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Statin Immunomodulation: Role in Transplantation and Disease Conditions

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ABSTRACT

The pleiotropic effects of statins suggest that their therapeutic benefits may probably extend beyond cholesterol lowering in cardiovascular disease to organ transplantation and other disease conditions, particularly autoimmune disease. This is attributable to their modulating influence on immune mechanisms mediated by inhibition of prenylated proteins. Isoprenoid intermediates generated by the mevalonate pathway are involved in post translational prenylation of signal transduction proteins. Reduction in allograft rejection is linked to immunomodulatory function of statins; graft rejection been enhanced by down regulation of pro-inflammatory T-helper 1 cells. Conclusively, the therapeutic potential of statins has been proven in organ transplantation and other disease conditions due to their potent immunomodulatory characteristic.

Key words: Autoimmune disease, Immunomodulation, Organ Transplantation, Protein prenylation, Statins, Therapeutic benefit.

INTRODUCTION

Clinical and experimental data support the protective role of statins against the rejection of organ transplants. Statins have been shown to be the most potent and effective drug for serum cholesterol lowering[1]. The therapeutic potential of statins as immunosuppressive agent has been demonstrated by clinical cases of transplant survival. Statins have been shown to offer protection against rejection in heart transplants[2] and found to be beneficial in pulmonary and renal transplantation[3-6]. Considerable interest has been shown in the therapeutic potential of statins in autoimmune disease conditions[7-9] such as rheumatoid arthritis, multiple sclerosis, encephalomyelitis; to conditions such as chronic kidney disease, respiratory disease and sepsis. This paper highlights the immunological response mediated by statins in organ transplantation and other disease conditions with particular reference to autoimmune diseases.

Statin Immunomodulation and Organ Transplantation

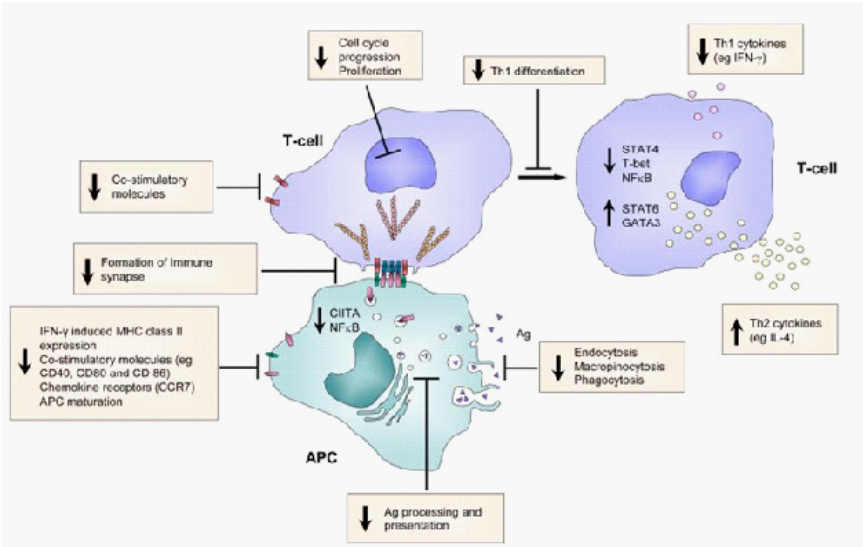
The prevalence of hypercholesterolemia in heart transplant patients necessitates the administration of statins to prevent transplant atherosclerosis. A decrease in graft atherosclerosis is consistent with immunomodulatory function of statins. The prevention of graft rejection can be enhanced by a shift towards T-helper 2 cell differentiation or down regulation of pro-inflammatory T-helper 1 cells. A study revealed diminution in host inflammatory cell recruitment without reduced lipid levels and attenuation of transplant graft arterial disease[10]. It has been shown that the inhibition of interferon-γ (IFN-γ) induced expression of MHC class II on antigen presenting cells is the major underlying mechanism of immunosuppression in organ transplantation[11]. Graft rejection after organ transplantion is influenced by MHC class II molecules which have direct effect on the control of immune responses.

The LFA1/ICAM1 interaction mediated by T-cell co-stimulation via statin modulation has an important role in pathophysiology of transplant rejection[12]. Nonetheless, in organ transplant recipients, the combination of an immunosuppressive effect with powerful cholesterol-lowering action would be particularly desirable. A study has noted that in many organ transplant recipients, there was a high incidence of hypercholesterolemia[13]. It was revealed that in patients, with pre-existing atherosclerosis, the highest incidence of post-transplantation hypercholesterolemia given as 80% was found, surprisingly in heart transplant patients. It is remarkable to note that hypercholesterolemia independent of transplantation has been linked to standard immunosuppressive agents (cyclosporine and corticosteroids) administered to transplant recipients. Significant decline in rejection rates has been reported in statin-treated patients following renal transplantation[4,5]. Data from a systematic review of 13 randomized controlled intervention trials indicated that the use of statins improved cardiovascular risk and reduced clinical cardiac events, although the risk of acute rejection after renal transplantation was not reduced[14].

