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An overview of statin-associated proteinuria

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Statins are an established therapeutic modality for the treatment of hypercholesterolemia. Although they generally exhibit a good efficacy and tolerability profile, their reputation has been tarnished as a result of reports of myotoxicity and, more recently, observations of proteinuria. The increased incidence of proteinuria with rosuvastatin was of particular concern, and raised questions about the renoprotective actions of statins. Different hypotheses have been put forward to explain the mechanisms of statin-induced proteinuria. The multifarious effects of statins, independent of their effects on cholesterol-lowering, form the basis of such hypotheses. However, rosuvastatin-associated proteinuria is transient and reversible and even at the highest dose did not affect renal function after prolonged treatment. It would appear that clinically relevant proteinuria is not associated solely with rosuvastatin and might represent a minor class effect of statins with a fairly low incidence. However, definitive proof of this assertion will need to be provided by rigorous testing.

The advent of hydroxymethylglutaryl-coenzyme-A (HMG-CoA) reductase inhibitors (popularly referred to as statins) has revolutionized the treatment of hyperlipidemia and dyslipidemia by providing an important and effective approach for lipid management. Hyperlipidemia is associated with increased low-density lipoprotein cholesterol (LDL-C), which is a risk factor for atherosclerosis and coronary heart disease (CHD). Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis, thereby reducing cellular sterol and LDL-C levels. Hypercholesterolemia and atherosclerosis are chronic conditions that require long-term treatment with statins. Therefore, it is imperative that statins exhibit a clean safety and tolerability profile. Clinical trials have established that statins are well-tolerated and effective in reducing cardiovascular risk, regardless of CHD history. However, side effects are a major reason for withdrawal of people from statin treatment in the first eight months [1,2].

Most of the therapeutically beneficial effects of statins have been assumed to result from inhibition of cholesterol synthesis, and subsequent reduction in its serum concentration. However, several preclinical studies suggest that statins have biological effects that are independent of their ability to lower serum cholesterol levels. These cholesterol-independent effects might be due to a reduction in the formation of various intermediates involved in the mevalonate pathway. A variety of statin-induced effects, such as their anti-inflammatory properties in atherosclerotic plaques, antiproliferative effects in vascular smooth muscle atherogenesis, anticoagulation effects [limiting thrombosis and improving vascular endothelial function through the augmentation of nitric oxide (NO) generation] are of particular interest [3]. Statins also exhibit various immunomodulatory, anti-inflammatory, osteogenic and anticancer effects, suggesting that they could have a role in treating rheumatoid arthritis [4], osteoporosis [5], cancer [6] and renal failure [7].

The withdrawal of cerivastatin from the market in August 2001 as a result of the unacceptable incidence of rhabdomyolysis and death has raised serious concerns about the safety profile of statins [8]. Recently, rosuvastatin-associated kidney damage has further increased concerns related to this class. The rate of reported kidney damage is ~75 times higher with rosuvastatin than for all other drugs in the same class combined (www.citizen.org/publications/release.cfm?ID=7341). The incidence of proteinuria, although not claimed to be significantly different from other statins, was considerably higher and dose dependent in case of rosuvastatin [9].

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This raised doubts as to whether some of the multifarious effects of statins might be problematic.

Proteinuria

Proteinuria is defined as abnormal loss of protein in the urine, and is recognized as a hallmark of renal disease. Urine is formed by ultrafiltration of plasma by the kidneys. Kidneys filter large volumes of plasma, retain plasma proteins and selectively reabsorb from or secrete into the filtrate. The importance of kidneys in the process of ultrafiltration can be gauged from the fact that they receive one-fifth of the cardiac output of the blood i.e. one litre per minute. The modification in the composition of the filtrate by reabsorption or secretion into the tubular system can impact glomerular filtration rate (GFR), which is regulated by crucial factors (Box 1). Proteinuria is also a feature of nephrotic syndrome, a kidney disease in which the glomeruli are damaged. Glomerulonephritis (inflammation of the glomeruli of the kidneys) can result in reduced GFR and a significant loss of albumin (~10 g or more per day) giving rise to the condition more precisely referred to as albuminuria. The steady loss of protein eventually leads to a serious reduction in blood albumin levels (hypoalbuminaemia). Albuminuria and proteinuria cause an appreciable drop in the plasma colloid osmotic pressure, which is responsible for retaining fluid in the capillaries throughout the body. This results in oedema, caused by fluid leaking from the circulation into the interstitial space. Persistent oedema can cause salt retention in the kidney and can result in heart failure.

