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ROSUVASTATIN (CRESTOR®) A NEW STATIN FOR THE TREATMENT OF DYSLIPIDEMIA

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Introduction

The American Heart Association estimates there are 102.3 million American adults with total cholesterol values of 200 mg/dL or higher and 41.3 million that have levels greater than 240 mg/dL.[1] Although there are numerous medications available for the treatment of hypercholesterolemia, the statin class is the most effective in lowering low-density lipoprotein cholesterol (LDL-C). Multiple clinical trials have demonstrated their ability to reduce morbidity and mortality. Rosuvastatin (Crestor®) is the newest statin that has demonstrated larger reductions in LDL-C than the current statins on the market. It was approved by the Food and Drug Administration (FDA) on August 12, 2003 for the treatment of hypercholesterolemia and is manufactured by AstraZeneca. This article will explore the pharmacology, pharmacokinetics, safety, and efficacy of rosuvastatin.

Lipid Metabolism

Cholesterol and triglycerides (TG) are synthesized in the liver and are incorporated into very low-density lipoproteins (VLDLs) that are secreted into the circulation for delivery to peripheral tissues. Because cholesterol and TG are not soluble in water, they circulate together as a lipid and protein complex (lipoprotein) in the blood. This complex is composed of particles of VLDL, intermediate-density lipoprotein (IDL) and LDL. Triglycerides are removed by lipases, while the modified VLDL is transformed into an IDL and then into the cholesterol rich LDL. The LDL particle contains apolipoprotein B–100 (ApoB-100) and fractions of high-density lipoprotein (HDL), which is thought to facilitate the reverse transport of cholesterol from tissues back to the liver.[2]

Pharmacology and Pharmacokinetics

Rosuvastatin is a selective and competitive inhibitor of hydroxymethyl glutaryl coenzyme (HMG-CoA) reductase, the rate limiting enzyme that converts 3 HMG-CoA to mevalonate, a precursor of cholesterol. Rosuvastatin decreases lipids through two main mechanisms: 1) it increases the number of hepatic LDL receptors on the cell surface to increase uptake and breakdown of LDL and 2) it inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles. Rosuvastatin increases HDL and reduces total cholesterol, LDL, Apo B, TG, and non-HDL in patients with homozygous and heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, and mixed dyslipidemias.[3-4]

Rosuvastatin's peak plasma concentration

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Table 1. Dose-response to rosuvastatin in patients with primary hypercholesterolemia[7]

Dose	N	Total-C*	LDL-C*	ApoB*	TG*	HDL-C*
Placebo	29	-2±1†	-4±2†	-2±2	-1±5	4±2
5	17	-3±2†	-43±2†	-37±2	-35±7‡	14±3
10	16	-35±2†	-51±2†	-41±2	-10±7	14±3‡
20	13	-40±2†	-57±3†	-49±3	-23±8	10±4
40	34	-46±1†	-63±2†	-54±1	-28±5†	10±2
80	31	-47±2†	-65±2†	-55±2	-23±6	13±3

N=number of patients, Total-C=total cholesterol, LDL-C=low density lipoprotein cholesterol, , ApoB=apolipoprotein B, TG=triglycerides, HDL-C=high density lipoprotein cholesterol.
*Values are the percent change from baseline at week 6 expressed as least-squares mean ± SE. † $p<0.001$ compared with placebo. ‡ $p<0.05$ compared with placebo.

(C_{max}) and area under the curve (AUC) increase in a dose-dependent manner. Following an oral dose, the C_{max} is reached in 3 to 5 hours, with an absolute bioavailability of about 20%. Food may delay the rate but not the extent of absorption of rosuvastatin. When given with food, peak plasma concentrations decreased by up to 20% while the AUC remained unaffected. Plasma concentrations did not differ following evening or morning drug administration and reductions in LDL were observed whether or not rosuvastatin was given with or without food and regardless of the time of day it was given.[3]

The mean steady state volume of distribution is 134 liters, with approximately 88% of rosuvastatin bound to plasma proteins, mainly albumin. Metabolism occurs through the cytochrome P450 isozyme 2C9. However, rosuvastatin is not extensively metabolized with only 10% of the radiolabeled dose recovered as its N-desmethyl metabolite. Following administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%), with a half-life of about 19 hours.

