REVIEW

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Immunomodulation by statins: mechanisms and potential impact on autoimmune diseases

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Abstract

Statins are inhibitors of the enzyme 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) and they are the most effective agents for lowering cholesterol in clinical practice for the treatment of cardiovascular diseases. However, it has become clear that statins also have pleiotropic immunomodulatory effects in addition to their lipid-lowering properties. As a result, much attention has been focused on their potential as therapeutic agents for the treatment of inflammatory autoimmune diseases. In this review the effect of statins on the expression and function of a variety of immune-relevant molecules will be discussed alongside the underlying mechanisms that contribute to the immunomodulatory effects of statins.

Key words: statins, cardiovascular diseases, autoimmune diseases.

Abbreviations: HMG-CoA – hydroxy-3-methyl-glutaryl coenzyme A, LDL – low-density lipoprotein, CAD – coronary artery disease, MHC – major histocompatibility complex, IL-2 – interleukin 2, ICAM1 – intercellular adhesion molecule 1, T_H – T helper, EAE – experimental autoimmune encephalomyelitis, SLE – systemic lupus erythematous, MK – mevalonate kinase.

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INTRODUCTION

In the last two decades there has been a significant reduction in cardiovascular mortality due to the lowering of plasma cholesterol by a variety of drugs. Among these agents, the statins, a family of drugs that inhibit the rate-limiting enzyme 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase in the mevalonate pathway for the biosynthesis of cholesterol in cells, are the most effective (Sacks et al. 1996; Shepherd et al. 1995; Tobert 2003). The blocking of HMG-CoA reductase by statins effectively lowers intracellular cholesterol levels. To maintain cholesterol homeostasis and compensate for the decreased cholesterol synthesis, cells such as hepatocytes will up-regulate the expression of low-density lipoprotein (LDL) receptors. This leads to an increase in the uptake of plasma LDL, the main carrier of extracellular cholesterol, which effectively lowers the blood LDL-cholesterol concentrations (Palinski and Tsimikas 2002).

The lowering of blood cholesterol by statins can influence a number of pathogenic mechanisms that are thought to contribute to coronary artery disease (CAD). Several large-scale intervention trials and epidemiological studies have shown that statin treatments significantly ameliorate vascular arteriosclerosis and reduce cardiovascular-related morbidity and mortality in patients with or without CAD (Downs et al. 1998; Sacks et al. 1996). However, mounting evidence suggests that some of the clinical benefits of statins may not be attributed to the lipid-lowering properties of these drugs (Maron et al. 2000; Palinski 2001); for instance, the reduction of ischemic stroke was not consistent with the degree of cholesterol reduction (Pfeffer et al. 1999; Shepherd et al. 1995). There is also accumulating evidence from numerous clinical studies and *in vitro* experiments to suggest that statins have anti-inflammatory properties (Maron et al. 2000; Weitz-Schmidt et al. 2001). Since coronary heart disease has an inflammatory component, the anti-inflammatory property of statins has important implications and may have contributed to the beneficial effects of statins in cardiovascular medicine. Similarly the immune system is associated with various facets of inflammatory responses and this has

resulted in extensive clinical and laboratory studies providing compelling evidence that statins have pleiotropic immunomodulatory effects and attenuate experimental inflammatory diseases (Baetta et al. 2002; Derk and Jimenez 2006; Jakobisiak and Golab 2003; McKay et al. 2004; Schonbeck and Libby 2004; Shovman et al. 2002). These results have generated considerable interest in their potential use as a therapeutic agent for various immune-related diseases since statins are well tolerated and have a good safety profile.

