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STATINS: ADVERSE RESPONSES, OXIDATIVE STRESS AND METABOLIC COMMUNICATIONS – A NARRATIVE REVIEW

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ABSTRACT

Statins, otherwise called HMG-COA reductase inhibitors, are a class of medications frequently recommended by specialists to help lower cholesterol levels in the blood. By getting down the levels, they help counteract coronary failures and stroke. Studies demonstrate that, in specific individuals, statins decrease the danger of coronary experience, stroke, and even demise from coronary illness by about 25% to 35%. Statin treatment has been appeared to decrease major vascular occasions and vascular mortality in a wide scope of people, yet there is vulnerability about its viability and security among more experienced individuals. We included a meta-examination of information from all enormous statin preliminaries to analyze the impacts of statin treatment at various ages.

INTRODUCTION

Hydroxymethylglutaryl coenzyme A reductase (HMG-CoA) inhibitors (commonly known as statins) have been one of the most widely prescribed groups of drugs in the world since their introduction to the market more than twenty years ago. Currently, there are six statin drugs available on the market – pitavastatin, atorvastatin, rosuvastatin, pravastatin, simvastatin, and fluvastatin. Because pitavastatin is more commonly prescribed in Asian patients, trial results are more generalizable to the wider Asian population [1]. These drugs are perceived to have a favorable safety profile [2-4] and have well-documented benefits to cardiovascular disease in many groups, including persons who are younger and older, male and female, at moderate and high cardiovascular risk. In addition, benefits have been objectively shown to exceed risks on average for total mortality and total morbidity (indexed by serious adverse events), specifically in clinical-trial equivalent middle-aged men who are at high cardiovascular risk [5-7]. Although many people treated with statins do well, no drug is without the potential for adverse effects (AEs). There is a need for awareness of risks as well as benefits of all drugs, particularly those that, like statins, are used on a wide scale where even uncommon effects can translate to significant public health impact. Statins inhibit HMG-CoA, which is a rate-limiting step in cholesterol biosynthesis [8]. Statin therapy is effective in lowering low-density lipoprotein cholesterol (LDL-C) levels 20-50%, as well as lowering triglyceride levels 10-20% and causing a possible rise in serum high-density lipoprotein cholesterol (HDL-C) levels (5-10%) [8-10]. Despite growing interest in the non-cardiovascular benefits of statins, there has so far been little evidence to support their use in this setting. The excessive or long-term use of statins can cause in vitro cytotoxicity, in vivo liver injury, liver necrosis,

kidney damage, and myopathy in both human beings and animals. Many studies indicate that oxidative stress is involved in the various toxicities associated with statins, and various antioxidants have been evaluated to investigate their protective roles against statin-induced liver, kidney, and muscle toxicities. Widespread attention has been given to statin-induced oxidative stress, with and without the use of other drugs. Much of the information about the mechanism for this reduction comes from cell culture and in experimental animal studies. The primary focus of this article is to summarize the research progress associated with oxidative stress as a plausible mechanism for statin-induced toxicity, as well as its metabolic interactions. This review summarizes the research conducted over the past five years into the production of reactive oxygen species, oxidative stress as a result of statin treatments, and their correlation with statin-induced toxicity and metabolism. Statin-induced metabolism involves various CYP450 enzymes, which provide potential sites for statin-induced oxidative stress, and these metabolic factors are also reviewed. The therapeutics of a variety of compounds against statin-induced organ damage based on their anti-oxidative effects are also discussed to further understand the role of oxidative stress in statin-induced toxicity [11].

ADVERSE EFFECTS

Muscle Adverse Effects

Myositis, Myalgia, and Rhabdomyolysis: The best recognized and most commonly reported AEs of statins are muscle AEs [12,13] and include muscle pain, fatigue and weakness as well as rhabdomyolysis. Nearly all of the statin drugs are associated with musculoskeletal side effects. Myalgia is the most common symptom, and myositis is less common and associated with a rise in creatine kinase (CK). Rhabdomyolysis is the most severe musculoskeletal form observed, with a rise in CK greater than 10x the upper limit of normal with associated features including myoglobinuria, renal impairment, and serum electrolyte abnormalities [14]. Large long-term randomized controlled trials show the excess risk of myopathy relative to placebo is typically up to 0.1%. This is with all currently marketed statins at up to their maximum recommended doses. Though individual trials report varied absolute difference in the rate of muscle-related symptoms, up to 1.4% in some data, robust meta-analysis currently shows such variation to be non-significant. This small risk of myopathy is greatest within the first year of therapy and after either a dose increase or the addition of a known interacting drug. Risk factors for myopathy and rhabdomyolysis include hypothyroidism, preexisting muscle disease, and renal impairment; other less robust associated factors include female gender, a pre-existing diagnosis of diabetes and East Asian descent [15].

