The role of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in modern rheumatology

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Abstract: Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase commonly known as statins are widely used for treating hypercholesterolemia. However, there is much evidence to suggest that statins may have other properties in addition to their cholesterol-lowering effect. In particular, statins may neutralize post-translational prenylation of vitally important regulatory small GTPases, which are involved in several processes such as tissue fibrosis, cell maturation, apoptosis, immune cell maturation, and immune response. The beneficial effect of statins has been reported in animal and *in vitro* models as well as in some clinical studies. As they have an acceptable safety profile, statins may be considered, in selected cases, as a valuable concomitant therapy in the treatment of rheumatic and autoimmune disorders.

Keywords: statins, connective tissue diseases, rheumatology, pleiotropic effect

Introduction

Statins, 3-hydroxymethyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, belong to a category of drugs that can inhibit a key enzyme in the pathway of cholesterol synthesis [Vaughan *et al.* 2000; Corsini *et al.* 1998]. They exert their biological effects by inhibiting the conversion of HMG-CoA to L-mevalonate (Figure 1). As a result, stimulation of low-density lipoprotein (LDL) receptor expression at the cell surface occurs, as the cholesterol level is the main negative regulator of LDL expression on hepatic cells. Increased cholesterol uptake occurs with LDL receptor expression, leading to a further reduction of blood LDL cholesterol. This mechanism was thought to be the main mode of action of statins. Marked reduction of LDL cholesterol was until recently believed to halt the progression of atherosclerosis. Despite the direct association between reduction of cholesterol level and improvement of clinical course in patients with cardiovascular events, not all beneficial effects can be explained by the inhibition of cholesterol synthesis only. It is often observed that in many cases the therapeutic effects of statins precede a reduction in lipid levels. This excludes reduction of LDL cholesterol as the main mechanism of action. In particular, inflammation and immune

response, which are often present in patients with atherosclerosis, may be sufficiently reduced as a result of statins therapy. This suggests that properties of the drugs other than their lipid-lowering properties have to be involved [Pierre-Paul and Gahtan, 2003]. The observation that the benefits of statins which occur just after the beginning of therapy are not restricted to patients with hypercholesterolemia, and also exceed those of other lipid-lowering drugs despite a similar lipid effect, was the background to seeking another mechanism through which statins may provide the pharmacologic effect. Considerable experimental and clinical evidence has shown that statins have effects of significant biological importance beyond their cholesterol-lowering properties.

Pleiotropic effects of statins

These diverse properties, which are separate from their lipid-lowering potential, are sometimes called pleiotropic effect (from the Greek: pleio meaning many, tropos meaning manner). The term is a little controversial, since it is difficult to differentiate *in vivo* the effects that are independent of cholesterol lowering, as the decreased cholesterol level itself may produce many biological consequences. It is of particular importance that statins may exert a biological

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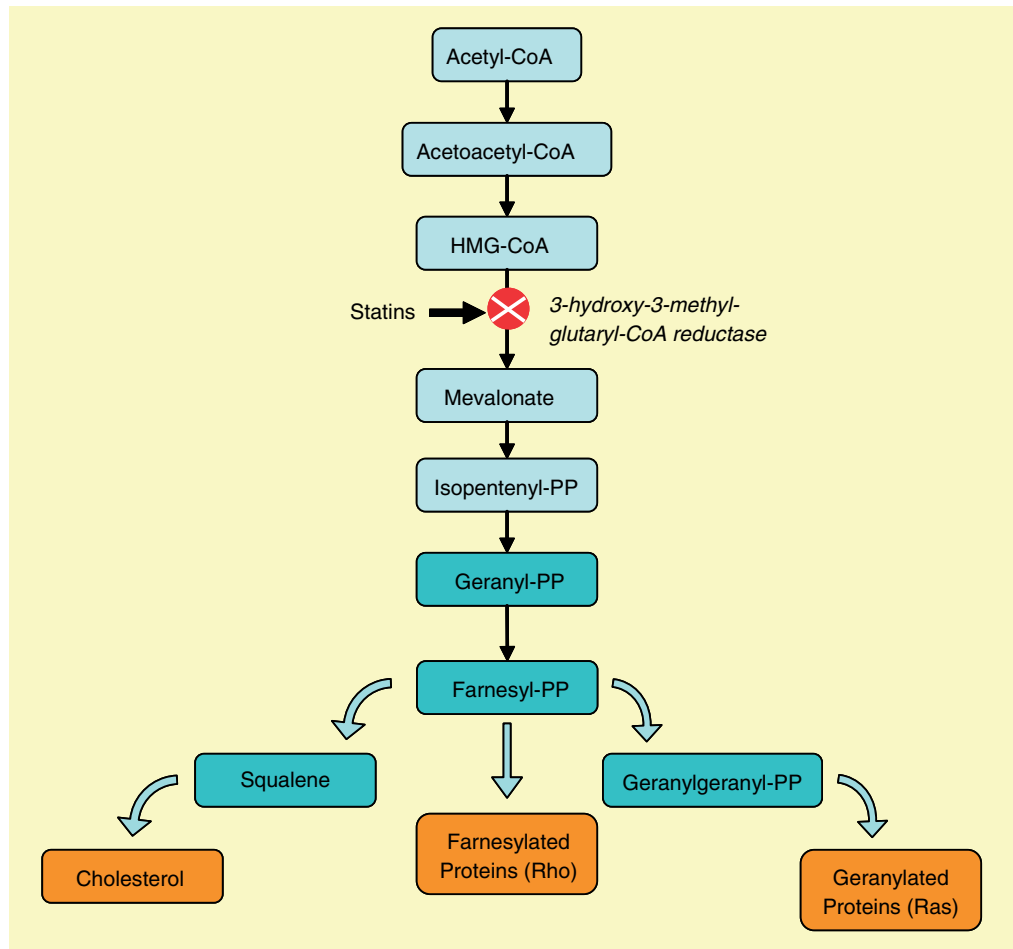**pkotyla@sum.edu.pl**

