REVIEW ARTICLE

Journey of Statins

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ABSTRACT

Statins are the most common drugs prescribed by doctors for lowering the levels of cholesterol or lipids in blood. These drugs are used for low-density lipoprotein concentration in plasma. These are also known as 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors. Statins are also used in cardiovascular ailments risk management. With many benefits of statins, certain side effects are linked with their use with varying degree of severity such as rhabdomyolysis associated with Cerivastatin that lead to its withdrawal from the market in 2001. In today's world, statins have come a long way from when the first statin being lovastatin was commercialized in 1987. At present, statins are a large part of present pharmaceutical market around the globe.

Key words: Statins, 3-hydroxy-3-methylglutaryl-Co-A reductase inhibitors, Types, Side effects, Safety

INTRODUCTION

Statins are a drug class of cholesterol reducing mediators utilized for the dyslipidemia treatment (irregular lipid amounts) and lowering the risk of atherosclerotic-cardiovascular disease. The potent and broad effects of statins on the lipid levels and cholesterol independent pleiotropic cardioprotective effects placed these drugs among the most recommended prescriptions globally.

Late in the 1980s and beginning of 1990s, these drugs were introduced as a new category of lowering cholesterol level drugs in effort to give patients with hypercholesterolemia an effective and safe way of reducing the cholesterol level in plasma. Research has presented that statins not only play a significant role in reduction of blood lipid levels, however as well in person's possibility of vascular ailment generally.

TYPES OF STATINS

There are two types of statins as follows:

1. Natural or type 1
2. Synthetic or type 2.

Natural or type 1

Originally, these were identified in the form of secondary fungi metabolites. All of the statins of this type show close homology of structure and vary from the synthetic or type two statins. It includes:

- Mevastatin
- Pravastatin
- Simvastatin
- Lovastatin.

Synthetic or type 2

Typically, these differ in the structure as these have a group of fluorophenyl instead of butyryl group that is there in natural statins. It includes:

- Fluvastatin
- Pitavastatin
- Rosuvastatin
- Atorvastatin
- Cerivastatin.

Furthermore, rosuvastatin and atorvastatin have hydrogen-binding interactions in addition.

The functional variance between the above-mentioned two varieties of statins mainly count on the capability to impede the 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase, nevertheless also on the lipophilicity. Because of the particular structure, synthetic statins incline to form much strong interactions with enzyme HMG-CoA reductase.

In addition, statins can also exist in the preparations in amalgamations of greater than 1 kind, which implies that a statin might be there as a salt (containing salts of calcium, potassium, and sodium), acid, for example, carboxylic acid or in closed ring of lactone, neutral form. The preferred grouping of statins be subject to the proposed end consumer, the final goal of the treatment, and solubility of the mixture.[1]

HISTORY

In 1976, Akira Endo, the biochemist employed at Sanko Merchandise derived a compound that came to be a

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competitive HMG-CoA reductase inhibitor. This compound termed mevastatin or compactin was derived from *Penicillium* fungus species citrinum. It was the primary compound given to humans.

Mevastatin demonstrated to reduce the levels of lipid in plasma in the monkey, rabbit, and dog. However, certain researchers were unconvinced with its action in rats.

Later, clinical and experimental research related to compact in followed in Japan and globally, respectively. In 1978, Alfred Alberts along with the team in 1978 identified a compound termed mevinolin at that time as a HMG-CoA reductase inhibitor with great potency. This discovery arose from fermentation of *Aspergillus terreus* species broth at Company of Merck Research. The compound later on was known as lovastatin.

Further, in 1980, the clinical trials commenced at Merck for lovastatin, which demonstrated great potency in low-density lipoprotein reduction in plasma with the absence of adverse effects. After demonstrating such promising results, lovastatin in 1987 came to be the first approved drug in statin class by the-Food and Drug Administration (FDA) in United States of America.

This followed the approval of various other statins globally stated as follows:

- Simvastatin-1988
- Pravastatin-1991
- Fluvastatin-1994
- Atrovastatin-1997
- Cerivastatin-1998
- Rosuvastatin-2003.[2,3]

MECHANISM OF ACTION

The statin drugs acting through HMG-CoA reductase competitive inhibiting, which is the degree-limiting enzyme for the pathway of mevalonate. As statins being analogous in configuration to β-hydroxy β-methylglutaryl-CoA on a degree of molecule, these will sit inside the active location of the enzyme and contend with the β-hydroxy β-methylglutaryl-CoA intrinsic substrate. The antagonism decreases the degree by which β-hydroxy β-methylglutaryl-CoA reductase is capable of producing mevalonate, the following molecule in the force that ultimately generates cholesterol. *Aspergillus* and *Penicillium* fungi as secondary metabolites generate varieties of type 1 statins. The type one statins possibly function to impede the enzyme β-hydroxy β-methylglutaryl-CoA reductase in fungi and bacteria that contend with the manufacturer.