On the basis of its origin, proteinuria can be categorized as glomerular, tubular or mixed in nature [10] (Table 1). Patients with proteinuria can be asymptomatic or symptomatic (i.e. for signs of renal disease). Furthermore, proteinuria can be persistent or transient, and action needs to be taken in the case of persistent proteinuria. The clinical diagnosis takes into account the pattern, composition and degree of proteinuria. Individuals with persistent proteinuria have elevated risk of cardiovascular disease and premature mortality compared with those with transient proteinuria.

Dyslipidemia and renal function

Renal function decline in healthy human beings starts after maturity and manifests as GFR decreasing by 8–10 ml/min/1.73 m^2 per decade at 40–60 years age, from a normal rate of 125 ml/min/1.73 m^2 in an average human adult. In addition, a large proportion of the population suffers from chronic renal failure and associated disorders (renal insufficiency) and end-stage renal diseases. According to US Renal Data System, 2003, nearly 392,000 people suffer from end-stage renal diseases per year, and nearly 67,000 die per year because of it, in the USA, with a prevalence rate of. Current prevalence is 0.14%, which is expected to increase because of a growing geriatric population and the associated co-morbidities, such as hypertension and diabetes. In addition, immune and nonimmune mechanisms are important contributors in the development of nephritis, progressive renal injury and renal failure. Proteinuria, hypertension and dyslipidemia are nonimmune risk factors implicated in the deterioration of kidney function [11]. Dyslipidemia can contribute to the development of glomerulosclerosis, in addition to ischemic heart disease, in patients with renal disease [12]. Patients with renal disease commonly exhibit quantitative and qualitative changes in lipoproteins [13]. In addition, the changes in blood lipid levels also accelerate the decline in renal function, as is evident from the Helsinki Heart Study [14]. Therefore, treatment of dyslipidemia by effective control of proteinuria and blood pressure is imperative for amelioration of renal dysfunction and protection from vascular diseases. Because of their good efficacy in lipid management and good tolerability, statins are of considerable interest for the treatment of patients suffering with hyperlipidemia associated with various renal abnormalities. These include renal nephritis, hyperuremic patients on continuous ambulatory peritoneal dialysis, renal transplant recipients and patients with unremitting nephritic syndrome [7,15].

BOX 1

Glomerular filtration of proteins: critical factors

Urine formation involves three main processes: glomerular filtration, tubular reabsorption and tubular secretion. Glomerular filtration involves the filtration of water and small molecules while retaining blood cells and most of plasma proteins. The semipermeable nature of glomerular capillaries and Bowman's capsule, in conjunction with hydrostatic pressure and osmotic pressures, allows the selective filtration of plasma components. The filtration barrier allows the free passage of substances based on size exclusion and ionic charge. Fixed negative charges, probably on basement membranes and podocyte cell membranes, cause negatively charged albumin to be retained and not filtered into tubules. The fluid that filters into Bowman's capsule is therefore more-or-less protein-free and exhibits similar composition to blood except for the absence of blood cells and proteins. The difference between the hydrostatic pressure and osmotic pressures in the glomerular capillaries and in the lumen of the Bowman's capsule defines glomerular filtration rate (GFR). In an average human adult, GFR is approximately 125 ml/min (180 l/day). Because the total volume of plasma is about three litres, the entire plasma volume is filtered about 60 times every 24 h. GFR is also dependent on the permeability of the filtration barrier and the filtration surface area.