A population pharmacokinetics analysis revealed no clinically relevant differences among Caucasian, Hispanic, and African Americans or African Caribbean groups. However, there was a 2-fold increase in the AUC in Japanese subjects living in Japan and in Chinese subjects living in Singapore when compared to Caucasians living in North America and Europe. No studies were done on Asians living in United States.

Precautions and Drug Interactions

Rosuvastatin, like other HMG-CoA reductase inhibitors, is absolutely contraindicated in women who are or may become pregnant, as it is a pregnancy category X drug. There are no pharmacokinetic differences due to gender or age. However, caution is advised in the elderly and those with renal insufficiency. Plasma concentrations of rosuvastatin increased 3-fold in patients with severe renal impairment (CrCl <30 mL/min) compared to healthy adults with normal renal function (CrCl >80 mL/min). Mild to moderate renal impairment (CrCl 30-80 mL/min) had no influence on plasma concentration when oral doses of rosuvastatin 20 mg were given for 14 days.

Because rosuvastatin's clearance is not dependent on cytochrome P450 3A4 metabolism, 3A4 inhibitors including ketoconazole and erythromycin are not expected to affect its metabolism.[5-6] However, since it is a substrate for cytochrome P450 2C9, there is a potential for interactions with other drugs that are also metabolized through this isozyme, including warfarin. Coadministration of rosuvastatin and warfarin did not change the warfarin plasma concentration but it resulted in significant increases in the INR (> 4 vs. baseline 2-3).[3] The INR should be monitored at baseline and frequently after initiating rosuvastatin.

Coadministration of rosuvastatin 80 mg and gemfibrozil resulted in a 2.2- and 1.9-fold increase in the AUC and C_{max} of rosuvastatin, respectively.[3] However, plasma concentrations of rosuvastatin did not significantly change when the 10-mg dose was used. If rosuvastatin is used concurrently with gemfibrozil, a lower maximum dosage of 10 mg/day of rosuvastatin is recommended. Coadministration with cyclosporine resulted in a 11– and 7-fold increase in the C_{max} and AUC of rosuvastatin respectively. It is advisable to avoid concurrent use of rosuvastatin and cyclosporine. However, if a statin must be used concurrently with cyclosporine, consider an alternative HMG-CoA reductase inhibitor

Table 2. Percent change in LDL-C from baseline to week 6 with available statins[8]

Treatment Group	Daily Dose (mg)			
	10*	20*	40*	80*
Rosuvastatin	-46	-52	-55	---
Atorvastatin	-37	-43	-48	-51
Pravastatin	-20	-24	-30	---
Simvastatin	-28	-28	-35	-46

LDL-C=low density lipoprotein cholesterol
*Values are the percent change from baseline at week 6 expressed as least-squares mean.

that is not metabolized by the CYP450 system or use lower initial and maximum recommended dosages of rosuvastatin.

Clinical Trials

Dose-Ranging Study

In order to determine the dose-response of rosuvastatin, Olsson and colleagues[7] conducted a 2-phase, placebo-controlled, multicenter study in patients with mild to moderate hypercholesterolemia. The first phase randomized 142 patients to receive placebo or rosuvastatin at doses of 1, 2.5, 5, 10, 20, or 40 mg for 6 weeks. The second phase extended this dosage range and randomized 64 patients to placebo or rosuvastatin 40 or 80 mg for 6 weeks. Over the 6-week period, rosuvastatin was well-tolerated and produced clinically and statistically significant dose-dependent reductions in LDL-C. It also produced elevations in HDL-C and reductions in TG that were statistically significant at some dose levels. (Table 1)

STELLAR Trial

The Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial was a multi-center, open-label, parallel group, dose ranging study of rosuvastatin in 12,569 patients with hypercholesterolemia. Rosuvastatin 10-80 mg was given as a single daily dose and total cholesterol, LDL, HDL, and TG were measured at baseline and after 6 weeks of treatment. Overall, rosuvastatin 10 mg lowered LDL cholesterol by up to 52% and by as much as 63% when given at the 40 mg dose. In patients with hypertriglyceridemia, rosuvastatin produced mean reductions from baseline in TG ranging from -10% to -28% ($p<0.001$).[8]