Inhibition of Lipid Production

Through β-hydroxy β-methylglutaryl-CoA reductase inhibition, statins wedge the conduit for producing lipid in the liver. It is important as most circulating lipid emanates from interior production instead of the diet. When there is no more production of cholesterol in the liver, levels of fat in the plasma will decline. Lipid production seems to happen maximally at nocturnal, thus statins with petite half-lives are typically administered at nighttime to make the most of the effect. Research has presented larger low-density lipoprotein (LDL) and overall cholesterol decreases in the interim duration of action simvastatin administered at nighttime instead of the morning, nevertheless has displayed no variance in atorvastatin the long duration action of the drug [Figure 1].

Elevating LDL Uptake

Liver cells of the bunnies nous decreased amounts of liver lipid and pursue to recompense through producing receptors of LDL to pull lipid out of the flow. It is completed by proteases, which split sterol membrane bound controlling component binding proteins that at that time travel to the center of nucleus and attach to the response components of sterols. The response elements of sterol afterwards assist amplified transcription of numerous further proteins, much particularly, receptors of LDL. The receptor of LDL is migrated to the cell membrane of the liver then attaches to transient very LDL and LDL elements, arbitrating the liver uptake, where the lipid is processed again into salts of bile and further derivatives. It leads toward a net result of reduced level of LDL circulation in plasma.

Reduction of Explicit Prenylation of Protein

Statins, through the β-hydroxy β-methylglutaryl-CoA reductase pathway inhibition, impede downstream

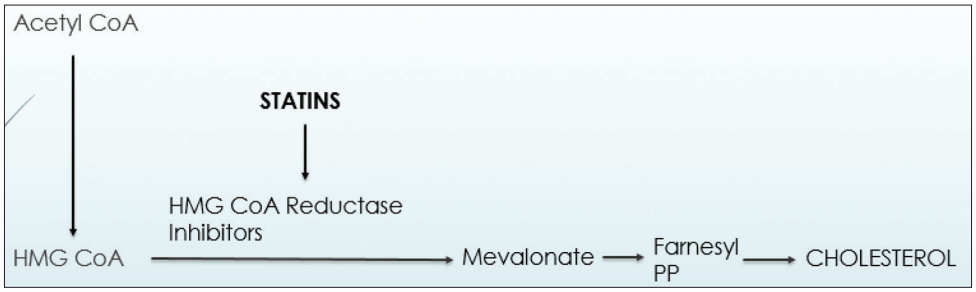


Figure 1: Schematic representation of statin's mechanism of action

production of isoprenoids, such as the geranylgeranyl pyrophosphate and farnesyl pyrophosphate. Reticence of prenylation of protein for proteins like the RhoA and following reticence of Rho-linked kinase protein might be convoluted, at least partly, in the progress of endothelial functioning, inflection of immune functioning, and further pleiotropic cardiovascular aids of statins. In addition, as the datum that a numeral of additional medications that reduce LDL levels have not displayed the similar cardiovascular risk aids in research as statins, plus might also reason of some of the aids comprehended in cancer decline by statins. In addition, the inhibitory result on prenylation of protein might also be included in a numeral of undesirable side effects linked using statins, involving myopathy that is pain in the muscles and diabetes meaning elevated sugar plasma levels.[4]

CHEMICAL CONFIGURATION

Chemically, the configuration of these statins is composed of two constituents:

1. Pharmacophore that is a segment of acid dihydroxyheptanoic and
2. The moiety constituted with following:
    - Complex ring configuration, which is hydrophobic and connected covalently to the analogue of substrate. It binds with the enzyme HMG-CoA reductase. There is variation in the structure of the ring
    - The different groups of substituents in the ring configuration characterize the solubility, resulting in pharmacokinetic determination of statins [Table 1].[5,6]

PHARMACOKINETICS

Once orally administered, absorption of each statin occurs through intestine efficiently, then through the liver extensive albeit initial metabolism takes place which results in consequent bioavailability decrease systemically to 50% from initial 5%. Administration of almost every statin occurs as acids of β-hydroxy with the exception of prodrugs such as simvastatin and lovastatin that are activated by hepatic metabolism.