Figure 1. Mevalonate biosynthetic pathway. HMG-CoA, 3-hydroxy-3-methyl-glutaryl coenzyme A; PP, pyrophosphate.

effect on the immune system. This may explain why the beneficial effect of statins is present just after the start of therapy and often precedes the reduction in cholesterol level. Perhaps what is more important is that the immunomodulatory effect of the drug might be used in the treatment of many conditions where a dysregulated immune response is responsible for causing the inflammation.

Inhibition of an early step in the cholesterol biosynthetic pathway resulted not only in a diminution in cholesterol synthesis, but also decreased other intermediate metabolites downstream including 15-carbon farnesyl pyrophosphate and 20-carbon geranylgeranyl pyrophosphate. These isoprenoids attract much attention since they are involved in the post-translational isoprenylation of intracellular signaling molecules [Liao, 2002; Zhang and Casey, 1996]. Almost 100 different

proteins may undergo prenylation, but importantly among these proteins is that approximately 40 small proteins belong to a small GTPase superfamily [Takai *et al.* 2001; Cohen *et al.* 2000]. GTPases are intercellular switches that are involved in many cellular processes, including apoptosis, gene expression, regulation of cytoskeleton actin, membrane trafficking, and migration [Colicelli, 2004; Etienne-Manneville and Hall, 2002]. The Rho and Rho-like proteins of the GTPases regulate the formation of the adhesion complex, as well as a number of inflammatory pathways, including mitogen-activated protein (MAP) kinase cascades [Braga, 2002; Mackay and Hall, 1998]. Data from experimental studies suggest that statins may inhibit inflammation mainly by the suppression of Rho family protein activity [Liao, 2002]. The GTPases that belong to the Ras family proteins are involved in signal transduction from growth factor receptors

but also play a role in MAP kinase regulation. Evidence from laboratory studies showed that there are various ways of activating Ras and Rho superfamily molecules. Rho proteins are typically geranylated, whereas activation of the Ras family requires farnesylation [Colicelli, 2004].

Small molecular weight G proteins of the Ras superfamily (Ras, Rac, and Rho) are also involved in the regulation of growth, cell-to-cell interaction and apoptosis [Comparato *et al.* 2001; Glomset and Farnsworth, 1994]. Isoprenylation of small G proteins is essential for those proteins to achieve new regulatory functions [Corsini *et al.* 1993]. Equilibrium between the activities of these proteins provides a strong positive stimulus on the endothelium and promotes vasorelaxation [Barandier *et al.* 2003]. The influence of cardiovascular risk factors on the cascade of small G proteins results in the activation of the small RhoA protein and Rho kinase (ROCK), leading to the destabilization of nRNA for endothelial nitric oxide (eNOS) synthase [Eto *et al.* 2001]. At the same time a strong positive regulatory effect on prepro-endothelin-1 (prepro-ET-1) synthesis can be observed. It provides an imbalance between NO synthesis and overproduction of ET-1. As a result vasoconstriction of the vessel is observed. Endothelial and muscle smooth cells also express another small G protein Rac1, which is the major component of NAD(P)H oxidase that acts as the source of free radical species in many pathological conditions. Free radical species can interact with NO and decrease its bioavailability leading to endothelial dysfunction [Barandier *et al.* 2003]. Another biological function of RhoA and ROCK proteins is the regulation of endothelial barrier dysfunction by increasing phosphorylation of the myosin light chain. RhoA also plays a role in signal transduction to muscle and non-muscle myosin II [Somlyo and Somlyo, 2000]. All these events eventually lead to contraction of the blood vessel and promote the development of atherosclerotic plaque. Statins may interfere with isoprenylation of the small G protein and block their pathophysiological function. It has been suggested that this is one of the main mechanisms that explains the pleiotropic properties of HMG-CoA reductase inhibitors [Takemoto and Liao, 2001].