The STELLAR study also compared rosuvastatin to the HMG-CoA reductase inhibitors atorvastatin, simvastatin, and pravastatin. Rosuvastatin was able to achieve larger reductions in LDL compared to the other statins, with the 10-mg dose being roughly equivalent to simvastatin 80 mg and atorvastatin 40 mg (Table 2). Rosuvastatin was also superior in reducing TG and increasing HDL compared to the other statins. A 10mg dose reduced TG by 20% compared to 18% with atorvastatin 10 mg, 12% with simvastatin 20 mg, and 12% with pravastatin 20 mg ($p<0.01$). Meanwhile, rosuvastatin 10-40 mg increased HDL cholesterol by 7.7% to 9.6% compared to 5.2% to 6.8% with simvastatin 10-80 mg, 3.2% to 5.6% with pravastatin 10-40 mg, and 2.1% to 5.7% with atorvastatin 10-80 mg.[8]

Rosuvastatin vs. Atorvastatin

In a 52-week, randomized, double blind, multicenter trial, Olsson and colleagues[9] compared the ability of rosuvastatin and atorvastatin to achieve LDL-C goals in 412 patients with primary hypercholesterolemia. Patient with LDL-C values between 160 and 250 mg/dL were randomized to receive atorvastatin 10 mg or rosuvastatin 5 or 10 mg for 12 weeks followed by 40 weeks in which dosages could be sequentially doubled up to 80 mg if National Cholesterol Education Program (NCEP) Adult Treatment Panel II (ATP-II) LDL-C goals were not achieved. At 12 weeks, LDL cholesterol goals were achieved in 76% of patients receiving rosuvastatin 10 mg versus 53% of patients receiving atorvastatin 10 mg ($p<0.001$). Furthermore, in the subgroup of patients with the most stringent LDL cholesterol goal of <100 mg/dL, 60% of rosuvastatin-treated patients (10 mg) versus 19% of the atorvastatin-treated patients (10 mg) achieved their desired LDL-C goal ($p<0.001$).[9]

Table 3. Percent change in lipid measures from baseline at 24 weeks[10]

Lipid Measure	Rosuvastatin 40 mg*	ER Niacin 2 g*	Rosuvastatin 40 mg + ER Niacin 1 g*	Rosuvastatin 10 mg + ER Niacin 2 g*
LDL-C	-48†	-0.1†	-42	-36‡
Total-C	-41	-7†	-38	-29†
TG	-42	-26	-46	-41
HDL-C	11	12	17	24†

ER=extended-release, LDL-C=low density lipoprotein cholesterol, Total-C=total cholesterol, TG=triglycerides, HDL-C=high density lipoprotein cholesterol.
* Percent change from baseline is expressed as least-squares mean.
† $p<0.001$; ‡ $p<0.01$ (all treatment comparisons vs. rosuvastatin 40 mg).

Rosuvastatin and Niacin

Capuzzi and colleagues[10] assessed the safety and efficacy of rosuvastatin and extended-release (ER) niacin alone and in combination in 270 patients with total cholesterol values =200 mg/dL, TG 200 to 800 mg/dL, and HDL<45 mg/dL. This 24-week, multicenter, open-label trial randomized patients to 1 of 4 treatment groups: rosuvastatin 10 to 40 mg, ER niacin 0.5 to 2 g, rosuvastatin 40 mg/ER niacin 0.5 to 1 g, or rosuvastatin 10 mg/ER niacin 0.5 to 2 g.

Rosuvastatin monotherapy produced the greatest decrease in LDL-C (-48%) and total cholesterol (-41%) at 24 weeks. Extended-release niacin 2 g alone did not significantly reduce LDL-C from baseline (-0.1%) and addition of ER niacin 1 g to rosuvastatin 40 mg did not lower LDL-C to a greater degree than rosuvastatin monotherapy (Table 3). The lack of effect of niacin can in part be explained by the significantly higher incidence of withdrawals and decreases in adherence to treatment seen in the niacin groups that were attributed to niacin's less favorable side effect profile.

