THE EFFECT OF IMMUNOSUPPRESSIVE AGENTS ON LIPID PROFILE OF POST RENAL TRANSPLANT PATIENTS

Mohammad Ghnaimat, MD*, Wafa' Nsour, MSc (Pharm)**, Rabe'a Abbadi, BSc (Pharm)**

ABSTRACT

Objective: To determine the effect of the different immunosuppressive medications on the lipid profile of renal transplant recipients with normal renal functions.

Methods: A Single blinded study was conducted on patients who underwent live-related renal transplants at Queen Alia Military Hospital between January 2001 and March 2003.
They were divided into two groups according to the immunosuppressive treatment. Group I: On tacrolimus and Group II: On ciclosporine (Neoral)®. Both groups received in addition steroids and either azathioprine or Mycophenolate Mofitel.
Inclusion Criteria includes normal blood glucose and normal lipid profile prior to transplantation.
Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides were measured monthly for at least three months after transplantation.
Statistical significance was considered if $P \leq 0.05$.

Results: In both groups, the mean total cholesterol, low-density lipoprotein cholesterol and triglycerides were indifferent; while there was a statistically significant difference between the two groups in high-density lipoprotein cholesterol in favor of the ciclosporine (Neoral) group.

Conclusion: Tacrolimus and ciclosporine have a similar effect on total cholesterol, low-density lipoprotein cholesterol and triglycerides; while Ciclosporine is better in raising the high-density lipoprotein cholesterol. Further long-term studies are required to determine the effect of these lipid profile changes on cardiovascular morbidity and mortality.

Keywords: Dyslipidemia, Renal transplantation, Immunosuppressive medications.

Introduction

It has long been debated whether renal transplantation, in addition to improving patients quality of life, also offers a survival benefit over continuation of dialysis, because when evaluating the success of renal transplantation, many studies focus on the initial results; especially the risk of acute rejection and the short term patient and graft survival [1].

Since transplantation is usually performed in the best candidates, a proper control group is difficult to compose. Nevertheless, recent studies have made it clear that transplantation improves survival [1,2].

The main causes of death after renal transplantation are infections, malignancies and cardiovascular disease [3].

The incidence of cardiovascular disease in the renal transplant population is more than four times higher than in the general population [4].

In addition to the well known risk factors for cardiovascular disease, most renal transplant recipients have gone through the stage of end stage renal failure.

Cardiovascular mortality in this population is 10-20 times higher than in the general population [5].

Hyperlipidemia is a significant management issue after renal transplantation; post transplant hyperlipidemia has been linked to cardiovascular disease morbidity and mortality [6].

In addition to multiple causes, the type and level of immunosuppressive agents used can also adversely impact post transplant hyperlipidemia [7].

This article reports comparing tacrolimus and ciclosporine (Neoral) on hyperlipidemia in patients with stable graft function.

Methods

Between January 2001 and March 2003, 104 patients underwent live- related renal transplant at Queen Alia Military Hospital were included in this single blinded study. The study was a non-randomized one and a convenient sample of 104 patients was selected.

To be included in the study, patients had to meet the following criteria: Follow up of at least 4 months after transplantation, stable renal function tests, fasting blood glucose less than 130mg/dl, normal lipid profile prior to transplantation.

Patients with diabetes mellitus, proteinuria, obesity or those on drugs known to alter the lipid profile were excluded.

Out of 104 patients who underwent living related renal transplant during the 27 months study period, 80 patients met the inclusion criteria, and 24 patients were excluded.

Patients were divided into two study groups (40 patients each), the tacrolimus (group I) and the ciclosporine (Neoral) (group II), the two groups were matched according to age and gender.

All patients were on hemdialysis prior to transplantation.

All patients were on steroids, Prednisolone 20 milligrams/day tapered to 7.5 milligram/day at the end of the third month.

Twenty-Five patients from the tacrolimus group were on azathioprine and 15 were on MMF, while in the second group (Neoral) 23 patients were on azathioprine and 17 on MMF.

The initial dose of tacrolimus was 0.15 mg/kg/day tapered according to blood level, and that of Neoral was 8mg/kg/day tapered according to ciclosporine after 2 hours (C2) level.

On each visit to the nephrology clinic blood samples were extracted for 12 hours, fasting blood glucose, serum creatinine, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides.

Statistical analysis using t-test was conducted to determine the difference between the effects of the two medications on lipid profile. P value $P \leq 0.05$ was considered significant.

Results

Table I shows the demographic characteristics of both study groups, comparing the results between pre and post transplant patients receiving cyclosporine treatment.

A statistically significant difference was present in total cholesterol, LDL cholesterol and HDL cholesterol, which were all elevated as shown in Table II.

Table III presents the tacrolimus effect on variables under study, among both pre and post transplant patients were only HDL cholesterol elevation was found to have a statistically significant difference ($P<0.0005$). Total cholesterol < 0.004 and LDL cholesterol <0.02, both are statistically significant but HDL cholesterol is highly significant.

Table IV demonstrates the post transplantation effect of both immunosuppressive medications, and as clearly shown ciclosporine has a more favorable effect on elevation of HDL cholesterol.

There was no difference between males and females in both groups in the study variables.

