(79.1%) were male and 38(20.9%) were female (Table-1). The patients were randomly allocated to two equal groups. The overall mean weight of patients was 54.41±11.144kg (95% Confidence Interval [CI]: 52.78 to 56.04). Despite improved appetite and effect of steroids, none of the patients had BMI $\geq$ 30 during the study. There was no significant difference in age, weight and gender observed between groups ($p \geq 0.05$).

Dyslipidaemia was found in 115(63.2%) patients: 61(67%) in group A, and 54(59.3%) in group B. Though there was numerical difference in the frequency of dyslipidaemia

Table-1: Demographics and frequency of dyslipidaemia.

Features	Values
No. of patients	182
Gender	Males=144 (79.1%)
	Females=38 (20.9%)
Mean Age (Years)	30.18 ± 9.57
Mean Weight (Kg)	54.41±11.144
Group A (Cyclosporine)	Males=71 (78%)
	Females=20 (22%)
	Total=91
Group B (Tacrolimus)	Males=73 (80%)
	Females=18 (18%)
	Total=91
Dyslipidaemia	Group A= 61 (67%)
	Group B= 54 (59.3%)
	P= 0.28
Dyslipidaemia among males	Group A=49 (69%)
	Group B=45 (61.6%)
	p=0.677
Dyslipidaemia among females	Group A= 12 (60%)
	Group B= 9 (50%)
	p=0.677

Table-2: Abnormal individual lipid profiles after 3 months of renal transplant.

Lipid Profile	Group A (91)	Group B (91)	Total (182)	p-values
Elevated total Cholesterol ≥200 mg/dl	20(22%)	15(16.5%)	35(19.2%)	0.347
Elevated Serum Triglycerides ≥150mg/dl	30(33%)	22(24.2%)	52(28.6%)	0.189
Serum HDL cholesterol <40 mg/dl	45(49.5%)	43(47.3%)	88(48.4%)	0.76
Elevated Serum LDL cholesterol ≥130mg/dl	16(17.6%)	13(14.3%)	29(15.9%)	0.54

HDL: High-density lipoprotein. LDL: Low-density lipoprotein.

between the two groups, it was not statistically significant (p=0.28). There was no statistically significant difference in terms of age, weight and gender in the two groups.

Regarding individual values of fasting lipid profile after 3 months of renal transplant, TC was raised in 35(19.2%), raised TG in 52(28.6%), reduced HDL in 88(48.4%), and raised LDL in 29(15.9%) cases (Table-2). Comparison of individual values of serum cholesterol, TG, HDL and LDL between the two groups did not reveal any statistically significant difference.

Discussion

Renal transplantation has revolutionised the management of patients with end-stage renal failure and it has survival advantage over haemodialysis.[13] However, the risk of premature death among renal allograft recipients is still much higher than the age-matched general population and cardiovascular diseases account for a significant number of deaths among transplant recipients.[14] Both cyclosporine and tacrolimus have been shown to be very effective in reducing the incidence of acute rejection, at the same time, both the calcineurin inhibitors increase the cardiovascular risks among renal allograft recipients. Although tacrolimus is associated with less risk of nephrotoxicity, hypertension and hyperlipidaemia compared to cyclosporine, it has more diabetogenic potential which can offset its benefit on cardiovascular morbidity and mortality.[15] It has been shown that despite statin treatment, renal transplant recipients can have a characteristic pattern of lipid disturbance with raised TC, LDL, HDL, and a concomitant increase in TG and more aggressive approach to manage post-transplant dyslipidaemias is warranted in patients with pre-existing dyslipidaemia.[16]

Among the patients included in our study, 63.2% developed hyperlipidaemia compared to approximately 34% transplant recipients in a study from Iran.[12] This difference may be due to differences in dietary habits and differences in the demographics of the two study populations.

Our study showed that there was no statistically significant difference in the occurrence of new onset hyperlipidaemia among renal transplant recipients taking cyclosporine and tacrolimus. This is similar to the earlier findings of a study[17] which showed significant deterioration in lipid profile after renal transplantation among renal allograft recipients taking either cyclosporine or tacrolimus. One study[18] observed that both cyclosporine and tacrolimus had a similar effect in raising TC, LDL and TG in renal transplant recipients, while cyslosporine also raised HDL cholesterol. The rise in HDL was not observed in our study and may be because of low dosage and rapid tapering of steroids. A study from Belgium[19] showed that the lipid levels remained stable in the long term after conversion from tacrolimus to cyclosporine among patients who had new onset diabetes mellitus after renal transplantation, but the use of statins increased significantly.

On the other hand, some studies have shown that in comparison with cyclosporine, tacrolimus has less effect on raising cholesterol levels.[6] It has been shown that with the conversion of cyclosporine to tacrolimus, the lipids' profile improves. A study from Greece showed that tacrolimus is an immunosuppressant agent with fewer and less severe adverse effects on lipid metabolism compared to cyclosporine.[20] Another study from Iraq showed that the use of low-dose tacrolimus-based immunosuppressive regimen is associated with a more favourable lipid profile than the use of cyclosporine and reduction in the dose of cyclosporine did not improve the changes in lipid profile.[21] However, a retrospective study from Turkey[22] found a positive correlation between blood level of cyclosporine and LDL cholesterol, but no such correlation was found with tacrolimus. A recent study showed that conversion from cyclosporine to tacrolimus in stable kidney transplant recipients resulted in improvement in lipid profile but there was no reduction in the number of medications and marginal reduction in cardiovascular risk parameters.[23] Sub-analysis of Symphony study revealed that patients receiving sirolimus (mTOR Inhibitor) had the worst lipaemic control and patients receiving sirolimus had highest LDL-cholesterol and triglyceides than patients receiving tacrolimus and cyclosporine while there was no difference in HDL levels.[24] The two mTOR inhibitors (sirolimus and everolimus) have similar effects on lipid levels.[25] At our institution, mTOR inhibitors are not used during the initial 3 months post-transplant and therefore mTOR inhibitors were not included in our study.

Although there are conflicting reports of superiority of tacrolimus over cyclosporine in terms of hyperlipidaemia, the low cost of cyclosporine is a major reason for its use in greater proportion of renal transplant recipients. As our study shows that tacrolimus is not superior to cyclosporine in terms of dyslipidaemia, it can help to save cost without compromising the patient care and use of available resources for larger patient volume. However, where there is convincing indication, cyclosporine can be switched to tacrolimus especially among children when cosmetic side effects are a concern and for patients with poor match.[8]

The limitation of the current study is that it did not include

individual values of serum lipids and only had noted two categories as 'normal' and 'high' levels. Probably it would have been better to take lipid levels as continuous variable. Secondly, our study included a small number of patients at a single centre. Larger and multi-centre studies are needed to further clarify this issue.

Conclusion

The occurrence of new onset hyperlipidaemia is similar in renal transplant recipients receiving either cyclosporine or tacrolimus in first 3 months post-transplant, but there is room for more research in this field as dyslipidaemia following successful renal transplantation is a frequent and persistent complication. This will have implication for economical use of available limited resources in developing countries like Pakistan.

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