

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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The Role of Statins in Vascular Protection

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H&O Could you give a brief overview of the role of statins in vascular protection?

JM At the moment, the role of statins in vascular protection is one of huge potential rather than defined reality. We know how useful statins are in patients with ischemic heart disease, particularly those who have hyperlipidemia. The potential, I think, lies in using statins prophylactically to protect the vasculature in patients considered to be at risk with, for example, systemic inflammatory diseases.

H&O How was this potential role of statins discovered?

JM One of the first people to identify this role was James K. Liao, MD, of Harvard Medical School in Boston, Mass., who reported beneficial effects on vascular endothelial function following treatment with statins, without any measurable change in cholesterol levels. These benefits are commonly referred to as cholesterol-independent pleiotropic effects. Since those first papers in the late 1990s/early 2000s, there has been a plethora of studies, initially in vitro, and subsequently using animal models and human volunteers. These suggest that there are clear benefits on vascular endothelial function, which are independent of the effect of the statins on serum cholesterol. A study by Landmesser and colleagues in 2006, comparing simvastatin and ezetimibe (Zetia,

Merck/Schering-Plough), was particularly important. Despite an equivalent reduction in serum cholesterol, only simvastatin improved endothelial function.

H&O Has there been an understanding of the mechanism of action of statins in this regard?

JM The understanding of the mechanism of action of statins, outside their cholesterol-lowering action, is not completely understood. In addition to reducing cholesterol synthesis, inhibition of the mevalonate pathway prevents synthesis of isoprenoid intermediates including geranylgeranylpyrophosphate. Geranylgeranylation is important in the posttranslational modification of intracellular signaling proteins, including Rho GTPases. This mechanism underlies many of the pleiotropic effects including the ability of statins to stabilize endothelial nitric oxide synthase mRNA and increase nitric oxide biosynthesis. However, further work is required in statin pharmacology.

H&O Could you discuss the effect of statins on the coagulation system?

JM Statins favor fibrinolytic over prothrombotic mechanisms, and this may be particularly relevant at sites affected by atherosclerotic plaques, where thrombosis can be life-threatening. The mechanisms favoring fibrinolysis are multiple and, in addition, statins inhibit the generation of tissue factor. The latter has been demonstrated in monocytes, macrophages, and endothelial cells. Much of the research in this area has been performed in vitro, but there is evidence for similar effects occurring in animal studies (eg, in rabbits), as well as in small clinical trials in humans. Statins may also modulate platelet function by inhibiting their activation. Again, the mechanisms here are probably multiple, but would include statin-induction of nitric oxide and inhibition of thromboxane A₂ synthesis. This ability to inhibit platelet function has also been shown in both animal and human studies. Statins increase expression of tissue plasminogen activator (tPA),

the profibrinolytic molecule, while inhibiting plasminogen activator inhibitor (PAI)-1. This expression is seen in endothelial cells, macrophages, and smooth muscle cells, and the mechanism appears to be the inhibition of geranylgeranylation. Though the clinical scenarios in which the effects of statins on the coagulation system might be useful are still to be defined, these actions are important in protecting patients with ischemic heart disease due to atherosclerosis.

H&O What is the role of statins in the protection of the vascular endothelium?

JM The benefits statins confer on vascular endothelial function are still underutilized clinically. Many clinicians tend to think of statins as drugs confined to the treatment of patients with defined ischemic heart disease or hypercholesterolemia. However, they are increasingly used to protect patients with renal failure and diabetes mellitus against atherosclerosis. One of my particular interests is the potential role of statins in patients with systemic inflammatory diseases, such as systemic lupus erythematosus or rheumatoid arthritis, in whom endothelial dysfunction and accelerated atherosclerosis are common. I believe there is a role in these diseases for the protection of patients prophylactically. For instance, if a diabetic, or, indeed, a healthy person is treated with a statin, after 24–48 hours a marked improvement in flow-mediated dilatation, a measure of endothelial function, is apparent. This benefit is rapidly lost when the statin is withdrawn, and occurs independently of the effect on cholesterol synthesis. A similar effect has been reported in patients with rheumatoid arthritis and, if sustained, this may reduce the risk of cardiovascular death. Important mechanisms here would include statin-mediated induction of eNOS and inhibition of endothelin-1, a potent vasoconstrictor. I suspect we have plenty to learn regarding vasculoprotective actions of the statins, but we do know, from both animal and human studies, that these agents have clinically important benefits.

Another important action of the statins is their ability to modulate oxidative stress, a major contributor to endothelial dysfunction. Thus, statins are able to reduce the generation of superoxide and other free radicals, by inhibiting nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase.

