Statins and Renal Diseases: From Primary Prevention to Renal Replacement Therapy

Giuseppe D'Amico

Department of Nephrology and Immunology, San Carlo Hospital, and Fondazione "D'Amico" per la Ricerca sulle Malattie Renali, Milan, Italy

In glomerular diseases with nephrotic syndrome or protracted severe proteinuria, alterations of the lipid metabolism occur and are characterized mainly by increase of LDL cholesterol and frequently also of triglycerides and by qualitative abnormalities of HDL cholesterol and LDL cholesterol. In all renal diseases, when renal insufficiency develops, hyperlipidemia also occurs, with a near-elective increase in VLDL and intermediate-density lipoprotein cholesterol and a decrease of mature HDL cholesterol. There is clear evidence that these abnormalities may induce cardiovascular complications and, probably, also an accelerated progression of the renal damage. The inhibitors of 3-hydroxy-3-methylglutaryl CoA reductase, the so-called statins, are effective in controlling hypercholesterolemia, even in the more advanced stages of renal failure and in patients who are on maintenance dialysis. This antilipidemic effect of statins combines with other effects—antioxidant, anti-inflammatory, immunomodulatory, and antithrombotic (called "pleiotropic" effects)—as a result of the inhibition of the mevalonate pathway induced by these agents. Also because of these non–lipid-dependent effects, statins could have an antiatherosclerotic and renoprotective effect, which has been demonstrated clearly *in vivo* on renal cells and in experimental models of nephropathy but is still less evident in human renal diseases. Ongoing large trials will establish more clearly whether such effects are present in renal patients.

J Am Soc Nephrol 17: S148–S152, 2006. doi: 10.1681/ASN.2005121341

Meta-analysis of the data of the literature reviewed all of the controlled trials on the effect of the various statins in hyperlipidemic patients and confirmed that all of these drugs are able to reduce dyslipidemia, although at different dosages (1). Moreover, it showed that statins can protect against the occurrence of cardiovascular events and stroke. The reduction of risk of ischemic heart disease events for a 1.0-mm/L decrease of LDL cholesterol concentration was 11% (4 to 18%) after 1 yr, 24% (17 to 30%) after 2 yr, 33% (28 to 37%) between the third and fifth years, and 36% (26 to 45%) after 6 yr or more (1). It now is universally accepted that the protective effect of this class of drugs is that it blocks the 3-hydroxy-3-methylglutaryl CoA reductase, so inhibiting not only the synthesis of cholesterol but also the mevalonate pathway and the synthesis of the so-called isoprenoids (farnesyl pyrophosphate and geranylgeranyl pyrophosphate) is not the simple consequence of the antilipidemic effect of the drugs (2–5). Isoprenoids are essential for the posttranslational modification of several proteins that are involved in important signaling pathways, such as the small GTP-binding proteins Ras and Rho, and their inhibition interferes with numerous important cellular functions, leading to many additional effects of the statins, called "pleiotropic." Because of this inhibition, statins protect the endothelial function (increased endothelial nitric oxide synthase expression and reduced endothelin-1 expression), act as antioxidants (inhibition of NAD[P]H oxidase, reduced superoxide formation, reduced LDL oxidation, and increased oxygen free radical scavenging), as anti-inflammatory agents (inhibition of proinflammatory cytokines, NF-κB activation, leukocyte–endothelial cell adhesion, and reduction of C-reactive protein), as immunomodulatory agents (reduced monocyte and T cell activation, inhibition of IFN-γ, and shift from TH_1 to TH_2), and as antithrombotic agents (reduced tissue factor expression and increased fibrinolytic activity), as reviewed recently by Mason (6,7).

It is highly probable that some of these effects of statins, together with their antilipidemic action, can be helpful in the treatment of proteinuric glomerular diseases as well as all renal diseases that induce chronic renal failure, including the terminal stage of maintenance dialysis. There is the rationale for a potential protective effect of these drugs on the rate of the progression of renal damage. However, the evidence still is insufficient, at least in humans. We briefly review the accumulated evidence, starting with the *in vitro* studies on cultured cells and the *in vivo* experimental models of renal diseases.

In Vitro Effects on Renal Cells and Leukocytes

Many studies have demonstrated the existence of non–LDL-dependent effects of statins on mesangial cells (8–17), on tubular cells (18–20), and, as already stressed, on endothelial vascular cells. These effects are potentially advantageous, especially in inflammatory glomerular diseases, because they could inhibit the cytokine activation network, proliferation,

Address correspondence to: Dr. Giuseppe D'Amico, Fondazione "D'Amico," per la Ricerca sulle Malattie Renali, c/o Ospedale San Carlo Borromeo, Via Pio II 3, 20153 Milan, Italy. Phone: +39-02-48705804; Fax: +39-02-40222222; E-mail: giuseppe.damico@scb.sined.net

ISSN: 1046-6673/1704-0148

production of extracellular matrix, glomerular sclerosis, and tubulointerstitial inflammatory processes.

