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ROSUVASTATIN: A REVIEW OF PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

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ABSTRACT

Rosuvastatin is a potent statin with pharmacologic and pharmacokinetic advantages. Its high degree of liver selectivity results in high hepatic concentration leading to superior efficacy at lowering low density lipoprotein cholesterol and triglycerides as well as improving high density lipoprotein cholesterol compared to other statins. Rosuvastatin has relatively low lipophilicity when compared with other statins and has minimal entry into peripheral cells. This along with its minimal cytochrome P450 metabolism presents relatively better tolerability, safety and drug interaction profile. Consistent with these features, rosuvastatin represents a step forward in the statin therapy. We conducted a literature search to identify rosuvastatin papers published in English. In this review, we have outlined the pharmacodynamics, pharmacokinetics of rosuvastatin, focusingits efficacy and safety. We have also emphasized on the major clinical trials involving rosuvastatin.

KEYWORDS: rosuvastatin, pharmacodynamics, pharmacokinetics

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INTRODUCTION

The advent of the inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase (HMGR) also known as "statins": Lovastatin, Simvastatin, Pravastatin, Fluvastatin, Atorvastatin, Cerivastatin, Rosuvastatin and Pitavastatin (NK-104), for the treatment of lipoprotein metabolism disorders, constitutes a milestone in the history of prevention and therapy of cardiovascular disorders.1,2Since the introduction of lovastatin in the USA in 1987, the use of statins has surpassed over 100 million prescriptions a year, with an estimated 25 million patients worldwide on the medication.3

Data arising from both primary and secondary prevention trials in which statins have been used (4S, WOSCOPS, CARE, LIPID, AFCAPS, HPS, ASCOT-LLA, CORONA, JUPITER)4,5,6,7,8,9,10,11 have been consistent in showing beneficial effects on total and cardiovascular mortality.

The overall clinical benefits observed with statin therapy, however, appear to be greater than that might be expected from changes in lipid profile alone, suggesting that the beneficial effects of statins may extend beyond their effects on serum cholesterol levels. Recent experimental and clinical evidence indicates that some of the statins involve improving or restoring endothelial function, enhancing the stability of atherosclerotic plaques, decreasing oxidative stress and inflammation, inhibiting the thrombogenic response in the vascular wall, inhibiting platelet aggregation, immunomodulation and stimulation of bone formation and inhibition of growth of tumor cells.12,13,14,15,16

Statins can be grouped into naturally derived and chemically synthesized.17,18 Statins derived from fungal fermentation include lovastatin, simvastatin, pravastatin and mevastatin, whereas fluvastatin, atorvastatin, cerivastatin, rosuvastatin and pitavastatin (NK–104) are synthetic compounds. Mevastatin (compactin) is the first statin identified, which is not in clinical use.19

Currently commercially available statins are lovastatin (Mevacor, Merck Frosst), pravastatin (Pravachol, Bristol-Meyers Squibb), simvastatin (Zocor, Merck Frosst), fluvastatin (Lescol, Novartis), atorvastatin (Lipitor, Parke-Davis) and rosuvastatin (Crestor, Astra-Zeneca). Cerivastatin (Baycol/Lipobay, Bayer) was voluntarily withdrawn from the market in 2001 after reports of rhabdomyolysis.20,21,22Pitavastatin is the latest addition to the statin class.23,24Lovastatin and simvastatin are prodrugs and are converted into their active forms (-hydroxy acid) in the liver, whereas the others are active in their parent forms.25 All statins function similarly by binding to the active site of 3-hydroxy- 3-methylglutaryl-coenzyme A reductase (HMGR) and thus inhibiting the enzyme. However, structural differences in statins may partially account for differences in potency of enzyme inhibition.26 Statins are

competitive inhibitors of HMGR. All statins share a structural component that is very similar to the HMG portion of HMG-CoA, and all differ from HMG-CoA in being more bulky and more hydrophobic (Figure 1).

