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Atorvastatin Beats Rosuvastatin in Protecting Kidneys in Diabetic and Nondiabetic Patients

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July 2, 2010 (Munich, Germany) — Results of 2 related trials investigating the effects of statins on urinary protein excretion and kidney function found atorvastatin (ATV) protective and rosuvastatin (RSV) unprotective, and possibly harmful, in diabetic and nondiabetic patients.

High-dose ATV significantly reduced proteinuria and did not affect renal function, whereas RSV was associated with a significant decline in function and had no effect on proteinuria, according to results of the PLANET trials, reported in a late-breaking trials session here at the XLVII European Renal Association-European Dialysis and Transplant Association Congress by Dick de Zeeuw, MD, PhD, a clinical pharmacologist and clinical trialist at the University Medical Center in Groningen, the Netherlands.

In diabetic and nondiabetic patients, proteinuria is a risk factor for further loss of kidney function and progression to end-stage renal disease, even when angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) are used to lower blood pressure. Experimental results have suggested that statins reduce proteinuria and preserve kidney function, but clinical studies have produced mixed results.

The ongoing Study of Heart and Renal Protection (SHARP) trial with simvastatin and ezetimibe aims to test this hypothesis. Data collection is scheduled to complete in late summer 2010.

The 2 randomized double-blind multinational PLANET trials tested the effects of ATV 80 mg/day or RSV 10 or 40 mg/day on urinary protein excretion and renal function in hypercholesterolemic patients with moderate proteinuria.

PLANET I involved 325 patients with type 1 or 2 diabetes, and PLANET II involved 220 patients without diabetes in the intent-to-treat populations. Patients had urinary protein/creatinine ratios of 500 to 5000 mg/g, a fasting low-density-lipoprotein (LDL)-cholesterol level of 90 mg/dL or higher, and had used ACE inhibitors or ARBs for at least 3 months prior to screening.

There was an 8-week lead-in period, and then patients were put on the drug. The patients randomized to receive RSV 40 mg/day or ATV 80 mg/day took half the daily dose for the first 4 weeks and then escalated to full doses.

Patients with severe renal disease, defined as an estimated glomerular filtration rate (eGFR) below 40 mL/min per 1.73 m^2, or PLANET I patients with a hemoglobin A_{1c} level above 11% were excluded from the study, as were people with active liver disease.

The primary end point of the studies was the change in urinary protein/creatinine ratio from baseline to week 52 or to the last on-treatment observation carried forward. In PLANET I, the 3 treatment groups were fairly well matched at baseline for age (range, 57 to 59 years), sex (62% to 77% male), mean body mass index (BMI) (31.8 to 32.5 kg/m^2), mean blood pressures (138 to 139/79 to 80 mm Hg), mean eGFR (68.8 to 72.6 mL/min per 1.73 m^2), geometric mean protein/creatinine ratio (1160 to 1260 mg/g), and geometric mean albumin/creatinine ratio (805 to 911 mg/g).

The nondiabetic PLANET II cohort had baseline characteristics fairly similar to those of PLANET I, except for younger age (48 to 50 years), lower mean BMI (27.4 to 29.0 kg/m^2), lower mean blood pressure (125 to 133/79 to 82 mm Hg), as would be expected for a nondiabetic population, and higher mean eGFR (71.5 to 78.3 mL/min per 1.73 m^2).

Dr. de Zeeuw summarized the findings of both studies. For PLANET I (diabetic patients), he said, "atorvastatin significantly reduces the proteinuria in these patients on top of ACE/ARB therapy, with around a 15% reduction in proteinuria, whereas rosuvastatin, both 10 and 40 mg, had no significant effect at all on proteinuria."

The effect of ATV was evident by week 26 and continued through week 52, but neither RSV dose lowered proteinuria at either time point.

In PLANET II (the nondiabetic cohort), "we see a similar pattern, even more pronounced," he said. ATV reduced proteinuria by more than 20% at 26 and 52 weeks, but there was no significant effect with either dose of RSV. The results for albuminuria were very similar to those for proteinuria.

