drug information perspectives

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ROSUVASTATIN

TRADE NAME: Crestor

CLASSIFICATION:
- Lipid-modifying drug
- HMG-CoA reductase inhibitor
- Statin

ACTION:
- Competitively inhibits the hepatic enzyme hydroxymethylglutaryl-CoA (HMG-CoA) reductase which catalyzes the rate-limiting step of *de novo* cholesterol synthesis
- Increases LDL-cholesterol (LDL-C) receptors and inhibits synthesis of VLDL in the liver
- Lowers C-reactive protein levels
- Anti-inflammatory effects are suspected but their clinical importance is unproven

PHARMACOKINETICS:
Half-life: 20 hours
Absorption:
- Absolute bioavailability 20-29%
- Undergoes first-pass active uptake into the liver by OATP1B1
- Cmax at 3-5 hours

Distribution:
- Extensive distribution
- Protein binding 88%

Metabolism:
- Only 10% metabolized
- Metabolized by P450 CYP2C9 and to a lesser extent by 2C19
- One metabolite formed by P450 enzyme CYP2C9 has half the activity of rosuvastatin; the lactone metabolite is inactive

Elimination:
- In feces (90%) and urine (10%), mostly as unchanged drug

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- Not a substrate for P-glycoprotein
Special populations:
- **Elderly**: No change
- **Hepatic impairment**: Severe liver disease (Child-Pugh score 8-9): increased exposure at least 2-fold. Mild-moderate impairment: increased Cmax 1.5-2-fold
- **Renal impairment**: Severe renal impairment (ClCr<30mL/min): 3-fold increase in AUC and Cmax
- **Gender**: no difference
- **Race**: Asian patients (Japanese, Chinese, Asian-Indian, Malay, Filipino, Korean, Vietnamese): 2-fold increased AUC and Cmax compared with Caucasians

USES AND EFFICACY:
Uses:
- Adjunct to dietary treatment for the reduction of LDL-cholesterol levels in persons with elevated LDL-cholesterol with or without slightly elevated triglycerides (**primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia)**. Reduces LDL-C by 40-63%, TC/HDL-C by 34-45%, and apolipoprotein B by 33-47% (depending on dose), increases HDL-C 9%, and reduces triglycerides by 19-28% (proportional to baseline and dose).
- **Homozygous familial hypercholesterolemia**

Clinical course:
- Maximum LDL-C reduction in 2 weeks
- If discontinued, lipid level effects are gone in 1-3 weeks

Major clinical trials

STELLAR (2003): A randomized, open-label trial compared rosuvastatin with atorvastatin, simvastatin and pravastatin across their approved dosage ranges in 2268 patients with average baseline LDL-C levels 4.9 mmol/L . After six weeks, LDL-C levels were reduced as follows: rosuvastatin 10mg: 46%; 20mg: 52%; 40mg: 55%; atorvastatin 10mg: 37%; 20mg: 43%; 40mg: 48%; 80mg: 51%; simvastatin 10mg: 28%; 20mg: 35%; 40mg: 39%; 80mg: 46%; pravastatin 10-40mg: 20-30%. The maximum doses of rosuvastatin (40mg) and atorvastatin (80mg) were highly effective and did not differ significantly in degree of LDL-C lowering or in the percentage of patients who met their Canadian or US ATP III goals (approx. 80%). Rosuvastatin 10mg did not significantly differ in LDL-C lowering from atorvastatin 40mg. Rosuvastatin was superior to simvastatin and pravastatin for LDL-C lowering at all doses. At maximum doses, rosuvastatin raised HDL-C levels significantly more than atorvastatin, but the effects were small, 10% vs. 2%. Rosuvastatin and atorvastatin had a similar effect on triglycerides. Side effects were similar.

ASTEROID (2006): The ability of rosuvastatin 40mg to induce regression of coronary artery disease was assessed in 394 patients with coronary artery obstruction. Most patients had hypertension, over 70% were male, 22-24% had a history of a myocardial infarction, and baseline, mean LDL-C was 3.0 mmol/L. After 2 years, LDL-C decreased by 53% to a mean 1.6 mmol/L, and HDL-C increased by 15%. Coronary atherosclerosis measured by IVUS imaging had regressed in 64% of patients and progressed in the remainder. Study limitations: No placebo group. A causal link between regression of atherosclerosis and LDL-C reduction or HDL-C elevation was not clear.