PHARMACOLOGY OF STATINS

The statin family of drugs can be divided into naturally occurring members, such as mevastatin, pravastatin, lovastatin, and simvastatin, and synthetic members, which include atorvastatin, cerivastatin, fluvastatin, and rosuvastatin (Bolego et al. 2002). All these drugs bind to HMG-CoA reductase and competitively displace its natural substrate, HMG-CoA. This prevents the conversion of HMG-CoA to L-mevalonate and inhibits the downstream biosynthesis of cholesterol (Fig. 1). Besides cholesterol, L-mevalonate is also the precursor for numerous isoprenoid metabolites; hence the blocking of HMG-CoA reductase would also inhibit the biosynthesis of intermediates such as geranyl-geranyl pyrophosphate and farnesyl pyrophosphate. Both these isoprenoid metabolites are important lipid attachments for the posttranslational prenylation of several important cell-signaling proteins (Zhang and Casey 1996). Among these proteins are members of the small GTPase family of proteins, which includes Ras, Rac, and Rho (Takai et al. 2001). These proteins are known to act as molecular switches and control multiple signaling pathways, such as those involved in the maintenance of cell shape, motility, factor secretion, differentiation, and proliferation. In addition, a large proportion of cellular proteins are prenylated proteins and the lipophilic prenyl group plays a crucial role in anchoring these proteins onto cell membranes, which in many cases are required for these proteins to function (Liao 2002; Zhang and Casey 1996). Given the central role of some of these prenylated proteins, it is not surprising that the blocking of HMG-CoA reductase by statins will inevitably modulate signaling pathways during immune responses, which is unrelated to the cholesterol-lowering properties of these agents.

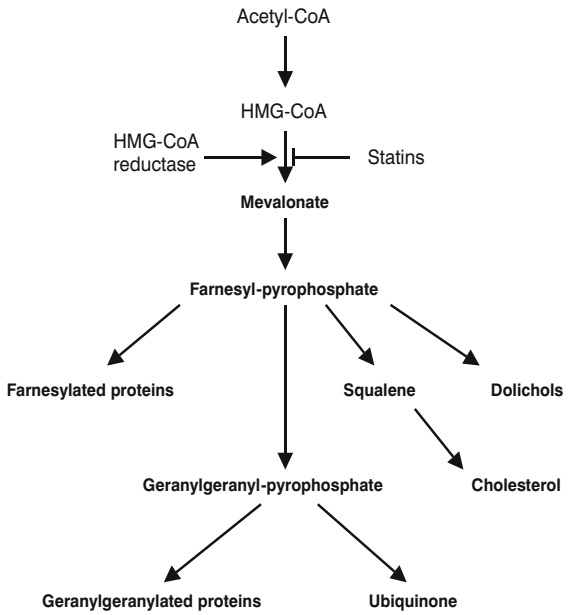

Fig. 1. The biosynthetic pathway for cholesterol and isoprenoid biosynthesis

IMMUNOMODULATORY EFFECTS OF STATINS

Major histocompatibility complex molecule expression

Antigen-specific immune responses involve the presentation of bound foreign peptides on major histocompatibility complex (MHC) class I and class II molecules expressed on antigen-presenting cells (APCs) and subsequent recognition by the T cell receptor on $CD4^+$ and $CD8^+$ T cells. To achieve an efficient T-cell activation, MHC-CD4/CD8 co-receptor interaction as well as co-stimulatory molecules and their ligands, such as CD80/CD86, CD28/CTLA-4, and CD40/CD154, and adhesion molecules, including the intercellular adhesion molecule (ICAM)1 and lymphocyte associated-function antigen (LFA)3, are required (Grakoui et al. 1999; van Der Merwe and Davis 2002). MHC class I molecules are expressed on the surface of most nucleated cells, whereas MHC class II expression is restricted to APCs, such as dendritic cells, B cells, and monocytes/macrophages. Besides the constitutive expression of MHC class II on APCs, a number of cell types will express MHC class II molecules upon cytokine stimulation, especially by the inflammatory cytokine IFN-γ (Reith and Mach 2001). The up-regulation of MHC class II molecule expression mediated by IFN-γ is now known to be inhibited by statins, which helps to explain some of the immunomodulatory effects of these drugs (Kwak et al. 2000). Both lipophilic and hydrophilic statins, including simvastatin, lovastatin, pravastatin, and atorvastatin, have been shown to block the up-regulation of MHC class II molecule expression induced by IFN-γ at nanomolar and micromolar concentrations. The mechanism now identified involves statins blocking the IFN-γ-inducible expression of the MHC class II transactivator (CIITA) promoter pIV, which is the master regulator of MHC class II expression (Kwak et al. 2001; Steimle et al. 1994). Of all the statins that are known to have this effect, atorvastatin is the most potent and more effective compared with pravastatin and lovastatin. More recently, statins were also found to inhibit another IFN-γ--inducible CIITA expression promoter, pI, suggesting that these drugs are not selective in blocking pIV, but may have effects on all IFN-γ-inducible promoters in