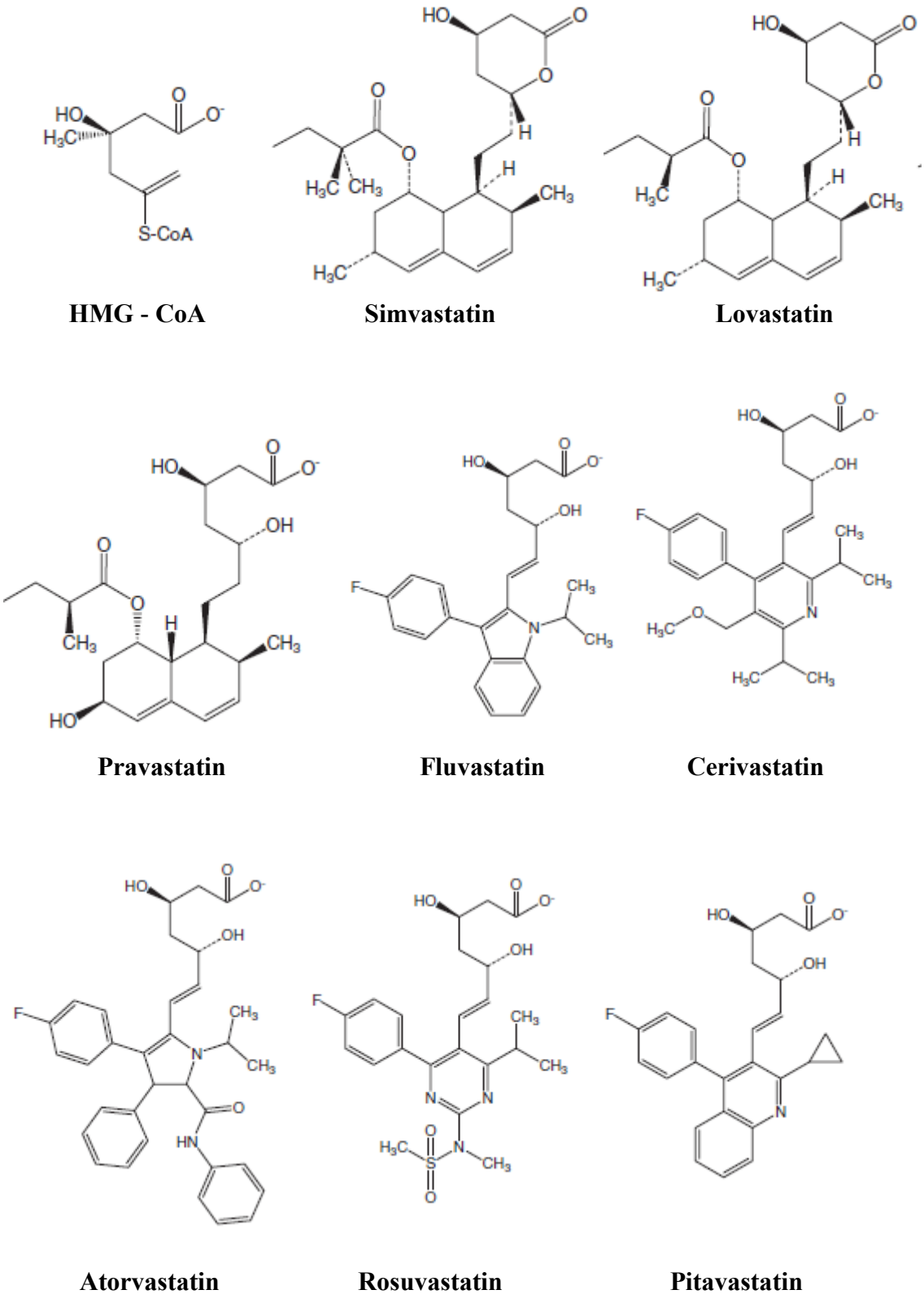

Figure 1: Chemical Structures of the Statins

Rosuvastatin is a new generation HMG-CoA reductase inhibitor which exhibits some unique pharmacologic and pharmacokinetic properties. It is a relatively potent inhibitor of HMG-CoA reductase, has low extrahepatic tissue penetration, low potential for cytochrome P450 interactions, relatively long elimination half life and a greater efficacy in lowering LDL-C and therefore has distinct advantages.27

MECHANISM OF ACTION

By inhibiting HMG-CoA reductase, rosuvastatin inhibits the rate-limiting step in the endogenous pathway for cholesterol production.28 The reduction of cholesterol production promotes the up-regulation of LDL-C receptors by hepatocytes. This action increases the removal of TG-rich lipoproteins from plasma, reduces synthesis of apolipoprotein B (apo B)-containing lipoproteins (eg, very low-density lipoprotein cholesterol [VLDL-C]) by the liver, and consequently reduces the transformation of VLDL-C to LDL-C. Rosuvastatin reduces TC, LDL-C, apo B, and VLDL-C and increases HDL-C in patients with hypercholesterolemia.29 In addition to its cholesterol-lowering effects, rosuvastatin increased vascular endothelial nitric oxide production30 and reduced tumor necrosis factor alpha, amyloid A, and fibrinogen production31 in animal studies, indicating an anti-inflammatory effect independent of plasma cholesterol lowering in the liver. These anti-inflammatory effects may improve vascular endothelial function.31