H&O How do statins affect inflammatory responses?

JM Statins are important in the treatment of atherosclerosis, which is now recognized to be an inflammatory disease, based on research by Dr. Russell Ross and

others. There is emerging evidence to suggest that statins influence the inflammatory process. An example is the use of statins in transplantation medicine, where there is reasonably good evidence for their beneficial effects on preservation of cardiac transplants, through anti-inflammatory and immunomodulatory mechanisms; the benefit is less clear in renal transplantation. Statins are able to inhibit interferon-gamma–induced major histocompatibility complex (MHC) class II expression and subsequent T-cell activation. Furthermore, they modulate leukocyte-endothelial cell interactions. This is mediated via inhibition of chemokine release, and by reduced adhesion molecule expression on the endothelial cell surface, most reliably demonstrated using *in vivo* models. The consequence of this action is reduced leukocyte trafficking to sites of inflammation. Again, the underlying mechanisms are not fully understood here. There is an emerging literature showing that statins modify transcription factor activation. For example, statins can inhibit nuclear factor kappa-B and activating protein-1 (AP-1), typically pro-inflammatory transcription factors. In the last 3 years, statins have also been reported to increase the activity of Kruppel-like factor 2 (KLF2), an anti-inflammatory, cytoprotective transcription factor in the endothelium. This research is very intriguing and likely to yield further important insights into the vasculoprotective actions of statins. Finally, an interesting article by Weitz-Schmidt and colleagues, showed that lovastatin can bind directly to the leukocyte integrin LFA-1 (CD11a/CD18), inhibiting adhesion to its ligand intercellular adhesion molecule-1 (ICAM-1) and reducing leukocyte trafficking. This is an example of an anti-inflammatory action of statins that is independent of HMG-CoA reductase inhibition.

H&O What is the effect of statins on angiogenesis?

JM There is a good deal of data on the role of statins in angiogenesis, although this is somewhat conflicting. This may in part reflect a dose-response relationship. There are well-conducted studies showing that a low dose (eg, 10–20 mg) of atorvastatin, is proangiogenic and protective against apoptosis. Higher concentrations, achieved by the upper limit of therapeutic doses, tend to be proapoptotic and antiangiogenic. The use of statins as a clinical modifier of angiogenesis is still unproven. A great number of patients have been treated with these drugs, and if they were potently proangiogenic, one might expect to see an increased risk of tumors. However, there is no evidence that these drugs encourage tumor development. Likewise, there is no definitive evidence for an antiangiogenic, tumor-modulating action of statins. We await further studies with interest.

A related area of study is the ability of statins to mobilize endothelial progenitor cells. Treatment with statins increases the number of circulating endothelial progenitors, through a phosphoinositide-3 (PI-3) kinase-dependent pathway. This action is likely to be important during angiogenesis and vascular repair, and patients with atherosclerosis have reduced numbers of these cells in their circulation.

H&O What concerns regarding comorbidities exist with statins?

JM One of the major, though rare, side effects of statins is myositis or muscle inflammation. This side effect was responsible for the withdrawal from the market of cerivastatin, a statin particularly prone to inducing myositis. This may be a worry in the treatment of patients with systemic lupus erythematosus, for example, where myositis is a feature of the disease. There has been concern about the use of statins in these patients, who are prone to accelerated atherosclerosis. However, our clinical experience, and that of others, suggests that there is only a slight increase in the incidence of myositis among patients with systemic lupus erythematosus who require a statin. The statins are remarkably safe drugs, providing that they are started at low dose and gradually titrated and that the patients are carefully monitored.

H&O What are the future directions of research for statins in vascular protection?

JM There are a number of areas of research worth pursuing. In terms of the vascular endothelium, there are studies now ongoing in the United States and Europe, in which patients are being followed prospectively, to assess whether early treatment with statins reduces endothelial

dysfunction and protects against accelerated atherosclerosis. Regarding immunomodulatory and anti-inflammatory responses, further studies (some already ongoing) are required to assess the disease-modifying effects of statins, reported in small studies of patients with rheumatoid arthritis and multiple sclerosis. These will help answer the question of whether statins exert an important and measurable effect in this setting. In terms of benefits conferred on the coagulation system, there have not been many studies, apart from those researching atherosclerosis. In hematologic terms, it would be interesting to see whether the known effects of statins on the coagulation system can be translated into clinical practice. An improved understanding of the mechanisms underlying the pleiotropic actions of statins, will allow the development of more specific drugs, targeting individual pathways, thereby opening up new areas of therapy. For example, researchers are looking at farnesyltransferase inhibitors, aiming to optimize specific cholesterol-independent beneficial effects of statins.

Suggested Readings

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