Pleiotropic effects of statins

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ABSTRACT

The lipid-lowering actions of statins are well known. However, recent studies provide compelling evidence that the clinical benefits of statin therapy may also be attributed to mechanisms independent of their cholesterol-lowering effects. These non-lipid-lowering (pleiotropic) effects of statin therapy are believed to include antiinflammatory actions, property to reverse endothelial dysfunction by decreasing LDL oxidation and increasing nitric oxide bioavailability. Their antioxidant actions, ability to provide plaque stability, favorable coagulation profile, ability to prevent platelet aggregation and normalize sympathetic outflow as well as their antiproliferative and immunosuppressive properties also contribute to the non-lipid-lowering effects. These pleiotropic effects shown by statin therapy offer many advantages over the currently available drugs for dyslipidemias. These additional benefits not only find therapeutic application in cardiovascular disorders but also in many other disease states.

KEY WORDS: HMG CoA reductase inhibitors, immunomodulation, antioxidant, vascular disease, antiplatelet activity

Introduction

HMG CoA reductase inhibitors (statins) promote reduction in plasma levels of low-density lipoprotein (LDL) cholesterol, a primary risk factor in coronary artery disease. Numerous primary and secondary prevention trials confirm clinical benefits with this class of agents.[1-4] The mechanisms involved have largely been attributed to the ability of these agents to inhibit cholesterol biosynthesis,[2] leading to upregulation of hepatic LDL receptors and corresponding reductions in circulating levels of low-density lipoprotein (LDL) and very high density lipoprotein (VLDL) particles[2] by increasing catabolism. Additionally, a significant increase[2] in high-density lipoprotein (HDL) is produced which ultimately results in favorable lipid ratio.[4] All these lipid actions have been strongly suggested to result in higher percentage of patients achieving National Cholesterol Education Program (US Department of Health and Human Services) and European LDL cholesterol goals.[2,3] However, a growing body of evidence suggests that some of the clinical benefits of statin therapy may be attributed to mechanisms independent of their cholesterol-lowering effects.[5-17] These so called *pleiotropic effects* are defined as, producing or having multiple effects from a single gene. Such effects are believed to include antiinflammatory actions, property to reverse endothelial dysfunction by prevention of LDL oxidation and increasing nitric oxide bioavailability. Their antioxidant actions and ability to provide plaque stability, favorable coagulation profile, preventing platelet aggregation and normalizing sympathetic outflow as well as their antiproliferative and immunosuppressive properties suggest a new face of statin therapy which make them very important not only in the treatment of dyslipidemias and associated complications but also in many other disease states. Numerous, *in vitro*, experimental and clinical studies suggest the pleiotropic actions of statins and some of these important pleiotropic actions of statins have been reviewed in the present article (Tables 1 and 2).

Pleiotropic effects and cardiovascular disorders

1. Antiinflammatory role of statins

Appreciation of the importance of inflammatory processes in the pathogenesis of atherogenesis is growing[18,19] and statins have been suggested to have an antiinflammatory role. High sensitivity C-reactive protein has been incontroversially shown to predict major adverse cardiac events among the healthy population,[20] in patients with stable coronary artery disease (CAD) or acute coronary syndrome (ACS)[21] and in those patients who undergo percutaneous coronary interventions (PCI).[22] C-reactive protein (CRP) reduces nitric oxide production by endothelial cells and increases endothelial expression of adhesion molecules.[23, 24] It plays a crucial role in the chemotaxis of monocytes and foam cell formation in atherosclerotic plaques.[25] Besides this, CRP promotes tissue factor release and potentiates the effects of killer-T cells on endothelial cells.[26, 27] In addition to its direct role in plaque formation, CRP also enhances vasoreactivity of unstable plaque.[23, 28] Indeed, higher CRP concentrations were found within ruptured plaques in patients who died from cardiac causes compared with those patients with stable coronary disease or patients who died from non-cardiac causes.[29] Statin-induced reduction in acute phase reactant proteins such as CRP provide strong evidence for an overall antiinflammatory effect of these