general (Youssef et al. 2002). Although all the statins examined appear to have similar capacity to down-regulate MHC class II expression, they display varying effects on MHC-I expression. For instance, atorvastatin has no effect on endothelial cell MHC class I expression, whereas simvastatin reduced both IFN-γ-induced and constitutively expressed MHC class I in various cell types (Kuipers et al. 2005; Kwak et al. 2000).

The blocking of IFN-γ-inducible expression of MHC class II molecules on macrophages, endothelial cells, and smooth muscle cells by statins suggests that these drugs may be beneficial in chronic inflammatory conditions and autoimmune diseases (Kwak et al. 2001). Furthermore, statins also inhibit the constitutive expression of MHC class II in B lymphocytes, activated T cells, and microglial cells (Kuipers et al. 2005; Kuipers et al. 2006; Lawman et al. 2004), which could result in a reduction in T-cell proliferation and differentiation. Indeed, statin-treated endothelial cells and smooth muscle cells in mixed lymphocyte reactions markedly inhibited T-cell proliferation and interleukin (IL)-2 production (Kwak et al. 2000). In addition, it is well documented that blocking MHC class II molecules with anti-I-A antibodies prevents the development of numerous autoimmune diseases, such as experimental autoimmune encephalomyelitis (EAE), experimental autoimmune myasthenia gravis, and experimental autoimmune thyroiditis in mice (Steinman et al. 1981; Vladutiu and Steinman 1987; Waldor et al. 1983). These results provide a compelling rationale for studying the effects of statins on T cell-mediated diseases, particularly in the autoimmune setting, which revealed the pleiotropic immunomodulatory effects of statins.

Co-stimulatory molecules

Besides recognizing antigens presented in the context of MHC class II molecules, T cells must also recognize other co-stimulatory molecules for an effective T-cell response to take place. Similar to MHC class II molecules, statins were also shown to inhibit constitutive as well as IFN-γ-induced up-regulation of co-stimulatory molecules, such as CD40, CD80, and CD86, in lymphocytes, macrophages, microglia, and endothelial cells (Kuipers et al. 2005; Kuipers et al. 2006). In professional APCs, statin treatment suppressed the cytokine-induced maturation of dendritic cells, resulting in the failure of these cells to express high levels of CC-chemokine receptor 7, CD40, CD83, CD86, and HLA-DR (Yilmaz et al. 2004). It is clear that statins can inhibit T-cell activation and proliferation at various stages and therefore not surprising that statin-treated APCs consistently fail to induce T-cell proliferation effectively. This is further corroborated in experimental autoimmune diseases in rodents where statin treatment consistently leads to a reduction in T-cell response or proliferation (Table 1). Whether this immunosuppression mediated by statins actually happens in humans is still unclear, although large-scale clinical trials as well as the increasing use of statins have not provided any indication of weakened immune responses at clinical doses of statins.

