A REVIEW ON ROLE OF STATINS IN HYPERLIPIDEMIA PATIENTS
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ABSTRACT: Statins (or HMG-CoA reductase inhibitors) are a class of used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. The best selling statin is atorvastatin which in of US $ 12.4 billion in 2008. Statins can lower LDL cholesterol by 1.8 mmol/l (70 mg/dl), which translates into an estimated 60% decrease in the number of cardiac events (heart attack, sudden cardiac death) and a 17% reduced risk of stroke after long-term treatment. Statins do not come with a no-risk guarantee. Side effects can include insomnia, rashes and gastrointestinal problems, which are relatively minor. But there can also be serious muscle inflammation, hepatitis, Rhabdomylosis and kidney failure.

KEYWORDS: Hyperlipidemia, HMG CoA Reductase inhibitor, Rhabdomylosis

1. INTRODUCTION
Statins (or HMG-CoA reductase inhibitors) are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. Increased cholesterol levels have been associated with cardiovascular disease, and statins have been found to prevent cardiovascular disease in those who are at high risk. Statins, bile acids sequestrants (colsevalam), fibric acid (Gemfibrozil), nicotinic acid (Niacin), cholesterolabsorption inhibitor (Ezetimibe) are used for the management of hypercholesterolemia. Statins are highly effective cholesterol-lowering agents, and have been shown to reduce cardiovascular morbidity and mortality in patients with and without CVD. Consequently, statins have become the therapy of choice for the treatment of many dyslipidemias. As of 2010, a number of statins are on the market including: simvastatin, atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, and rosuvastatin.\textsuperscript{1}

Based on 2003 prescribing data from the Department of Health, Based on the best selling order of statin is atorvastatin, Simvastatin, pravastatin, fluvastatin, rosuvastatin.\textsuperscript{2}

Specific statins also appear to have a favorable effect, including dementia, lung cancer, nuclear cataracts, hypertension, and prostate cancer. Simvastatin is associated with a reduced incidence of dementia and Parkinson’s disease. Rosuvastatin lowers total serum cholesterol and low-density-lipoprotein (LDL) concentrations thereby reducing the risk of atherosclerosis and its complications – myocardial infarction and stroke.

OBJECTIVE AND SCOPE OF THE STUDY
The annual cost of statins estimated from this method is £273; this represents a 14% decrease from the trial weighted cost of £317. Use of this cost in the model would not, however, take into account any potential change in efficacy resulting from using a different mix of statins to that on which the trial evidence is based. The best selling statin is atorvastatin which in of US $ 12.4 billion in 2008. Statins can lower LDL cholesterol by 1.8 mmol/l (70 mg/dl), which translates into an estimated 60% decrease in
the number of cardiac events (heart attack, sudden cardiac death) and a 17% reduced risk of stroke after long-term treatment. Currently, about 40 million patients worldwide (including about 20 million in the United States) are being treated with statins. In 2009, the statins market was worth over $25 billion and looks to be even more profitable in the future with the looming health issues in the United States and Europe. It is estimated that approximately 2.1 million patients in the U.S. were prescribed a product containing 80-mg simvastatin in year 2010.

In primary prevention the estimated ICERs (incremental cost-effectiveness Ratio) varied according to risk level and age. Around £20,000 to £28,000 for men between 3 and 0.5% CHD risk, and between £21,000 and £57,000 for women. There was significant variation with age within risk levels. At an annual CHD risk of 3%, the estimated cost per QALY (quality-adjusted life-year) ranged from £10,000 to £37,000 for men and from £14,000 to £48,000 for women between the ages of 45 and 85. At the age of 85 years the estimated cost per QALY rose from £37,000 and £48,000 for men and women, respectively, at 3% CHD risk, to around £105,000 and £111,000 for men and women at 0.5% CHD risk.

This review suggested that about 40 million patients worldwide (including about 20 million in the United States) are being treated with statins and the statins market was worth over $25 billion per year. Current statin prescribing is estimated at around £675 million per annum. The estimated additional prescribing cost to the NHS for primary prevention ranges from £300 million at an annual CHD risk level of 3% to £1.9 billion at a risk of 0.5%.