Discussion

Post transplant hyperlipidemia has been linked to cardiovascular disease with its high morbidity and mortality rate, in addition to its correlation with atherosclerosis; there is an indirect association of hyperlipidemia with the progression of chronic transplant nephropathy [8,9].

Atherosclerosis is a multifactorial disease, the initial step is endothelial dysfunction which increases the permiability of the endothelium for atherogenic lipid particles especially LDL cholesterol. They accumulate in the vessel wall, undergo oxidation and stimulate the production of monocyte chemotactic protein-1 which invites inflammatory cells to the vessel wall.

This inflammation is clinically known as fatty streaks, the initial stage in the atherosclerotic process [10].

Endothelial function is influenced by all of the classical risk factors known from epidemiological studies: Hypertension, hyperlipidemia, diabetes mellitus, smoking, renal failure and hyperhomocysteinemia.

The most commonly used immunosuppressive drugs to prevent rejection; steroids and Calcineurin inhibitors are also known to cause endothelial dysfunction [10].

Hollander et al [11] reported an 8% higher incidence of cardiovascular death 8 years after transplantation in patients treated with ciclosporine and steroids than in patients converted to azathioprine and steroids.

The prevalence of hyperlipidemia after transplantation is high and up to 60% of all transplant patients have high cholesterol levels.

Steroid increase both total and LDL cholesterol but also increase HDL cholesterol [10].

Ciclosporine also induces hyperlipidemia in a dose dependent way, mainly increase total and LDL cholesterol.

In the main US trial comparing tacrolimus to ciclosporine, hyperlipidemia especially hypercholesterolemia was less frequent in tacrolimus treated patients , Friemann S, *et al* [12] and Thomas R *et al* [7] suggested that in patients with hyperlipidemia after renal transplantation switching to tacrolimus will improve lipid profile.

In the present study there was a 15.2% rise in total cholesterol over the pre transplant values in the ciclosporine treated group and 11.8% rise in the tacrolimus group while LDL cholesterol increased by 13.5%in the ciclosporine group compared to 12.2% in the tacrolimus group. In both groups there was an 8% rise in triglycerides levels over the baseline values.

In contrast to other studies, the elevation in HDL cholesterol was more in the ciclosporine treated group.

Conclusion

Patients who are candidates for renal transplantation are often at risk for hyperlipidemia due to pre existing conditions. This risk increases several folds post transplantation as a result of the immunosuppressive drugs used to prevent rejection.

Tacrolimus and ciclosporine have similar effect on total cholesterol, LDL cholesterol and triglycerides, while ciclosporine is better in raising the HDL cholesterol.

Further long-term studies are required to determine the effect of these lipid profile changes on cardiovascular morbidity and mortality.

Limitations of the study

Further study is needed to show the differences in lipid profile into:

- Ciclosporine and Azathioprine
- Tacrolimus and Azathioprine
- Ciclosporine and Mycophenolate Mofitel
- Tacrolimus and Mycophenolate Mofitel
- The study group was all on hemodialysis and none was on peritoneal dialysis.

Table I. Demographic variables of the study groups

Variable	Tacrolimus	Ciclosporine
Mean age (years)	32.90	36.38
Males	26	28
Females	14	12
Mean body (Weight. (Kg))	67	65

Table II. Ciclosporine effect on different variables before and after renal transplant.

Variable	Pre-transplant	Post-transplant	P. Value
Total cholesterol(mg%)	171$\pm$41	197.48$\pm$40.98	< 0.005
LDL-cholesterol (mg%)	104$\pm$21.72	118.73$\pm$23.69	<0.005
HDL-cholesterol (mg%)	33.62$\pm$3.98	42.45$\pm$4.19	<0.0005
Triglycerides (mg%)	167$\pm$33.21	181$\pm$64.85	>0.23
Fasting blood sugar (mg%)	90$\pm$17	92$\pm$16	>0.6

Table III. Tacrolimus effect on different variables before and after renal transplant.

Variable	Pre-transplant	Post-transplant	P. Value
Total cholesterol (mg%)	169.71$\pm$38.62	189.9$\pm$45.35	< 0.05
LDL-cholesterol (mg%)	106.22$\pm$22.46	119.23$\pm$25.09	<0.05
HDL-cholesterol (mg%)	32.87$\pm$3.81	38.21$\pm$4.49	<0.0005
Triglycerides (mg%)	164.28$\pm$79.7	181.41$\pm$82.15	>0.3
Fasting blood sugar (mg%)	87.2$\pm$14.48	97$\pm$24	>0.05

Table IV. The effect of Ciclosporine and Tacrolimus on both groups after renal transplantation.

Variable	Group I (post- Transplant)	Group II(Post-transplant)	P. Value
Total cholesterol (mg%)	197.48 $\pm$ 40.98	189.9 $\pm$ 45.35	> 0.05
LDL-cholesterol (mg%)	118.73 $\pm$ 23.69	119.23 $\pm$ 25.09	>0.05
HDL-cholesterol (mg%)	42.45 $\pm$ 4.19	38.21 $\pm$ 4.49	<0.05
Triglycerides (mg%)	181 $\pm$ 64.85	181.41 $\pm$ 82.15	>0.05
Fasting blood sugar (mg%)	92 $\pm$ 16	97 $\pm$ 24	>0.05

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