Hyperlipidemia & its Management by using Rosuvastatin : A review

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Abstract

Hyperlipidemia is the leading risk factor for cardiovascular diseases. It is a medical condition characterized by an increase in one or more of the plasma lipids, including triglycerides, cholesterol, cholesterol esters, phospholipids and or plasma lipoproteins including very low-density lipoprotein and low-density lipoprotein along with reduced high-density lipoprotein levels. Cholesterol and triglycerides together make it difficult for blood to pass by narrowing the blood vessels. The present review focuses mainly on the types of hyperlipidemias, lipid metabolism, treatments using Rosuvastatin. It inhibits HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase and have beneficial effects on atherosclerosis including plaque stabilization, reduction of platelet activation, and reduction of plaque proliferation and inflammation. As with other statins, rosuvastatin is an appropriate therapy in addition to antihypertensive treatment to reduce cardiovascular risks. Rosuvastatin is a potent statin, which appeared to raise levels of HDL-cholesterol, in addition to marked reductions in levels of LDL-cholesterol. These effects on lipids are associated with a beneficial impact of rosuvastatin on progression of various stages of atherosclerosis and cardiovascular outcomes.

Keywords: Hyperlipidemia, Cardiovascular diseases, Lipids, Rosuvastatin, HMG-CoA coenzyme

Introduction: Hyperlipidemia is the most common risk factor related to the various cardiovascular diseases. Hyperlipidemia is very common. About ninety-three million American adults (age 20 and older) have a total cholesterol count above the recommended limit of 200 mg/dL. Patients with hyperlipidemia are about twice as likely to develop cardiovascular disease (CVD). It is a condition that incorporates various genetic and acquired disorders which increases the lipid levels within the human body. Lipids typically include cholesterol levels, lipoproteins, chylomicrons, VLDL, LDL, apolipoproteins, and HDL[3] .Epidemiological studies have established a strong correlation between cholesterol and the incidence of cardiovascular disease. The associated morbidity and mortality is positively correlated to low density lipoprotein cholesterol (LDL-C) and inversely related to high density lipoprotein cholesterol (HDL-C). [7,8]

Cholesterol is involved in building the membrane of the cells and hormones. Cholesterol's physiological roles include[9]

(1) cell membrane constituent;

(2) precursor for synthesis of steroid hormones, bile acids, and oxysterols;

(3) modifier of neuronal signalling molecules.

Liver produces approximately 80% of the cholesterol whereas rest of the cholesterol is obtained from the food like fish, eggs, meat, etc[1] . Elevated levels of LDL cholesterol increase a person's risk for the development of atherosclerotic plaques and subsequent vascular disease. The main etiology of elevated cholesterol in blood is high intake of several saturated fats [5]

Hyperlipidemia, also known as hyperlipoproteinemia or high cholesterol, is a disorder characterized by abnormally high concentrations of lipids (fats) in the blood that are correlated with the development of atherosclerosis, the underlying cause of coronary heart disease (CHD) and stroke[2]

Inside arterial vessel there is formation of atherosclerotic plaques due to the presence of hyperlipidemia [4] Blood flow may obstruct by plaque rupture as it may cause a clotting of blood which may lead to heart attack.

Plaque is comprised of cholesterol, fat & different substances found in the blood.

Lipoproteins are basically categorized into three types [10]:

- LDL (Low Density Lipoprotein)
- HDL (High Density Lipoprotein)
- VLDL (Very Low Density Lipoprotein)
- IDL (Intermediate-density lipoproteins)
- Chylomicrons (CM)

Here is normal lipid profile:

1. Fasting triglyceride level:
- Normal: less than 150 mg/dL
- Mild hypertriglyceridemia: 150 to 499 mg/dL
- Moderate hypertriglyceridemia: 500 to 886 mg/dL
- Very high or severe hypertriglyceridemia: greater than 886 mg/dL

