

Summary

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History and development of HMG-CoA reductase inhibitors

An encouraging development in the treatment of hypercholesterolemia has been the introduction of a new class of fungal-derived compounds that are potent competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-controlling enzyme in the biosynthetic pathway for cholesterol. HMG-CoA reductase (HMGR) inhibitors (statins) are established drugs for the treatment of hypercholesterolemia and have been shown to induce regression of vascular atherosclerosis, as well as reduction of cardiovascular-related morbidity and death, in patients with and without coronary artery disease. In the early '70s, Endo and Kuroda, while searching for HMGR inhibitors of microbial origin, assayed over 6,000 microbial strains for their ability to block lipid synthesis, and they isolated compactin. Since their original work, the search for additional HMG-CoA reductase inhibitors continued for several years, leading to the discovery of several HMGR inhibitors. More recently, several fully HMG-CoA reductase synthetic enantiomeric inhibitors are being developed or are already in clinical testing.

Key Words: Anti-atherosclerotic drugs, atherosclerosis, atorvastatin, cerivastatin, coronary artery disease, fluvastatin, hypolipidemic drugs, lipid-lowering, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, statins.

Summary

Margaret E. Brousseau and Ernst J. Schaefer

Structure and mechanisms of action of HMG-CoA reductase inhibitors

The efficacy of LDL reduction in the prevention of coronary heart disease has clearly been demonstrated in a number of primary and secondary intervention trials. Drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis, constitute a major advance in the treatment of patients with elevated plasma concentrations of LDL cholesterol. Treatment with HMG-CoA reductase inhibitors, or statins, has been shown to significantly reduce plasma LDL cholesterol and apolipoprotein (apo) B levels in hypercholesterolemic subjects, independent of the underlying metabolic disorder. However, although the cholesterol-lowering ability of this class of drugs is irrefutable, the mechanisms responsible for their hypocholesterolemic effects are yet to be completely defined. While the inhibitory effect of statins on the *de novo* synthesis of cholesterol has consistently been observed, the effect of this class of drugs on apoB metabolism is less clear. The majority of experiments performed in cell culture systems have demonstrated that statins decrease apoB secretion by increasing apoB degradation, rather than by decreasing apoB synthesis. Decreased production of LDL apoB-100 has similarly been shown in a number of human *in vivo* kinetic studies. Conversely, early studies on the action of statins in patients with hypercholesterolemia have attributed the reduction in plasma cholesterol levels to upregulation of the LDL receptor pathway, secondary to a decrease in intracellular free cholesterol pools. The goal of this work is to review the results of recent *in vitro* and *in vivo* studies that have investigated the mechanisms by which statins reduce plasma LDL concentrations, with particular emphasis on the metabolism of apoB-containing lipoproteins in humans. Data from two studies that have examined the effect of statins on the *in vivo* kinetics of high density lipoprotein (HDL) apoA-I will also be reviewed.

Key Words: Apolipoprotein B, HMG-CoA reductase inhibitors, hyperlipidemia, kinetics, lipoprotein metabolism, statins.

Summary

Jörg Kotzka, Wilhelm Krone and Dirk Müller-Wieland

Sterol-regulatory element binding proteins (SREBPs): gene-regulatory target of statin action

Many clinical as well as morphological and cell biological studies have indicated, that statins appear to affect many aspects of life beside LDL-cholesterol lowering, indicating that plasma cholesterol lowering by induction of the hepatic LDL-receptor gene is only one effect of statin-mediated reduction of cholesterol synthesis. Therefore, it is a current issue of interest to understand the molecular mechanisms of statin action. There is a growing body of evidence, that inhibition of the cholesterol biosynthesis pathway might affect posttranslational modification of proteins by e. g. farnesyl pyrophosphate and geranylgeranyl pyrophosphate, thereby modulating many different signalling cascades within the cell. An other result of cholesterol synthesis inhibition is alteration of cellular gene expression. Statins and sterols have an interplay with different transcription factors, e. g. sterol-regulatory element binding proteins (SREBPs). SREBP-isoforms, SREBP-1a and SREBP-1c as well as SREBP-2, belong to the family of bHLH proteins and their intranuclear abundance is controlled by intracellular sterol levels. It has been shown, that SREBP-2 is a main regulator of cholesterol synthesis, whereas SREBP-1c affects mainly the synthesis of fatty acids, and SREBP-1a both pathways. Studies using transgenic animals and different cell lines indicate, that the intracellular abundance of SREBPs modulate the effectivity of statin action and mediate their effects on the induction of the LDL-receptor gene in liver. We have shown recently, that transactivity of SREBPs can be controlled by insulin, growth factors and cytokines, thereby being a gene regulatory link for metabolites, hormones and inflammatory signals. In addition, there appear to be many other gene targets of SREBPs indicating, that these cholesterol regulated transcription factors might be mediators of some so called pleiotropic statin effects. SREBPs appear to play an essential role in molecular signalling mechanisms of cholesterol and might be intracellular mediators linking metabolic alterations to gene regulatory events.

