

## Review Article

# Pharmacokinetic Interactions of Rosuvastatin: A Review

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Received Date: 9 September 2012

Revised Date: 12 October 2012

Accepted Date: 18 October 2012

### Abstract

Rosuvastatin was claimed a “super-statin” to lower the LDL cholesterol comparing with other statins. An excellent benefit-risk profile of Rosuvastatin makes it more acceptable to treat dyslipidemia. Safety profile is also comparable with other marketed statin. This statin is widely prescribed to treat hyperlipidemics in combination with other drugs. Interactions with other co-prescribed drugs might potentiate or lower its therapeutic effectiveness.

This review accentuates the origin of rosuvastatin in the family of statins and highlights the various interactions specifically pharmacokinetic interactions with other drugs that are commonly prescribed in its combination.

**Keywords:** Rosuvastatin, Interactions, Statins, Hyperlipidemia

### 1. Statins

The statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase competitively. HMG-CoA reductase has a key role in biosynthesis of cholesterol. The HMG CoA reductase inhibitors (statins) can cause comparatively large decline in plasma cholesterol levels (Corsini et al., 1999; Havel and Rapaport, 1995). Triglycerides are also reduced in plasma by increased doses of potent statins like Atorvastatin and Simvastatin. Various clinical trials suggests that statins reduces CHD events, strokes and overall mortality (Goodman Gilman, 2006). Simvastatin, Fluvastatin, Lovastatin, Pravastatin, Atorvastatin, Rosuvastatin and Pitavastatin are seven statins that are available in pharmaceutical form now a day's (Steinmetz et al., 2002; Asztalos et al., 2002). Classification of statins can also be made as natural and synthetic (Corsini et al., 1995; Thompson et al., 2000). After the reports of rhabdomyolysis in 2001, manufacturers withdrew Cerivastatin from market (Farmer, 2001; Staffa et al., 2002). All the statins are present in active form except Lovastatin and simvastatin as these are pro-drugs and are transformed in to its active forms in liver (Corsini et al., 1995). Some of the major procedures that have a role in the formation of atherosclerotic lesions are hindered by some of the statins, this phenomena is proved by variety of

clinical and experimental supports, so statins also have other roles other than hypolipidemic properties (Bellosta et al., 1998; Corsini et al., 1998; Herd et al., 1997; Driscoll et al., 1997; Rosenson and Tangney, 1998; Williams et al., 1998).

## 2. History of Statins

Isolation of Statins was carried out from *penicillium citrinum*, a mold. In 1976 Endo and colleagues suggested that statins has a role in the inhibition of cholesterol biosynthesis. Further studies by Brown and Goldstein confirmed that the target of statins is HMG-CoA reductase. Compactin was the first statin studied, it is also called Mevastatin. However first statin was Lovastatin, it was a work of Alberts and colleagues at Merck. *Aspergillus terreus* was a source of Lovastatin. The chemical modification of Lovastatin leads to Pravastatin and Simvastatin. Other Statins like Rosuvastatin, Atorvastatin, and Fluvastatin are synthetic compounds having different chemical structure (Goodman Gilman, 2006).

## 3. Rosuvastatin

Rosuvastatin is a new and latest drug in the statin group; it was first of all synthesized by Shionogi and Co, Ltd. Later Rosuvastatin accomplished phase-3 clinical studies at AstraZeneca. Rosuvastatin is indicated for several dyslipidemic conditions. In Clinical Studies, Rosuvastatin 1-80 mg reduced low density Lipoprotein cholesterol to a great extent. It also reduced the level of triglycerides (Ken-Ichi Nezasa et al., 2002). Statin family also consists of Atorvastatin, Simvastatin, pravastatin, Fluvastatin, Lovastatin (Thammera et al., 2006). Rosuvastatin is an active inhibitor of 3-hydroxy-3-methylglutaryl coenzyme (HMG-CoA reductase inhibitors) (Ke Lan, 2007). Rosuvastatin is taken by the liver to a great extent specifically (Dong-Hang Xu et al., 2006). Description has been summarized in table 1.

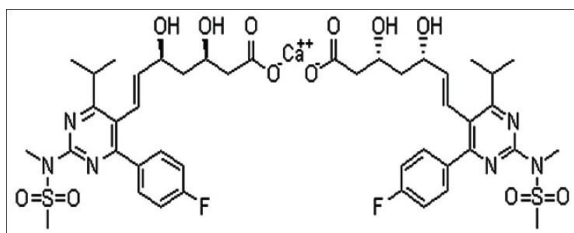
**Table 1:** General description of rosuvastatin

