

Statins - Between the Cholesterol-Lowering and Pleiotropic Effect

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ABSTRACT: Cardiovascular disease (CVD) ranks the first place in the world in terms of mortality, accounting annually for about one third of all deaths and representing an important part of the morbidity in the world. Studies have shown that blood cholesterol level is directly involved in the production of atherosclerosis and CVD. That is why cholesterol-lowering medication (especially statins) became absolutely necessary in reducing the risk of CVD with all its consequences. Statins are a class of drugs which, in addition to the main effect of lowering blood cholesterol levels, have numerous pleiotropic effects with important role in stabilization of plaque, thereby reducing vascular events. The first randomized controlled trials with statins were conducted in 1990, then a lot of other research led to precise recommendations (found in guidelines and protocols) for the use of this class of drugs. Today, statins are used both in primary and secondary prevention of vascular disease, whether cerebral or coronary.

KEY WORDS: statins, cholesterol, pleiotropic, atherosclerosis, cardiovascular disease.

Introduction

Statins are a class of drugs that in addition to their main effect of lowering blood cholesterol levels also have anti-inflammatory, antioxidant and antithrombotic effects. These effects are the ones responsible for the plaque stabilization by influencing the process of atherogenesis, making statins occupy an important place among drugs which reduce mortality and morbidity from vascular disease (cerebral and coronary). Cardiovascular disease - stroke, angina pectoris (AP), myocardial infarction (MI) - is the most important cause of mortality, accounting for about one third of all annual deaths. Also, CVD is a major cause of morbidity worldwide. High cholesterol, the most important risk factor, is directly involved in the production of cardiovascular events [1]. Reducing the cholesterol level is the primary goal of stroke or coronary artery disease prevention and statins are used for this purpose as medication of first choice.

Five years have passed between the identification of the first inhibitor agent of HMG CoA (Mevastatin) by the Japanese in 1971, and placing on the market of the first lipid-lowering agent of this class (Lovastatin). Since then, numerous studies have been conducted to demonstrate the effectiveness of these drugs. Nowadays, after more than 40 years, statins have

conquered their place well established in the treatment of cardiovascular disease.

Mechanisms of Action

Statins (HMG CoA Reductase Inhibitors) lower the blood cholesterol through their action in the liver, affecting cholesterol metabolism by competitively inhibiting the enzyme HMG CoA Reductase with a resulting reduction in LDL-cholesterol. Studies have shown that prolonged treatment with statins reduces LDL-cholesterol by 1.8 mmol/l (70 mg/dl), which represents a 60% decreased risk of cardiac events and a 17% decreased risk of stroke [2]. A recent meta-analysis (CTT - Cholesterol Treatment in Trialists) has shown that lowering LDL-cholesterol with 40mg/dl has reduced cardiovascular events by 21% and the mortality by 12%.

Lowering of LDL-cholesterol results in multiplying the number of hepatic membrane receptors for LDL-cholesterol by increasing its uptake by the liver and decrease in the blood. Statins reduce LDL-cholesterol by 25-45% depending on the type and dose used. They also reduce serum triglyceride levels and produce a slight increase in HDL-cholesterol effects demonstrated especially after Rosuvastatin [3].

Cholesterol synthesis increases during the night, which is why statins are recommended to be taken in the evening, especially statins with short half-life [4].

Lipid-lowering effect occurs in about 3 weeks and it is dependent on the type and dose of statin. It has been shown that dose doubling reduces only by 6% LDL-cholesterol [5].

In addition to their lipid-lowering therapeutic role statins are also involved in the atheromatosis and atherosclerosis processes, helping to prevent cardiovascular disease through pleiotropic effects (anti-inflammatory and antioxidant effect by reducing lipoprotein susceptibility to oxidation, antithrombotic effect, improves endothelial dysfunction by increasing nitric oxide synthesis and stabilizes the atheromatous plaque), exerted on the vessel wall and on the atheromatous plaque, highlighted by numerous clinical studies, out of which ASTEROID study. It showed the direct action of regression of the atheromatous plaque under treatment with statins, demonstrated by ultrasound techniques [6].

Their anti-inflammatory effect is proven by the reduction in the serum concentration of C-reactive protein (CRP) [7]. JUPITER study (2008) pointed out the reduction in cardiovascular events in patients with elevated levels of blood CRP and normolipemic patients [8]. The results of PROVE-IT study showed that the low level of CRP is associated with fewer cardiovascular events independent of LDL cholesterol.

Kiener et al. noticed that the differentiated effects of statins are partly related to their composition. Thus, it was shown that lipophilic statins such as Atorvastatin and Simvastatin have the most important anti-inflammatory effect [9].

Comparative studies conducted for different types of statins found out that at normal doses there is no statistically significant difference as regards the reduction of cardiovascular mortality and morbidity [10].