**LITERATURE SURVEY**

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J R Coll Physicians Edinb 2009; 39:362–4, KS Lyons; 2M Harbinson, Statins: in the beginning, concluded that The story of statin development will always be seen as a great success, both scientifically and financially. It illustrates how epidemiological data can provide the evidence for theories on disease processes, which can in turn lead to the development of targeted therapies to modify these processes.

The Asia-Pacific Journal Of Cardiovascular Medicine Vol I Issue I 2009, Shosaku Nomura, Pitavastatin in the Management of Hypercholesterolemia concluded that Pitavastatin exerts its potent pharmacological actions by strongly binding to the active sites on HMG-CoA reductase, and is one of the more potent statins along with atorvastatin and rosuvastatin. Pitavastatin has been reported to be associated with a lower frequency of adverse effects such as hepatic dysfunction and rhabdomyolysis, and therefore may be judged as one of the safer drugs among strong statins.

Jpn Pharmacol Thevol.36no.82008, Yuji Kurihara Takashi Douzono Koji Kawakita Yo shimasu Nagasaka, A large-scale, long-term, prospective post marketing surveillance of pitavastatin concluded that analysis of the data on pitavastatin collected during 2 years of the study revealed no particular problems pertaining to the safety or effectiveness of pitavastatin.

Journal of Lipid Research Volume 33, 1992, Akira Endo, The discovery and development of HMG-CoA reductase inhibitors, Concluded that No Mevastatin is apparently somewhat less active than are lovastatin and pravastatin. Nonetheless, the effects of these drugs on blood cholesterol and lipoprotein levels are quantitatively similar when administered at equivalent doses. Major serious side effects
associated with MG-CoA reductase inhibitors have been reported, despite their extensive use. Undoubtedly, MG-CoA reductase inhibitors have been established as effective and safe cholesterol-lowering agents.

CLASSIFICATION AND HISTORY OF STATIN

**Classification of statin by their discovery**

- Mevastatin (1970): sankyo pharmaceuticals in Tokyo (not yet marketed because of its adverse effect)
- Lovastatin (1976): Merck Research Laboratories
- Pravastatin (1979): pharmaceutical company Sankyo Co, Ltd
- Atorvastatin (1985): Pfizer
- Cerivastatin (1998): pharmaceutical company Bayer A.G. (withdrawn from the market due to reports of fatal rhabdomyolysis)
- Pitavastatin (2003): Nissan Chemical Industries

**MEVASTATIN**

In 1970 the first statin was discovered by a research group working at sankyo pharmaceuticals in Tokyo. They were headed by a young researcher, Akira Endo. With his research team, the substance was derived from cultures of Penicillium citrinum, a mould isolated from the rice of a vendor in Kyoto, and purified by solvent extraction, chromatography and crystallisation. The molecule contained a portion with a chemical structure very similar to mevalonate, the product of the HMG CoA reductase reaction. This finding fitted well with the theory that it acted via competitive inhibition of the enzyme HMG CoA reductase. It was never marketed because of its adverse effect. Patients with myopathy generally have muscle pain, tenderness or weakness, and an elevation of a muscle enzyme in the blood (creatine kinase), but some time death in laboratory dogs. Since early 1979, clinical trials of mevastatin were carried out in patients with severe hypercholesterolemia by over 10 groups in Japan. In mid 1980, however, most of these clinical trials were suspended, because mevastatin had been found to produce toxic effects in some dogs at higher doses in a long-term toxicity study. In this experiment mevastatin was given to the animals at doses of 25, 100, and 200 mg/kg per day for 104 weeks. Although details of the experiment have not been reported, the purported toxicity was apparently due to the accumulated toxicity of the drug. It should be noted that mevastatin is effective in humans at as low as 0.2 mg/kg or less; thus a dose of 200 mg/kg given to dogs is 1000 times higher than the effective dose in man.

**LOVASTATIN**

In July 1976, Merck Research Laboratories, signed a confidentiality agreement with Sankyo and obtained samples of compactin and confidential experimental data. In 1978 after carried out independent studies with compactin, Merk independently isolated new HMG-CoA reductase inhibitor from an Aspargillus terreus funge. In February 1979 Albert isolated a statin very similar to compactin, called mevinolin (lovastatin). Which is sold under name Mevacor, Advicor or Altoprey.