GFR is measured by any substance that is filtered freely and neither secreted nor reabsorbed by the nephron. Inulin, a polymer of fructose, is such substance, which is used to estimate GFR by intravenous infusion. However, in clinics, serum creatinine and creatinine-clearance rate are the most commonly used methods for the estimation of glomerular filtration rate, and hence renal functions. Creatinine is an endogenous substance that is primarily filtered, not secreted, and reabsorbed from the kidney, and can therefore be readily used as an estimate of GFR. However, creatinine clearance, used as an overall and more precise estimate of renal function, is defined as the volume of blood that is cleared of creatinine per time period. The normal value for a healthy adult is 120 ml/min. Creatinine clearance is inversely related to serum creatinine and hence poor renal function.

Assuming a normal GFR of 125 ml/min, approximately 7.5 l of urine per hour or 180 l per day is filtered. In normal conditions, each litre of blood carries 45 g of albumin. Therefore, nearly 8100 g of albumin-carrying plasma is filtered every day. Of about 45 g of albumin per litre, only 0.2 g is filtered. Therefore, nearly 36 g of albumin is filtered into tubular secretion and reabsorbed completely in tubules. The substances filtered at the glomerulus into the tubule subsequently undergo tubular reabsorption and secretion.

Statins and urinary protein excretion

Increased urinary protein excretion is an important risk factor for cardiovascular and renal morbidity and mortality. Statins, due to their pivotal role in the management of dyslipidemia, have been

TABLE 1

Types of proteinuria based on their origin

Property	*Glomerular*	*Tubular*	*Mixed*
Characterized by	Loss of moderate and high Mr proteins (~30 times greater than normal)	Loss of low Mr (<50 kDa) proteins	Mixed in nature; Primarily drug induced
Characteristic proteins	Albumin (~10 fold more than normal); IgG (~250 fold more than normal)	β_2-Microglobulin, retinol binding protein, lysozyme, α_1-acid glycoprotein, Immunoglobulin light chains	Both high and low molecular weight proteins e.g. immune complexes
Etiologies	Systemic diseases (amyloidosis, carcinoma, lymphoma, multiple myeloma); Congenital nephritic syndrome, renal transplant rejections; Infectious diseases (malaria, hepatitis B, syphilis), diabetes	Systemic diseases (Wilson's disease, galactosemia, Balkan nephropathy, systemic lupus eryhtromatosus); Congenital anomalies (Fanconi syndrome, Bartter's syndrome, polycystic kidney disease); Sepsis and acute renal diseases	Immune complex formation stimulatory drugs (trimethadione, lithium, d-penicillamine); Non-denatured antibody inducing drugs (hydralazine, griesofulvin, α-methyldopa); Anaphylactic agents; Drugs with direct toxic action on renal tubules; (aminoglycosides, cyclosporine); Drugs causing interstitial nephritis (phenindione, phenacetin)
Crucial factors	Altered glomerular permeability in terms of increased pore size, number of pores and changes in the charge of the glomerular basement membrane	Impairment of tubuler reabsorption	Exercise, metabolic state of patients, renal transplant rejection, trauma, chronic renal failure