Table 1

Important pleiotropic effects of statins and cardiovascular implications

Effect	*Mechanism of action*	*Change*	*Statins*	*Implications*
Antiinflammatory	• C-reactive protein	↓	Cerivastatin [C,30]	Useful in CAD, ACS and PCI
		↓	Pravastatin [C,31]	
		↓	Fluvastatin [C,33]	
		↓	Fluvastatin [C,36,E,37]	Prevent chemotaxis
	• MCP-I	↓	Fluvastatin [I,38]	
		↓	Pravastatin [I,39]	Prevent chemotaxis
		↓	Lovastatin [I,40]	
	• Growth and proliferation of macrophages	↓	Cerivastatin [E,41, landE,42]	
	• Apoptosis	↓	Pravastatin [E,43]	Retard hyperplasia and restenosis
		↑	Fluvastatin [E,43]	thereby, provide plaque stability initially
		↑	Simvastatin [I,44,I,45]	
		↑	Lovastatin [I,45]	
		↑	Atorvastatin [I,45]	
	• Collagen gene expression	↑	Pravastatin [E,43]	Plaque stability later
	and Synthesis of collagen	↓	Fluvastatin [E,43]	
	• mRNA for cyclooxygenase-2	↓	Lovastatin [I,46]	Reduce vascular inflammation
		↓	Simvastatin [I,46]	
	• Monocyte infiltration and VCAM-1	↓	Cerivastatin [E,86,I,87]	Prevent chemotaxis
Immunomodulatory				
	• T-cell proliferation	↓	Lovastatin [I,50]	Reduce vascular inflammation,
		↓	Provastatin [I,51]	antirejection role and antiproliferative action
		↓	Simvastatin [I,51]	
	• Expression of MHC-II	↓	Atrovastatin [I,52]	
	antigen presenting	↓	Lovastatin [I,52]	
	cell and T-cell activation	↓	Pravastatin [I,52]	
	• TNF-α	↓	Pravastatin [I,53]	
	• Interleukin-1ß	↓	Pravastatin [I,53]	
	• IL-8	↓	Simvastatin [I,54]	
	• IL-6	↓	Simvastatin [C,55]	
	• PPAR α and γ	↓	Lovastatin [I,46]	
		↓	Simvastatin [I,46]	
	• Isoprenylation of Ras and Rho genes	↓	Pravastatin [C,60]	Vascular antiproliferation in transplant associated arteriosclerosis
Endothelial dysfunction improvement				
↑ NO bioavailability	• Isoprenylation of Rac and Rho genes	↓	Atorvastatin [I,58,E,59]	Cardiovascular homeostasis vasodilator, antithrombotic and antiproliferative properties
	• Activation of eNOS	↑	Simvastatin [E,61]	
	through proteinkinase	↑	Rosuvastatin [E,13]	
	• Aortic caveolin-I protein, an inhibitor of NOS	↓	Rosuvastatin [E,12]	
↓ LDL oxidation	• Scavenge	↑	Fluvastatin [I,16]	Antiatherogenic effect
	superoxide	↑	Simvastatin [I63]	
	free radical	↓	Fluvastatin [I,16]	
	• NAD(P)H	↓	Simvastatin [I63]	
	Oxidase	↓	Fluvastatin [I,16]	
	• Inflammation cascade	↓	Simvastatin [I63]	

↑ - increase; ↓- decrease; I=*In vitro* study; E=experimental study; C=clinical trial, superscript numerals are reference numbers. ICAM -1= Intercellular adhesion moleucle-1, MCP-1=Monocyte chemotactic protein-1, PPAR α and γ=Peroxisome proliferator activated receptor α and γ, CAD=Coronary artery disease, ACS=Acute coronary syndrome, PCI=Percutaneous coronary interventions