STRUCTURE AND HMG-CoA REDUCTASE BINDING

Rosuvastatin is a synthetic compound consisting of a single enantiomer (3R5S) formulated and administered as the calcium salt of the active hydroxy acid. The molecule consists of a di hydroxyheptenoic acid portion, the characteristic statin pharmacophore (Figure 2), which binds to the active site of the target enzyme, 3-hydroxy-3-methylglutaryl coenzyme A (HMG–CoA) reductase. The remainder of the molecule is structurally distinct from the corresponding portions of other statins. This latter non-HMG-CoA reductase binding domain of the rosuvastatin molecule includes a polar methane sulphonamide group that confers relatively low lipophilicity.32 Rosuvastatin (log D at pH 7.4, ¬- 0.33) therefore more closely resembles pravastatin (log D, - 0.84) in terms of lipophilicity when compared with other statins (log D >1 and >2 for atorvastatin, fluvastatin, simvastatin, and cerivastatin)33 Given its relative hydrophilicity, rosuvastatin exhibit limited access to non hepatic cells as a result of low passive diffusion and avid hepatic cell uptake via selective organic anion transport. In addition, the relative water solubility of the compound is associated with reduced need for cytochrome P450 (CYP) enzyme metabolism.

X-ray crystallography studies of binding between the catalytic domain of human HMG-CoA reductase and a number of statins indicate that statins inhibit this enzyme by attaching to its

active site and sterically inhibiting substrate binding.34 Compared with other statins (mevastatin, simvastatin, fluvastatin, cerivastatin, and atorvastatin), rosuvastatin has the greatest number of bonding interactions with HMG-CoA reductase, including a unique polar interaction between the Arg568 side chain of the enzyme and the electronegative sulfone group of rosuvastatin (Figure 3), as well as a variety of other interactions that occur in other enzyme–statin complexes. Another binding characteristic seen only with rosuvastatin and atorvastatin is a hydrogen bond between Ser565 and a sulfone oxygen atom (rosuvastatin) or a carbonyl oxygen atom (atorvastatin). Overall, the interactions between rosuvastatin and the active site of the enzyme distinguish this statin as the most potent HMG–CoA reductase inhibitor developed to date.