Leukocyte adhesion molecules

Leukocyte adhesion to vascular wall and extravasation (migration into tissue) are known to play an important role in the pathophysiology of inflammatory and autoimmune diseases (Greenwood et al. 2006; Moreno et al. 1994). Leukocyte migration is dictated by the correct expression pattern of adhesion molecules, which play a cooperative role in the pattern and extent of migration. One of the key adhesion molecules which has a crucial role in adhesion and extravasation is LFA1, expressed on the surface of all leukocytes. LFA1 binds to ICAM1 and, in addition to leukocyte migration, it also provide co-stimulatory signals for T cells during T-cell activation (Reape and Groot 1999; Weitz-Schmidt et al. 2001). Several statins are now known to block selectively the interaction of LFA1 to ICAM1. The underlying mechanism appears to involve the binding of statins to the lovastatin-binding site (L-site) on the extracellular domain of LFA1. This blocks the binding of ICAM1 to LFA1 and results in the inhibition of both lymphocyte adhesion and co-stimulation (Weitz-Schmidt et al. 2001). The inhibition of LFA1 binding to ICAM1 by statins appears to be independent of the cholesterol-lowering properties because the lactone forms of statins, which lack HMG-CoA reductase inhibitory activity, was still effective. In addition, statins also inhibit the expression of other cell adhesion molecules, such as CD11b, CD18, and CD49, in monocytes and T cells (Weitz-Schmidt et al. 2001). This could result in an impaired ability of leukocytes to adhere to vascular wall and extravasation. Indeed, a marked decrease in leukocyte infiltration into target organs during statin therapy is evident in a number of experimental autoimmune diseases in rodents (Table 1).

Effects of statins on the cytokine network and the T_H1 and T_H2 responses

It is well established that the cytokine milieu following T-cell activation plays a crucial role in determining T-cell differentiation into T helper 1 (T_H1) or T_H2. The effects of statins on the production and secretion of cytokines both *in vitro* and *in vivo* have been investigated extensively (Grip et al. 2000; Hillyard et al. 2004; Pahan et al. 1997; Rosenson et al. 1999; Youssef et al. 2002). Collectively, these studies suggest that statins inhibit the secretion of pro-inflammatory cytokines such as IFN-γ, TNF-α, IL-1β, and IL-6 in various cell types such as microglia, astrocytes, and mononuclear cells. These studies also implicate statins in mediating the switch from a T_H1 to a T_H2 response during an immune response. This is illustrated by the compelling evidence from *in vivo* studies showing that atorvastatin prevents or reverses EAE in rodents (Aktas et al. 2003;

Table 1. Summary of the impact of statins in animal models of autoimmune disease

Statin	Animal model	Effect	References
Experimental autoimmune encephalomyelitis			
Atorvastatin	SJL/J mice	Disease was attenuated; shift in cytokine profile from T_H1 to T_H2	Youssef et. 2002
Atorvastatin	SJL/J mice	Disease was attenuated; increase in T_H2 cytokine levels and decrease in T-cell proliferation	Aktas et al. 2003
Lovastatin	Biozzi ABH mice	Disease was attenuated; inhibited leukocyte infiltration	Greenwood et al. 2003
Simvastatin	Brown Norway rats	No effect on disease	Sattler et al. 2005
Lovastatin	Lewis rat	Disease was attenuated; inhibited pro-inflammatory cytokine production	Stanislaus et al. 1999
Lovastatin	Lewis rat	Disease was attenuated; increase in T_H2 cytokine transcription	Paintlia et al. 2004
Lovastatin	Lewis rat	Disease was attenuated; shift from T_H1 to T_H2 cytokine profile	Stanislaus et al. 2002
Experimental arthritis			
Simvastatin	DBA/1 mice	Disease was attenuated; decrease in T cell proliferation and blockade of pro-inflammatory cytokine production	Leung et al. 2003
Simvastatin	DBA/1 mice	Disease was attenuated, but with severe side effects	Palmer et al. 2004
Rosuvastatin	DBA/1 mice	No effect on disease	Palmer et al. 2004
Atorvastatin	DBA/1 mice	No effect on disease	Palmer et al. 2004
Atorvastatin	Holtzman rats	Disease was attenuated; inhibited pro-inflammatory cytokine production	Barsante et al. 2005
Experimental autoimmune uveoretinitis			
Atorvastatin	B10RIII mice	Mild attenuation of disease	Gegg et al. 2005
Atorvastatin	B10RIII mice	No effect on disease	Thomas et al. 2005
Lovastatin	B10RIII mice	Disease was attenuated; suppression of leukocyte infiltration	Gegg et al. 2005
Atorvastatin	Lewis rat	Disease was attenuated; decrease in leukocyte infiltration	Kohno et al. 2007
Lovastatin	Lewis rat	Disease was attenuated; decrease in T-cell proliferation	Kohno et al. 2007
Experimental systemic lupus erythematosus			
Atorvastatin	NZB/NZW mice	No effect on disease	Graham et al. 2008
Atorvastatin	NZB/W F1 mice	Delayed progression of the disease and decrease in T-cell proliferation	Lawman et al. 2004
Experimental autoimmune myocarditis			
Atorvastatin	Lewis rat	Improvement in cardiac function and shift from T_H1 to T_H2 cytokine profile	Liu et al. 2005
Fluvastatin	Lewis rat	Improvement in cardiac function, decrease in T_H1 cytokines and inhibit leukocyte infiltration	Azuma et al. 2004
Experimental autoimmune diabetes			
Atorvastatin	NOD mice	Failed to prevent diseases development	Lozanoska-Ochser et al. 2006
Simvastatin	CD-1 mice	Delayed and protected against disease	Rydgren et al. 2007
Simvastatin	NOD mice	Disease was attenuated	Rydgren et al. 2007