In July 1982, Merck made lovastatin available, under an arrangement approved by the FDA to Roger Illingsworth of Oregon Health Sciences University and Scott Grundy and David Billheimer of the University of Texas Southwestern Medical Center.

In February 1987, a US FDA advisory panel fully considered the various safety issues arising out of the animal toxicology studies discussed below and the clinical results summarized above. The panel voted unanimously for the approval of the drug, and FDA approval was obtained on 31 August 1987. Lovastatin is highly effective in reducing concentration of total cholesterol &LDL-C in the plasma of patients with heterozygous FM. Slightly more active in inhibit HMG CoA Reductase than the parent compound.

**PRAVASTATIN**

Pravastatin (trade name Pravachol) is a statin drug
discovered in Japan by scientists at pharmaceutical company Sankyo Co, Ltd (now Sankyo Daiichi Sankyo Co.) in 1979. Pravastatin is produced by chemical modification of the related drug lovastatin in a two-step fermentation reaction performed by the bacterium Nocardia autotrophica. In 1991, following FDA approval, pravastatin was introduced to the US market by Bristol-Myers Squibb (BMS) who had acquired the rights to sell it outside of Japan.

**FLUVASTATIN**

Fluvastatin, which is produced by Swiss pharmaceutical company Novartis, and sold under the name Lescol or Lescol XL, is a synthetic derivative of lovastatin, developed in the mid-1980s. Recent research in Japan has found that fluvastatin can help healing in patients with arterial stents. There is also research in rats that suggests fluvastatin can help with osteoporosis in those with diabetes. Fluvastatin has protective effects against impaired re-endothelialization after sirolimus treatment.

Fluvastatin was first tested in humans in 1986 and received FDA approval in December 1993. Potential side-effects, in addition to those common to all statin include insomnia and, very rarely, dysaesthesia, hypoesthesia, peripheral neuropathy, oedema, angioedema, thrombocytopenia, vasculitis and lupus erythematosus-like reactions.

**SIMVASTATIN**

Simvastatin (trade name zocor, lipex) was developed in 1981 and patented by Merck & Colleagues, Merk scientist synthetically derived from a fermentation product of aspargillus terreus which was designated MK-7339 (Simvastatin). Simvastatin was first approved for use in Sweden in 1988; it did not receive United States FDA approval until December of 1991.

Approximately 60% of the cases of myopathy were associated with a genetic variant which affects the coding of the transporter responsible for simvastatin uptake into the liver. This variant increases the plasma concentration of simvastatin, thus increasing the risk of myopathy.

Fatal rhabdomyolysis associated with the 80-mg dose of simvastatin has been higher in comparison with lower doses of simvastatin or lower doses of most other statins. The higher the dose of statin used, the greater the risk of developing myopathy.

**ATORVASTATIN**

Atorvastatin was developed in 1985 by Pfizer and sold under the name of Lipitor. Atorvastatin may also be used to reduce triglycerides as well as reducing blood pressure and lowering LDL levels, they caused side effects such as stomach pain and nausea. The lowering of elevated CRP levels by atrovastatins may reduce the risk of cardiovascular events independently of the effect of statins on lipid levels. Atherosclerotic plaque growth may be attenuated with therapy aimed at minimizing inflammation. Because increased levels of CRP have been associated with arterial-wall inflammation, the reduction in CRP levels may reduce the extent of endothelial-cell opsonization, macrophage recruitment, and blunting of nitric oxide release. Prevention of vasoconstriction by attenuating the proinflammatory process and preserving vasodilation may allow sufficient perfusion to prevent myocardial ischemia. Further research is needed to determine the extent to which CRP contributes to the inflammatory process. The use of statins may prevent ischemia by both inhibiting deposition of lipids and decreasing inflammation. Several trials have been aimed at developing a correlation between statin-induced reductions in CRP and a subsequent decline in coronary events. Potential side-effects, in addition to those common to all statins, include insomnia, dizziness, hypoesthesia, arthralgia, back pain and asthenia; uncommonly, alopecia, anorexia, malaise, muscle cramps, thrombocytopenia and tinnitus; rarely, peripheral neuropathy, pancreatitis and peripheral oedema; and very rarely, erythema multiforme, hypoglycaemia, hyperglycaemia, peripheral neuropathy and Stevens–Johnson syndrome.

