Review: Pharmacological role and organic effects (good & adverse) of Statins

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ABSTRACT

Statins are a group of compounds with a polyketide structure that are produced by fungal secondary metabolism and have the ability to suppress the activity of HMG-CoA (hydroxyl methyl glutaryl-coenzyme A)enzyme. The impact of statins on histone deacetylase a regulator genetic modifier. Simvastatin, rosuvastatin, atorvastatin, fluvastatin, and pravastatin are the five statins with worldwide authorizations for use. Medications that separate and purify *Aspergillus tamari* are statin. Due to the existence of methane-sulphonamide and their hydroxyl-moiety molecules, some statins are lipophilic while other are hydrophilic. Numerous studies have demonstrated the usefulness of statins as an anticancer, antifungal, antioxidant, and cholesterol-lowering drug. Statins are known to reduce platelet activation by various mechanisms. Numerous studies have demonstrated that this class of statins we used either alone or in combination with other drugs as an anticancer drug. If statins are used with cytochrome P450 inhibitors or other statin metabolism inhibitors that increase blood levels, myopathy and Rhabdomyolysis are the most serious adverse effect of statin intake, but they occur rarely. This article reviews and discusses available information on Simvastatin and atorvastatin as a statin

Keywords: Statins, Effects, Adverse effect, Cholesterol, Simvastatin, Atorvastatin.

1. Introduction

Statins are well known for their ability to decrease cholesterol. By lowering hepatic cholesterol production and raising LDL clearance from the blood, these medications reduce LDL cholesterol.with the use of statins, HDL cholesterol and triglyceride levels were improved (1).The primary mechanism of action of the pharmacological class known as statins is to inhibitthe enzyme 3 hydroxy 3 methylglutaryl coenzyme A (HMG-CoA) reductase, a key enzyme in the production of cholesterol, which lowers levels of fat in the body (2). Statins also work in additional ways to decrease platelet activation. An experimental swine model was also used to investigate the acute and direct inhibitory effects of statins on platelet activity, and intravenous lovastatin significantly decreased platelet-rich thrombus size in a damaged carotid artery (3). In addition, the "pleiotropic effects" of statins, which do not involve inhibition of cholesterol biosynthesis, have been linked to some of the positive effects associated with their use. These effects include endothelial protection, antioxidant and anti-inflammatory properties, a decrease in thrombotic response, pro-angiogenic effects, and immunomodulatory effects (4). The ability of statins to combat microorganisms has also been studied. In one investigation evaluating the effect of statin on community-acquired pneumonia (5). Another

side effect of statins is the relative and absolute risk of high blood sugar and type 2 diabetes (6). Statins have three basic units that make up a compound's structure are the analogue of HMG-CoA. a side chain ring structure that governs the compound's solubility and pharmacokinetics, and aids in the binding of the statin molecule to the HMG-CoA reductase enzyme(7). Statins work by preventing the committed step in the mevalonate route, which is a more contemporary name for this process in the manufacture of cholesterol. statins also increase HDL-C and lower triglyceride levels (8). Additionally, apolipoprotein-B100 manufacturing is inhibited by statins, and the liver's production of triglyceride-rich lipoproteins is decreased(9). The enzyme that converts HMG-CoA to mevalonate in the cholesterol production pathway is called hydroxymethylglutaryl-CoA (HMG-CoA) reductase, and statins are a selective, competitive inhibitor of this enzyme. LDL receptors are upregulated, and there is a greater hepatic absorption of LDL cholesterol from the circulation, as hepatic cholesterol production is reduced (10).

The Specific Activity of statins such as atorvastatin, cerivastatin, fluvastatin, and pravastatin is given as the active ingredients (acid form). However, Simvastatin and lovastatin are given as an inactive lactone form; these active forms must be produced through enzymatic hydrolysis (11).

Diversity of Statin Pharmacodynamics

The extra-hepatic HMG-CoA reductase enzyme is inhibited by different statins depending on their hydrophilic/lipophilic properties (12). Hydrophilic statins cannot pass through the cell membranes of extrahepatic cells due to the lipid bilayer of the membrane. On the other hand, lipophilic statins' affinity for fat promotes their entry into hepatic and extrahepatic cells. Some statins' supratherapeutic effects in extrahepatic organs are caused by this characteristic of lipophilic (13). These include heme A, farnesylated proteins, ubiquinone (CoQ10)and inhibition of dolichol production (14). Lipophilic statins reduce ATP synthesis in the heart muscle which leads to exacerbation of ischemic region symptoms (15).