Numerous controlled and randomized trials conducted since 1990 and many comments regarding the beneficial effects of statins have been published, emphasizing the reduction in the number of cardiovascular events, especially in persons with a history of vascular disease (secondary prevention), but proved to reduce the risk, as well, in healthy persons with a risk of CVD (primary prevention), but there were not sufficient data regarding the possible risks of side effects. The analysis of the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE, by 2011 from 18 randomized trials and 19 observational studies, conducted within the period 1994-2008, shows

that out of 1000 patients treated with statin for 5 years, 18 avoided an important cardiovascular event and that the risk of serious side effects did not increase.

There are many controversies regarding the administration of statins in patients without cardiac disease, most evidence supporting their use in the secondary prevention of cardiovascular events and their management in patients without cardiovascular history only if blood cholesterol remains high (cardiovascular risk- SCORE risk, increased by over 20% every 10 years) [11], [12], despite the change in the lifestyle and diet.

There have been many debates regarding the benefits of statins in patients with hypercholesterolemia, but without other vascular risk factors. Some studies have found that statins do not significantly affect mortality and quality of life [13], [14] in patients with high risk but without CVD [15], while other studies have demonstrated their usefulness in terms of mortality and morbidity.

An important step in demonstrating the beneficial effects of statins has been made with the publication of four major statin studies and comparison of the results of these studies by assessing absolute risk reduction and estimating the number of patients who need medication to prevent a cardiovascular event. All 4 studies: 4S study (Scandinavian Simvastatin Survival Study) with Simvastatin and placebo in patients with myocardial infarction or angina pectoris, CARE study (Cholesterol and Recurrent Events) with pravastatin 40 mg / day or placebo for 5 years, LIPID study (Long-term Intervention in Ischemic Disease) with pravastatin 40 mg / day or placebo, with 6-year follow-up and WOSCOPS study (West of Scotland Coronary Prevention Study) with pravastatin for 5 years have demonstrated the beneficial effect of statins in reducing coronary cardiovascular morbidity (heart attack, angina pectoris or need for revascularization) or brain morbidity (cerebral stroke) and reduction of all-cause mortality in patients with coronary disorders, emphasizing their important role in secondary prevention. Furthermore, CARE study also had as secondary objective the monitoring of the risk of cerebral stroke in patients who received Pravastatin after a myocardial infarction and demonstrated a significant reduction in the risk of cerebral stroke in patients without a history of cerebral stroke [16].

WOSCOP study showed that statins have a role in reducing the rate of death in men with

cardiovascular risk but with no history of myocardial infarction, being an additional argument for the use of statins in primary prevention.

Most researches in the field have shown that this class of drugs reduces both mortality and morbidity in patients with already existing CVD [11], so that their use has become widespread for secondary prevention.

Today, more and more evidence comes to support the hypothesis that statins also have a neuroprotective role, a role that seems to be insured through their pleiotropic effects but also the chemical structure, the degree of lipophilicity, the blood-brain barrier potential and other chemical and enzymatic mechanisms.

Thus, statins improve the quality of life and significantly extend survival when used in secondary prevention and less in primary prevention.

Side Effects

Data from randomized clinical trials emphasize the existence of side effects in about 39% patients compared to placebo [17], [18], out of which 2/3 are represented by myalgias (less frequently myopathy with risk of rhabdomyolysis), and elevated values of transaminases [18]. The study conducted in 2008 indicated the increased risk of myopathy at higher doses of statins (40-80 mg). [19] The existence of these side effects requires transaminase monitoring every 3-6 months. Other possible reactions have been mentioned: cognitive dysfunctions, polyneuropathy, digestive, hepatic and pancreatic disorders, sexual dysfunction [17], [20], elevated levels of glycaemia, with an increased risk of diabetes mellitus (DM) [21]. Following a meta-analysis regarding JUPITER study, the Food and Drug Administration (FDA) reported an increase by approximately 27% in the risk of DM in statin-treated patients compared to placebo. Furthermore, a review of 13 studies with statins has concluded that out of the 91,140 subjects, 9% had an increased risk of DM [21]. The Modern Humanities Research Association (MHRA) highlighted the risk of hyperglycaemia in some patients with existing DM or glycaemia increase in patients at risk of developing DM, but the risks in these cases are much lower than the overall benefits [22].

A recent study conducted by Culver et al. reported that there is an increased risk of developing DM in postmenopausal women receiving statin [23]. There were suspicions

regarding the risk of neoplastic disease, but several studies, including that of 2006, conducted on a very large number of subjects (87,000) indicated that there is no connection with neoplasia [24], whereas other meta-analyses showed a statistical relationship between cancer and low levels of LDL-cholesterol, but to support these data, further investigations are still required [25].

Conclusions

Although they passed the test of time, having, today, well-established indications for the prevention and treatment of cardiovascular disease, there are still many questions waiting for answer, as regards this class of drugs.

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