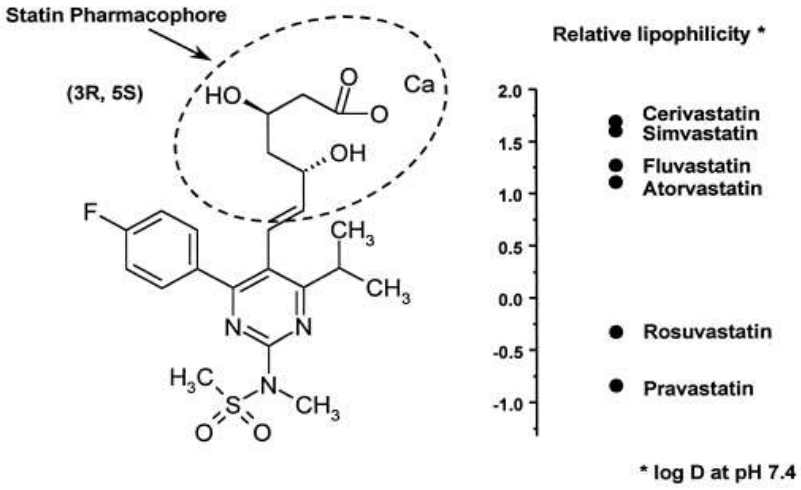

Figure 2: **Chemical Structure of Rosuvastatin**

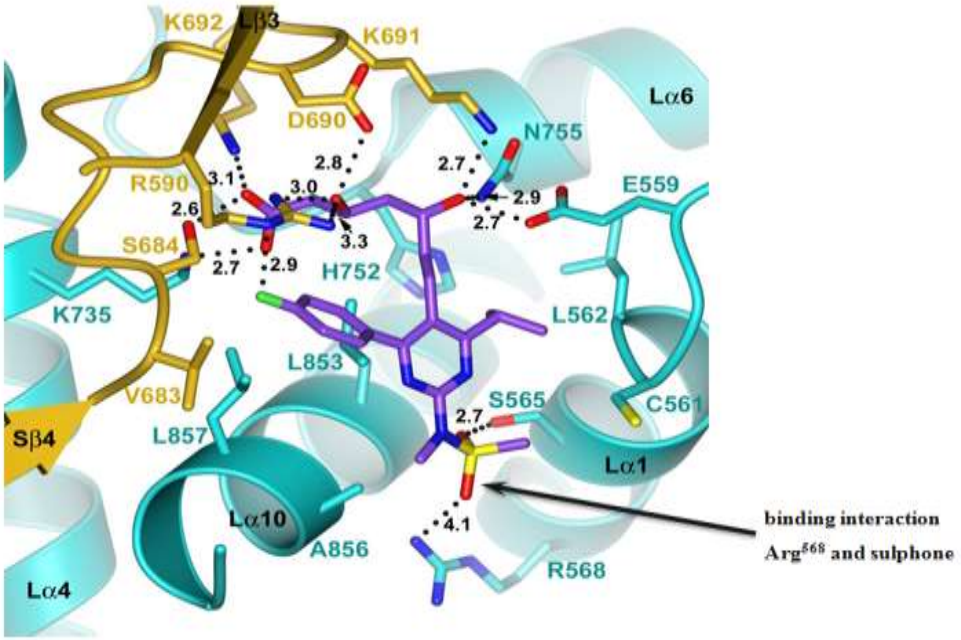

Figure 3: Rosuvastatin X-Ray Crystallography: Interaction between the Arg^{568} side chain of HMG-CoA reductase and Sulphone Group of Rosuvastatin.[34]

In accord with these binding characteristics, rosuvastatin exhibits a high affinity for the active site of HMG-CoA reductase, with an inhibition constant (Ki) of approximately 0.1 nM. Studies in a purified cloned catalytic fragment of human HMG-CoA reductase showed that rosuvastatin had a numerically lower 50% inhibitory concentration (IC50) value (5 nM) than atorvastatin (8 nM), cerivastatin (10 nM), simvastatin (11 nM), fluvastatin (28 nM) and pravastatin (44 nM) - statistically significant compared with simvastatin, fluvastatin, and pravastatin.35 In particular, rosuvastatin is about 8-fold more potent than pravastatin, which is closest to rosuvastatin in physicochemical properties.

PHARMACOKINETICS

In a pharmacokinetic study of 6 adult volunteers (mean age, 43.7 years) taking rosuvastatin 10 to 80 mg/d PO for 10 days, the time to maximum plasma concentration ranged from 3 to 5 hours.36 Both peak concentration and area under the plasma concentration-time curve increased in proportion to the rosuvastatin dose.36 In another pharmacokinetic study in 24 healthy volunteers, the pharmacokinetic profile determined after administration of rosuvastatin 10 mg/d for 14 days was not affected by time of drug administration (either morning or evening).37 The bioavailability of rosuvastatin 40 mg PO was determined to be 20% in 10 male volunteers.37 Administration of rosuvastatin with food reduces the rate of drug absorption by 20% but does not affect the extent of absorption.37 Rosuvastatin has a mean volume of distribution at steady state of 134 L and is 88% bound to plasma protein, mostly albumin. The protein binding is reversible and independent of plasma rosuvastatin concentration.37 Only 10% of the administered dose of rosuvastatin is metabolized by the cytochrome P-450 (CYP) 2C9 enzyme into N-desmethylrosuvastatin.38 This metabolite has 17% to 50% of the HMG-CoA reductase inhibitor activity of rosuvastatin. Rosuvastatin and its metabolite are 90% eliminated by the fecal route. The elimination half-life of rosuvastatin is 19 hours.38 In a study of the effect of age and sex on the pharmacokinetic profile of rosuvastatin, 16 men and 16 women (overall age range, 18-73 years; 8 of each were aged 18-35 years and >65 years) were given rosuvastatin 40 mg/d for 4 days. The pharmacokinetic profiles of rosuvastatin after 4 days were similar regardless of age and sex.39 In another study, rosuvastatin 10 mg was administered to 6 patients with mild hepatic dysfunction (Child-Pugh class A), 6 patients with moderate hepatic dysfunction (Child-Pugh class B), and 6 patients with normal hepatic function for 14 days.40 The maximum plasma concentrations of rosuvastatin were increased by 60% and 100%, respectively, and the areas under the plasma concentration-time curve were increased by 5% and 21%, respectively, in patients with mild and moderate hepatic dysfunction as compared with healthy subjects.40 However, the degree of LDL-C reduction was similar to that of subjects with normal hepatic

function.40 Mild to moderate renal dysfunction has no effect on rosuvastatin pharmacokinetics. However, plasma concentrations of rosuvastatin were increased by 3-fold in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m2) as compared with healthy subjects. It has also been demonstrated that, when given the same dose, Japanese and Chinese subjects have a 2-fold elevation in median exposure (area under the concentration-time curve) compared with white subjects.29