Pravastatin, lovastatin, and simvastatin are derivative of fungous metabolites with half-life elimination in the middle of 1 and 3 h. Rosuvastatin, atorvastatin, pitavastatin, and fluvastatin are completely synthetic drugs, with half-life elimination ranging from 1 h for fluvastatin to 19 h for rosuvastatin.

Simvastatin, lovastatin, atorvastatin, pitavastatin, and fluvastatin are comparatively lipophilic drugs. Statins that are lipophilic are more vulnerable to breakdown through the P (450) cytochrome structure, with the exemption of pitavastatin that undertakes restricted breakdown by such pathway. Kidney and liver are main performers in the removal of these drugs from the circulation through the bile resulting into the feces [Table 2].[5]

SIDE EFFECTS

With the use of statins for lowering cholesterol, the dug class is associated with some side effects with varying degree of severity and occurrence. Some of the most conventional effects are as follows:

- Sleeping difficulty
- Headache
- Skin flushing
- Drowsiness
- Weakness, tenderness, or ache in muscles called as myalgia
- Dizziness
- Pain or abdominal cramping
- Vomiting or nausea or vomiting
- Gas or bloating
- Constipation
- Diarrhea
- Rash.

In addition, there are certain severe and rare side effects as follows:

1. Muscle inflammation
2. Rise in creatine kinase levels
3. Rhabdomyolysis.

Muscle Inflammation

It also called myositis, wherein there are increased chances of injury of muscles if statins are administered along with some other medicines. For instance, in case of administration of a statin drug simultaneously with some other drug class used for lowering cholesterol such as fibrate drug class. This will heighten the chances of damage of muscles largely in comparison to sole administration of a statin.

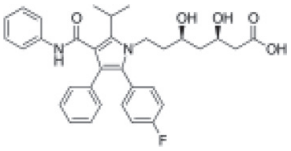
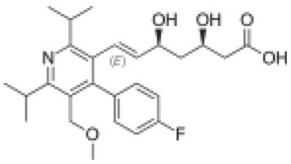
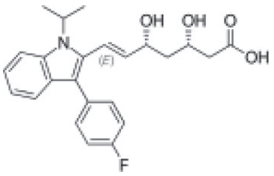
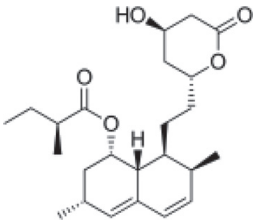
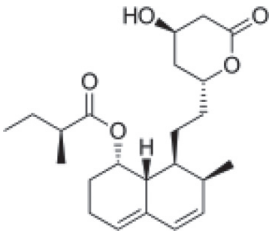
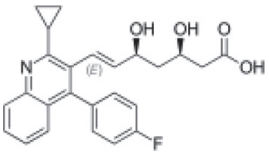
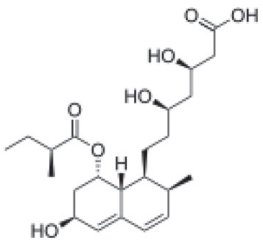
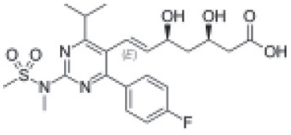
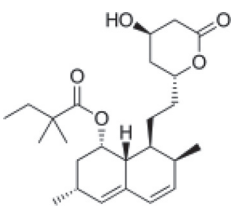
Rise in Creatine Kinase Levels

It is an enzyme of muscles that when increased cause mild inflammation, pain, and weakness in muscles. It is a rare condition, however takes much longer to overcome.

Rhabdomyolysis

This is a condition, wherein there is extreme damage and inflammation of muscles. In this, all body muscles become weak and painful, such severely injured muscles discharge proteins in the plasma, which is accumulated in kidneys. This causes damage to kidneys due to the elimination of muscle collapse in huge amounts. Ultimately resulting in failure of kidneys or even death of individuals to whom