Keywords: Lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, G-proteins, SREBP, ADD1, Lipid toxicity, metabolic syndrome, insulin resistance, insulin, growth factors, cytokines.

Summary

Gerd Schmitz and Michael Torzewski

Cellular effects of HMG CoA reductase inhibitors on blood cells (monocytes, macrophages, platelets)

Independent of their ability to reduce plasma cholesterol, three potential targets for statins are emerging concerning leukocyte differentiation: first, bone marrow progenitor cells leading to the maturation of less CD14⁺ cells; second, the blood compartment itself influencing differentiation and extravasation of monocytes; third, statins are able to reduce the in vitro cholesterol accumulation in macrophages (either directly or via reduction of plasma levels of potential opsonins like CRP) and expression of matrix metalloproteinases, resulting in plaque stability. Repressing the induction of MHC-II, and subsequent T-lymphocyte activation, statins further provide a new type of immunomodulation. These activities, which affect major processes involved in the formation of atherosclerotic lesions, are linked to the local modulation of the mevalonate pathway. Accordingly, statins exert their cardiovascular benefits through direct anti-atherogenic properties in the arterial wall, beyond their effects on plasma lipids. Following plaque disruption, statins may influence thrombosis through variable inhibitory action on platelet deposition and aggregation, coagulation factors, thrombin generation, rheology, and fibrinolysis. These effects of statins may contribute to the primary or secondary prevention from CHD in large clinical studies. However, the clinical significance of diverse effects of statins on factor VII, fibrinogen, plasma viscosity, PAI-1 and lipoprotein(a) has been not yet determined. Accordingly, understanding the

effects of statins on hemostasis with respect to prevention or treatment of atherosclerosis will require further basic and clinical research.

Key Words: Atherosclerosis, innate immunity, adaptive immunity, macrophages, dendritic cells, C-reactive protein, peripheral blood monocytes, cholesterol esterification, mevalonate pathway, plaque stability, T lymphocytes, platelet aggregation, fibrinogen, thrombin, plasminogen activator inhibitor-1.

Summary

Koichi Node and James K. Liao

Pleiotropic effects of HMG-CoA reductase inhibitors on cells of the vascular wall

The 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors or statins are potent inhibitors of cholesterol biosynthesis. Several large clinical trials have demonstrated the benefits of cholesterol lowering with these agents in the primary and secondary prevention of coronary heart disease. However, the overall clinical benefits observed with statin therapy appear to be greater than what might be expected from changes in lipid profile alone, suggesting that the beneficial effects of statins may extend beyond their effects on serum cholesterol levels. Indeed, recent experimental and clinical evidence indicates that some of the cholesterol-independent or "pleiotropic" effects of statins involve improving or restoring endothelial function, enhancing the stability of atherosclerotic plaques, decreasing oxidative stress and inflammation, and inhibiting the thrombogenic response in the vascular wall. Many of these pleiotropic effects of statins are mediated by their ability to block the synthesis of important isoprenoid intermediates, which serve as lipid attachments for a variety of intracellular signaling molecules. In particular, the inhibition of small GTP-binding proteins, Rho, Ras, and Rac, whose proper membrane localization and function are dependent upon isoprenylation, may play an important role in mediating the direct cellular effects of statins on the vascular wall.

Key Words: HMG-CoA reductase inhibitor, endothelium, vascular smooth muscle, platelets, atherosclerosis, inflammation, cholesterol, low density lipoprotein, G-proteins, gene expression, plaque stability, vasodilation.