Lessons derived from experimental models suggest that statins upregulate eNOS expression and inhibit smooth muscle proliferation through the inhibition of the Rho-ROCK pathway. The effect is enhanced by the simultaneous inhibition of Ras. Animal models showed that Ras plays a significant role in the formation of atherosclerotic plaques, which has been demonstrated in apolipoprotein knock-out mice [George *et al.* 2002].

Immunomodulatory effects of statins

Many studies have shown that statins may possess immunomodulatory properties that might be of particular benefit in the treatment of autoimmune disorders. Statins may inhibit nuclear factor κB resulting in the inhibition of endothelial activation [Vaughan and Gotto, 2004; Meroni and Tremoli, 2003]. Statins regulate the class II transactivator, which reduces induction by interferon gamma (IFNγ) expression of major histocompatibility complex (MHC) class II molecules on antigen-presenting cells (APCs). MHC molecule expression on the surface of APCs is required for antigen presentation, thus the antigen is recognized by T cells in the context of MHC II antigens. Decreased expression results in antigen tolerance and downregulation of the T-cell response [Sadeghi *et al.* 2001; Kwak *et al.* 2000]. Interaction with the process of MHC II presentation contributes to the shift in the T cell from the Th1 response to the protective Th2 response [Lawman *et al.* 2004; Aktas *et al.* 2003].

Taking into account endothelium involvement, which is almost universal among connective tissue diseases, the role of statins is to repair the endothelium damage. Statins downregulate expression of the adhesion molecules on endothelial cells as well as reducing the levels of circulating soluble intravascular cell adhesion molecule-1 (ICAM-1), and E- and P-selectins [van Haelst *et al.* 2001; Romano *et al.* 2000a]. Recently the role of the integrin lymphocyte function-associated antigen-1 (LFA-1 CD11a–CD18) on lymphocytes has been debated. This integrin binds to the immunoglobulin superfamily molecule ICAM-1 and this is a key interaction that facilitates both adhesion/migration and costimulation. Some statins have shown the ability to block LFA-1/ICAM-1 interaction through direct binding to the so-called lovastatin binding site (L-site on the extracellular domain of LFA-1). As a result of this process inhibition both lymphocyte adhesion and costimulation occurs [Watts *et al.* 2005]. LFA-1, a β2 integrin, is critical in the development of inflammatory arthritis in the B/BxN serum transfer mouse model of arthritis. When statins

(except pravastatin, which does not bind to the L-site) bind to LFA-1, they cause allosteric changes in the integrin structure preventing ICAM-1 binding [Watts *et al.* 2005; Weitz-Schmidt *et al.* 2001]. Another major player in leukocyte endothelium interaction is monocyte chemotactic protein-1 (MCP-1), a main chemoattractant for monocytes and T lymphocytes. MCP-1 is produced by human endothelial cells after stimulation by C- reactive protein, interleukin 1β (Il-1β), or lipopolysaccharide. Simvastatin inhibits *de novo* synthesis of MCP-1 in endothelial cells [Weitz-Schmidt *et al.* 2001]. Simvastatin and also lovastatin decreases synthesis of MCP-1 in human peripheral monocytes [Han *et al.* 2005; Romano *et al.* 2000a].