Another inhibitory effect of statins was demonstrated recently on the proximal tubular cells of opossum (21) and of human (22): Inhibition of the receptor-mediated mechanisms of reabsorption of the proteins that reached the tubular lumen in physiologic and pathologic conditions. This inhibition, which can be reversed by mevalonate, may increase the urinary excretion of proteins, especially after administration of the more potent statins that usually are metabolized also at the renal level. As correctly stressed by Agarwal (23), we cannot say at the moment whether such effect is renoprotective (the reabsorptive load of proximal tubular cells, especially when abnormal amounts of high molecular weight proteins transit in the tubular lumen, may have an injuring effect on these cells) or toxic.

In Vivo Effects in Animal Models of Renal Disease

In 1990, the group of Klahr (24) demonstrated that the administration of 4 mg/kg per d lovastatin in rats with puromycin aminonucleoside–induced nephrosis reduced not only hypercholesterolemia but also histologic lesions (global sclerosis) while increasing inulin clearance; proteinuria was not modified. In a model of mesangial proliferative glomerulonephritis induced by anti–Thy-1 in rats, simvastatin (4 mg/kg per d), while reducing hypercholesterolemia, decreased proteinuria and serum creatinine, induced a 70% suppression of mesangial cell proliferation and of mesangial matrix expansion and type IV collagen synthesis, inhibited monocyte-macrophage recruitment in glomeruli, and reduced the PDGF-β chain protein and mRNA expression in glomeruli (25). In diabetic nephropathy that was induced by streptozotocin in rat, lovastatin (4 mg/kg per d) administration, started at day 1, reduced proteinuria at 3, 6, and 12 mo and suppressed the increase of TGF-β1 RNA in isolated glomeruli between 2 wk and 12 mo; all these effects were reversed by mevalonate (26). In the same experimental model, cerivastatin (0.5 mg/kg per d) reduced proteinuria and BP, decreased macrophage infiltration and intercellular adhesion molecule-1 expression in glomeruli, and partially suppressed renal NF-κB activity (27). Finally, in the same model of diabetic nephropathy, Qin *et al.* (28) demonstrated the protective effect of simvastatin (2 mg/kg per d) on proteinuria, histologic lesions (both glomerular and tubulointerstitial), and overexpression of TGF-β1 and vascular endothelial growth factor; all these effects were potentiated by the combination of the statin and losartan. In a model of unilateral ureteral obstruction in mouse, fluvastatin (10 or 40 mg/kg per d) but not pravastatin (10 mg/kg per d) reduced interstitial fibrosis, appearance of α-smooth muscle actin–positive myofibroblasts in the interstitium, and induction of heme oxygenase-1 mRNA 12 h after ligation of the ureter (29). In a rat model of chronic cyclosporine-induced nephropathy, pravastatin at two dosages (5 and 20 mg/kg per d) suppressed afferent arteriolopathy, striped interstitial fibrosis, and tubular atrophy; reduced the number of recruited macrophages, TGF-β1, and osteopontin mRNA; and increased endothelial nitric oxide synthase protein (30). Finally, in the rat transgenic for human renin and angiotensinogen (dTGR), cerivastatin (0.5 mg/kg per d), given from weeks 4 to 7, induced reduction (60%) of proteinuria, serum creatinine, and arterial hypertension and attenuated leukocyte infiltration and intercellular adhesion molecule-1 expression in the kidney (31).

It is worth stressing that the beneficial effects in these various animal models have been obtained with dosages that exceeded those of therapeutic use in human and with all of the available statins, independent of their prevalent hydro- or lipophilicity. Many of these effects seem to be independent of the cholesterol-lowering action of the drugs, related to an antioxidant, anti-inflammatory, immunomodulatory pleiotropic action.