LIVER SELECTIVITY

The polar methyl sulfonamide moiety of rosuvastatin confers relative hydrophilicity to the molecule. In a study measuring octanol-water coefficients of the statins (all measured in open acid form), values of log D at pH 7.4 were -0.84 for pravastatin and -0.33 for rosuvastatin, compared with values of > 1.0 to < 2.0 for atorvastatin, fluvastatin, simvastatin, and cerivastatin. Thus, rosuvastatin and pravastatin are relatively hydrophilic, compared with the other statins.41

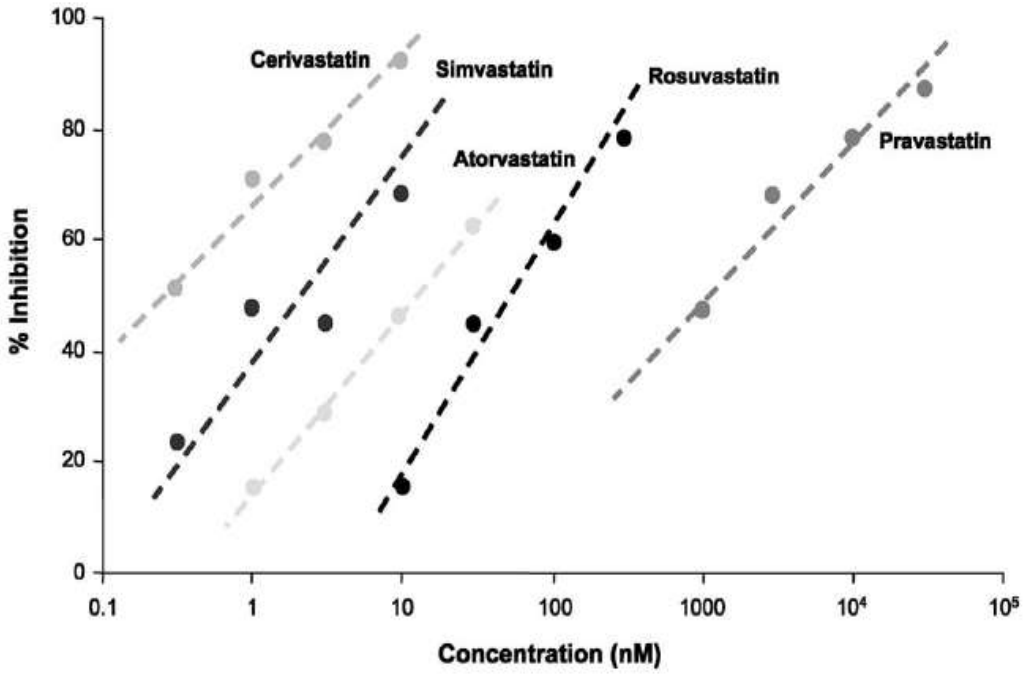

Figure 4: **Concentration-related Inhibition of Cholesterol Synthesis in Primary Cultures of Human Skeletal Muscle Cells by Rosuvastatin, Pravastatin, Atorvastatin, Simvastatin, and Cerivastatin.[43]**

The importance of this characteristic resides in the fact that the more lipophilic molecules are likely to have unrestricted access to many cell types throughout the body by passive diffusion across the cell membranes. In contrast, statins with greater hydrophilicity would have lower rates of passive diffusion and exhibit high rates of uptake only in cells such as hepatocytes that express active transporters with high affinity for organic anions, such as the statins. Studies have demonstrated that rosuvastatin is taken up into hepatocytes by both passive

diffusion and active transport, with the latter mechanism predominating at low concentrations. It has also been shown that rosuvastatin is a substrate for the human liver-specific organic anion transport protein OATP-C, with an apparent Km of 7.3 µM.41,42 The effect of the statins in inhibiting cholesterol synthesis in cultured human skeletal muscle cells has also been examined, since muscle toxicity is a characteristic though infrequent adverse effect of statin treatment. As shown in Figure 4, results of experiments with primary cultures of human myocytes showed that the hydrophilic statins pravastatin and rosuvastatin were approximately 50- to 1000-fold less potent in inhibiting cholesterol synthesis in these cells, compared with the more lipophilic examples, atorvastatin, simvastatin, and cerivastatin.43