Physical Characteristics	Chemical characteristics	Dosage form and strength	Indication
<p><b>Colour</b> White</p> <p><b>State</b> An amorphous powder</p> <p><b>Melting point</b> 122 °C</p> <p><b>Solubility</b> It is moderately soluble in water and methanol and soluble in Ethanol to some extent.</p>	<p><b>Molecular Formula</b> 2(C<sub>22</sub>H<sub>27</sub>FN<sub>3</sub>O<sub>6</sub>S).Ca; C<sub>44</sub>H<sub>54</sub>CaF<sub>2</sub>N<sub>6</sub>O<sub>12</sub>S<sub>2</sub></p> <p><b>Molecular Weight</b> 1001.14</p> <p><b>Structure Chemical Name</b> 7-{4-(4-Fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl) amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid</p> <p><b>Chemical Class</b> HMG CoA reductase inhibitors; Statin</p>	<p>Film coated Tablets: 5mg, 10mg, 29mg, and 40m</p>	<p>Hyperlipidemia Hypertriglyceridemia Primary Dysbetalipoproteinemia Homozygous Familial Hypercholesterolemia Slow down progression of Atherosclerosis Primary prevention of cardiovascular diseases</p>

### 3.1 Chemistry of Rosuvastatin

Rosuvastatin is prepared synthetically, it is a single enantiomer (3R, 5S) prepared and is available as Rosuvastatin Calcium in market. Its chemical name is bis {(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl (methylsulfonyl) amino] pyrimidin-5-yl]-3, 5-dihydroxyhept-6-enoic acid} calcium salt, shown in figure 1. Its empirical formula is (C<sub>22</sub>H<sub>27</sub>FN<sub>3</sub>O<sub>6</sub>S)<sub>2</sub>Ca. Molecular weight of Rosuvastatin calcium is 1001.14 (Anders G. Olsson, 2002). In the molecular structure of Rosuvastatin, the presence of heptenoic acid fraction is the distinguishing statin Pharmacophore. The remaining part of Rosuvastatin molecule is different from other members of statin group (Fergus McTaggart, 2003).

The presence of a polar hydroxyl group and methane sulphonamide group makes Rosuvastatin more hydrophilic (Michael Schachter, 2004).



**Figure 1:** Chemical structure of Rosuvastatin Calcium

### 3.2 Mechanism of Action of Rosuvastatin

As Rosuvastatin is a new HMG-CoA reductase inhibitor, it reduces low density lipoprotein and cholesterol level in plasma. It does so by inhibiting production of Mevalonate, a main step in the Cholesterol synthesis. Liver is the site of action where Rosuvastatin inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase. High cholesterol level is one of the main causes of cardiovascular problems; these risks are prevented by the use of drugs that lowers the cholesterol level in plasma (Yoshihisa Shitara et al., 2006). 3-Hydroxy-3-methylglutaryl fraction is present in the structure of newer statins, due to this newer statins shows high inhibitory effects, because HMG-moiety have more affinity towards HMG-CoA reductase (Yoshihisa Shitara et al., 2006). The activity of Rosuvastatin is specific for liver cells, where it shows its effect by blocking the biosynthesis of Cholesterol. Rosuvastatin is more potent drug than Atorvastatin; its activity is 7-times more than atorvastatin. As compared to other statins Rosuvastatin shows high activity and decrease in the cholesterol and low density lipoprotein level in the body (Fergus McTaggart, 2003).

Cholesterol level in plasma is reduced by Rosuvastatin by inhibiting biosynthesis of cholesterol in liver. As a result LDL receptor gene expression is increased.

As free cholesterol level in hepatocytes is decreased, as a result cleavage of membrane bound SREBPs takes place and translocation to the nucleolus occurs. This cleavage occurs due to protease. LDL receptor gene has sterol-responsive element, which are bounded by transcription factors, as a result transcription is increased and synthesis of LDL receptors also increased. There is a marked decrease in LDL receptors degradation, and increased number of LDL receptors is available on the surface of Hepatocytes. Which plays an important role in increased removal of LDL from blood, as a result LDL-C levels in blood is

decreased (Goodman Gilman, 2006).

### *3.3 Rosuvastatin affinity to HMG-CoA reductase*

Along with a specific Pharmacophore that is present in all statins, Rosuvastatin also have a polar sulfonamide fraction. This fraction exhibits exclusive interaction with HMG-CoA reductase. As other Statins experience various Vander Wall and polar attractive forces with HMG-CoA reductase, Along with these forces, Rosuvastatin also build a bond that is polar in nature, between electronegative sulfone fraction and the Arg568 part of HMG-CoA reductase (Fergus, 2003).