Effects in Human Renal Diseases

Effects on Lipid Abnormalities and Cardiovascular Complications

Lipid abnormalities are present not only in patients with glomerular diseases and massive proteinuria (increase in LDL cholesterol, with a high proportion of dense LDL, and frequently also hypertriglyceridemia, but also in all chronic renal diseases with impaired renal function (discrete lipoprotein qualitative abnormalities in the earlier stages of renal insufficiency; a more evident near-elective increase in VLDL and intermediate-density lipoprotein cholesterol, with slightly increased LDL cholesterol characterized by a small dense LDL phenotype; and often a reduced HDL cholesterol, in patients with more severe functional impairment or on maintenance dialysis). These abnormalities increase the cardiovascular risk in patients with nephrotic syndrome (32). In chronic renal failure, the risk for cardiovascular complications also is very high, but it is more difficult to distinguish the role of dyslipidemia from that of the many other coexisting risk factors (*e.g.*, cardiomyopathy, high BP, fluid overload, anemia, vascular calcifications, hyperhomocysteinemia). This relative risk was 1.8 greater in the >6000 participants who participated in the Second National Health and Nutrition Examination Survey and had mild to moderate renal insufficiency (33). In another study in >1000 adults, adjusted risk was 3.4 greater in patients with GFR <15 ml/min than in patients with normal renal function (34). All statins induce a marked reduction of LDL cholesterol, and the most powerful statins even induce a marked reduction of triglycerides in patients with nephrotic syndrome (35). Clinical and pharmacokinetic studies have demonstrated that, even in patients who have chronic renal failure and are on maintenance dialysis, statins are well tolerated and effective, providing equivalent control of lipid levels to that seen in matched control subjects (36–40). In particular, pravastatin was able to reduce intermediate-density lipoprotein in patients who were on hemo- and peritoneal dialysis (41).

As for the protection that statins might provide from the cardiovascular complications as a result of these antilipidemic effects and eventually from their pleiotropic effects, the available data still are insufficient and controversial. Pravastatin significantly reduced the incidence of cardiovascular events, especially major coronary events, in the subgroup of 1711 patients who had chronic renal insufficiency (creatinine clearance

≤75 ml/min) and participated in the large Cholesterol and Recurrent Events (CARE) study (42).

A noncontrolled study of 3716 patients who were on dialysis in the United States demonstrated that the subgroup of patients who were using statins at baseline had a 36% reduced risk for cardiovascular-specific mortality (43). A more recent retrospective analysis of data from the Dialysis Outcomes and Practice Pattern (DOPPS) study on 17,221 patients who were randomly selected from representative dialysis facilities in France, Germany, Italy, Spain, the United Kingdom, Japan, and the United States demonstrated that patients who had been prescribed statins for any reason (11.8% of the total population) had a 23% lower relative risk for cardiac mortality and 31% lower risk for death (44). Three ongoing controlled clinical trials among patients with chronic renal disease, mainly dialyzed patients, presumably will give a more clear answer about the effect of statins on cardiovascular risk.

Effects on Renal Disease Progression

There now is much evidence that dyslipidemia can favor progression of renal damage both in diabetic and in nondiabetic diseases (45–52). A secondary analysis of the Modification of Diet in Renal Disease (MDRD) Study demonstrated that HDL cholesterol and triglyceride-rich lipoproteins were correlated with an unfavorable effect on the progression of renal disease (53). Also in the Atherosclerosis Risk in Communities (ARIC) study of 12,728 individuals who had baseline serum creatinine <2 mg/dl and were followed for 2.9 yr, high triglycerides and low HDL cholesterol predicted an increased risk for renal functional impairment (54).

In correcting dyslipidemia, statins, even independent of their additional pleiotropic protective effects on the renal and vascular system, should have a protective effect on the progression of renal damage. However, the evidence still is scanty. In patients with nephrotic syndrome, a mild protective effect is suggested by the meta-analysis of Fried *et al.* (55), who reported on 13 randomized trials of a small number of patients who were treated for short periods of time. More recently, Bianchi *et al.* (56), who reported on 56 patients who had chronic renal disease and were randomly assigned to atorvastatin or placebo for 12 mo, found that in treated patients, proteinuria was significantly reduced starting from the sixth month, and the rate of decline of renal function was lower at the end of the study. In a *post hoc* subgroup analysis of the large CARE randomized trial of pravastatin *versus* placebo, patients who had a calculated creatinine clearance <40 ml/min and were treated with the statin had a reduced rate of renal loss in comparison with nontreated patients, especially when their baseline proteinuria was elevated (57). Finally, in the controlled, randomized Greek Atorvastatin and Coronary Heart Disease (GREACE) study of dyslipidemic patients with coronary heart disease, a subgroup analysis reported that, whereas untreated patients showed a 5.2% decrease in creatinine clearance, treated patients had a 4.9% increase of clearance, and the difference was statistically very significant (58).

Conclusions

The statins, because of their antilipidemic effect and other pleiotropic lipid-independent effects, are potentially useful not only in controlling dyslipidemia in patients with renal disease but also in protecting them from the cardiovascular complications that are particularly frequent in these patients. Recent evidence does suggest that statin therapy also may have a renoprotective effect. However, large studies are needed and, in part, are already ongoing, to confirm these additional beneficial effects.

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