2. LDL-C level:
- Optimal: less than 100 mg/ dL
- Near optimal/above optimal:100 to 129 mg/dL
- Borderline high: 130 to 159 mg/dL
- High: 160 to 189 mg/dL
- Very high: greater than 190 mg/dL

3. HDL level:
- Low: less than 40
- High: greater than or equal to 60

Total cholesterol – It is a measure of the total amount of cholesterol in your blood. It includes both LDL and HDL.
LDL cholesterol - LDL is known as 'bad' cholesterol due to higher ratio of cholesterol content to protein which increases the risk of developing heart disease, stroke, etc. It is the main sourceof cholesterol buildup and blockage in the arteries.
HDL cholesterol – HDL is good cholesterol as it helps to remove cholesterol from your arteries
Non-HDL - this number is your total cholesterol minus your HDL. Your non-HDL includes LDL and other types of cholesterol such as VLDL (very-low-density lipoprotein).
Triglycerides - another form of fat in your blood that can raise your risk for heart disease, especially in women.

Types of Hyperlipidemia: The main types of hyperlipidemia having different effects on the body are the following: [45]

- **Type I**: Children are mostly by this type of hyperlipidemia. It may cause infections in pancreas, enlargement of liver and also cause abdominal pain. This is hereditary and also known as LPL deficiency which may destruct the breakdown of fats.
- **Type II:** This is the high level of LDL which may deposits fat around the eyes.
- **Type III:** This basically affects the level of lipoproteins. The level of LDL is low and HDL is normal. It may cause yellowish grey plaques around the eyes. It increases the early onset of cardiovascular disease .
- **Type IV:** The cholesterol level decreased whereas the level of triglycerides elevated which may leads to obesity

Complications of hyperlipidemia: [45]
Atherosclerosis

Coronary Artery Disease (CAD)
Myocardial Infarction (MI)
Ischemic stroke

Causes:

Cholesterol, saturated fat, trans fat in the following food may raise the lipid level in blood

• Dairy products.
• Ice cream pastries.
• Fried and junk foods.
• Meat etc.[11]

Other disorders like obesity, diabetes mellitus and hypothyroidism is major causes for hyperlipidemia. Smoking and low exercising may lead to hyperlipidemia[12].

Excessive use of alcohol also increases the risk of hyperlipidemia. Certain drugs as steroids and β– blockers may cause hyperlipidemia . Lipoprotein lipase mutations[13].

Several other causes of hyperlipidemia are:

• Obesity.
• Genetic or inheritance.
• Smoking.
• Several drugs such as corticosteroids, estrogen, betablockers may risk for hypertriglyceridemia.
• Alcohol, steroids, hypothyroidism, kidney failure etc.
• Low exercise [14]

SYMPTOMS OF HYPERLIPIDEMIA

Hyperlipidemia usually has no noticeable symptoms and tends to be discovered during routine examination for atherosclerotic cardiovascular disease [15]

•chest pain (angina), heart attack or stroke.
• When levels are exceed high, cholesterol may be deposited in tendons or just beneath the skin under the eyes.
• liver, spleen or pancreas are swelled .
• blood vessels block in brain and heart.
• Higher rate of obesity and glucose intolerance.
• Pimple like lesions across the body[16]

Diagnosis:

No any other specific symptom for Hyperlipidemia it can be only detected by a blood test. Hyperlipidemia may be diagnosed by a regular checkup of LDL, HDL, VLDL and Triglycerides in blood test [17]

TREATMENT:

Pharmacological Treatments: [18,49]

• Statins
• Fibrates
• Bile acid binding resins,
• Nicotinic acid derivatives

Non-Pharmacological Treatments: The following lifestyle modification may lower the cholesterol level:

- Proper diet.
- Less weight of the body.
- Regular exercise.
- Having non-oily food.