Persistent Muscle Effects: Muscle effects arising on statins do not uniformly resolve fully with statin discontinuation [16]. A range of cases has now been reported in which statin use has “uncovered” previously clinically silent or clinically tolerated conditions, ranging from McArdle disease to myotonic dystrophy to acid maltase deficiency to possible Kennedy disease [17-19]. Statins have also exacerbated known muscle conditions, such as myasthenia gravis [20]. In the case of mitochondrial myopathies, the relative degree to which statins have unmasked vs induced disease may not always be clear [21].

Hepatic Dysfunction: Statins act in the liver to inhibit HMG-CoA reductase which temporarily depletes intracellular cholesterol and in turn induces production of LDL receptors. Statins have liver effects that range from mild transaminase elevation to very rare hepatotoxicity with severe liver injury. In about 1% of patients, statins cause asymptomatic and dose-related elevations in transaminases greater than 3 times the upper limit of normal, although this does not indicate either hepatocellular injury or liver synthetic dysfunction. Such increases nearly always demonstrate an ALT greater than AST, important in distinguishing liver from muscle-related sources of the latter. While no clear mechanism has been clarified as to why low-level transaminase elevation occurs in some and not others, to-date no clinical sequelae have been noted. Clinically significant statin hepatotoxicity is an extremely rare event, occurring in about 0.001% of patients. No clear pattern of prior transaminase elevation has been found in those patients, and it is no longer recommended to routinely monitor transaminase levels on statin therapy. Some experts suggest that the clinician should obtain baseline liver function studies before statin

initiation, either for future comparison or to identify those individuals with pre-existing dysfunction who may be at theoretical risk of drug-related injury. It is not currently possible to predict which patients will develop hepatotoxicity, and providers must be alert to symptoms and signs of this rare complication. The clinical significance of this "transaminitis" is uncertain, with the majority of patients being asymptomatic. Cases of hepatic failure due to statin use have otherwise been exceedingly rare, with case reports providing the primary bulk of evidence. Although it is useful to access baseline liver function, routine monitoring of liver function tests is not recommended. Patients with mild derangement of LFT's use can safely continue statin therapy with close monitoring [22-25].

DIABETES MELLITUS: The trend of newly-diagnosed or new-onset diabetes is another oft-cited effect of statin therapy. A potential causal relationship between statin therapy and the risk of developing diabetes was first noted in a post hoc analysis of the WOSCOPS (West of Scotland Coronary Prevention Study) trial, which revealed a borderline significant lower association of new diagnosis over 5 years (HR 0.7, placebo). The first prospective analysis occurred in the JUPITER (Crestor 20mg Versus Placebo in Prevention of Cardiovascular Events) trial, which had a prespecified outcome of newly diagnosed diabetes; it showed an incident increase of 0.6% (relative increase 24%) over 1.9 years by physician report with notably no change in fasting glucose levels over this time. Subsequent large meta-analyses depending on study-level data have differed in their conclusions, showing proportional increases (OR) for the new diagnosis of diabetes to be around 10%. All of these analyses are limited by the varied definition and criterion for diabetes between trials, as well as the lack of diabetes as a pre-specified outcome in the overwhelming majority of studies. The diabetogenic risk of statin therapy appears largely confined to patients with obesity, metabolic syndrome, and pre-diabetes. One interpretation is that statin therapy accelerates the onset of diabetes amongst those most at risk for insulin resistance. What remains unclear is whether the duration of statin therapy affects this possible risk; whether the diabetogenic effect of statins would be reversible at all is an active area of research. In summary, statin therapy seems to modestly increase the risk of developing diabetes, albeit via mechanisms that are not well understood, with intensive dosing over 5 years. The absolute increase in average hemoglobin A1c is small and of questionable clinical significance, particularly in light of clinical evidence that suggests A1c and blood sugar control alone are coarse measures for cardiovascular and macrovascular outcomes in diabetes. The increased risk of diabetes appears highest for a population similarly at risk for CVD (preexisting obesity, metabolic syndrome). Since statins are well established to substantially reduce cardiovascular events in those with and without diabetes, there is no reason to stop therapy. Clinical care should focus on increased efforts toward lifestyle modification, periodic diabetes screening, and statin initiation and persistence [22-25]. There is evidence to suggest that some statins are potentially diabetogenic, and the risk appears to be dose-related [26]. However, diabetic patients are one of the groups that benefits most from statin therapy with regards to cardiovascular risk. There is no convincing evidence indicating that statin therapy in diabetics may contribute to worsening glycaemic control. Overall, the cardiovascular protective benefits of statins outweigh the concerns associated with the risk of diabetes mellitus [27]. Patients must be informed of this risk before commencing therapy and routine monitoring of blood glucose levels is recommended.