For eGFR, Dr. de Zeeuw said the results were "very surprising," in that in the PLANET I trial, patients on RSV lost more kidney function over 52 weeks than did those on ATV. Patients on ATV lost about 1 to 2 mL/min per 1.73 m^2 over 52 weeks, those on RSV 10 mg/day lost about 4 mL/min per 1.73 m^2, and those on RSV 40 mg/day lost close to 8 mL/min per 1.73 m^2.

In nondiabetic patients (PLANET II), the effects of the treatments on kidney function were slightly less pronounced. There was a significant decline in eGFR with RSV 40 mg/day but not in the other 2 treatment groups.

Dr. de Zeeuw explained that the differential effects on proteinuria and eGFR in the treatment groups was not a result of differences in lipid lowering. All the treatments lowered total and LDL cholesterol, and there were no significant differences in the amount of lipid lowering.

All the treatments were well tolerated in both trials. A total of 6 deaths occurred, and all were reported as not of a renal etiology. Although determined by investigators to be not related to drug, the incidence of renal adverse events was higher in the RSV 40 mg/day group in PLANET I but not in PLANET II.

PLANET I: Summary of Renal Adverse Events (%)

Adverse Event	**RSV 10 mg/day (n = 116)**	**RSV 40 mg/day (n = 123)**	**ATV 80 mg/day (n = 110)**	***P* value**
Any renal adverse event	7.8	9.8	4.5	nonsignificant
Acute renal failure	0.0	4.1	0.9	<.05
Serum creatinine doubling	0.0	4.9	0.0	<.01
Serum creatinine doubling or acute renal failure	0.0	7.3	0.9	<.01

One limitation of the study was that there was no placebo control group; ethical committees overseeing the study would not allow the investigators to have a no-statin group, "which was quite a surprise to us because I think there is no proof yet that statins actually help in these patients," Dr. de Zeeuw said.

He concluded from these findings that in diabetic and nondiabetic patients with proteinuria, using optimal therapy, including ACE inhibitors and ARBs:

- ATV 80 mg/day significantly reduced proteinuria by about 20%
- RSV 10 or 40 mg/day had no effect on proteinuria
- RSV 40 mg/day was associated with a significant decline in eGFR of about 8 mL/min per 1.73 m^2 per year
- ATV 80 mg/day had no effect on eGFR

- ATV 80 mg/day has a clear advantage over RSV 40 mg/day in terms of renal protection and renal damage.

After many trials and many years of statin use, cardiologists have largely concluded that most of the lipid effects they see with statins are a "class effect" and not necessarily unique to any particular one. However, Dr. de Zeeuw said this trial "sort of dismembers the class effect," at least for the parameters studied here. ATV and RSV were obviously exerting different effects from each other on proteinuria and renal function. "I think this 'class' discussion is going to be extremely important," he said.

One big question remaining is whether ATV is actually protecting the kidneys or whether RSV is damaging them. Based on the current results, Dr. de Zeeuw advised that "if you are considering putting such a patient on a statin, you should not put them on rosuvastatin."

Taking the 2 PLANET trials together, David Harris, MD, professor of medicine at the University of Sydney in Australia, said: "It's a very important study because it has dispelled the idea about class effects of statins and has shown that 2 drugs that we thought were extremely similar have very different effects and, clinically, very significant effects on kidney disease. . . . It certainly would point any practicing nephrologist toward using atorvastatin rather than the other drug in this situation."

But he noted that until there are data on hard end points, such as patients progressing to dialysis or dying, the full story on these drugs in this setting will not be known.

The PLANET trials were funded by AstraZeneca. Dr. de Zeeuw reports being a consultant to and receiving honoraria (to his institution) from Abbott, Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Hemocue, Novartis, Noxxon, Merck Sharp & Dohme, and Johnson & Johnson. Dr. Harris has disclosed no relevant financial relationships.

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