Physicochemical Properties with source of Statins

Lovastatin, pravastatin, and simvastatin are statins obtained from fungi, while atorvastatin, cerivastatin, fluvastatin, pravastatin, pitavastatin, and rosuvastatin are the synthetically made statins (16). Some statins, such as lovastatin, atorvastatin, simvastatin, and fluvastatin, are lipophilic; however, rosuvastatin and pravastatin are hydrophilic due to the presence of their respective methane-sulphonamide- and hydroxyl-moiety molecules(17). As a gene modulator and regulator, histone deacetylase is affected by statins (18).

Application of the isolated Fungal Statins

Statins are a group of compounds with a polyketide structure that are produced by secondary fungal metabolism and have the ability to suppress the activity of the enzyme HMG-CoA (hydroxyl methyl glutaryl-coenzymeA) reductase. Statins' ability to modulate endogenous cholesterol levels in this way makes them appropriate for therapeutic usage (19). For many years, statins were first found in fungi (20). Simvastatin, rosuvastatin, atorvastatin, and lovastatin are examples of statins. Fusarium, Rhizopus, Excerohilumsp., Candida albicans, Candida krusei, Candida glabrata, and Candida tropicalis are among the cultures. Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Aspergillus, fusarium, and Rhizopus spp are also present. On potato dextrose agar, the fungi were kept alive at a temperature of 28 °C. The biological effects of statins are diverse and include anticholesterolemic, antibacterial, and antioxidant characteristics. Determine the Aspergillus tamarii fungal statin's potency as an antioxidant, antifungal, anticancer, and anticholesterolemic with isolate and purify fungal statin (21). The steroid-metabolizing enzymes that statins and steroid hormones compete for candiverge (22). Given that statins prevent the local synthesis of the substrate for androgens, it would be physiologically

predicted that they would diminish (testosterone) (23). DHEA is one of the main hormones secreted by the adrenal gland, and statin use was linked to reduced levels of DHEA in both men and women (24).

Simvastatin

Statins have a significant financial influence on the pharmaceutical industry. For instance, Merck produced simvastatin initially under the trade name ZocorTM; in 2005, ZocorTM was Merck's top-selling medication and the second-highest selling statin globally (25). Simvastatin is given as a lactone pro-drug, which is enzymatically hydrolyzed in the body to become its active, hydroxy-acid form (26). Simvastatin was demonstrated in the studies to have no effect on dehydroepiandrosterone sulfate, indicating that it had no impact on the production of adrenal steroid hormones (DHEAS). Simvastatin had an impact on the hypothalamo-pituitary axis (27). Over the course of three months, the statin group saw a greater decline in luteinizing hormone (LH) levels whereas follicle stimulating hormone (FSH) levels remained essentially same. According to the study, the effects of simvastatin on the ovary cannot be differentiated from those on the hypothalamus and pituitary (28). The size of the ovary is also decreased by statin drugs (29). Testosterone levels were observed to be lowered by statin medication in virtually all investigations using simvastatin and the majority of studies using atorvastatin (27). Inactivity and poor eating practices, particularly in young people and adolescents, have led to a rise in the usage of statins to lower cholesterol levels (30). Given that, statin exposure may hinder female rats from producing follicle-stimulating hormone, this may have an effect on the pituitary's capacity to function (31). Comparatively, atorvastatin was linked to an increased risk of stage I of ovarian cancer whereas simvastatin was linked to a higher risk of cervical cancer and adenocarcinoma of the cervix (32). Simvastatin has anti-inflammatory properties by reducing cytokines in leukocytes and endothelium (33). In cardiac cell lines and mice hearts, simvastatin triggered autophagy (34) also it had ability to increase bone synthesis and decrease bone loss (35).

Atorvastatin

It is called super statin which is known for its remarkable ability to raise high-density lipoprotein cholesterol levels while significantly lowering levels of low-density lipoprotein cholesterol when compared to other available drugs (36). It was initially created in 1985 by Bruce Roth of Parke-DavisWarner-Lambert Company (now Pfizer), who also gave it the brand name A Lipitor TM for commercial use. reduction in central nervous system inflammation induced by atorvastatin is beneficial for a mouse model of experimental autoimmune encephalomyelitis (37). Atorvastatin was found to have favorable effects on disease activity and systemic inflammation in the randomized clinical trial of atorvastatin on rheumatoid arthritis (TARA) (38). Androgenetic alopecia and polycystic ovaries have been linked to simvastatin, while serum testosterone levels and androgenetic alopecia have been linked to atorvastatin. It is interesting to note that all of these negative effects were associated with higher testosterone levels (39).