## **4. Pharmacokinetic Interactions of Rosuvastatin**

### *4.1 Effect of erythromycin*

A study was conducted by Cooper KJ et al., (2003) to observe the change in pharmacokinetics of Rosuvastatin when co-administered with Erythromycin. As erythromycin is a powerful inhibitor of CYP3A4 and increases the level of other statins in plasma. The study conducted did not show any increase in the plasma level of Rosuvastatin when administered along with Erythromycin. It shows that CYP3A4 mechanism of Rosuvastatin metabolism is not much important. When Atorvastatin is compared with Rosuvastatin, studies show that there is marked increase in Atorvastatin plasma levels when co-administered with Erythromycin. The mean  $C_{max}$  of Atorvastatin is increased up to 37.7%, and AUC is increased up to 32.5% when co-administered with Erythromycin, because statins like Atorvastatin, Simvastatin, and Lovastatin all are targets for CYP3A4, Rosuvastatin is not a substrate for CYP3A4. It indicates that metabolism involving CYP3A4 is not a significant clearance mean for Rosuvastatin (Cooper KJ et al., 2003).

### *4.2 Effect of Lopinavir/Ritonavir*

A study conducted in seronegative volunteers, to assess the pharmacokinetics of Rosuvastatin when administered alone and along with Lopinavir/Ritonavir. As a result AUC of Rosuvastatin was amplified 2.1 times when administered along with Lopinavir/Ritonavir; similarly  $C_{max}$  is increased 4.7 times, when given in combination. This interaction between Lopinavir/Ritonavir and Rosuvastatin is surprising, the mechanism of their interaction is not known up till now. But it is understood that unlike Atorvastatin and Simvastatin, Rosuvastatin does not depend upon CYP3A4. Ritonavir is a strong inhibitor of CYP3A4, the presence of Ritonavir and other Statins at the same time results the accumulation of Statins and their plasma level is increased (Jennifer J. Kiser et al., 2008).

### *4.3 Effect of Antifungals*

Fluconazole belongs to azole group of antifungals. Fluconazole is a strong inhibitor of CYP2C9 and CYP2C19. When a HMG-CoA reductase inhibitor Fluvastatin is administered along with Fluconazole, the level of Fluvastatin is increased in plasma, because Fluvastatin is metabolized by CYP2C9. So a study was carried out to evaluate the effects of Fluvastatin on the pharmacokinetics of Rosuvastatin.

In the study of Cooper KJ et al., (2002) it is concluded that co-administration of Rosuvastatin and fluconazole does not increase AUC and  $C_{max}$  of Rosuvastatin up to significant levels. As Fluconazole is a strong inhibitor of CYP2C9 and CYP2C19, but it do not affect the Pharmacokinetics of Rosuvastatin (Cooper KJ et al., 2002). Similarly the effects of Ketoconazole an important antifungal, on the pharmacokinetics of Rosuvastatin were also studies and evaluated by K.J. Cooper. The results of the study shows that AUC and  $C_{max}$  of Rosuvastatin were same after the co-administration with Ketoconazole and

then with placebo. So it is concluded that as pharmacokinetics of Rosuvastatin is not changed In vivo, so CYP<sub>450</sub> has no role in the clearance of Rosuvastatin (Cooper KJ et al., 2002).

#### 4.4 Effect of Rifampicin

Rifampicin is an antibiotic and widely used in the treatment of Tuberculosis. Rifampicin has a property to induce the enzymes taking part in drug metabolism. As Warfarin and Gliclazide is metabolized by CYP2C9, so their metabolism is induced by Rosuvastatin, and as a result the level of these drugs is altered in plasma. Up till now there is no report regarding drug-drug interaction of Rosuvastatin and Rifampicin, so a study is conducted to evaluate the change in the pharmacokinetics of Rosuvastatin, when co-administered with Rifampicin. The results of the study shows that there is no change in the pharmacokinetics of Rosuvastatin, because the plasma level of Rosuvastatin is not altered, so it is concluded that Rifampicin does not effects the pharmacokinetics of Rosuvastatin (Wei zhang et al., 2008).

#### 4.5 Effect of Silymarin

Milk Thistle (*silybum marianum*) is a source of Silymarin. Flavonoids are present in Silymarin, as Flavonoids are present in most of the plants, fruits, vegetables and herbs. The major Flavonoids present in Silymarin are Silybin, Silydianin, and Silychristine. Silymarin is indicated in Liver diseases, like Hepatic Cirrhosis, and gall bladder diseases etc, since Silymarin is hepatoprotective in nature. As there is possibility of Flavonoids- Drugs interaction, so a study was conducted to evaluate the effects of Silymarin on the Pharmacokinetics of Rosuvastatin, Is there any drug interaction, but the result showed that there is no such interaction and Pharmacokinetics of Rosuvastatin is not altered by Silymarin (Jian Wei Deng et al., 2008).

### 5. Conclusion

Rosuvastatin is usually co-prescribed with other numerous agents and the indicated interactions of this statin can guide the prescriber to treat all the classes of patients.

### List of Abbreviations

HMG-CoA – hydroxymethyl glutaryl Co-enzyme A

CHD – chronic heart diseases

LDL – low density lipoproteins

AUC – area under the curve

C<sub>max</sub> – maximum plasma concentration

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