investigated for their ability to regulate urinary protein excretion. Simvastatin was reported to decrease the urinary albumin excretion rate in hypercholesterolemic nondiabetic patients [16] and normotensive microalbuminuric hypercholesterolemic type 2 diabetic patients [17]. Consequently, it was hoped that statins would provide an additional means of preventing renal dysfunction in hypercholesterolemic patients. However, no significant changes in GFR and urinary albumin excretion rate were observed in type I and type II diabetic patients with microalbuminuria and hypercholesterolemia after longterm simvastatin treatment [18,19]. In animal models of renal disease, lovastatin reduced proteinuria and the degree of glomerulosclerosis [20]. However, lovastatin treatment in patients with unremitting nephrotic syndrome (heavy proteinuria with hyperlipidemia) for six months was unable to change proteinuria and renal albumin clearance. The GFR was unaltered in these patients, but was increased (118.2 ml/min/1.73 m^2) at the end of six months of treatment in patients with relatively good pretreatment renal function (>70 ml/min/1.73 m^2) [21]. In a randomized clinical trial, pravastatin treatment for six months in proteinuric patients significantly reduced proteinuria by 54% compared with baseline values [22]. However, recently, in the PREVEND (prevention of renal and vascular end stage disease) intervention trial in microalbuminuric subjects, pravastatin (40 mg) did not result in a significant reduction in urinary albumin excretion [23]. Other clinical findings indicated that fluvastatin could cause hematuria (blood in the urine), proteinuria and rhabdomyolysis in a hyperlipidemic patient [24]. Contrary to this, a reduction in the urinary albumin excretion rate has been reported in nephrotic patients [16], proteinuric type 2 diabetes patients [25], as well as in moderately proteinuric patients with immunoglobulin A nephropathy [26] following longterm treatment with statins. As a result of these contradictory clinical observations, longterm and comparative studies are required to ascertain the role of statins in urinary protein excretion.

Rosuvastatin: in focus

Rosuvastatin (Crestor®, AstraZeneca; licensed from Shinogi and Co.) was the first statin approved by regulatory authorities following the withdrawal of cerivastatin in August 2001. Rosuvastatin is highly effective in reducing LDL-C and raising high-density lipoprotein cholesterol (HDL-C) and, as such, is of great value in assisting patients to attain normocholesterolemia. The efficacy, safety and tolerability of rosuvastatin have been evaluated in several longterm, multicentre clinical trials at doses ranging from 5 to 80 mg in subjects with hypercholesterolemia [27], hypertriglyceridemia [28] and hyperlipidemia [29]. The typical licensed dose of rosuvastatin for the treatment of hypercholesterolemia and associated morbidities is between 10 and 40 mg/day. The usual recommended starting dose of rosuvastatin is 10 mg/day. The 80 mg dose of rosuvastatin has been associated with severe side effects, especially myopathy and urine abnormalities. This dose was indicated solely for use in patients with severe hypercholesterolemia and for those with marked CHD risk (e.g. heterozygous familial hypercholesterolemia).

What was surprising with rosuvastatin were the urine abnormalities, specifically proteinuria and hematuria, which had not been reported previously with this class of drug. This raised concerns with respect to the safety of statins and demanded a thorough investigation of the presumed drug effect on the kidney. Moreover, it paved the way to discussion and investigation as to whether urine abnormalities, specifically proteinuria, are a class effect or specific solely to rosuvastatin.

Rosuvastatin and proteinuria

Twelve percent of patients receiving 80 mg rosuvastatin experienced an increase in dipstick proteinuria of ≥2 [30]. Although the proteinuria appeared to be transient and not associated with impaired renal function, it was sufficient to cause concern for the regulatory agencies. The renal failure of two patients receiving

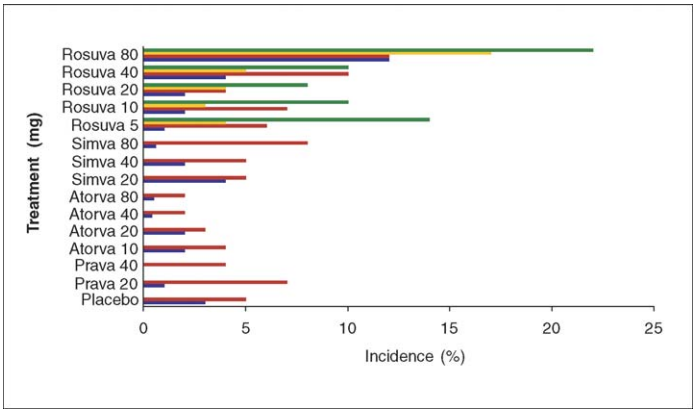

FIGURE 1

Incidence of proteinuria and hematuria in controlled, uncontrolled and RTLD pools. The data include only patients with an increase of at least one protein category above baseline. Key: blue, urine dipstick proteinuria ≥(++); red, urine dipstick hematuria ≥(+); yellow, (samples from open-label extension trials) urine dipstick proteinuria ≥(++); green, (samples from open-label extension trials) urine dipstick hematuria ≥(+). Data taken from the FDA AV_LBUR.xpt data file (of controlled, uncontrolled and RTLD data) 20 May 2003.