A beneficial effect on chronic allograft nephropathy was reported by retrospective study aimed at determining the impact of statins on graft outcome in the first year following transplantation[6]. The study further lent credence to the fact that improved functional and histological outcome in the first year results following early introduction of statins, post-transplantation; which impacts on the pathology of chronic allograft rejection significantly.

Statin Immunomodulation in Disease Conditions

Statins have been shown to exhibit therapeutic potential in immunological disorders due to their potent immunomodulatory characteristics. Chronic and relapsing paralysis in multiple sclerosis was not only prevented by atorvastatin but reversed[15,16]. Beneficial effects of statins in multiple sclerosis and rheumatoid arthritis have been reported[17,18]. A study reported that lovastatin treatment over a 12 month period resulted in a decrease in the mean number of gadolinium



The interferon-γ induced expression of MHC class II under the influence of MHC-II transactivating factor and expression of co-stimulatory molecules by APCs are inhibited by statins. Statins inhibit Signal Transducer and Activator of Transcription 4 (STAT4) necessary for T helper1 cell differentiation, while enhancing the effect of STAT6 and GATA3 responsible for that of T helper2 cell. Modified and Adapted from- Greenwood J., Steinman L. and Zamvil S.S. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. *Nature*. 6: 358-370 (2006).

Fig. 1: Mechanisms of Statin Immunomodulation on T-cell and APC Functions

enhancing lesions but no accompanying reduction in the expanded disability status scale (EDSS) score, in a purely observational study of seven patients with relapsing-remitting multiple sclerosis[19]. Although, it is well known that statins reduce cardiovascular risk in individuals with normal renal function[20,21]; there are some encouraging data indicative that this effect is also seen in individuals with chronic kidney disease. Pravastatin reduced rates of cardiovascular events in patients with or at high risk of coronary disease plus the combination of diabetes and stage 2 or early stage 3 chronic kidney disease, in a sub-study of three randomized clinical trials: Cholesterol and Recurrent Events (CARE), West of Scotland Coronary Prevention Study (WOSCOPS) and Long-Term Intervention with Pravstatin in Ischemic Disease (LIPID)[22]. Results from clinical trial involving rosuvastatin indicate that the drug might arrest the progression of kidney disease[23]. The fact that pravastatin moderately reduced the rate of kidney function decline was further revealed by pooled analysis of data from WOSCOPS, CARE, and LIPID trials. Analysis of the GREeK Atorvastatin and coronary heart disease evaluation (GREACE) study showed that atorvastatin prevented decline of creatinine clearance and improved renal function[24]. The role of statins in decreasing blood pressure has been demonstrated in a model of normocholestrolemic spontaneously hypertensive rat[25]. Nitric oxide production, a crucial mediator of vascular homeostasis and blood flow is enhanced by statin[26,27]. It has been shown in humans that hypercholesterolemia results in blood pressure rise due to angiotensin II enhancement induced by AT1 receptor overexpression[28]. Atorvastatin decreased blood pressure and protected against end-organ damage in an experimental model of hypertensive Dahl salt-sensitive rats prone to cardiovascular, renal and endothelial damage when fed on high salt diets[29]. A study revealed that the addition of pravastatin to the treatment regimen of hypertensive proteinuric patients treated with antihypertensives decreased the severity of proteinuria and this was attributable to a decline in urine endothelin I levels[30]. The same pravastatin was reported to lower diastole, systole and pulse pressures in a randomized placebo controlled study involving individuals with untreated hypertension and moderate hypercholesterolemia[31]. There are still obvious differences amongst various statins with regards to their pharmacokinetics, clinical efficacy and potency. It is unclear which statins will provide the best therapeutic benefit in a given disease condition. However, it remains controversial whether the benefits of statins demonstrated in animal studies translated to humans are mediated by the same mechanism.

In conclusion, statins possess proven therapeutic benefits in organ transplantation and other disease conditions attributable to their immunomodulatory properties. Notwithstanding, the need for large scale and long term clinical trials to ascertain the need for widespread recommendation and use of statins in autoimmune and other disease conditions can never be overemphasized.

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