Role of statins in atherosclerosis

Statins not only reduce morbidity and mortality in coronary heart disease but also prolong life span in patients with hyper- and normocholesterolemia. The most recent evidence suggests that the action of statins is at least partially independent of the lipid-lowering properties of HMG-CoA reductase inhibitors. It may be speculated that not only the reduction in cholesterol synthesis but also the inhibition of lipid oxidation are the mechanisms through which statins may halt the progression of atherosclerosis. Atherogenesis and plaque formation begin with the accumulation of LDL cholesterol in the endothelial compartment of the blood vessel followed by its oxidation. Oxidized lipoproteins accumulate within the endothelial space and are the main target for monocytes and macrophages. Enzymes released from the monocytes/macrophages break down the fibrous cap at the top of the plaque and this leads to rupture [Navab *et al.* 1996; Henney *et al.* 1991]. Statins possess the ability to stabilize atherosclerotic plaques. Several clinical studies have shown the potential of statins to decrease the evolution rate of atherosclerotic lesions towards rupture. One of the possible mechanisms involved in this process is the suppression by statins of cyclooxygenase-2 and microsomal prostaglandin synthase-1. As a result plaque stabilization occurs, which prevents rupture and subsequent thrombus formation, the main mechanism leading to acute myocardial infarction [Mezzetti, 2005; Cipollone *et al.* 2003].

Platelet activation and aggregation are a key step in thrombus formation; several factors are released upon their activation which generate a further amplification of the process [Daniel *et al.* 1999; Fuster *et al.* 1992]. Platelets can be activated by different stimuli including thrombin, adenosine diphosphate (ADP), and pro-inflammatory cytokines (including Il-1 and IFNγ) [Schror, 1995]. Platelets are also an important source of thromboxan A_2, one of the most potent vasoconstrictors in the body. Statins, acting on the Rho-dependent pathway, may minimize platelet aggregation and thromboxan release through the partial inhibition of ADP and adenosine-5′-triphosphate (ATP) release from activated platelets and by exerting antioxidant effects [Kaneider *et al.* 2002].

Fibrinogen, an important factor in coagulation, exerts its pro-atherosclerotic action by stimulation of the proliferation and migration of smooth cells. These processes are realized by affecting the permeability of the vascular endothelium and function of the platelets and monocytes/macrophages as well as exerting proinflammatory and procoagulatory effects [Heinrich and Assmann, 1995; Warkentin, 1995]. Results obtained from the studies indicate that the effect of statins on the level of fibrinogen is relatively mild [Rosenson *et al.* 2001; Song and White, 2001]. However, in patients suffering from connective tissue diseases the level of fibrinogen may reflect the level of inflammation. This is why fibrinogen is well known as an acute phase marker and its level is raised significantly during the course of inflammation [Krysiak *et al.* 2003]. Statins may act in this area by cooling the inflammation following a decrease in fibrinogen level.

Another potent coagulation factor that is found in atherosclerotic plaques is the tissue factor (TF) [Rosenson and Tangney 1998]. It is synthesized by damaged or stimulated monocytes, macrophages, and smooth muscle and endothelial cells. After binding to activated factor VII, the TF promotes coagulation [Dahlback, 2000]. Statins reduce the level and activity of the TF in human monocyte cultures activated, but also nonactivated, by inflammatory stimuli [Ferro *et al.* 2000; Colli *et al.* 1997]. This effect is not only restricted to mononuclear cells but can also be seen in the smooth muscle cells of the artery wall as well as in endothelial cells [Camera *et al.* 2002; Eto *et al.* 2002].

Several studies have addressed the influence of statins on thrombin formation. Particular emphasis was put on thrombin generation parameters

such as thrombin fragment (F1+2), fibrinopeptide A, and thrombin-antithrombin III complexes [Krysiak *et al.* 2003]. According to data obtained from studies, simvastatin inhibits conversion of prothrombin to thrombin [Musiał *et al.* 2001]. In addition, in *ex vivo* studies, simvastatin decreased thrombin generation and the total activity of the enzyme in patients with a significantly high cholesterol level [Szczeklik *et al.* 1999]. Statins were also shown to inhibit platelet-dependent formation of thrombin. The presumed mechanism of this activity is the improvement of the impaired interaction between platelets and coagulation factors, since platelet activity does not change during treatment [Aoki *et al.* 1997].

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disorder of unknown origin that serves as a prototype for other autoimmune disease. It affects mainly young people, especially women, which is a population not at risk of atherosclerosis development. Many years ago, the acute course of lupus with lupus nephropathy, hematological complication, and infection attracted the attention of physicians. Improvement of the management of lupus contributes significantly to improvement in prognosis and prolongation of life span. However, many years after the onset of lupus, survivors of the acute lupus phase face the problem of unexpected premature cardiovascular incidents.