METEOR (2007): The ability of rosuvastatin 40mg to induce regression of coronary artery disease was assessed in a placebo-controlled, randomized, double-blind study in 984 patients with subclinical atherosclerosis, based on carotid intima media thickness assessed with B-mode ultrasound, but who had a low 10-year risk of coronary heart disease. Subjects had no clinical symptoms of atherosclerosis, and were 67 years old on average, and 60% were male, with a baseline mean LDL-C of 4mmol/L. After 2 years, rosuvastatin lowered LDL-C by 49% and raised HDL-C by 8%. Atherosclerosis did not progress in the rosuvastatin group, a significant difference from the progression seen in the placebo group. Rosuvastatin did not induce regression of atherosclerosis. Study limitations: The 40mg dose is not a recommended starting dose due to the increased risk of myopathy. Further research is needed to evaluate the impact on clinical events.

Comparisons
Vs. other statins:
- Despite concerns, there is currently no evidence of greater toxicity with rosuvastatin than with other statins.

- Maximum rosuvastatin dose 40mg reduces LDL-C levels by up to 63%, similar to the maximum dose of atorvastatin. More effective for LDL-C reduction than maximum dose monotherapy with simvastatin or pravastatin.
- More potent LDL-C reduction on a mg per mg basis than other statins.
- Slightly superior at raising HDL-C levels compared with atorvastatin, but not as effective as niacin.

Vs. statins plus ezetimibe:
- Maximum rosuvastatin dose 40mg reduces LDL-C levels slightly less (4% less) than the maximum dose of simvastatin combined with ezetimibe. The combination may increase the risk of liver enzyme elevation and myopathy.

Advantages:
- Highly effective for lowering LDL cholesterol
- Reduces C-reactive protein and all subfractions of LDL-C
- Many patients achieve their LDL-C reduction goal with the initial dose: 95% of patients at low risk of cardiovascular events started on 5-10mg; 79% of patients at high risk started on 20mg; 57% of patients at very high risk started on 40mg. This speeds benefit and reduces the need for dose titration.
- Does not interact with digoxin (unlike some other statins)
- Simple dosage regimen

Disadvantages:
- Lacks clinical outcome data
- Lacks long-term safety data

Place in therapy:
- Among the most potent LDL cholesterol-lowering therapies available
- Most useful for non-Asian patients who require extensive reduction in LDL-C to reach their goal, but have not responded to other statin drugs that have demonstrated long-term safety and reduced CHD risk
- For diabetic patients, triglycerides are reduced, with even greater reductions if combined with fenofibrate

Investigational/Unapproved Uses:
- **Heart failure**: Two randomized, placebo-controlled trials are investigating the benefit of rosuvastatin to treat heart failure patients (NYHA class II-IV) already receiving medications: GISSI-HF and CORONA. Benefit has been seen with other statin drugs. Hypothetically, benefit may derive from the relationship between coronary artery disease and heart failure, and anti-inflammatory action. However, the potential for cardiac muscle dysfunction is a concern.

CONTRAINDICATIONS AND PRECAUTIONS:

Contraindications:
- **Hypersensitivity** to rosuvastatin
- **Active liver disease** (risk of liver toxicity)
- **Severe liver impairment** (40mg dose contraindicated; increased myopathy risk due to increased drug levels)
- **Pregnancy** (another statin is teratogenic in animals)
- **Lactation** (inhibition of cholesterol synthesis could be dangerous to nursing infants)
- **Cyclosporine** (11-fold increase in rosuvastatin levels)
- **Fibrate drugs** (rosuvastatin 40mg dose contraindicated; gemfibrozil contraindicated; increased myopathy risk)
- **Niacin** (rosuvastatin 40mg dose contraindicated; increased myopathy risk)
- **Asian patients** (40mg dose contraindicated due to increased drug levels)
- **History of statin-induced myopathy** (40mg dose contraindicated)
- **Family or personal history of muscle disorders** (40mg dose contraindicated)
- **Severe renal impairment** (40mg dose contraindicated; increased myopathy risk due to increased drug levels)
- **Hypothyroidism** (40mg dose contraindicated; increased myopathy risk)
- **Alcoholism** (40mg dose contraindicated; increased myopathy risk)
- **Any situation where rosuvastatin levels may be elevated** (40mg dose contraindicated; increased myopathy risk)