a dose of 80 mg/day of rosuvastatin in the STELLAR (statin therapies for elevated lipid levels compared across doses to rosuvastatin) trial further alarmed the regulators [31]. Pooled analysis of data from controlled clinical trials in an attempt to make comparative assessment of the renal effects of rosuvastatin (5–40 mg/day) with atorvastatin (10–80 mg/day), simvastatin (10–80 mg/day), pravastatin (10–40 mg/day) or placebo demonstrated positive proteinuria results by dipstick testing [30,32]. The FDA performed a comparison of the occurrence of dipstick proteinuria and hematuria across all statins included in trials in the rosuvastatin clinical development program. The most current urinalysis data (Figure 1) identified patients with at least a (++)-grade of proteinuria and patients with urine dipstick positive hematuria of ≥(+)-grade. The data indicates an increase in dipstick-positive proteinuria and hematuria at a dose of rosuvastatin of 80 mg/day. There is a trend suggesting an intermediate effect at 40 mg/day, whereas the 20 mg/day and lower doses have levels that are similar to the range observed with other statins and, most notably, with placebo groups (www.fda.gov/ohrms/dockets/ac/03/briefing/3968b1.htm). Although the incidence of (++)-grade proteinuria with atorvastatin (10–80 mg/day), rosuvastatin (5–40 mg/day), simvastatin (20–80 mg/day) and pravastatin (20 and 40 mg/day) were not significantly different from placebo (3%), rosuvastatin (80 mg/day) demonstrated a relatively higher incidence (12%) compared with placebo. Compared with other statins, a significant increase of 26% ('none or trace' to ≥1+) and 10.3% ('none or trace' to ≥2+) in proteinuria (detected by shifts in protein-dipstick categories) was also observed in Phase III studies of rosuvastatin in subjects receiving a dose of 80 mg/day (www.fda.gov/cder/foi/nda/2003/21-366_Crestor.htm).

Polyacrylamide gel electrophoresis data demonstrated a predominance of low molecular weight proteins (molecular weights lower than albumin), suggesting reduced tubular reabsorption of normally filtered proteins. This was in contrast to the detection of high molecular weight proteins observed during glomerular leakage. The identification of β_2-microglobulin and *N*-acetyl-β-d-glucosaminidase (NAG) in the urine of some subjects treated with rosuvastatin who had at least a (++)-category shift in urine dipstick proteinuria, further confirmed it to be tubular rather than glomerular in origin. Of the other renal functions examined, serum creatinine levels were essentially unchanged in placebo and rosuvastatin group. Furthermore, renal function, as assessed by mean GFR, did not deteriorate in patients who received longterm (≥96 weeks) rosuvastatin treatment at any dose, irrespective of age, gender, hypertensive or diabetic status, level of renal function at baseline or presence of a positive result for proteinuria before or during the period of treatment [32]. The beneficial effects on the progression of renal disease could be explained by the lipid reduction (reduction in LDL-C by 46–51% from baseline) achieved with a 10 mg/day dose of rosuvastatin [33]. This highlights that, despite proteinuria, prolonged treatment with rosuvastatin does not cause renal impairment in itself. Simultaneously, this in-part confirmed the renoprotective status of statins, although the increased incidence of proteinuria remains a moot point.

Stain-associated proteinuria

The mechanisms by which statins affect proteinuria remain undefined. The highly desirable renoprotective effects of statins with respect to reduced albumin excretion have to be tempered by the observed increased incidence of proteinuria seen with rosuvastatin. Several hypotheses have been put forward to explain the mechanism of statin-induced proteinuria.

