

# Statin Induced Proteinuria: Renal Injury or Renoprotection?

RAJIV AGARWAL

*Division of Nephrology, Department of Medicine, Indiana University School of Medicine, and Richard L. Roudebush VA Medical Center, Indianapolis, IN*

Meticulous blood pressure control, particularly with antiproteinuric medications, such as ACE inhibitors and angiotensin receptor blockers (ARBs), have proven to be effective in slowing the progression of kidney disease and are pillars in the modern management of chronic kidney disease (CKD). However, despite careful attention to blood pressure lowering and the use of ACEi and/or ARBs, progression of renal disease remains the rule. Furthermore, blood pressure control and renin angiotensin system (RAS) blockade has not been successful in reducing the extremely high incidence of cardiovascular disease in patients with CKD. Thus, an unfulfilled need exists for reducing progression of renal and cardiovascular disease patients with CKD. HMG-CoA reductase inhibitors (statins) represent a particularly attractive class of medications for CKD patients. Statins have dramatically improved cardiovascular outcomes in patients without significant kidney disease and may prove to have similar effects in patients with kidney disease. However, careful attention should be paid to some new data on the renal effects of statins.

Preclinical studies done with all statins have shown to produce renal tubular degeneration in high doses (1). Proteinuria commonly occurs with high dose statin therapy. Although this adverse effect has long been recognized, the phenomenon resurfaced as a result of clinical trials conducted with a highly potent statin, rosuvastatin. With the highest dose of rosuvastatin tested in clinical trials (80 mg) a high incidence of proteinuria and hematuria was seen and was accompanied by isolated cases of renal failure some of which were associated with myopathy (2). The 80 mg dose of rosuvastatin was not approved by the FDA for clinical use. Nevertheless, an interest into the mechanism of this phenomenon of proteinuria was kindled.

Receptor mediated endocytosis (RME) is the process that is responsible for albumin uptake in proximal tubular cells. RME of proteins in the proximal tubules occurs via megalin and cubulin receptors (3) requires the presence of prenylated GTP binding proteins. Statins reduce the activity of mevalonate, which is required for the generation of isoprenoid pyrophosphates. Isoprenoid pyrophosphates are required for prenylation

of GTP binding proteins and can impair RME. Sidaway *et al.* performed experiments in cell cultures of proximal tubular cells derived from the opossum kidney to test the hypothesis that statins reduce RME by reduced prenylation of GTP binding proteins (4).

The following set of observations made by Sidaway *et al.* support the hypothesis that statins reduce albumin uptake by RME (4). First, there was a dose dependent reduction in RME. Second, the degree of inhibition in RME was related to the *in vitro* inhibition of HMG-CoA reductase that was related to the lipophilicity of the statin. Thus, the IC<sub>50</sub> of simvastatin in reducing cholesterol synthesis was <1/50th that of pravastatin, and predictably simvastatin produced greater impairment in RME. Third, the reduction in RME was not related to binding of albumin to the receptor but receptor mediated albumin endocytosis and was shared by other proteins such as  $\beta_2$ -microglobulin.

What was the mechanism of reduction in RME? The authors provide evidence that impairment of prenylation of GTP-binding proteins may be etiologically related to reduced RME. Inhibition of RME was associated with the time-dependent appearance of unprenylated Rap1A, a GTP-binding protein. Second, the impairment in RME was reversed by the addition of mevalonate and by the addition of the isoprenoid, geranylgeranyl pyrophosphate. Third, RME was impaired independently by reduction of prenylation induced by the addition of farnesyl and geranylgeranyl transferase inhibitors. Finally, addition of cholesterol did not correct the impairment in RME providing further evidence that RME was not impaired due to reduction in cholesterol synthesis but as a direct result of prenylation of GTP-binding proteins.

Whether the above phenomenon is replicated in human kidney cells was evaluated by Verhulst *et al.* (5). In primary cultures of human kidney cells harvested from the intact kidney region of cancerous kidneys, the authors demonstrated RME by microscopy, flow cytometry, and spectrofluorometry in the proximal tubular cells that was inhibited in a dose-dependent way by statins (simvastatin > rosuvastatin > pravastatin) without altering cell viability. Mevalonate reversed the impairment of RME induced by statins.

These data provide a mechanism for the occurrence of proteinuria with rosuvastatin. Gel electrophoresis of urine in patients receiving rosuvastatin showed a “tubular pattern”, which was confirmed by increased levels of low-molecular-weight proteins such as  $\alpha_1$ -microglobulin,  $\beta_2$ -microglobulin, and retinal binding proteins, that also undergo RME (1). Back titration showed greatest reductions in low-molecular-weight

Correspondence to Dr. Rajiv Agarwal, VAMC, 111N, 1481 West 10<sup>th</sup> Street, Indianapolis, IN 46202. Phone: 317-554-0000 x2241; Fax: 317-554-0298; E-mail: ragarwal@iupui.edu

1046-6673/1509-2502

Journal of the American Society of Nephrology

Copyright © 2004 by the American Society of Nephrology

DOI: 10.1097/01.ASN.0000143720.71748.79

proteins. The occurrence of proteinuria with rosuvastatin may be related to 28% of the systemic clearance by renal route by predominantly tubular secretion together with its high potency of HMG-CoA reductase inhibition (1). For other statins, the degree of renal excretion and HMG-CoA reductase inhibition is less than that observed with rosuvastatin. Although these set of studies provide important data on the mechanism of proteinuria seen with statins, the *in vitro* data in cell cultures are incapable of explaining the occurrence of hematuria that also accompanies the use of high dose rosuvastatin. To investigate the occurrence of hematuria will require intact animal models.