Statins: According to several national guidelines,[19] statins are recommended as first-line therapy for CAD(coronary artery disease) because a significant body of literature supports their use for primary prevention, particularly in higher risk patients. Statin therapy is also supported for secondary prevention in known cardiovascular disease patients or those with the risk equivalent.[20] A meta-analysis of over 90,000 participants determined that reducing LDL-C levels by an average of 39 mg/dL will yield a 23% reduction in cardiovascular risk over 5 years.[21]

Rosuvastatin belongs to a new generation of methane-sulphonamide pyrimidine and N-methane sulfonyl pyrrole-substituted 3, 5- dihydroxy-heptenoates. Although the characteristic statin pharmacophore remains similar to other statins, the addition of a stable polar methane-sulphonamide group provides low lipophilicity and enhanced ionic interaction with HMG-CoA reductase enzyme thus improving its binding affinity to this enzyme.[16–18]

Newer, so-called high-intensity statin therapy (second or third generation statins, e.g., 20–40 mg/day of Rosuvastatin) was developed and has had even more success in lowering LDL-C levels.[22,23]

Pharmacodynamics

Rosuvastatin has demonstrated comparable reductions in triglyceride (TG) concentrations to other statins with the greatest benefit seen in patients with high baseline TG levels. Studies have shown rosuvastatin to increase HDL-C by 8%–12% with no clear relationship between the dose and response, although the increase is greatest in patients with low baseline HDL-C levels.[28,29] The affinity of rosuvastatin for the active site of the enzyme is four times greater than the affinity of HMG-CoA for the enzyme. It has the highest affinity for HMG-CoA reductase among statins marketed in Europe. Rosuvastatin and other statins improve endothelial function by increasing the production of endothelial nitric oxide and reducing the production of oxygen derived free radicals. This in turn reduces endothelial dysfunction that has been implicated in atherosclerosis[46]. Rosuvastatin inhibits platelet aggregation to leukocytes which inhibit formation of clots in injured endothelium[30].

Pharmacokinetics

The oral bioavailability of rosuvastatin is 20%, which is comparable to atorvastatin, pravastatin and fluvastatin, and qualitatively higher than simvastatin and lovastatin. After a single oral dose the peak plasma concentration is reached at 5 hours. This is longer than other HMG-CoA inhibitors which achieve maximum plasma concentrations in less than 3 hours. Food intake decreases the rate of absorption of rosuvastatin by 20% but not the extent of absorption. This does not reduce the cholesterol lowering potency; therefore rosuvastatin can be taken with or

without food, and in the morning or evening. Rosuvastatin is metabolised to an N-desmethyl metabolite which is less potent than the parent drug in inhibiting HMG-CoA reductase activity. The parent drug rosuvastatin is responsible for approximately 90% of plasma HMG-CoA inhibitor activity. Rosuvastatin is less likely to cause metabolic drug to drug interactions since it has limited metabolism by CYP isoenzymes. Rosuvastatin has a plasma half life of 19 hours. Approximately 72% of absorbed rosuvastatin is eliminated in bile and 28% via renal excretion.[31]

Mechanism of action:

Statins inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase. This inhibition occurs early in the hepatic pathway that produces not only cholesterol but also other vital metabolic products.[24] Rosuvastatin therefore decreases hepatic sterol synthesis, which, in turn, leads to a decreased concentration of hepatocellular cholesterol. Cholesterol itself is an intermediate product in pathways that produce corticosteroids, sex steroids, Vitamin D, and bile acids. Decreased cholesterol synthesis results in upregulation of LDL-C receptors on the surface of the hepatocyte and greater clearance of LDL-C from the plasma. Effective statin therapy will reduce LDL-C, reduce triglycerides, and modestly raise HDL levels. Statins have other beneficial effects on atherosclerosis including plaque stabilization, reduction of platelet activation, and reduction of plaque proliferation and inflammation.

In the **JUPITER** (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) study, rosuvastatin was also found to be effective in reducing the occurrence of symptomatic venous thromboembolism[32].

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 [41,42,43].

