



Statins in Organ Transplant

RP Mathur

Head, Department of Medicine & Nephrology, Jagjivan Ram Hospital, Mumbai-400 008.

77

ABSTRACT

An advanced 'vasculopathy' is the common denominator of all failing organ transplants. Cardiac allograft vasculopathy (CAV) is one of the major causes of mortality late after heart transplantation. In kidney, this vasculopathy is described as a 'fibroproliferative endarteritis' involving the interlobular and arcuate arteries. A similar long-term graft dysfunction is also described in liver and lung transplant recipients. There are multiple immune and non-immune risk factors associated with above vasculopathic process, one of which is hyperlipidemia.

Use of lipid lowering agents, specifically HMG-CoA reductase inhibitors (statins) appear to have outcome benefits from heart and kidney clinical studies by delaying the graft vasculopathy, retardation of progression of atherosclerosis and by their immunomodulatory effects.

FACTORS INFLUENCING LONG TERM OUTCOMES AFTER ORGAN TRANSPLANTATION

Advances in immunosuppressive therapy and in the treatment of opportunistic infections have largely improved outcomes after organ transplantation. More often, post-transplant patients die with a functioning graft. Cardiac vascular disease (CVD) is now a leading cause of such deaths. Premature CVD is a major target for intervention in patients undergoing renal transplantation.

An increased risk of CVD is not seen to the same extent in liver transplant recipients. This difference suggests that the root of the problem in renal transplant lies in the damage to the vasculature caused by chronic renal failure, rather than by transplantation itself. Pre-transplant vascular disease is the strongest predictor of post-transplant vascular disease. Some factors contributing to the risk of CVD (such as volume overload, anaemia and abnormalities in calcium and phosphorus metabolism) may improve after renal transplantation. However, other risk factors e.g. hypertension and lipid abnormalities may persist after transplantation, partly due to the effect of immunosuppressive drugs. Age, smoking, male sex, lipid abnormalities and diabetes are independent risk factors for CVD after renal transplantation. Thus, risk factor reduction for prevention and management of CVD after organ transplantation is an important strategy to extend patient and graft survival.

Besides CVD, long term allograft dysfunction is also a significant cause of morbidity and mortality in organ transplantation.

Cardiac allograft vasculopathy (CAV) is an accelerated form of obliterative coronary artery disease occurring in heart transplant recipients and is one of the leading cause of death in long term cardiac transplant patients. This disease process occurs to a lesser extent in patients with other donor organs however, a similar chronic graft dysfunction is also described in kidney, liver and lung transplant recipients. Both immune and non-immune risk factors are associated with development of CAV. Hyperlipidemia is one of the most important non-immune risk factors.

DYSLIPIDEMIA AFTER ORGAN TRANSPLANTATION

The etiology of lipid abnormalities seen after organ transplantation is multifactorial, including drug treatment with steroids, cyclosporine and anti-hypertensives, impaired renal function, proteinuria and persistent hyperparathyroidism. The typical pattern includes marked hypercholesterolemia and moderate hypertriglyceridemia and increased apolipoprotein B. In addition, cyclosporine-treated patients have increased susceptibility of LDL to oxidation and increased lipoprotein(a). Hyperlipidemia after transplantation is also associated with obesity.

In view of close association between hyperlipidemia and CVD in general population, lipid abnormalities after transplantation may exert an adverse effect on cardiovascular morbidity and mortality, and may also contribute to chronic graft dysfunction.

There is a tendency of physicians to be more sensitive to cardiovascular risk factors in older rather than in younger individuals. This practice seems to be erroneous because renal transplant

patients of all ages, but particularly the young, have an increased cardiovascular risk as compared to general population.

Role of Lipid - lowering therapy in Organ Transplantation

As per third report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Panel III or ATP III) the management of hyperlipidemia includes therapeutic lifestyle changes, reduced intake of saturated fat and cholesterol, weight reduction, increased physical activity and the use of lipid lowering drugs. In the organ transplant, population drug therapy is invariably required. Various clinical trials have proved that HMG-CoA reductase inhibitors or statins are the safest and most effective cholesterol lowering agents. The overall beneficial effects of statins may be due to cholesterol-lowering as well as cholesterol-independent properties of the drug and other cardiovascular effects. Statins affect long-term graft survival through several mechanisms:

- a. Prevention of atherosclerosis.
- b. Improvement of graft vasculopathy.
- c. Retardation of progression of renal graft dysfunction.
- d. Immunosuppressive effect.

Prevention of atherosclerosis

An initial inflammatory response in the coronary artery endothelial cells initiates atheroma formation in non-transplant patients. Subsequent inflammation of an atheromatous lesion may result in plaque disruption and vessel lumen occlusion and progression of atheromatous plaque. In cardiac transplant cases, a chronic inflammatory response from the recipient to the endothelial cells of the donor coronary arteries occurs, leading to the development of CAV. Thus, it appears that there may be common mechanisms involved for the development of atherosclerosis in non-transplant and transplant patients.