MINIMAL CYTOCHROME P450 METABOLISM

Consistent with its relatively hydrophilic character, rosuvastatin exhibits minimal metabolism via the cytochrome P450 (CYP) system, including little or no metabolism via CYP 3A4, the isoenzyme implicated in a wide variety of drug-drug interactions. Rosuvastatin appears to undergo minimal metabolism in vivo.44 No metabolism of rosuvastatin has been detected in experiments in which rosuvastatin was incubated with human hepatic microsomes, and no effect on the metabolism of specific probe substrates by a range of CYP isoforms was detected. Incubation of human liver cells with rosuvastatin for 48 h resulted in only low rates of metabolism, with this low degree of metabolism being attributable to CYP 2C9 and, to a lesser extent, CYP 2C19. No significant metabolism by CYP 3A4 was observed.

The lack of importance of P450 isoenzymes to rosuvastatin clearance is also evident from a series of clinical drug interaction studies with known CYP 3A4 and CYP 2C9 inhibitors45,46,47. The minimal metabolism of rosuvastatin by the CYP system differentiates it from simvastatin and atorvastatin, both of which undergo extensive CYP 3A4 metabolism. Cerivastatin undergoes metabolism by CYP 2C8 and 3A4 isoenzymes. Several statins, including simvastatin, lovastatin, rosuvastatin, atorvastatin, and cerivastatin, are conjugated by glucuronidation.48

SYSTEMIC AVAILABILITY

The known high-affinity uptake of rosuvastatin into liver cells is consistent with clinical studies that show a high degree of hepatic extraction after oral dosing and a low degree of systemic bioavailability that is consistent with other statins, such as pravastatin. Relatively lower systemic availability can be considered an important attribute of a statin, as well as the selectivity for uptake into hepatic versus non-hepatic cells.

PROLONGED ELIMINATION HALF-LIFE

In the context of potent HMG-CoA reductase inhibition in combination with selective uptake into and activity in hepatic cells and moderate-to-low systemic availability, a prolonged

elimination half-life can constitute a relative advantage for a statin, in that it can ensure maintained inhibition of the liver enzyme during the dosing interval and maximal associated upregulation of hepatic LDL receptors. Of available statins, rosuvastatin has the longest elimination half-life, approximately 20 h 49 compared with 14 h for atorvastatin and 1-2 h for fluvastatin, pravastatin, and simvastatin (2-3 h for cerivastatin).

CLINICAL TRIALS

There have been a number of clinical studies evaluating rosuvastatin on its own, against placebo and against other statins in various clinical settings.

The GALAXY Program is a comprehensive global research initiative involving series of clinical studies investigating the efficacy and tolerability of rosuvastatin in line with the hypothesis that the statin with the greatest efficacy for improving the atherogenic lipid profile and beneficially modifying inflammatory markers will also slow progression of atherosclerosis and improve cardiovascular outcomes. Some of the important clinical trials under this programme are listed below:

Studies designed to investigate the effect of rosuvastatin on the 'atherogenic lipid profile' are STELLAR, MERCURY I, MERCURY II, ORBITAL, DISCOVERY, COMETS, LUNAR, PLUTO, POLARIS, PULSAR, CENTUARUS. Two of these studies, COMETS and LUNAR also assess the effects of rosuvastatin on inflammatory markers. Studies designed to investigate the effect of rosuvastatin on 'atherosclerosis' are METEOR, ASTEROID, ORION, COSMOS, SATURN.Studies designed to investigate the effect of rosuvastatin on 'cardiovascular morbidity and mortality' are AURORA, CORONA, JUPITER.

Clinical Trials on Primary Prevention

Clinical studies have demonstrated the benefits of statins in primary prevention. This is supposed principally to be secondary to reduction in LDL-C, high sensitivity C-reactive protein (hsCRP) and elevation of HDL-C though other effects are recognised. The Cholesterol Treatment Trialists' Collaborators (CTT) meta-analysis established that a 1 mmol/L reduction in LDL cholesterol results in a 20% reduction in cardiovascular risk.50

The benefit of statins in low risk populations was showed in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study where reduction of cholesterol using pravastatin 10 mg reduced cardiovascular events by 33%.51

JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) marked a significant juncture in primary cardiovascular disease prevention with statins.52 The participants had a mean Framingham risk score at baseline of 11.6% and would otherwise not have qualified for lipid lowering therapy. They were apparently healthy

individuals with normal levels of LDL-C and increased high-sensitivity C-reactive protein (hs-CRP).