Summary

Hans-P. Thomas and Elisabeth Steinhagen-Thiessen

Indications and contra-indications for statin treatment (primary and secondary prevention of hypercholesterolemia)

Cardiovascular diseases continue to be the most common cause of death in western countries. Epidemiological studies clearly showed that there is a replicable and independent relationship between the total cholesterol levels and the incidence of coronary heart disease. Moreover, the treatment of lipid disorders with HMG-CoA reductase inhibitors (statins) has proved to be highly effective in a series of studies. The effects of statins are independent of pre-treatment LDL-cholesterol levels, gender and show the clear benefit for older patients up to the 75-year-old age group. On average, the overall risk of cardiovascular events fell by 30% and overall mortality was able to be reduced by 21%. Effective cholesterol reduction also has a beneficial influence on stroke.

Contra-indications primarily concern hypersensitivity, active liver disease or persistent elevations of liver enzymes, muscle diseases, pregnancy and lactation. Other side effects that would limit treatment employing a statin therapy are very rare.

The use of statins can surely serve as a perfect example of a sensible therapy approach. If we actually put into practice what we know from numerous studies, a further reduction in morbidity and mortality from cardiovascular diseases will be the consequence.

Key Words: Lipid lowering, primary prevention, secondary prevention, statins.

Summary

Helena K. Gylling and Tatu A. Miettinen

Clinical experience: studies with HMG-CoA reductase inhibitors

Since 1994, five large clinical trials of the beneficial effect of statins on coronary disease have been published. These trials have revealed that extensive serum cholesterol reduction by HMG-CoA reductase inhibitors was followed by a marked reduction in clinical manifestations of arterial atheromatosis not only in coronary arteries, but also in cerebral, carotid and peripheral arteries. In spite of different statins, study populations and baseline cholesterol values, the relative risk reduction of coronary recurrences, 24-34%, was of similar magnitude in the different studies. In addition, statin treatment also reduced total mortality. There is, however, little information on non-responsiveness to statin treatment. An example of a possible genetic cause of non-responsiveness, as well as an example of a metabolic cause, i.e., high baseline cholesterol absorption and low synthesis, are presented. Long-term statin treatment increased serum plant sterol levels markedly, but the clinical relevance of this observation remains to be settled.

Key Words: Coronary artery disease, LDL cholesterol, HDL cholesterol, triglycerides, glucose, statin, serum cholesterol precursor sterols, serum plant sterols, stanol ester.

Summary

Colin Berry, Andrew Davie and John McMurray

Cost-effectiveness of statins in primary and secondary prevention of coronary heart disease

Coronary heart disease (CHD) remains a major cause of ill health and premature death worldwide. As a result, the healthcare costs and welfare costs for patients with CHD are substantial. Consequently, both the primary and secondary prevention of CHD are major objectives of healthcare systems worldwide. Recently, large, multicentre, clinical trials have consistently demonstrated that these objectives can be achieved through cholesterol-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) therapy.

In this article, the economic impact of statin therapies is reviewed. Cost-effectiveness analyses of results obtained from large, multi-centre, randomised, placebo-controlled trials of statin therapy both for the primary (e.g., The West Of Scotland COronary Prevention Study (WOSCOPS) and The AirForce Coronary/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPs)), and secondary (e.g., Scandinavian Simvastatin Survival Study (4S)) prevention of CHD have demonstrated that these interventions are cost-effective, and compare favourably to other healthcare interventions. Other cost-effectiveness analyses suggest both primary and secondary statin therapy can be cost-effective in both men and women, and in the elderly. Other analyses of different statin therapies have found that atorvastatin 10 mg, fluvastatin 20 mg, lovastatin 20 mg, pravastatin 20 mg, or simvastatin 10 mg are similarly cost-effective.

Healthcare providers must decide at what level of risk for future CHD events should statin therapy be introduced. Secondary prevention with statin therapy is very cost-effective, and is now generally recommended. The economic case for primary prevention of CHD with statin therapy is less clear. Although in many countries, including Scotland, primary prevention is currently recommended for individuals with an annual CHD risk of 3%, we and others take the view that primary prevention therapy with statins can also be cost-effective in individuals at lower risk (e.g., 2%).

Key Words: Statin, coronary heart disease, cost-effectiveness analysis, health economics, risk.

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