The clinical benefits observed in statin-treated heart transplant cases are most probably due to the powerful cholesterol-lowering effects of statins; however a possible cholesterol-independent immunomodulatory effect is also suggested. Hypercholesterolemia is linked with increased lipid peroxidation and increased oxidative stress; oxidized LDL leads to stimulation of macrophage activation, DNA synthesis of smooth muscle cells, expression of HLA-DR antigens and IL-2 receptor expression in resting T cells. Activated macrophages and endothelial cells mediate LDL oxidation, which can stimulate macrophages further to secrete cytokines, chemokines and growth factors which in turn promote vascular intimal thickening. Reduction of lipid levels by statins may decrease these oxidation sensitive pathways leading to suppression of inflammation, atherogenesis and plaque rupture.

Improvement of Graft Vasculopathy by statins

An advanced 'vasculopathy' is the common feature of all failing transplanted organs termed as 'cardiac allograft vasculopathy' in heart transplant recipients and 'fibroproliferative endarteritis' involving the interlobular and arcuate arteries in kidney transplant patients. The progressive narrowing of these vessels ultimately leads to ischaemia and graft loss. These lesions are very similar

to atherosclerotic lesions. By controlling the hyperlipidemia by statins, the progression of graft vasculopathy may be significantly delayed.

Retardation of progression of renal graft dysfunction

Hyperlipidemia is a significant factor in the progression to end-stage renal disease and its control by administration of statins may improve graft survival.

Immunosuppressive effects of statins

Statins have beneficial effects beyond their lipid-lowering effect. In transplant patients statins have been shown to modulate the rejection reaction leading to suppression of acute rejections, chronic vascular rejections and a general improvement of graft survival.

In a four year randomised trial of 72 heart transplant patients, Wenke et al demonstrated a lower incidence of CAV in simvastatin-treated patients (18%) as compared to control patients (42%). In addition, intravascular ultrasound performed at baseline and at one year interval revealed less progression of intimal thickness in the simvastatin group. Statins have shown protective effects on coronary vasomotor function and the decreased coronary sinus release of IL-6 and tumor necrosis factor-alpha (TNF-alpha) in cardiac transplant patients, suggesting that endothelial functions are improved and inflammatory cytokine release is reduced. Besides this effect, inhibition of natural killer cells by statins has been demonstrated in vitro.

The other immunomodulatory effects of statins include repression of MHC-II, selective blocking of the beta-2 integrin, leucocyte function antigen-1 (LFA-1) and increased formation of nitric oxide which promotes arterial vasodilatation and inhibits atherogenesis. The above effects are cholesterol-independent, and many of the above effects are due to protein prenylation. Inhibition of proliferation and induction of apoptosis in smooth muscle cells, inhibition of integrin-dependent leukocyte adhesion, and increased fibrinolytic activity.

Statins potentiate the effects of cyclosporine through competition with cytochrome P 450 responsible for cyclosporine metabolism, and also through lowering of lipoproteins, thus liberating the cyclosporine bound to them.

CONCLUSION

The statins are a new addition to the immunosuppressive protocol. The early introduction of statins may lead to retardation of progression of renal disease, delay graft vasculopathy, halt the progression of atherosclerosis and add its beneficial immunomodulatory effects.

REFERENCES

1. Kendrick E. Cardiovascular disease and the renal transplant recipient. *Am J kidney Dis* 2001;38 (suppl 6): S 36-S 43.
2. Kobashigawa JA. Statins in solid organ transplantation: Is there an immunosuppressive effect? *Am J Transplantation* 2004;4:1013- 1018.
3. Stephan A, Barbari A, Karam A, et al. Hyperlipidemia and graft loss. *Transplant Proc* 2002;34:2423-2425.
4. Castello IB. Hyperlipidemia: A risk factor for chronic allograft dysfunction. *Kidney International* 2002;61(Suppl 80): S 73 - S 77.

5. Andrews PA. Renal transplantation. *BMJ* 2002;324:530-534.
6. Dimeuy EM. Cardiovascular disease after renal transplantation. *Kidney International* 2002;61(Suppl) 80: S78-S 84.
7. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998;32 (suppl 3):S 112-S 119.
8. Kobashigawa JA, Kasiske BL. Hyperlipidemia in solid organ transplantation. *Transplantation* 1997;63: 331-338.
9. Bumgardner GL, Wilson GA, Tso PL, et al. Impact of serum lipids on long term graft and patient survival after renal transplantation. *Transplantation*, 1995;60: 1418-1421.
10. Munford RS. Statins and the acute phase response. *N Engl J Med* 2001;344: 2016-2018.