JUPITER was a randomised, double blind, placebo-matched, multicentre trial conducted at 1315 sites in 26 countries. 17,802 participants received either 20 mg of rosuvastatin, or matched placebo, and were followed up every six months. 12 months into the study, the rosuvastatin group had a 50% lower median LDL-C, 37% lower median hsCRP and 17% lower median triglyceride level which persisted to study completion. The observed increase in HDL-C was transient. Results showed that rosuvastatin was linked with a significant reduction in first major cardiovascular events which was the primary endpoint. Reductions were further observed in the incidence of the individual components of the trial end point including myocardial infarction (54%), stroke (48%), arterial revascularisation (47%), unstable angina and death from cardiovascular causes. This is important as up to 50% of all myocardial infarctions and strokes occur in patients with LDL cholesterol concentrations that are considered normal.53

Clinical Trials on Secondary Prevention

As per STELLAR study (Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses)at different doses, rosuvastatin reduced total cholesterol better than other statins, and triglycerides better than simvastatin and pravastatin. Also a larger proportion of rosuvastatin patients achieved National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) LDL-C targets when compared with atorvastatin.54,55 PULSAR (Prospective Study to Evaluate Low Doses of Atorvastatin and Rosuvastatin) demonstrated that in hypercholesterolaemic patients with vascular occlusive disease rosuvastatin 10 mg was better than atorvastatin 20 mg at reducing LDL-C, improving other lipid parameters and enabling achievement of US and European treatment goals. 55,56,57

Impact of high dose rosuvastatin on regression of atherosclerosis was investigated by ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-derived Coronary Atheroma Burden). The results showed that rosuvastatin 40 mg produced significant reduction in LDL-C (53% from baseline; $P < 0.001$), increase in HDL-C (14.7% from baseline; $P < 0.001$) and regression of atheroma volume in the most diseased coronary arteries in 78% of participants. A median reduction of 6.8% in atheroma volume was recorded by IVUS (intravascular ultrasound).58,59

Rosuvastatin 40 mg achieved a 49% LDL-C reduction and slowed progression of atherosclerosis as assessed by carotid intima-media thickness (CIMT) but did not result in regression of CIMT these findings were demonstrated by ORION (Outcome of Rosuvastatin

Treatment on Carotid Artery Atheroma: a Magnetic Resonance Imaging Observation) and METEOR (Measuring Effects on Intima Media Thickness: an Evaluation of Rosuvastatin). The lack of plaque regression may have occurred because low risk patients with minimal subclinical carotid atherosclerosis were used in the study. The COSMOS (Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects) study established that rosuvastatin achieved significant reduction of coronary plaque volume with good safety in stable Japanese CHD patients.60,61

SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin) study compared maximal doses of rosuvastatin and atorvastatin on coronary atheroma. This study reported that although rosuvastatin achieved lower LDL-C and higher HDL-C, both agents produced similar percentage reduction in atheroma volume.62

As per NCEP ATP III guidelines, intensive statin treatment should be used in patients admitted with acute coronary syndrome (NCEP 2001). The European Society of Cardiology (ESC) and the American College of Cardiology (ACC) have recommended LDL-C levels of 1.8 mmol/L as the optimal target for very high risk patients (established CHD, type I diabetes with end organ damage, moderate to severe chronic kidney disease (CKD) or a SCORE level >10%).63

SPACEROCKET (Secondary Prevention of Acute Coronary Events—Reduction of Cholesterol to Key European Targets Trial) study showed that a larger proportion of patients on rosuvastatin 10 mg achieved ESC, ACC and American Heart Association (AHA) optimal LDL-C target of less than 1.81 mmol/L when compared to those on simvastatin 40 mg. A critical observation of SPACEROCKET was that in both treatment arms, most patients did not achieve these targets, highlighting the importance of intensive statin therapy to meet these goals. The superior lipid lowering effect of rosuvastatin makes it a good candidate for intensive lipid lowering.64

Rosuvastatin20 mg produced similar changes in ApoB:ApoA-1 ratio at 3 months when compared with atorvastatin 80 mg, these were the findings of CENTAURUS (Comparison of the Effects Noted in The ApoB:ApoA-1 ratio Using Rosuvastatin or Atorvastatin in Patients with Acute Coronary Syndrome). ApoB:ApoA-1 ratio is an important predictor of myocardial infarction. In the same study rosuvastatin 20 mg achieved similar LDL-C reduction as atorvastatin 80 mg. This study therefore showed that rosuvastatin 20 mg is as effective as atorvastatin 80 mg in intensive statin therapy.65