Nonlipid functions of statins: focus on receptor-mediated endocytosis

Statins exert a range of effects on cells not related to cholesterol homeostasis. These include proliferation [34], signal transduction [35] and apoptosis [36], each of which results in a wide range of physiological consequences. Most of these effects stem from depletion of mevalonate and its nonsterol metabolites, particularly isoprenoid pyrophosphates, such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). Isoprenoids have an important role in the posttranslational modification of various cellular proteins, including the small GTP-binding protein superfamily [37,38]. GTP-binding proteins have been implicated in a multitude of cellular functions related to receptor-mediated endocytosis (RME) [39]. These include control of membrane trafficking [40], formation of endocytic vesicles [41], transcytosis [42], fusion of secretion granules with the plasma membrane [43] and cross-talk between different signalling networks related to endocytotic trafficking of receptors [44].

RME is a process that is responsible for protein uptake in proximal tubular cells. It is mediated by multiple-ligand endocytic receptors megalin (glycoprotein 330) and cubilin, which are expressed in high concentrations on the apical surface of renal proximal tubules [45]. Megalin, a member of the low-density lipoprotein receptor family, is a type I transmembrane protein that binds several ligands, such as apolipoproteins B, E and J/clusterin (apo J), lipoprotein lipase and Ca^{2+} [45,46]. By contrast, cubilin, a 460 kDa peripheral membrane glycoprotein binds intrinsic factor-cobalamin, immunoglobulin light chains, albumin, apolipoprotein A-1 (apo-A1), Ca^{2+} and megalin [47,48]. In the process of ligand uptake, megalin can mediate the endocytosis of a complex of cubilin and ligand [49].

The endocytosis of the ligand–cubilin complex, and the subsequent intracellular trafficking mediated by megalin and transcytosis

to lysosomes is regulated by G proteins, including GTPase-activating proteins (GAP), regulators of G-protein signaling (RGS), small molecular weight GTPases such as Rab5/Rab7 proteins and so on. [50,51]. The activity of various G proteins, such as Rho, Rac and several members of the Rab family, is further controlled by their prenylation [52]. Therefore, it is plausible that statins, by affecting the activity of GTP-binding proteins, might impair receptor mediated endocytosis and hence protein reabsorption by proximal tubular cells, which might be responsible for the observed proteinuria.

This hypothesis was supported by Sidaway *et al.* [53], who demonstrated the inhibition of uptake of albumin and β_2-microglobulin in an opossum kidney cell line (OK) by statins (fluvastatin, simvastatin, atorvastatin, rosuvastatin and pravastatin). The results indicated that the inhibition of protein uptake was related to the degree of inhibition of HMG-CoA reductase. The addition of mevalonate prevented the inhibition of albumin uptake by atorvastatin and rosuvastatin. Similar findings have been reported in human proximal tubular cells [54]. The results suggested that statins, as a result of HMG-CoA inhibition, cause the depletion of geranylgeranyl pyrophosphate or one of its products, which are crucial to protein reabsorption during the early stages of endocytosis. Taken together, these observations support an undescribed class pharmacological effect of statins on proximal tubular protein reabsorption. The findings from this *in vitro* study and the clinical trials of rosuvastatin suggest that the statin-associated proteinuria did not indicate a renal toxic effect either of statins in general or of rosuvastatin in particular.