Precautions:
- **Patients at risk for myopathy** (40mg dose contraindicated; includes history of statin-induced myopathy; age over 70; family or personal history of muscle disorders; fibrate drug; niacin; severe liver impairment; severe renal impairment; hypothyroidism; alcoholism; excessive exercise; surgery; trauma): monitor, discontinue if muscle weakness or pain, measure creatine kinase levels (risk of rhabdomyolysis and renal failure)

- **Liver function**: perform liver tests before and three months after therapy, and if 40mg dose is used (liver toxicity possible). Discontinue or reduce dose if liver transaminases rise to 3 x ULN. Use with caution if past history of liver disease.
- **Proteinuria**: consider discontinuation (clinical importance unknown)
- **Report** unexpected or serious reactions to the Canadian Adverse Drug Reaction Monitoring Program

PREGNANCY AND LACTATION:
- Avoid during pregnancy
- Insulin is the treatment of choice for pregnant diabetic patients
- Excessively high doses in animals associated with low birthweight in offspring, adverse effects on embryonic development, and increased incidence of gallbladder agenesis or small gallbladder
- Lovastatin is teratogenic in animals
- Only one reported case of human pregnancy exposure during first 24 weeks of pregnancy; no adverse effects on neonate
- Avoid during breast-feeding; human data lacking. Unknown if excreted in human breast milk. Inhibition of cholesterol synthesis could be dangerous to nursing infants.

SIDE EFFECTS:
Generally well tolerated. A dose of 80mg is not approved due to unacceptable side effects: myopathy (0.9% of patients), proteinuria (12-15%), and hematuria (12%).

CNS: Headache (3-6% vs. placebo 0); dizziness (1-10%). Memory loss (cases with positive dechallenges).
Endocrine/Metabolic: Increased or decreased lipoprotein(a) levels.
Gastrointestinal: Nausea (6-12% versus placebo 3%, not dose-related); diarrhea (6% vs. placebo 3%, not dose-related); constipation (0.9%); abdominal pain (2%); pancreatitis (1 case).
Genitourinary: Proteinuria (1-4% versus placebo 3%, dose-related, mainly with 40mg dose (9%); transient and usually not associated with renal impairment; tubular origin and may reflect inhibition of albumin uptake; clinical importance unknown); hematuria (6-10% versus placebo 5%, mainly with 40mg dose).
Hepatic: Increased transaminases (ALT >3 times ULN in 0.5%, dose-related; usually mild, transient and rarely indicates liver damage; usually resolves with continued therapy or discontinuation); jaundice, hepatitis (very rare). Autoimmune hepatitis (cases).
Musculoskeletal: Muscle pain (3-8%, dose-related); myopathy (pain, tenderness, weakness, with creatine kinase >10 times ULN; dose-related: 0.1% with 10 and 20mg doses, 0.4% with 40mg dose; creatine kinase may increase without muscle symptoms and may resolve despite continued therapy); rhabdomyolysis with renal impairment (rare, 1 in 10,000 patients, may be fatal, most common in patients with risk factors, see CONTRAINDICATIONS AND PRECAUTIONS).
Other: Angioedema.

INTERACTIONS:
Does not induce or inhibit P450 enzymes**.**

DRUG	**EFFECT**	**MECHANISM**	**IMPORTANCE**
Antacid, aluminum- magnesium	Decreased statin levels 50%	Unknown	Dose antacid 2 hours after statin
Cyclosporine	Increased rosuvastatin levels 11-fold	Inhibition of OATP-mediated liver uptake	Contraindicated
Ethinyl estradiol and norgestrel oral contraceptive	Increased levels of both hormones	Unknown	Choose low dose contraceptive