Beneficial effects of Statins

Nowadays, Statins are used therapeutically for conditions such as cardiovascular health, anti-inflammatory and immunosuppressive properties, prevention and treatment of sepsis, autoimmune diseases, osteoporosis, kidney and neurological disorders, and even cancer treatment (40). Some research has found statins to be effective in reducing depressive symptoms in people (41) or animals , while other investigations have found no association between the two (42). In addition to their anticoagulant properties, statins have been associated with decrease platelet aggregation, which may contribute to explaining the overall decrease in cardiovascular mortality (43). Effects of acetyl LDL on cholesterol esterification and its accumulation in macrophages (44). Th anti-inflammatory effects of statins on heart tissue have been shown to reduce cardiac fibrosis and hypertrophy in animal experiments (45).

Statins appear to be a desirable alternative for the treatment of patients with autoimmune or inflammatory illnesses in light of a wealth of experimental evidence. In fact, clinical data indicates that statins may be helpful for a number of pathological conditions, including sepsis, allergic asthma, Alzheimer's disease, Parkinson's disease, multiple sclerosis, osteoporosis, and osteoporotic bone fractures. (46) KI. Paraskevas & et al ., (2007) showed that statins are affordable drugs with few side effects that can be used to treat a variety of cancers. Statins are now being researched either alone or in conjunction with other anticancer medications in a number of clinical trials [47]. Along with a decrease in serum Fe++ and glucose, statins significantly increased the liver function enzymes AST, ALT, ALP, and bilirubin [48]. The cellular depletion of geranylgeranyl pyrophosphate (GGPP), which causes autophagic responses, is the primary mechanism by which statins activate autophagy through the AMPK-mTOR signaling pathway [49].Similar to this, earlier research has demonstrated that statins influence immune function by obstructing dendritic cell (DC) development and activity [50].

Adverse effects of Statin therapy

Myotoxicity, rhabdomyolysis, headache, dizziness, and gastrointestinal (GI) dysfunction are common adverse effects of statin medication and one of the main reasons people stop taking them (51). Muscle and liver damage are the most significant negative effects. Inhibitors of cytochrome P450 or other statin metabolism are provided along with statins, causing their blood concentration to rise, and this can result in myopathy (52). The most dangerous side effect of statin use is rhabdomyolysis, although it occurs very rarely . Hepatic transaminases can occasionally rise. Usually, this increase is a temporary consequence that goes away with more therapy or after a small break from it. To monitor use of these drugs without signs of hepatotoxicity like unusual weakness , fatigue, jaundice, and black urine, the FDA no longer endorses liver function testing (53).

Discussion and Conclusion:

The true efficacy of statins' pleiotropic therapeutic effects, the introduction of statins is required along with more thorough and thorough studies. Clinical studies will provide more details on the precise effects of each statin medicine and how they affect the decrease of CVD symptoms via SIRT-related signaling pathways. Statins, a class of medications that have been used for a while to decrease cholesterol, have the same potential as autografts to promot bone regeneration in both entochondrostosis and intramembranous ossification(35). Interestingly, we've identified that statins' anticancer impacts on tumor cells depend on both time and dose, so that smaller statin doses delivered over longer times may be just as effective as larger doses given more quickly (54). side effects associated with statins including liver damage and muscle pains may be a drawback.

In conclude. The goal of the present review has focused on compare existing studies on hydrophilic and lipophilic statins in order to identify any differences in the hypolipidemic efficacy of these medications and to demonstrate that hydrophilic statins have a much superior impact on the total lipid profile. Statins also have a remarkable safety record and are widely tolerated. In addition, statins interfere with bone-forming processes independently of their hypolipidemic effects. HMG-CoA reductase inhibitors were also shown to decrease the development of tumor cells. We also offer ideas for future clinical trials of the anti-cancer potential of statins that will be carefully planned.

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8. Conflicts of interest

The authors state that they have no conflicts of interest regarding the contents of the manuscript.

9. References

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