Table 2

Important pleiotropic effects of statins and cardiovascular implications

Effect	*Mechanism of action*	*Change*	*Statins*	*Implications*
Antioxidant action	• Bio-availability of NO, which can antagonize vasconstrictive properties of ROS	↑	Simvastatin [E,62]	Reduces cardiovascular oxidative stress
	• Lipid peroxidation and ROS production	↓	Simvastatin [C,64]	
	• Myeloperoxidase derived ROS	↓	Atorvastatin [C,8]	
Plaque stability	• Matrix metalloproteinases (MMP-9)	↓	Cerivastatin [I,11,E,71]	Useful in ACS ,MI and UA
		↓	Pravastatin [I,73]	
	• Cholesterol ester content	↓	Pravastatin [I,73]	
	• Volume of collagen contents	↑	Pravastatin [I,73]	
	• Monocyte infiltration in artery wall	↓	Atrovastatin [E,74]	
	• Apoptosis	↓	Pravastatin [E,43]	
		↑	Fluvastatin [E,43]	
		↑	Simvastatin [I,44,I,45]	
		↑	Lovastatin [I,45]	
		↑	Atrovastatin [I,45]	
Favorable coagulation	• Activation of extrinsic coagulation pathway	↓	Simvastatin [C,76]	Impede thrombogenesis
		↓	Fluvastatin [C,15]	
	• Platelet adhesion and aggregation	↓	Pravastatin [C,77]	
	• Improve rheologic profile	↑	Pravastatin [C,77]	
Normalization of sympathetic outflow	•NO synthesis	↑	Rosuvastatin [E,13]	Useful in hypertension, MI, cerebral ischemia and CHF
		↑	Simvastatin [E,62]	
	• Angiotensin-II and AT_1 receptor expression	↓	Cerivastatin [C,80]	
	• ET_A receptor expression	↓	Atrovastatin [I81]	
		↓	Simvastatin [I,81]	
	• Normalization of sympathetic reflex regulation	↑	Simvastatin [E,62]	
Effect in peripheral arterial disease (PAD)	• NO Synthesis	↑	Simvastatin [E,62]	Improve lower extremity functioning in PAD patients
	• Platelet function	↓	Atrovastatin [C,76]	
	• Endothelin-1	↓	Simvastatin [I,81]	

↑- increase; ↓- decrease. I =*In vitro* study; E =experimental study; C= clinical trial, Superscript numerals are reference numbers, ACS= Acute coronary syndrome, MI= Myocardial infarction, UA=Unstable angina, CHF= Congestive heart failure

agents, independent of their cholesterol-lowering effects.[10,30-32] Statins have been attributed to early benefits among patients with acute coronary syndrome or vascular injury and inflammation[10, 33, 34] by reducing high-sensitivity CRP independent of their lipid-lowering actions.

Intercellular adhesion moleucle-1 (ICAM-1): A critical function of acute inflammation is delivery of leukocytes to the site of injury mediated by adhesion and transmigration which occur as a result of interactions between complementary adhesion molecules on the leukocytes and on the endothelium. ICAM-1 is of pivotal importance to carry this function.[35] Statin therapy can result in reduction of endothelial adhesion molecule (ICAM-1).[36, 37]

Monocyte chemotactic protein-1 (MCP-1)

Macrophages are the major cellular players in chronic inflammation. They are derived from peripheral monocytes that have been induced to emigrate across the endothelium by chemokine e.g. monocyte chemotactic protein-1 (MCP-1). When the monocyte reaches the extravascular tissue, it transforms into a larger phagocytic cell, 'the macrophage'. Fluvastatin has been shown to decrease adhesive interaction between monocytes and the vascular wall.[38] Whereas pravastatin and lovastatin have been shown to decrease monocyte chemotaxis

by interfering with MCP-1.[39, 40] Similarly, growth and proliferation of macrophages is also inhibited by statin therapy.[41, 42]

Apoptosis (programmed cellular death)

Apoptosis which is thought to be responsible for numerous physiological and pathological events[35] decreases with the use of pravastatin[43] but is induced with fluvastatin,[43] simvastatin,[44, 45] lovastatin[45] and atorvastatin[45] which may be beneficial initially to retard hyperplasia and restenosis, thereby providing plaque stability.