Contrary to this hypothesis, several aspects related to proteinuria remain unexplored and need further investigation. An important aspect of great relevance is that rosuvastatin is a highly potent HMG-CoA reductase inhibitor in hepatocytes compared with other comparator statins. The rank order of hepatoselectivity (i.e. selective inhibition of cholesterol synthesis in liver over extrahepatic tissues) over tubular cells for various statins is as follows: rosuvastatin $\gg$ pravastatin $\approx$ atorvastatin $>$ simvastatin $\approx$ fluvastatin (Table 2). Hepatoselectivity is an important index that can be used to establish the safety of statins, especially in the context of myotoxicity [55]. The high hepatoselectivity of rosuvastatin, associated with poor uptake into tubular cells, would seem to make it unlikely for it to cause proteinuria. Furthermore, if that was the situation, then simvastatin and fluvastatin, owing to their moderate potency, high uptake into kidney cells due to passive diffusion, poor hepatoselectivity and potent inhibition of the albumin uptake, would be expected to have a greater propensity than rosuvastatin to affect protein reabsorption, and hence cause proteinuria. However, the findings from comparative clinical trials paint a totally different picture. The implications are that there are other confounding factors, which might be responsible for statin-associated proteinuria.

Alternative possible mechanisms

Rosuvastatin, owing to its high potency and unusually high systemic exposure at a dose of 80 mg/kg in humans (C_{max} 30 ng/ml, compared with 10.3 ng/ml at 40 mg dose) [56], might impair tubular reabsorption of proteins in the kidney. At doses of $\leq$40 mg/day, the rate of proteinuria with rosuvastatin was within the range observed with other statins and, notably, placebo. A correlation of rosuvastatin plasma concentration and serious adverse events was performed with a limited clinical dataset. Few patients treated with rosuvastatin at 40 mg/day (2%) and a greater proportion of patients treated with 80 mg/day (33%) achieved a steady-state plasma drug concentration (>50 ng/ml). This analysis suggests a potential threshold in the drug level at which risks of renal toxicity are increased (www.fda.gov/ohrms/dockets/ac/03/briefing/3968B1_02_A-FDA-Clinical%20Review.pdf). The increased systemic exposure of rosuvastatin, combined with its high potency and renal excretion (10%), could explain the relatively high incidence of proteinuria at doses of 80 mg/day. Pravastatin, at the marketed doses of 10–80 mg/day, also exhibits appreciable renal excretion (20%), but might not have significant effects on the tubular reabsorption of proteins, because it is not such a potent inhibitor of cholesterol synthesis as rosuvastatin.

Impaired endosomal acidification caused by drug accumulation could be an alternative hypothesis for statin-associated proteinuria. Endocytic uptake and transfer to lysosomes depends on endosomal acidification, maintained by H^+-ATPase coupled to a chloride conductance channel. The voltage-gated chloride channel ClC-5 is almost exclusively expressed in kidney-proximal tubular cells and is localized in endosomes. The importance of lysosomal acidification in low molecular weight proteinuria has been established from knockout studies and inactivating mutations in Dent's disease [57]. Drugs reported to abrogate vacuolar acidification did not affect the rate of endocytic uptake but inhibited recycling or arrested transfer to lysosomes. This results in impairment in the reabsorption of proteins, especially low molecular weight proteins [57]. The accumulation of rosuvastatin

TABLE 2

Comparative selectivity (tissue and functional selectivity) of different statins

Statin	Inhibition of cholesterol synthesis[a] (IC_{50}) nM		Inhibition of albumin uptake[a] (IC_{50}) μM	Selectivity	
	Primary rat hepatocytes	OK[b] cells	OK cells	Cholesterol Synthesis Inhibition (Hepatocytes vs OK cells)	Inhibition of Cholesterol synthesis vs albumin uptake (OK cells)
Rosuvastatin	0.16	100	10	625	100
Atorvastatin	1.15	60	6	52	100
Pravastatin	6.93	300	100	43	333
Simvastatin	2.74	10	0.3	3.6	30
Fluvastatin	3.78	10	0.3	2.6	30

[a] www.fda.gov/cder/foi/nda/2003/21-366_Crestor.htm.
[b] Abbreviations: OK, opossum kidney.

caused by drug insolubility or crystallization in the renal tubules at higher doses is another possibility, which needs to be confirmed (www.fda.gov/ohrms/dockets/ac/03/briefing/3968B1_02_A-FDA-Clinical%20Review.pdf).