Greenwood et al. 2003; Paintlia et al. 2004; Stanislaus et al. 2002; Stanislaus et al. 1999; Youssef et al. 2002). These preclinical studies suggest that the beneficial effects of atorvastatin were due to its specific induction of a T_H2 bias *in vivo* by shifting the pattern of T-cell cytokine secretion. More specifically, there was an induction of the secretion in T_H2 cytokines (IL-4, IL-5 and IL-10) and a concomitant decrease in the production of inflammatory T_H1 cytokines such as IL-2, IL-12, IFN-γ, and TNF-α. The molecular mechanism that underlies the T_H2 bias induced by atorvastatin involves the activation of the signal transducer and activator of transcription 6 (STAT6), which is involved in IL-4--dependent T_H2 differentiation. In contrast, STAT4 activation, which is required for IL-12-dependent T_H1 differentiation, was markedly inhibited. Statin treatment has also been shown to promote the expression of GATA-binding protein 3 (GATA3), a transcription factor involved in T_H2 differentiation in T cells, and downregulate nuclear factor-κB and T bet, both transcription factors known to be associated with T_H1 differentiation (Murphy and Reiner 2002; Robinson and O'Garra 2002). The ability of statin to induce a T_H2 bias is not restricted to EAE, but was also observed in a T_H1-driven model of experimental autoimmune myocarditis (Table 1), where artovastatin was able to promote a shift in the T-cell phenotype from a T_H1 to a T_H2 bias (Azuma et al. 2004; Liu et al. 2005). In contrast, fluvastatin was found to decrease the production of both T_H1 as well as T_H2 cytokines in this mouse model (Azuma et al. 2004).

Accumulating evidence suggests that not all statins are capable of inducing a T_H2 bias during statin therapy *in vivo*. For instance, simvastatin effectively inhibits the development and expansion of T_H1 cells in collagen--induced arthritis in mice without promoting any corresponding increase in T_H2 activity or increase in T_H2-type cytokines (Leung et al. 2003). Furthermore, not all statins are effective, as demonstrated in a similar arthritis model in which only simvastatin, but not atorvastatin or rosuvastatin, attenuated the disease (Palmer et al. 2004). Similarly, in acute experimental autoimmune uveoretinitis (an autoimmune retinal disease), both lovastatin and atorvastatin attenuated the disease but had no effect on T_H2 cytokine secretion, although both T-cell proliferation and leukocyte infiltration were inhibited (Gegg et al. 2005; Kohno et al. 2007). In sharp contrast, atorvastatin had virtually no effect on the disease and did not modulate the immune response in a similar mouse model (Thomas et al. 2005). The same controversy exists for autoimmune diabetes and systemic lupus erythematous (SLE). In the former, atorvastatin failed to prevent disease development in NOD mice, but simvastatin appeared to have some beneficial effect (Lozanoska-Ochser et al. 2006; Rydgren et al. 2007). For the latter, atorvastatin appeared to delay the progression of the disease and inhibited T-cell proliferation, but failed to have any beneficial effect in another study (Graham et al. 2008; Lawman et al. 2004).