Synthesis of collagen

Pravastatin increases collagen gene expression and synthesis of collagen whereas fluvastatin has no effect on this parameter.[43] Increase in the synthesis of collagen may be one of the mechanisms responsible for providing plaque stability.

Cyclooxygenase-2

One of the studies has also suggested the antiinflammatory role of statin therapy by reduction of mRNA for cyclooxygenase-2.[46] Therefore, statins can reduce vascular inflammation by numerous mechanisms.

2. Immunomodulatory role of statins

Many studies have suggested the immunomodulatory roles of statins.[47, 48] Macrophages can be activated by cytokine-like Type-I Interferon-α (IFN-α) produced by immune activated T-cells to secrete numerous factors like toxic oxygen metabolites, proteases, neutrophil chemotactic factors, coagulation factors, arachidonic acid metabolites, nitric oxide, growth factors, fibrogenic cytokines and angiogenesis factors involved in tissue injury and fibrosis.[35] Statins have been shown to decrease the T-cell proliferation.[49-51] Atorvastatin, lovastatin and pravastatin have been shown to reduce the expression of major histocompatibility complex-II (MHC-II) on antigen presenting cells and MHC-II mediated T-cell activation.[52] Statins have also been suggested to reduce inflammatory cytokines production like tumor necrosis factor-α (TNF-α) and Interleukin-1ß (IL-1ß),[53] chemotactic cytokine like IL-8[54] and IL-6 which are associated with natural immunity.[55] In addition, it appears that statins can disrupt the oxidative stress/inflammation cycle[56] by decreasing the release of inflammatory mediators and lipid peroxidation. Chronic administration of statins can also inhibit peroxisome proliferator activated receptor (PPAR) α and γ, which are known inflammatory mediators.[46] These pleiotropic actions may help in reducing vascular inflammation and in antirejection regimens following graft arterial disease (GAD)

3. Statins and endothelial dysfunction

Endothelial dysfunction has relevance to the pathogenesis, progression and prognosis of a wide spectrum of cardiovascular diseases. It is characterized by reduced bioavailability of nitric oxide (NO), LDL-oxidation in the vascular wall and the vascular inflammatory response. All these pathological processes fundamental to the development and progression of endothelial dysfunction, are modulated by increased vascular oxidative stress in dyslipidemia.[56] Statins have been shown to improve endothelial dysfunction by increasing nitric oxide bioavailability as well as by reducing LDL oxidation and vascular inflammatory response.

a) Effect of statin therapy on nitric oxide bioavailability

Nitric oxide is a crucial mediator of cardiovascular homeostasis. In vascular endothelium, statins increase the concentration of nitric oxide, which has vasodilator, antithrombotic and antiproliferative properties.[57] Recent cell culture studies demonstrate that statin therapy suppresses superoxide formation and enhances NO generation by vascular endothelial cells *via* inhibition of isoprenylation of Rac and Rho.[58, 59] Rac is a component of the NAD(P)H oxidase complex of both leukocytes and vascular cells[58] whereas Rho is a small GTPase involved in cell signaling.[59] Inhibition in Rho isoprenylation in endothelial cell has been shown to mainly result in enhanced NO production. Because Ras and Rho also regulate the cell cycle, they are, in addition, likely targets for the direct antiproliferative effects of statins. Indeed, statins inhibit vascular smooth muscle cell proliferation in transplant-associated arteriosclerosis.[60] While others have shown that statins enhance the activity of eNOS through protein kinase activation.[61] Simvastatin[62] has been shown to enhance the production of NO in the vascular endothelium and attenuate myocardial injury following ischemia and reperfusion in normocholesterolemic, hypercholesterolemic[62] mice. A recently introduced new statin (rosuvastatin)[12,13] has been shown to increase vascular endothelial NO production and attenuate myocardial necrosis following ischemia and reperfusion in mice, thereby providing cardio-protective effects independent of lipid-lowering actions.