Fibrates (other than gemfibrozil)	Risk of myopathy	Unknown; no kinetic interaction with fenofibrate	Rosuvastatin 40mg dose contraindicated
Gemfibrozil	Myopathy, renal failure, increased statin levels	Unknown; possibly additive toxicity and altered kinetics	Contraindicated
Itraconazole	Small increase in statin levels	Unknown	Caution
Niacin	Myopathy risk	Unknown	Rosuvastatin 40mg dose contraindicated with niacin
Warfarin	Increased INR and bleeding	Unknown	Caution, monitor

Interactions lacking
A lack of pharmacokinetic interaction has been documented with
- Cholestyramine
- Digoxin
- Erythromycin
- Fenofibrate
- Fluconazole
- Ketoconazole

DOSAGE:
Guidelines
- Used in conjunction with diet
- May be taken with or without food at any time of day, because of its long half-life
- 2-4 times more potent for LDL-C reduction than the same mg dose of atorvastatin
- Assess patient's level of cardiovascular risk and LDL-C reduction goal:

Dose	%decrease in LDL-C	Maximum absolute LDL-C decrease (based on baseline LDL-C of 4.8mmol/L)
1 mg	34%	
2.5mg	41%	
5mg	38-43%	2.06 mmol/L
10mg	43-51%	2.45 mmol/L
20mg	48-57%	2.74 mmol/L
40mg	53-63%	3.02 mmol/L

Adults:
- Dyslipidemia:
- Oral: Initially 10mg once daily. Severe hypercholesterolemia or familial hypercholesterolemia: initially 20mg once daily.
- Range 5-40mg once daily.
- Specialist supervision is required at the 40mg dose, due to increased risk of myopathy. A 40mg dose is used only in patients with high cardiovascular risk due to severe hypercholesterolemia when lower doses are not effective.
- Adjust dose at 2-4 week intervals.
- Switching from another statin drug: start with rosuvastatin 10mg daily unless lipid levels are severely uncontrolled.

Elderly:
- No dosage adjustment is usually necessary.

Hepatic impairment:
- No dosage adjustment necessary in mild to moderate impairment.
- Severe hepatic impairment: maximum dose 20mg once daily.

Renal impairment:
- No dosage adjustment necessary in mild to moderate impairment.
- Severe renal impairment: start with 5mg once daily. Maximum dose 20mg once daily.

Pharmacogenetics:
Asian patients: start with 5mg once daily. Maximum dose 20mg once daily.

NURSING IMPLICATIONS:
Once-daily doses may be given at any time of day, with or without food.

Usually well tolerated.

Carefully observe for and report signs of muscle cramps or aches and pains, especially in patients receiving a high dose or combinations of medications.

If there is a sudden reduction in the patient's liver or kidney function, as indicated by symptoms or tests, notify physician.

Encourage the patient to follow the prescribed low fat diet.

PATIENT INSTRUCTIONS:
Rosuvastatin (roe-SOO-va-sta-tin) is given to modify the levels of cholesterol in the blood. The goal is to prevent complications of atherosclerosis, including heart attack and stroke. It is one of the "statin" drugs.

Before starting this medication, be sure that your physician is aware if you have any of the following conditions: liver disease, kidney disease, history of side effects from other "statin" drugs, muscle disorders, personal or family history of muscle disorders, hypothyroidism, pregnancy or breast-feeding.

Take this medication exactly as prescribed; to be effective it must be used in conjunction with a low fat diet. It is usually taken once daily. It may be taken at any time of day; however, taking it at the same time each day will help you to remember. It may be taken with food or on an empty stomach. It must be taken regularly to be effective.

This drug may interact adversely with certain other drugs. Be sure to tell your physician and pharmacist about any other drugs that you are taking. Antacids can reduce the benefit of this drug. Take antacids 2 hours after taking this drug.

Serious side effects seldom occur. If you notice unexplained muscle pain or weakness, or any other unexpected side effects, notify your physician or pharmacist.

If you have experienced an unexpected or serious reaction to this drug, this can be reported to Health Canada's monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789). Note that this is not an emergency number.

Store this drug in its original container, away from heat, light and moisture, and out of the reach of children.

PRESENTATION:
Tablets: 5, 10, 20, 40 mg.

References are available on request.