The premature atherosclerosis in young lupus patients was first described by Urowitz and colleagues [Urowitz *et al.* 1976]. They coined the term 'bimodal mortality' and showed that the first peak of mortality was caused by the acute phase of disease, but the second was attributed to the fatal complication of atherosclerosis. The same conclusions came from the study of Bulkey and Roberts who in series of autopsies of young lupus female patients found significant atherosclerotic lesions in at least one coronary artery in the majority of cases [Bulkley and Roberts, 1975]. These findings were substantiated by subsequent studies that additionally showed that the incidence of myocardial infarction was five times higher in lupus patients than in the general population. Moreover, the specific target population for the disease was a group of young women in which an age-specific incidence that increased by a factor of as much as 50 was observed [Manzi *et al.* 1997; Johnsson *et al.* 1989].

The mechanism of accelerated atherosclerosis in lupus patients is not completely understood. It is speculated that atherosclerosis in SLE is the result of a combination of traditional risk factors, treatment, and inflammation [Esdaile *et al.* 2001; Petri, 2000]. However, the traditional risk factors fail to explain fully the process of accelerated atherosclerosis that suggests a main role of the inflammatory process in the beginning and progression of atherosclerotic lesions among patients with SLE. Moreover, the role of corticosteroid therapy and subsequent development of atherosclerosis in SLE patients is still subject to controversy and the results obtained from studies are contradictory [Roman *et al.* 2001]. Since the traditional risk factors and corticosteroid use are unable to explain fully the burden of accelerated atherosclerosis, SLE alone (also other connective tissue disorders) should be recognized as a novel independent risk factor.

Since the work of Ross, who explained that atherosclerosis is an inflammatory disease, we now better understand the mechanism of atherosclerosis in connective tissue diseases [Ross, 1999]. In recent years this new understanding of the pathogenesis of atherosclerosis has included insights into the role of inflammatory mediators in cardiovascular disease, and characterization of immunologic phenomena that are present in coronary vascular disease but may also be found in classic autoimmune diseases [Mustafa *et al.* 2000; Liuzzo *et al.* 1999; Cristea *et al.* 1986]. This contributes to the recognition of atherosclerosis in SLE as a chronic inflammatory disease characterized by circulating auto-antibodies, activated T and B lymphocytes, immune complexes, and pro-inflammatory cytokines. The level of inflammation in the course of SLE is high enough to start and progress atherosclerosis in patients.

Evidence derived from experimental models has shown that statins may deeply interfere with the immunological system leading to a reduction in SLE activity. In spite of the fact that SLE is not a typical Th1-mediated autoimmune disease, upregulation of MHC class II molecules, and increased production of IFNγ are involved in the pathogenesis and progression of the disease. Statins can ameliorate IFNγ-induced overexpression of MHC molecules class II on most APCs, but have no influence on MHC class I [Kwak *et al.* 2001, 2000]. This finding may be of particular importance as many data suggest that

overexpression of MHC class II molecules is a key mechanism in autoimmune disorders [Botazzo *et al.* 1983]. Reduced expression of MHC is responsible for the impaired formation of the immunological synapse between the T cell-receptor complex and MHC. This ultimately leads to impaired antigen recognition and finally to antigen tolerance. Moreover, interaction with the process of MHC II presentation contributes to the shift of the T cell from the Th1 response to the protective Th2 response [Hakamada-Taguchi *et al.* 2003].

The term 'protective response' in the case of lupus is controversial, since this response leads to increased B-cell reactivity and auto-antibody production. Indeed the presence of antinuclear antibodies and lupus-like syndromes has been reported in patients on statins therapy [Hanson and Bossingham, 1998]. A question thus arises regarding the utility of statins in this setting. However, the immunomodulatory potential of statins may also be explained not by the switch to a Th2 response but by their ability to activate T regulatory cells (Tregs). Tregs are a unique population of CD4+ cells that suppress autoreactivity and are critical regulators of immune tolerance [Baecher-Allan *et al.* 2001]. Much data suggests that in many autoimmune disorders including lupus the Treg population is reduced or functionally suppressed [Valencia *et al.* 2007; Liu *et al.* 2004]. In animal models simvastatin can mediate the induction of mouse Fox3p+ Tregs that may stabilize equilibrium between activated and regulatory T cells [Kim *et al.* 2010].