SAFETY

The incidence of adverse events during rosuvastatin therapy was comparable to those of other statins as per the safety data of controlled Phase II/II trials. Rosuvastatin has a comparable

safety profile to other available statins when used at 10 mg to 40 mg daily dose a shown by meta-analysis of clinical trials and post marketing experience 66

The most commonly reported adverse events (>2%) include pharyngitis, headache, diarrhea, dyspepsia, nausea, myalgia, asthenia, back pain, flu-like syndrome, urinary tract infection, rhinitis, and sinusitis. In comparative trials with other statins, the most commonly reported adverse events thought to be related to rosuvastatin were myalgia, constipation, asthenia, abdominal pain, and nausea.67,68,69,70 In JUPITER, hepatic injury, myopathy and cancer did not occur more frequently with rosuvastatin than with placebo, despite the fact that LDL-C <55 mg/dL (1.4 mmol/L) were achieved in half of the rosuvastatin group.71

All statins were associated with a dose dependent increased risk of myopathy with the exception of fluvastatin, these were the findings of a recent large prospective cohort study of primary care patients. All statins were associated with a dose dependent increased risk of liver dysfunction.The highest risk was associated with fluvastatin while pravastatin and rosuvastatin had the lowest risks.72

Frequency of rhabdomyolysis with rosuvastatin is very rare (<0.01%) which is in line with that reported for other marketed statins.29 Combination of statins with other medications may lead to increased risk if these medication increase plasma concentrations of the statins.

EFFICACY

Clinical trials like STELLAR, showed the greater efficacy of rosuvastatin in improving LDL-C, triglycerides and HDL-C. It is the most effective statin at increasing HDL-C and has a positive effect on apolipoprotein and lipid ratios.54 PULSAR compared the efficacy and safety of rosuvastatin 10 mg with atorvastatin 20 mg in high risk patients with vascular occlusive disease. Rosuvastatin 10 mg was better than atorvastatin 20 mg at improving LDL-C, HDL-C, triglycerides and ApoB/ApoA-1 ratio. Rosuvastatin also facilitated a greater proportion of treated patients to NCEP ATP III and ESC goals.57

ROSUVASTATIN'S PLACE IN THERAPY

Rosuvastatin is a potent statin with pharmacologic and pharmacokinetic advantages. Its high degree of liver selectivity results in high hepatic concentration leading to superior efficacy at lowering low density lipoprotein cholesterol and triglycerides as well as improving high density lipoprotein cholesterol compared to other statins. Rosuvastatin has relatively low lipophilicity when compared with other statins and has minimal entry into peripheral cells. This along with its minimal CYP450 metabolism presents relatively better tolerability, safety and drug interaction profile. As the circulating half life is 19 hrs it can be taken once daily at any time of the day regardless of meals.

Clinical trial data and post marketing surveillance have demonstrated important information about rosuvastatin. Several cardiovascular outcome studies have confirmed the beneficial effects that had been anticipated from vascular imaging studies. JUPITER showed the reduction in cardiovascular events and all cause mortality of rosuvastatin in primary prevention in patients with lower cardiovascular risk.71This is the only statin that has been shown to reduce cardiovascular and all cause mortality. Comparative studies have shown the potential benefits of rosuvastatin in secondary prevention and high intensity therapy54,57.

Patients with a 10 year cardiovascular risk of >20% require intensive treatment to achieve required LDL-C goals. These include patients with established CHD, moderate to severe CKD, type 1 and type 2 diabetes. Only rosuvastatin 20 mg–40 mg and atorvastatin 80 mg achieve this reduction as monotherapy. A large proportion of these patients are on multiple drug therapy and thus it is crucial to limit pill burden and avoid drug interactions. Most lipid therapy is now aimed at achieving treatment goals from guideline bodies such as ESC, JBS and NCEP ATP III. A new category of patients is thus created by those who fail to achieve these goals with various treatments. Such patients should be considered for treatment with rosuvastatin.27

CONCLUSION

Rosuvastatin is a potent statin with pharmacologic and pharmacokinetic advantages. Its high degree of liver selectivity results in high hepatic concentration leading to superior efficacy at lowering LDL-C and TGs as well as improving HDL-C compared to other statins. Rosuvastatin has relatively low lipophilicity when compared with other statins and has minimal entry into peripheral cells. This along with its minimal CYP450 metabolism presents relatively better tolerability, safety and drug interaction profile. It can be taken once daily at any time of the day regardless of mealsas it is having a half life of around 19 hrs. Consistent with these features, rosuvastatin represents a step forward in the statin therapy.

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