In human studies, lovastatin, simvastatin, and mevastatin have all failed to induce a T_H1 or T_H2 bias in human peripheral blood mononuclear cells (PBMCs) from patients with multiple sclerosis (Neuhaus et al. 2002). Furthermore, no change in the cytokine profile was observed in activated T cells from multiple sclerosis patients showing clinical improvement following simvastatin treatment (Vollmer et al. 2004). With the numerous large-scale clinical trial studies carried out and the increasing use of statins, there is no indication to date of T_H2 bias or an increase in any disorders associated with increased T_H2 activity in humans. Recent studies have suggest that atorvastatin has no effect on the differentiation of T_H0 cells into T_H1 and T_H2 cells in human T cells *in vitro* (Coward and Chow 2006). In addition, the T_H1/T_H2 balance in human T cells was unaffected by atorvastatin. The differences in the activity of atorvastatin on T_H1/T_H2 responses in the human and murine systems can be due to a number of reasons. It is well established that there are major differences between mice and humans in their T_H1/T_H2 dichotomy and the demarcation between T_H1 and T_H2 in the mouse is very well defined, whereas this is less so in humans (Mestas and Hughes 2004). Overlapping responses are often seen with T cells differentiating in defined T_H1 or T_H2 environments in humans. In addition, being different species it is unlikely that the responses in humans are identical to those in mice.

Pro-inflammatory effects of statins

In contrast to the established anti-inflammatory properties of statins, a number of studies have also shown that the lipophilic statins, such as fluvastatin, simvastatin, atorvastatin, and lovastatin, are capable of inducing pro-inflammatory responses in some model systems (Matsumoto et al. 2004; Montero et al. 2000; Sadeghi et al. 2000; Sun and Fernandes 2003). Fluvastatin was shown to activate caspase-1 and enhance the secretion of inflammatory cytokines such as IL-1β, IL-18, and the T_H1 cytokine IFN-γ in PBMCs stimulated with *Mycobacterium tuberculosis* (Montero et al. 2000). This T_H1 bias in activated PBMCs mediated by fluvastatin is in sharp contrast to the T_H2 bias induced by atorvastatin and simvastatin in mice both *in vitro* and *in vivo* (Aktas et al. 2003; Youssef et al. 2002). On the other hand, lovastatin has been shown to enhance the production of IL-6, IL-12, and TNF-α in bone marrow--derived dendritic cells (Sadeghi et al. 2000) and promote TNF-α secretion in a macrophage cell line by inhibiting the Rho family of GTPase (Monick et al. 2003). Similarly, simvastatin was found to augment the lipopolysaccharide-induced pro-inflammatory response in macrophages by differential regulation of transcription factors (Matsumoto et al. 2004).

These findings suggest that statins can have both anti-inflammatory as well as pro-inflammatory properties. Indeed, using human PBMCs, both atorvastatin and simvastatin were found to induce the production of pro-inflammatory cytokines such as IFN-γ, IL-1β, and

IL-18 in activated T cells *in vitro* (Coward et al. 2006). Although clinical doses of statins are unlikely to produce these effects in hypercholesterolemic patients, blocking the mevalonate pathway for cholesterol synthesis has been shown to induce pro-inflammatory responses. This is best illustrated in human disorders associated with impaired isoprene biosynthesis, such as hyperimmunoglobulinemia D and mevalonic aciduria, in which periodic fever syndrome is often seen associated with increased in pro-inflammatory cytokines (Drenth et al. 1999; Houten et al. 1999a; Houten et al. 1999b). These disorders are caused by different mutations in the gene encoding mevalonate kinase (MK), the next enzyme after HMG-CoA reductase in the biosynthesis of isoprenoids. The mutations result in patients exhibiting different degrees of deficiency in MK activity. Hyperimmunoglobulinemia D syndrome (HIDS) patients have very low MK activity and mevalonic aciduria patients have little or no activity of this enzyme (Drenth et al. 1999; Houten et al. 1999a; Houten et al. 1999b). As a result, the mevalonate levels in the plasma of these patients are markedly elevated. The levels of pro-inflammatory cytokines such as IFN-γ and IL-6 were markedly increased during fever attacks in HIDS patients and the PBMCs from these patients secreted large amounts of the pro-inflammatory cytokine IL-1β (Houten et al. 1999a). Interestingly, no T_H2 type cytokine levels were increased in these patients, indicating that blocking the mevalonate pathway for cholesterol biosynthesis does not promote a T_H2 bias in humans.