Endothelium involvement in the course of SLE is almost universal and contributes significantly to the development of atherosclerosis. Statins also work in this area. The understanding of endothelium activation as an initial step in its dysfunction and damage lead to a search for potential targets for statins. The expression of endothelial cell adhesion molecules that reflects endothelial activation is strongly modulated by the use of statins. In particular, inhibition of RHO and RHO-mediated gene expression by statins leads to downregulation of P- and E-selectins [Romano *et al.* 2000b]. Statins may also interfere with second signal transmission, since they are able to decrease expression of the CD80/86 molecule on APCs (mainly on B cells). Costimulation is essential to evoke the full activation of T cells; in the absence of a strong costimulation signal,

T cells may develop immune tolerance and subsequent lack of activity [Youssef *et al.* 2002]. In this model treatment with atorvastatin stopped the progression of lupus in lupus-prone New Zeland F_1 mice [Lawman *et al.* 2004].

These promising results unfortunately have not been translated into clinical practice. So far only a few trials have been designed to verify the immunomodulatory properties of statins in humans. The study of Abud-Mendoza and colleagues in patients with refractory SLE and lupus nephropathy may serve as an example where a good therapeutic response has been observed [Abud-Mendoza *et al.* 2003]. These results should, however, be interpreted with caution as the group of patients comprised only eight subjects and it was not a controlled trial. In another study, 4 weeks of treatment with simvastatin in patients with SLE resulted in a marked suppression of the tumor necrosis factor (TNF)-α level and decreased lupus activity on the systemic lupus erythematosus disease activity index scale [Kotyla *et al.* 2006].

The influence of statins on SLE is not only restricted to disease activity but also comprises their effect on vessel function. Ferreira and colleagues reported improvement in arterial vasodilation in an 8-week controlled trial where flow-mediated dilatation was increased in SLE patients [Ferreira *et al.* 2007].

It should be mentioned that probably not all statins provide a pleiotropic effect in patients with connective tissue disease. The absence of immunomodulatory properties in pravastatin has been proven in the study of Costenbader and colleagues where two dose of pravastatin failed to affect lupus activity and had no influence on C-reactive protein reduction [Costenbader *et al.* 2007]. This indicates that pravastatin may differ from other statins with regard to pleotropic properties [Kotyla, 2009].

The lack of anti-inflammatory effect was also shown in a study by de Kruif and colleagues where rosuvastatin was tested in a group of 15 SLE patients with mild disease [de Kruif *et al.* 2009]. It is speculated that, in this particular trial, the effect of statins may have been ameliorated by concomitant steroid use and statin-induced apoptosis, which in turn activated the immune response or the shifting from the Th1 to Th2 response resulting in B-cell hyperactivity

and overproduction of auto-antibodies [de Kruif *et al.* 2009].

As shown in the above cited study, the pleiotropic effect does not seem to be a class effect of statins. Various compounds may differ from each other with regard to immunomodulatory/immunosuppression properties. Currently we do not know the main mechanism of immunomodulation. Some statins have the ability to bind to the L-site on the LFA-1 and inhibit the LFA-1–ICAM-1 interaction [Watts *et al.* 2005]. Contradictory results obtained from the study where various statins were used may be explained by the inability of pravastatin and rosuvastatin to bind to the L-site.

Understanding of the new role of statins in the treatment of SLE should result from the recognition of SLE as a complex systemic disease with late complications arising from the cardiovascular system. HMG-CoA reductase inhibitors have proven their efficacy in the treatment of atherosclerosis in a population not affected by connective tissue diseases and showed noncholesterol-lowering properties, so it may be reasonable to use this group of compounds in the primary and secondary prevention of cardiovascular diseases among patients with SLE. It is clear that statins will never substitute glucocorticosteroids and immunosuppressants in the treatment of SLE, but having a neutral, possible beneficial influence on immune response, HMG-CoA reductase inhibitors should always be considered as a valuable concomitant therapy in SLE patients.