b) LDL oxidation

Oxidation of LDL cholesterol is critical to the pathogenesis of endothelial dysfunction. Oxidative modification of LDL appears to play a key role in mediating the uptake of lipoprotein cholesterol by macrophages and in other processes including cytotoxicity within lesions. LDL cholesterol is subsequently oxidized by superoxide generated by macrophage NAD(P)H oxidase. Hypercholesterolemia potentiates LDL oxidation by increasing substrate and promoting LDL conformations that are more susceptible to oxidation. Oxidized LDL mediates a number of redox-sensitive processes that are deleterious to endothelial function. Through inhibition of eNOS and inactivation of NO, oxidized LDL promotes an inflammatory phenotype through activation of NF–κB triggering an elaboration of inflammatory cytokines and adhesion molecules through redox-sensitive pathways. Inflammatory-mediated release may in turn activate enzymatic source of reactive oxygen species, including NAD(P)H oxidase and xanthine oxidase, potentiating the already established oxidative stress. Thus, this can lead to a self-perpetuating cycle.[56] Statins reduce the susceptibility of lipoproteins to oxidation both *in vitro* and *ex vivo* i.e. they decrease the LDL oxidation.[16,63] This is done by increasing NO which can scavenge superoxide free radical anions responsible for LDL oxidation, by inhibiting NAD(P)H oxidase, the inflammatory cascade or through their antioxidant actions.

c) Vascular inflammatory response

Vascular inflammation is also supposed to account for endothelial dysfunction. Statins by their vascular antiinflammatory actions as shown in Tables 1 and 2 can improve endothelial dysfunction.

4. Antioxidant actions of statin therapy

There is an assumption that oxidative stress mediates atherosclerotic dysfunction. Reactive oxygen species (ROS) including superoxide ($O_2^{\bullet -}$), hydroxyl radical ($OH^{\bullet}$), hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^-$) have oxidative property and contribute to oxidative stress. Normal endothelial function is characterized by a dynamic balance between NO and other oxidants. As a scavenger of superoxide anions, the potent vasodilator and antioxidant NO antagonizes the vasoconstrictive properties of the ROS. Thus, statins possess antioxidant properties by increasing the NO bioavailability,[62] by reducing lipid peroxidation[64] and ROS production.[65] One recent study[8] suggested that statins promote systemic antioxidant effects through the suppression of distinct oxidation pathways. The major pathways inhibited include myeloperoxidase-derived and nitric oxide-derived oxidants, implicated in atherogenesis. Most importantly, this study suggested that these effects were largely independent of lipid-lowering and antiinflammatory actions.

5. Statins and plaque stability

Atheromatous plaque rupture and subsequent thrombosis are the main causes of acute coronary syndrome including acute myocardial infarction (MI), unstable angina (UA) and sudden cardiac death.[66,67] Plaque instability is associated with a high macrophage content and a thin fibrous cap. Matrix metalloproteinases have the capability to degrade the extracellular matrix of the fibrous cap, predisposing to plaque rupture.[68] Macrophages are the major source of the matrix metalloproteinases of which MMP-9 is the most prevalent form. Several lines of evidence suggest that MMP-9 could play a potential role in atheromatous plaque disruption and in the molecular mechanism of acute coronary syndrome.[69, 70]

Animal experiments and clinical studies have shown that statins can stabilize plaque by increasing the collagen content and inhibiting metalloproteinases.[71-73] Plaque stabilization could be achieved by direct inhibition of MMP-9 by statins.[14] Statins may foster plaque stability through a reduction in macrophage[71] and cholesterol ester contents[73] and by increasing the volume of collagen contents.[73] The thrombotic sequelae caused by plaque disruption are mitigated by statins through the inhibition of platelet aggregation and maintenance of a favorable balance between prothrombotic and fibrinolytic mechanisms.[15] Statins can stabilize atherosclerotic plaques by reducing oxidative stress and by decreasing vascular inflammation.[73] They appear to inhibit monocyte infiltration in the artery wall in a rabbit model as well.[74] They also appear to modulate the cellularity of the artery wall by inhibiting proliferation of smooth muscle cells and enhancing apoptotic cell death, which can be beneficial initially to retard hyperplasia and restenosis.[75]