The results of the hypercholesterolemia trials justified an expedited review by the FDA and approval was granted for atorvastatin just six months after submission of the New Drug Application (NDA).
CERIVASTATIN

Cerivastatin (brand names: Baycol, Lipobay) is a synthetic member of the class of statins used to lower cholesterol and prevent cardiovascular disease. It was marketed by the pharmaceutical company Bayer A.G. in the late 1990s. Cerivastatin was first approved for use in the United Kingdom in 1997 and was authorized in all European Union countries through the mutual recognition procedure. Subsequently, it was approved for use in at least 16 other countries throughout the world.

Between 1997 and 2000, a total of 549 cases of rhabdomyolysis in association with cerivastatin had been reported to the WHO Collaborating Centre for International Drug Monitoring and in 1999 a signal was issued concerning an association between cerivastatin, myopathy and rhabdomyolysis. The most serious form of myopathy is called rhabdomyolysis. It occurs when a protein (myoglobin) is released as muscle fibers break down. Myoglobin can damage the kidneys. Patients with rhabdomyolysis may have dark or red urine and fatigue, in addition to their muscle symptoms. Damage to the kidneys from rhabdomyolysis can be so severe that patients may develop kidney failure, which can be fatal.

Cerivastatin was voluntarily withdrawn from the market worldwide in 2001, due to reports of fatal rhabdomyolysis.²

ROSUVASTATIN

Rosuvastatin is a potent, orally available inhibitor of hepatic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase the major rate-limiting enzyme in cholesterol synthesis. which is sold by the pharmaceutical company AstraZeneca under the name of Crestor. Rosuvastatin was approved for use in the United States in 2003 and currently several million prescriptions are filled yearly. Rosuvastatin is indicated for coronary, cerebrovascular and peripheral artery disease. Rosuvastatin is available in tablets of 5, 10, 20 and 40 mg. Rosuvastatin is one of the more potent statins available and is typically used in a comparably lower dose. The recommended dose in adults is 5 to 40 mg once daily based upon tolerability and lipid levels. Common side effects include muscle cramps, joint aches, headache and weakness.

Rosuvastatin lowers total serum cholesterol and low-density-lipoprotein (LDL) concentrations there by reducing the risk of atherosclerosis and its complications – myocardial infarction and stroke.³

PITAVASTATIN

Pitavastatin is a member of the medication class of statins, marketed in the United States under the trade name Livalo. Like other statins, it is an inhibitor of HMG-CoA reductase, the enzyme that catalyses the first step of cholesterol synthesis. The drug substance was originally synthesized by Nissan Chemical Industries, Ltd., and further formulation of drug product was performed by Kowa Company, Ltd. This drug exerts its potent pharmacological actions by strongly binding to the active sites on HMG-CoA reducetase, and is one of the more potent statins along with atorvastatin and rosuvastatin. One unique characteristic of this statin is that it is minimally metabolized by the CYP isozymes, and is therefore associated with a reduced incidence of any drug interactions. Pitavastatin has been reported to be associated with a lower frequency of adverse effects such as hepatic dysfunction and rhabdomyolysis, and therefore may be judged as one of the safer drugs among strong statins. Various in-vitro and in-vivo studies have suggested that pitavastatin also has many pleiotropic effects; it reduces the inflammatory response and generation of reactive oxygen species, improves endothelial function, increases nitric oxide production, inhibits cell adhesion, attenuates smooth muscle cell contraction, increases thrombomodulin expression, enhances angiogenesis, promotes apolipoprotein (apo) A-I production, and prevents the progression of aortic atherosclerosis.²⁴-²⁸

In the US, it received FDA approval in 2003. Pitavastatin, was approved by the FDA in August 2009. It is marketed in the US by Eli Lilly.³

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