Rheumatoid arthritis

Epidemiologic studies in rheumatoid arthritis have consistently found that subjects with rheumatoid arthritis (RA) are at increased risk of cardiovascular disease, and this burden cannot be easily explained by the traditional risk factors alone. The mechanism underlying the high frequency of cardiovascular morbidity that occurs in patients is not fully understood. Research carried out over last decade has demonstrated, however, that similar to patients with other connective tissue diseases, RA is a cardiovascular risk factor. This is due to the fact that RA is an autoimmune disorder involving various types of inflammation that shares many similarities with atherosclerosis. Obviously inflammation present in RA patients is not restricted to the joints and synovial membrane but has a systemic character and is also present at the level of blood vessels. Vessel involvement is the same as in SLE patients and comprises several steps in vessel dysfunction and damage. An early step in vessel damage is endothelium dysfunction. This process is mainly driven by increased levels of circulating Il-6, TNF-α and C-reactive protein, which by working together ultimately lead to the inhibition of endothelium-dependent vasodilation, arterial stiffness, and subclinical atherosclerosis [Esteve *et al.* 2007; Mahmud and Feely, 2005]. Systemic inflammation also leads to deep changes in many physiological processes such as impairment of vascular injury repair, insulin resistance, hypercoagulable state, elevated homocysteine levels, and upregulation of immunocompetent cells. More importantly, endothelial damage and subclinical arterial stiffness, the first steps in atherosclerosis, often precede RA. The results from a study may serve as an example where the risk of myocardial infarction was particularly high within the 2 years before formal diagnosis of RA was made [Maradit-Kremers *et al.* 2005]. Patients with RA may differ from patients with no symptoms of connective tissues disease. Compared with patients suffering from atherosclerosis, low body mass in RA patients is linked to a higher risk of a serious cardiovascular event, mainly due to the influence of inflammatory cytokines that possess catabolic properties. The results regarding the lipid profile in RA patients in general gave contradictory results. Indeed the routine test used for the detection of lipid profile abnormalities usually returns as normal. On the other hand, inflammation is known to alter lipoprotein metabolism in a manner that promotes atherogenicity [Libby *et al.* 2002].

Prevention of atherosclerosis in RA patients can be easily achieved with statins, but again the question arises of the additional, anti-inflammatory or immunomodulatory activities of the drugs. The results of a collagen-induced arthritis study that represents an animal model of RA, offers support for the thesis that statins may be useful in RA patients. In this study simvastatin significantly suppressed articular inflammation and decreased pro-inflammatory cytokine synthesis, IFNγ, TNF-α, and Il-12 [Leung *et al.* 2003]. Similar results were reported by Lin and colleagues who examined the influence of simvastatin on peripherial monocytes from patients with active RA. Inhibition of the Rho pathway in this study resulted in the suppression of

Toll-like receptor-2 activation and subsequent reduction of cytokines synthesis [Lin *et al.* 2010].

Suppression of inflammation could be also observed *in vivo*, in patients with refractory RA, where administration of the HMG-CoA reductase inhibitor simvastatin contributed to the reduction in number of swollen joints and improvement in self-assessed disease activity [Abud-Mendoza *et al.* 2003; Kanda *et al.* 2002]. This effect was confirmed in a large double-blind, randomized, placebo-controlled trial with atorvastatin (TARA study). According to the data obtained from the study, atorvastatin has a significant impact on disease activity and reduces the markers of inflammation [McCarey *et al.* 2004]. In another study, Yokota and colleagues reported the inhibition of production of IL-6, IL-8, and TNF-α in fibroblast-like synoviocytes from patients with RA [Yokota *et al.* 2006]. Two years later the same authors suggested a biphasic mode of action of simvastatin on fibroblast-like synoviocltes. They postulated that reduction of cytokine synthesis is observed in lower doses of simvastatin since higher doses predispose the fibroblast-like synoviocltes to apoptosis [Yokota *et al.* 2008].

Systemic sclerosis (scleroderma)

Systemic sclerosis is a connective tissue disease characterized by immune alterations that often correlate with organ injury. The main feature of the disease is the thickening and hardening of skin due to uncontrolled fibroblast proliferation and collagen synthesis. Although the skin is the most visible problem, it is internal organ involvement that is responsible for the reduction in life span and the development of serious complications. The accumulation of collagen fibers in almost all organs and the vascular bed contributes significantly to the presence of internal organ and vessel injury.

Lung involvement can be observed in most connective tissue diseases, however pulmonary manifestation in systemic sclerosis attracts much attention from physicians. It may occur as lung fibrosis and pulmonary arterial hypertension. In the course of systemic sclerosis lung fibrosis reflects profibrotic activity in the body rather than local inflammation. In scleroderma patients the attention on lung fibrosis has shifted from chronic inflammation to aberrant wound repair mechanisms with special emphasis on the interplay of fibroblasts and alveolar epithelial cells. As

a consequence the therapeutic approach has changed from traditional anti-inflammatory drugs to those that may possess the ability to modify the fibrotic process. Unfortunately at present there is a lack of such agents that may dramatically change the course of fibrosis in systemic sclerosis. Theoretically fibrosis may be halted/reversed by increased apoptosis of the fibroblasts. In some laboratory models lovastatin has been shown to induce apoptosis of the fibroblasts from normal and fibrotic lungs. The process was associated with inhibition of the Ras signaling pathway, which explained the mode of action of statins in this model [Tan *et al.* 1999]. Apoptosis of the fibroblasts is not the only mechanism through which statins may affect fibroblast function.