Similarly, there is no indication of elevated T_H1 activity or disorders associated with an increase in T_H1 activity in humans despite the increasing use of statins. This could be due to the short elimination half-life of most statins, with the exception of atorvastatin (Corsini et al. 1999), and therefore they are incapable of inducing the pro-inflammatory response. Although atorvastatin has a longer elimination half-life, its level in the plasma is very low and is unlikely to cause any inflammation (Posvar et al. 1996). However, their systemic exposure can be markedly increased when co-administered with medications that share their metabolic pathways, such as inhibitors and drugs competing of cytochrome p450-3A4 isoenzymes (Corsini et al. 1999; Jacobson 2004). For instance, anti-retroviral drugs are well-known inhibitors of cytochrome p450-3A4, and long-term anti-retroviral therapy in HIV patients is associated with the unwanted side effects of cholesterolemia and hypertriglyceridemia and increased risk of cardiovascular diseases (Ault 1997). To counter these side effects, statins are often administered to these individuals to reduce cholesterol and triglyceride levels (Murillas et al. 1999). However, the co-administration of retroviral protease inhibitor and statins has been shown to increase several-fold the peak concentrations of statins in the plasma (Clotet and Negredo 2003; Clotet et al. 2003; Hsyu et al. 2001). Whether the abnormally high concentration of statins found in the plasma of HIV patients will induce any pro-inflammatory effects is unclear and further studies are clearly necessary.

Like HIV patients, SLE patients have a high prevalence of risk factors for cardiovascular disease and premature CAD is a major contributor to the morbidity and mortality in these patients (Gurevich et al. 2005). Statin therapy has been used to lower the cholesterol level in SLE patients in order to reduce the risk of cardiovascular disease. However, besides reducing the incidence of cardiovascular disease in the patients, statin therapy has been shown to trigger or aggravate autoimmune diseases (Hanson and Bossingham 1998; Noel and Panizzon 2004). This unwanted side effect, which appears to be a lupus-like syndrome, is of considerable concern especially when considering the use of statins in the treatment of inflammatory autoimmune diseases.

CONCLUSION

There is a growing body of evidence suggesting that statins have the ability to modulate immune responses mediated by both the innate and adaptive immune system. Most of these findings suggest that statins have beneficial effects in a broad range of autoimmune diseases and that some of these effects may not involve attenuation of the T_H1 and T_H2 responses. Although the immunomodulatory actions of statins are currently being unraveled, the molecular mechanisms involved are complex and may involve cholesterol-dependent and/or -independent effects. Recent work highlighted the therapeutic potential of statins in several experimental animal models of autoimmune diseases. It is clear that the therapeutic success of statins can be attributed to their ability in suppressing a broad range of pro-inflammatory responses. Coupled with their relative safety and their ease in delivery, statins provide a compelling case for their evaluation in the clinical setting. Whether these promising results will be translated to the clinic is too early to predict, and the ongoing clinical trials will reveal whether these agents are effective in the treatment of inflammatory diseases in general. Nevertheless, evidence supporting the potential use of statins in the treatment of multiple sclerosis is emerging and the results from two small open-label clinical trials are encouraging. However, caution must be exercise since statins are known to cause toxic side effects such as rhabdomylosis and lupus-like syndrome in patients.

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