6. Statins and coagulation

Statins may impede thrombogenesis by inhibiting the activation of the extrinsic coagulation pathway, by inhibiting platelet adhesion and aggregation and improving rheologic profile.[76] They also support fibrinolysis and thus maintain a favorable balance between prothrombotic and fibrinolytic mechanisms.[15, 77]

7. Normalization of sympathetic outflow

Because statins are neuroprotective, partially, by a nitric oxide (NO)-dependent mechanism[78] and because NO is sympathoinhibitory,[79] it is proposed that chronic administration of a statin would lower sympathetic outflow. The ability of statins to enhance NO synthesis in the endothelium,[13,62] to reduce angiotensin II-induced injury and AT_1 receptor expression[80] and reduce endothelial (ET_A) receptor expression,[81] all point to its potential role in regulating the sympathetic and vagal outflow in the central nervous system. Moreover, statins have been shown to produce beneficial effects in hypertension, after myocardial infarction and after cerebral ischemia[82-84] possibly by normalization of the sympathetic outflow. Most recently, one study[9] has supported this hypothesis by showing that non-lipid-lowering effects include normalization of sympathetic outflow and reflex regulation in congestive heart failure (CHF). However, the precise neural and cellular pathways involved in these responses need further clarification.

8. Statins in peripheral arterial disease (PAD)

Statins, by increasing the production of nitric oxide[11,62] in the endothelium, have local vasodilatory property in addition to antithrombogenic, antiproliferative and leukocyte adhesion inhibiting effects. Other mechanisms by which statins favorably influence atherosclerosis include enhancement of endothelium-dependent relaxation,[62] inhibition of platelet function[76] and inhibition of endothelin-1,[81] a potent vasoconstrictor and mitogen. These mechanisms suggest that statins might improve lower extremity functioning in PAD by retarding the deleterious effects of atherosclerosis on leg arteries. This fact was supported by one recent study.[11]

Pleiotropic effects of statins and other disease states

1. Diabetic dyslipidemia

Atorvastatin[85] beneficially alters the atherogenic lipid profile in these patients and significantly decreases the density of LDL particles resulting in a shift from small, dense LDL to more buoyant and less atherogenic particles.

2. Glomerulonephritis

Monocytes play a determinant role in the progression of both glomerulosclerosis and atherosclerosis. Monocyte infiltration and the expression of the vascular cell adhesion molecule (VCAM-1) were shown to be reduced by cerivastatin treatment.[80] Platelets are known to enhance monocyte activity, and cerivastatin reduces monocyte and platelet activities.[86] Recently, Buemi *et al* [87] reported that another statin, fluvastatin, was effective in decreasing proteinuria in patients with IgA nephropathy probably by immunological mechanism.

3. Alzheimer's disease

Vascular and lipid-related mechanisms are thought to have a role in the pathogenesis of Alzheimer's disease and vascular dementia. An epidemiological study has suggested that individuals of 50 years and older who were prescribed statins had a substantially lowered risk of developing dementia, independent of the presence or absence of untreated hyperlipidaemia, or exposure to non-statin lipid-lowering agents (LLAs).[88] A recent review also suggests the same for Alzheimer's dis-

ease.[89]

4. Cancers

Lovastatin not only induces apoptosis, but also promotes redifferentiation in anaplastic thyroid cancer cells, and this suggest that the statins merit further investigation as differentiation therapy for the treatment of anaplastic thyroid cancer.[90] One study[91] identified a subset of various pediatric cancers and squamous cell carcinomas that are sensitive to lovastatin-induced apoptosis and this study showed HMG-CoA reductase as a potential therapeutic target of these cancers. Because Ras and Rho also regulate the cell cycle, they are, in addition, likely targets for the direct antiproliferative effects of statins. Indeed, statins may have clinical benefits in inhibiting certain breast cancers.[92]