Statin-associated proteinuria: confounding factors

The lack of sufficient high-dose data for statins (other than rosuvastatin) regarding the incidence rate of proteinuria could be equally important in the parallel comparison. The estimates of the incidence of rosuvastatin-associated proteinuria were made in the post-cerivastatin withdrawal period, when the regulatory agencies became more sensitive to any reported adverse effects. Furthermore, the median duration of treatment with various doses of statins other than rosuvastatin in the controlled periods of these clinical trials was approximately eight weeks, compared with 3.8 years for rosuvastatin (www.fda.gov/cder/warn/2004/12779.pdf). Therefore, direct comparison of rosuvastatin with other statins is neither justified nor valid. Another confounding factor is the lack of placebo data for the analysis, because much of the data came from open-label safety studies. The absence of a non-statin-treated control group makes it almost impossible to reach a definitive conclusion about the role of rosuvastatin in renal function.

In addition, the proteinuria findings were based on dipstick assays on random urine samples. Such tests are crudely quantitative and make no adjustment for urine osmolality. These tests are relatively inaccurate (they have a false positive rate of 10%) and nonspecific, and because they are read manually, investigators can introduce a significant error. No large-scale studies have yet confirmed the effects of statins on proteinuria using accurate quantitative measures. Moreover, intermittent, nonpathologic, dipstick-positive hematuria and low-level dipstick proteinuria are extremely common urinalysis findings.

In an attempt to examine the association of urine-dipstick abnormalities with changes in renal function, AstraZeneca and the FDA further analyzed the data and measured the levels of serum creatinine. The available information precludes the definitive findings of toxicity. The incidence of creatinine elevations in patients with proteinuria or combined proteinuria and hematuria were very low. None of the patients with these abnormalities (either alone or combined) developed kidney failure (www.fda.gov/cder/warn/2004/12779.pdf). The analysis showed that no patients receiving rosuvastatin at doses of 5–40 mg/day for $\geq$96 weeks had an increase in serum creatinine of greater than 30%. The results indicate that no patient in this cohort developed significant renal function deterioration. The average decrease in serum creatinine among patients receiving 40 mg/day rosuvastatin might indicate a beneficial effect on kidney function. However this hypothesis needs to be tested formally. More precisely, the urine dipstick and serum chemistry data as well as the adverse-event data from the clinical trials do not support renal toxicity or compromised renal function caused by rosuvastatin treament.

The incidence of renal insufficiency and/or failure in three patients in the preapproval studies and two in the postapproval studies of rosuvastatin were confounded by co-morbid medical conditions that could contribute to the development of renal disease. These confounding factors include diabetes, warfarin coagulopathy resulting in renal hemorrhage, dehydration, preexisting renal disease and concomitant drugs with potential renal adverse events.

Conclusion

Drug-induced proteinuria is of great clinical concern, especially if it is persistent in nature. The reputation of rosuvastatin, which was already in some doubt as a result of myotoxicity issues, has been further compromised because of proteinuria. However, preclinical studies have demonstrated that all statins have the potential to induce proteinuria as a result of their propensity to inhibit albumin uptake. Findings obtained from *in vitro* studies and clinical trials with rosuvastatin suggest that statin-associated proteinuria does not indicate a renal toxic effect of either statins in general or of rosuvastatin specifically. The incidence of creatinine elevations in patients with proteinuria or combined proteinuria and hematuria were very low, but detectable. None of the patients with these abnormalities developed renal failure. This was consistent with a transient or intermittent effect of the drug producing these abnormalities. The reduction in frequency of proteinuria after dose titration from 80 to 40 mg/day indicates that proteinuria is a reversible pharmacological effect of rosuvastatin. Furthermore, the decrease in serum creatinine among patients on 40 mg/day rosuvastatin indicated that rosuvastatin could have beneficial effects on kidney function. The induction of proteinuria might not be restricted to rosuvastatin and could represent a minor class effect of statins with fairly low incidence. However, the hypothesis needs to be tested formally before one can make a definitive ruling.

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