Preclinical data show increased protein trafficking to be associated with tubulointerstitial disease (6) and clinical trials have found an association of reduction in proteinuria and improved renal outcomes (7). Statins, unlike ACE inhibitors and angiotensin receptor blockers, increase protein excretion by reducing RME. Thus, is it possible that statins will be deleterious for the kidney? It would be prudent to monitor renal function and protein and RBC excretion at baseline and periodic intervals when using higher doses of rosuvastatin in particular and statins in general especially when used in patients with CKD. Although there are no definitive human trials to suggest renal protection with statins, a meta-analysis of randomized trials suggests that statins may be renoprotective (8).

Data presented by Verhulst *et al.* and Sidaway *et al.* provides a unique tool to assess the hypothesis if proteinuria is itself damaging to the kidney. In spite of increase in protein excretion, due to reduced protein trafficking across the proximal tubular cells, statin use may be associated with less inflammation, endothelial dysfunction and tubulointerstitial fibrosis. Statins may be thus be associated with renal protection in spite of increased protein excretion and may provide an example of a class of drugs that confers renal protection despite increased proteinuria. The *in vitro* experiments of Sidaway *et al.* and Verhulst *et al.* thus pave the way for *in vivo* experiments to test the above hypothesis.

The use of the combination of simvastatin and azetimibe in patients with CKD to prevent progression of renal disease and cardiovascular outcomes are currently under way. The AURORA study (A study to evaluate the Use of Rosuvastatin in subjects On Regular hemodialysis: an Assessment of sur-

vival and cardiovascular events) is a placebo-controlled, double-blind study using 10mg rosuvastatin in hemodialysis patients. Launched in early 2003, the study will enroll approximately 3000 patients, aged 50-80 years, in almost 20 countries in Europe, North America, and Australia. Mortality and cardiovascular events will be the primary endpoints. The AURORA study is expected to be completed in May 2007. The ability to potentially inhibit the HMG-CoA reductase enzyme in the proximal tubule with rosuvastatin provides us with another important drug to study the renoprotective effect of statins.

## References

1. Department of Health and Human Services. Food and Drug Administration Center for Drug Evaluation and Research. Endocrinologic and Metabolic Drugs Advisory Committee. July 9, 2003. (<http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3968T1.doc> accessed July 5, 2004)
2. Advisory Committee Briefing Document. Pharmacology/Toxicology. NDA 21-366 Crestor July 9, 2003. ([http://www.fda.gov/ohrms/dockets/ac/03/briefing/3968B1\\_02\\_FDA-PharmTox%20Review.pdf](http://www.fda.gov/ohrms/dockets/ac/03/briefing/3968B1_02_FDA-PharmTox%20Review.pdf) accessed July 5, 2004)
3. Christensen EI: Pathophysiology of protein and vitamin handling in the proximal tubule. *Nephrol Dial Transplant* 17 [Suppl 9]: 57–58, 2002
4. Sidaway J, Davidson R, McTaggart F, Orton T, Scott R, Smith G, Brunskill N. Inhibitors of 3-Hydroxy-3-Methylglutaryl-CoA Reductase Reduce Receptor-Mediated Endocytosis in Opossum Kidney Cells. *J Am Soc Nephrol* 15: 2258–2265, 2004
5. Verhulst A, D'Haese P, DeBroe M. Inhibitors of HMG-CoA reductase reduce receptor-mediated endocytosis in human kidney proximal tubular cells. *J Am Soc Nephrol* 15: 2249–2257, 2004
6. Abbate M, Zoja C, Corna D, Capitanio M, Bertaini T, Remuzzi G: In progressive nephropathies, overload of tubular cells with filtered proteins translates glomerular permeability dysfunction into cellular signals of interstitial inflammation. *J Am Soc Nephrol* 9: 1213–1224, 1998
7. De Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, Snapinn S, Cooper ME, Mitch WE, Brenner BM: Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: Lessons from RENAAL. *Kidney Int* 65: 2309–2320, 2004
8. Fried LF, Orchard TJ, Kasiske BL: Effect of lipid reduction on the progression of renal disease: A meta-analysis. *Kidney Int*. 59: 260–269, 2001

See related articles, “Inhibitors of 3-Hydroxy-3-Methylglutaryl-CoA Reductase Reduce Receptor-Mediated Endocytosis in Opossum Kidney Cells,” on pages 2258–2265; and “Inhibitors of HMG-CoA Reductase Reduce Receptor-Mediated Endocytosis in Human Kidney Proximal Tubular Cells,” on pages 2249–2257.