5. Osteoporosis

One recent review[93] suggested that there are several *in vitro* and *in vivo* studies in animals which demonstrate that statins stimulate the production of bone morphogenetic protein (BMP-2), which is a potent regulating protein in osteoblast differentiation and activity. This suggests that statins may have an anabolic effect on bones, making them a potentially interesting treatment option for osteoporosis. Additionally, several studies in humans showed that some statins may have a beneficial effect on bone turnover and may lead to an increase in bone mineral density. However, one of the most recent studies[94] showed contradictory results, suggesting that none of the statins produce beneficial effects. Therefore, to conclusively assess the potential of statins in the prevention and treatment of osteoporosis, randomized controlled trials need to be performed

6. Multiple sclerosis (MS)

Treatment of brain endothelial cells (EC) *in vitro* with lovastatin inhibits Rho-mediated transendothelial T-cell migration. In a relapsing-remitting mouse model of MS, lovastatin inhibited leukocyte migration into the CNS and significantly attenuated the development of both acute and relapsing clinical disease. This study[95] demonstrates that the indirect pharmacological inhibition of Rho proteins in brain EC by statins can inhibit a key stage in the pathogenesis of neuroinflammation, namely leukocyte migration across the blood-brain barrier. This novel effect of statins in modulating the immune response in neuroinflammtory diseases may provide additional rationale for their use in the treatment of MS.

7. Ischemic stroke

The observation that statins decrease the incidence of ischemic stroke, highlights some of their non-cholesterol effects since serum cholesterol levels are poorly correlated with the risk for ischemic stroke.[96]

8. Graft rejection

Despite the development of effective immunosuppressive therapy, transplant graft arterial disease (GAD) remains the major limitation to long-term graft survival. Clinically, statins attenuate GAD in murine heart transplants, diminish host inflammatory cell recruitment, and do not alter cholesterol levels. These results indicate an important potential role of statins.[97]

9. Vitiligo

Recently, one report supported the hypothesis that immune mechanisms play a role in the development of vitiligo and statins as an immunomodulator could be of use for the treatment of vitiligo.[98]

Lipophilic/Hydrophilic statins and differences in pleiotropic effects

The lipophilic statins (like lovastatin and simvastatin) would be expected to penetrate cell membranes more effectively than the more hydrophilic statins (like pravastatin and rosuvastatin), causing more side effects but at the same time, eliciting more pleiotropic effects. However, the observation that hydrophilic statins have pleiotropic effects similar to those of lipophilic statins raises the question whether there are really any cholesterol-independent effects of statins.[99] Indeed, recent evidence[100] suggests that some of the cholesterol-independent effects of these agents may be mediated by the inhibition of hepatic HMG-CoA reductase, leading to subsequent reduction in circulating isoprenoid levels. This hypothesis may help explain why hydrophilic statins such as pravastatin and rosuvastatin are still able to exert cholesterol-independent benefits on the vascular wall without directly entering vascular wall cells. In this respect, the word "pleiotropic" probably does not reflect the hepatic versus non-hepatic effects of these agents.[100] All pleiotropic effects need not be applicable to all clinically relevant statins, as these effects may vary according to the drug. Pleiotropic variations among statins are presented in Tables 1 and 2.

Dose response relationship

In one study[13] the lowest and highest doses did not significantly attenuate the degree of myocardial injury. Whereas intermediate doses significantly produced these pleiotropic effects. Similarly, in another study,[9] only moderate and higher doses produced pleiotropic effects. Presently data is scanty to establish clearly a dose response relationship of statins and pleiotropic effects. Hence, this aspect needs further elucidation.

In conclusion, a wide number of drugs are available today for effective treatment of dyslipidemia. The pleiotropic effects of statins offer advantages over other available lipid-lowering agents, as they are effective, well tolerated and can provide additional benefits not only in cardiovascular disorders but in other disease states too.

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