In the **ASTEROID** (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound Derived Coronary Atheroma Burden) study, rosuvastatin 40 mg daily for 24 months produced a significant regression of coronary atherosclerosis in 349 patients with coronary heart disease

statins have pleiotropic effects on vascular function, with mechanisms that of vascular nitric oxide, inhibition of vascular smooth-muscle cell proliferation and migration, anti-inflammatory actions, down regulation of angiotensin II type 1 receptor expression, and antioxidative effects.36–38 It has been suggested that most patients with hypertension should take statin treatment to reduce cardiovascular risk in addition to their antihypertensive treatment[50].

Cornonary Heart Disease:

The STELLAR study (Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses) showed that at different doses, rosuvastatin reduced total cholesterol better than other statins, and triglycerides better than simvastatin and pravastatin. Additionally 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 [37,38] PULSAR (Prospective Study to Evaluate Low Doses of Atorvastatin and Rosuvastatin) showed that in hypercholesterolaemic patients with vascular occlusive disease rosuvastatin 10 mg was better than atorvastatin 20 mg at reducing LDL-C [46].

Familial hypercholesterolaemia (FH): Many FH guidelines recommend a .50% reduction of LDL-C in heterozygous FH. Studies comparing different lipid lowering regimens demonstrate that only high impact therapy with rosuvastatin 40 mg or atorvastatin 80 mg achieves this goal when administered as monotherapy[39].

Stroke:

JUPITER showed a 51% reduction in ischaemic stroke with rosuvastatin, though no beneficial effects were observed for transient ischaemic attacks or haemorrhagic strokes. These benefits were present in all patient groups including women, non smokers and other low risk patients[46]. Rosuvastatin not only reduces the risk of stroke as shown in JUPITER but also slows the rate of progression of carotid atherosclerosis as observed in the ORION and METEOR studies[36]

Uses:

Rosuvastatin is employed in conjunction with a correct diet to assist lower "bad" cholesterin and fats (such as β-lipoprotein, triglycerides) and lift "good" cholesterin (HDL) within the blood. It belongs to a gaggle of medicine referred to as "statins." It works by reducing the quantity of cholesterin created by the liver. Lowering "bad" cholesterin and triglycerides and raising "good" cholesterin decreases the danger of cardiovascular disease and helps to stop strokes and heart attacks [33-35]. In addition to ingestion a correct diet (such as an occasional cholesterol/low-fat diet), alternative style changes which will facilitate this medication work higher embrace elbow grease, losing weight if overweight, and stopping smoking[47]

Efficacy:

The STELLAR study 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. Most of the lipid modifying benefit observed in the study was achieved at a 10 mg daily dose [40]

Rosuvastatin drug interactions: [46]

Drugs that increase plasma concentrations of rosuvastatin

A. Drugs that antagonise organic anion transporting polypeptide 1B1
- Gemfibrozil
- Protease inhibitors: ritonavir, liponavir, Cyclosporin

B. Drugs that reduce plasma concentrations of rosuvastatin
- Antacids
- Erythromycin

C. Drugs affected by co-administration with rosuvastatin
- Warfarin increased INR
- Ethinyl oestradiol: increased concentrations

Adverse Effects: [44]

- Creatinine kinase of greater than ten times the upper limit of normal
- Severe myopathy
- Rhabdomyolysis
- Development of type 2 diabetes mellitus [48]
- The most common toxic side effect of rosuvastatin is myalgia.
- This medication could seldom cause liver issues.

Rare adverse effects include hematuria, proteinuria, and hypersensitivity.

Other reported symptomatic adverse effects include headache, dizziness, nausea, constipation, interstitial cystitis, arthralgia, and weakness.

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. Prescribing and monitoring the patient depend upon communication between the physicians, cardiologists, pharmacists, nursing staff. Although there is a slightly increased risk of incident diabetes with rosuvastatin, as with other statins, the absolute benefit of statin therapy on cardiovascular events overweighs this risk in patients with moderate or high cardiovascular risk, including many patients with hypertension or diabetes or those with documented CVD. The prescriber should determine the risks versus benefits of the medication in conjunction with the patient after an informed consent discussion with shared decision making.

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