Dosage

The recommended initial rosuvastatin dose is 10 mg by mouth once daily. However, 5 mg once daily should be used for patients who do not require aggressive LDL-C reductions, patients with renal insufficiency (CrCl <30 ml/min), or patients at a high risk for myopathy. The 20 mg dose is recommended for patients with marked hypercholesterolemia who require aggressive lipid lowering therapy (LDL-C >190 mg/dL), while the 40 mg dose should be reserved for those patients who have not achieved their LDL-C goal despite being on the 20-mg dose.[3]

Toxicity and Safety

The safety profile of rosuvastatin throughout the dose range of 10 to 40 mg was reviewed in 12,569 patients with hypercholesterolemia.[11] The adverse event profile is similar to that of atorvastatin, simvastatin, and pravastatin and includes myalgia, asthenia, nausea, and abdominal pain (Table 4). Elevation of hepatic enzymes >3 times the upper limit of normal on 2 or more consecutive occasions occurred in <0.5% of patients. Nevertheless, the manufacturer recommends that practitioners check liver function tests (LFTs) at baseline, 12 weeks, and semiannually thereafter.[3]

Myopathy defined as muscle symptoms of pain and tenderness plus serum creatine phosphokinase (CPK) levels >10 times the upper limit of normal occurred in =0.03% of patients. However, it is advisable to check a CPK level at baseline and at any time symptoms of myopathy develop. There were 7 reported cases of rhabdomyolysis in clinical trials; however, these occurred in patients receiving higher than recommended doses (i.e. 80 mg) of rosuvastatin. No cases of rhabdomyolysis or death have been reported with the 40 mg dose to date. Factors that may predispose patients to myopathy include advanced age (=65 years), hypothyroidism, and renal insufficiency.

In clinical trials, 2 patients taking rosuvastatin 80 mg/day developed acute renal failure of uncertain etiology; however, they recovered after discontinuation of the medication. Dipstick-positive proteinuria and microscopic hematuria were observed in 6.1%, 1.3%, 0.3%, and 0.3% of patients receiving 80, 40, 20, and 10 mg of rosuvastatin respectively. Despite the recommendations from an FDA Advisory Committee for periodic monitoring of renal function when the 40-mg dose is used, the

Table 4. Adverse events in placebo-controlled studies[3]

Adverse Event	Rosuvastatin (N=744)	Placebo (N=382)
Pharyngitis	9.0 %	7.6 %
Headache	5.5 %	5.0 %
Diarrhea	3.4 %	2.9 %
Dyspepsia	3.4 %	3.1 %
Nausea	3.4 %	3.1 %
Myalgia	2.8 %	1.3 %
Asthenia	2.7 %	2.6 %
Back Pain	2.6 %	2.4 %
Flu syndrome	2.3 %	1.6 %
Urinary tract infection	2.3 %	1.6 %
Rhinitis	2.2 %	2.1 %
Sinusitis	2.0 %	1.8 %

final labeling only provides a precaution to reduce rosuvastatin dosage in patients receiving the 40 mg/ day dosage who have unexplained persistent proteinuria during routine urinalysis testing.

Cost

The mean retail cost for a 30-day supply of rosuvastatin 5, 10, 20, and 40 mg is $84.64.

Summary

Rosuvastatin is the newest HMG CoA reductase inhibitor to be approved by the FDA. Although it has the same mechanism of action as the other agents in the statin class, there are some differences in its pharmacokinetic profile. At equivalent doses, rosuvastatin is slightly superior than the other available statins in decreasing TG and increasing HDL. Rosuvastatin is the only statin to be significantly cleared renally; therefore, it should be used with caution in patients with renal insufficiency (CrCl <30 ml/min) such as the elderly and people with diabetes. Outcome data that will evaluate rosuvastatin's effect on cardiovascular events and overall mortality are not available however studies are under way.

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Aloxi™ (palonosetron HCl) is a new 5-HT_3 receptor antagonist for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy. It is given as a 0.25 mg IV single dose 30 minutes before the start of chemotherapy. It is not recommended to repeat dosing within a 7-day interval and practitioners should use it with caution in patients who are at risk for QT prolongation or on medications that may prolog the QT interval.

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Vardenafil (Levitra®) is a new PDE type 5 inhibitor approved for the treatment of erectile dysfunction. The recommended starting dose is 10 mg by mouth 60 minutes before sexual activity, with a maximum recommended dose of 20 mg. The dose should be lowered to 2.5 or 5 mg in the elderly and in patients who are taking CYP 3A4 inhibitors like ritonavir, ketoconazole, indinavir, itraconazole, and erythromycin.

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