Table 1: Different statins

Name	Brand name	Structure	Mechanism of action
Atorvastatin	Lipitor		It inhibits competitively the enzyme HMG-CoA reductase
Cerivastatin*	Baycol*		Competitive inhibitor of HMG-CoA reductase
Fluvastatin	Lescol		Selectively and competitively inhibits
Lovastatin	Mevacor, altocor		It inhibits competitively the enzyme HMG-CoA reductase
Mevastatin	Compactin		It inhibits-competitively the enzyme HMG-CoA reductase.
Pitavastatin	Livalo		It inhibits competitively the enzyme HMG-CoA reductase
Pravastatin	Pravachol		It acts through two pathways: 1. Reversible competitive inhibitor of HMG-CoA reductase 2. Inhibits the synthesis of very low-density lipoproteins
Rosuvastatin	Crestor		It inhibits competitively the enzyme HMG-CoA reductase
Simvastatin	Zocor		It is a prodrug hydrolyzed *in vivo* to generate the beta-, delta-dihydroxy acid and then competes with HMG-CoA for HMG-CoA reductase

*Withdrawn from market. HMG: 3-hydroxy-3-methylglutaryl

Table 2: Comparison of different statins

Drug name	TC drop (%)	TG drop (%)	HDL-C rise (%)	LDL-C drop (%)	Doses (mg)	Protein binding (%)	Metabolism	Hydrophobic	Half-life (h)
Fluvastatin	16–27	12–25	3–11	22–36	20,40,80	98	CYP2C9	Yes	0.5–3.0
Atorvastatin	25–45	17–53	5–13	26–60	10,20,40,80	98	CYP3A4	Yes	13–30
Lovastatin	16–34	6–27	2–10	21–42	10,20,40	>95	CYP3A4	Yes	2–4
Rosuvastatin	33–46	10–35	8–14	45–63	5,10, 20,40	88	CYP2C9	No	19
Pravastatin	16–25	15–24	2–12	22–34	10,20,40,80	43–67	Sulfation	No	2–3
Simvastatin	19–36	12–34	8–16	26–47	5,10,20,40,80	95–98	CYP3A4	Yes	1–3

TC: Total cholesterol, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

statins are being administered. Luckily, it is the rarest side effect that takes place.[7]

Withdrawal of Cerivastatin

In 2001, there was market withdrawal of the statin Cerivastatin or Baycol (brand name) globally due to the occurrence of the rarest side effect rhabdomyolysis associated with statin administration. The probability of its occurrence came to be 10–100 times greater in comparison to those with administration of the other various statins.[8]

CHANGES TO STATIN SAFETY LABEL

There was introduction of certain safety changes in the statin labels in 2012, by the US FDA. This includes the following:

1. The novel labels do not include routine checking of enzymes of liver
2. Lovastatin label now includes information for
   - Drug-drug interactions
   - Dose limitations
   - Contraindications.
3. Further, it involves a slight elevated probability of high concentration of sugar in plasma, which could lead to diabetes mellitus
4. In addition, it includes statement for possible intellectual effects such as loss of memory and confusion memory loss encountered in a few patients

Certain dose limitations for the novel lovastatin label are as follows:

1. Contraindication when administered with:
   - Ketoconazole
   - Itraconazole
   - Erythromycin
   - Posaconazole
   - Clarithromycin
   - HIV protease inhibitors
   - Telithromycin
   - Telaprevir
   - Boceprevir
   - Nefazodone.
2. Lovastatin avoidance with gemfibrozil and cyclosporine.[9]

PATENTS AND ORANGE BOOK

Each type or form of statin has numerous granted patent rights all around the globe. The patents associated with statins vary in number from statin to statin in different countries with atorvastatin having the maximum patents while mevastatin with minimum number of patents.

The patents for the statins along with the primary publication date in orange book are as follows, respectively:

1. Atorvastatin – 335, November 30, 2011.
2. Simvastatin – 205, December 20, 2006
3. *Cerivastatin – 31, not applicable
4. Fluvastatin – 89, April 11, 2011
5. Pitavastatin – 82, December 20, 2016
6. Lovastatin – 165, December 17, 2001
7. Mevastatin – 27
8. Pravastatin – 191, April 24, 2006
9. Rosuvastatin – 155, April 29, 2016.[10]

*Withdrawn from market.

CONCLUSION

It is concluded that statins are prescribed as the first line medications for lowering cholesterols levels with each statin drug varying in efficacy and potency to inhibit HMG-CoA reductase enzyme. Atorvastatin and simvastatin are the most popular statins today. Even with statins being beneficial there are, certain side effects associated with their use such as muscle pain, diarrhea, dizziness, and nausea. Nevertheless, the benefits overweigh the side effects of these drugs, hence continuing the use of statins in today's world.

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