The main player in fibrosis, that is characteristic of systemic sclerosis, is transforming growth factor beta (TGF-β), the growth factor involved in such processes as embryonic development immune responses, and regulation of tissue repair after injury [Clark and Cooker, 1998]. One of the most important effects of TGF-β is the stimulation of synthesis of the extracellular matrix proteins. As a result, increased production of collagens and other matrix proteins, such as fibronectin, can be observed [Varga *et al.* 1987]. The systemic sclerosis fibroblasts expressed increased levels of TGF-β receptors on their surface. This may explain increased collagen production by fibroblasts. The TGF-β also contributes to the imbalance between collagen synthesis and collagen-degrading metalloproteinases. As a result, collagen overproduction is seen. The process is augmented by stimulation of the production of protease inhibitors that prevents the breakdown of the extracellular matrix [Postlethwaite, 1995]. Data on statins influence on TGF-β synthesis gave contradictory results; some studies suggest that statins have the ability to block TGF-β synthesis, while others suggest they do not [Li *et al.* 2005; Porreca *et al.* 2002]. On the other hand, reduction of TGF-β may potentially be dangerous for the blood vessels. Some data indicate that TGF-β may exert a protective role in atherosclerosis development [Ryan *et al.* 2003]. Beneficial effects observed in vessels after statins therapy suggest that statins may use other signaling pathways increasing TGF-β levels but neutralizing its activity at more advanced stages of signaling. TGF-β is a potent inducer of connective tissue growth factor (CTGF), which is a fibroblast mitogen and promoter of

collagen deposition and has been implicated in the pathogenesis of tissue fibrosis [Frazie *et al.* 1996]. Laboratory data showed simvastatin inhibited TGF-β-stimulated CTGF activity through a Rho-dependent mechanism [Watts and Spiteri, 2004]. This mechanism may explain why antifibrotic activity is observed in spite of the statins' potential to induce TGF-β synthesis. Similar results, such as the reduction in fibroblast proliferation, could be observed after inhibition of cyclin D1 gene expression on fibroblasts that is mediated through the RhoA signaling pathway. This finding is of special pathophysiological importance, as cyclin D1 is a critical regulator in the progression of the cell cycle and cyclin gene, and its product is upregulated in idiopathic pulmonary fibrosis-derived lung fibroblasts. Simvastatin, an established Rho molecule inhibitor, significantly reduced cyclin D1 mRNA and protein synthesis as well as suppressing cell proliferation [Watts *et al.* 2006].

Another potential mechanism of statin action is the inhibition of vascular smooth muscle synthesis of thrombospondin-1, a potent activator of TGF-β. However, the role of this mechanism in fibrosis is still unclear [Riessen *et al.* 1999].

The other proposed targets in the treatment of fibrosis are the genes encoding collagens. Those genes that encode collagens type I and III have attracted much attention. This is because tissue fibrosis in scleroderma, the main clinical manifestation of the disease, is caused by the accumulation of these two types of collagen and other connective tissue components in the extracellular space. In the study of Rosenbloom and colleagues, GGTI-296, a specific inhibitor of geranylgeranyl transferase, inhibited type I gene expression in normal and systemic sclerosis fibroblasts [Rosenbloom *et al.* 2000]. This observation was further confirmed by a study with simvastatin, where a marked reduction of gene expression in cultures of normal and systemic sclerosis dermal fibroblasts caused a substantial reduction of collagen synthesis [Louneva *et al.* 2006].

Conclusions

At present it is not clear whether statin therapy will be important in the treatment of systemic sclerosis. Results from animal and *in vitro* models should be interpreted with caution and perhaps cannot be translated directly into the human clinic. Taking into account accelerated macrovascular disease among patients with systemic sclerosis, statins should be the first choice. However, additional immunosuppressive and antifibrotic properties should be proven in well-designed clinical trials.

The promising results of statins from various models of human auto-immunity and connective tissue diseases confirm the potential of HMG-CoA reductase inhibitors in the treatment of diseases. We are steadily accumulating research in this field. Unfortunately, most studies utilize animal and *in vitro* models, where very high doses of statins are used, and promising results cannot be found in the majority of connective tissue disease presentation in humans. However, treatment with statins may give us a unique opportunity to stop the burden of accelerated atherosclerosis and perhaps modulate immune response and fibrotic processes. It is clear that statins will not be substitutes for steroids and other immunosuppressants but may lead to a reduction in doses/amounts of classic drugs.

Conflicts of interest statement

None declared.

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