RENAL: Statins can influence the kidney in two main pathways. Rhabdomyolysis can induce tubular obstruction causing tubular injury and ischemia. Statin therapy can be associated with benign proteinuria due to inhibition of the tubular reabsorption of small molecular weight proteins. The clinical significance of this mild proteinuria is unknown, as the protein differs from that of other glomerular diseases. There has been no evidence of long-term renal dysfunction from statin therapy [28]. Rosuvastatin can cause dipstick-positive proteinuria and microscopic hematuria at the maximal dose of 40 mg/day, an effect that is generally transient and not associated with reduced renal function. Meta-analyses and prospective trials (JUPITER) have shown no increase in renal injury or a decline in renal function with long-term rosuvastatin use

(albeit on 20mg). All statins have been shown to cause AKI, albeit via the mechanism of diffuse skeletal muscle injury, rhabdomyolysis and subsequent myoglobinuria. Such events are more likely with higher doses of statins and amongst patients with known interacting medications. However, in individuals without rare rhabdomyolysis, statins do not cause acute renal injury or worsen proteinuria long term [22-25].

MALIGNANCY: The role of statins in malignancy is somewhat clouded by an array of mixed evidence suggesting both a protective role as well as being a potential risk factor. Animal studies have shown the link between high dose statin therapy and liver tumors in rodent models [29]. However, a recent clinical trial showed a reduction in liver cancers with statin use [29]. Both the Cochrane Review of statin therapy in primary prevention and the Cholesterol Treatment Trialists' meta-analyses have not shown any increase in cancer risk with statin therapy [30-35]. The Heart Protection Study and the West Scotland Coronary Prevention Study (WOSCOPS), which have extended follow-up periods of more than 10 years, have also not shown any difference in the rates of malignancy with long-term statin therapy [34]. A recent meta-analysis suggested that long-term statin use reduced the risk of some hematological malignancies [35]. Statin use was associated with a reduction in malignancy risk in post-menopausal women in the Women's Health Initiative [36]. The sources of evidence will continue to improve once long-term follow-up data of the early statin trials are published. However, it is reassuring that long-term statin therapy appears to be safe for the majority of patients.

NEUROLOGICAL: There have been case reports of statin use associated with peripheral neuropathy, mood symptoms and irritability [37]. To date, there is no proven association between statin use and an increase in suicide [38]. Despite some early reports of an increase in haemorrhagic stroke with statin use, this has not been substantiated in larger clinical trials and the protective aspects from recurrent ischaemic stroke outweigh these potential risks [39].

ROLE OF STATINS IN OXIDATIVE STRESS: Sudden Cardiac Death (SCD) accounts for over 4,00 000 deaths per year [40]. In the United States, more than 50% of all cardiac-related death occurs. Ventricular arrhythmias cause most of these deaths [41]. The only treatment for ventricular arrhythmias with proven mortality benefit is the internal cardioverter-defibrillator (ICD). Two recent observational trials have demonstrated that Hydroxymethylglutaryl coenzyme a reductase inhibitors (statins) decrease the incidence of ventricular arrhythmias as well as increase survival in patients with ICDs [42,43]. This survival benefit exists for both ischemic (MADITII) and non-ischemic cardiomyopathies (DEFINITE) and the reduction in ICD discharges is independent of statins' cholesterol-lowering effects. One proposed mechanism for the anti-arrhythmic effect of statins is their antioxidant properties. Statins reduce the generation of reactive oxygen species by inhibition of vascular NADPH oxidase [44,45], inhibiting the respiratory burst of phagocytes [46] antagonizing the pro-oxidant effect of angiotensin II and endothelin-1[47], and increasing the synthesis of vascular nitric oxide [48,49]. Besides, some statins and their metabolites are direct free radical scavengers. As inflammation is closely linked to the production of reactive oxygen species (ROS), statins may also have important anti-inflammatory effects. The molecular basis of these observed anti-inflammatory effects of statins may relate to their ability to block the production and/or activity of ROS.

METABOLIC COMMUNICATIONS

Grapefruit juice contains a chemical that can interfere with the enzymes that break down (metabolize) the statins in your digestive system. While you won't need to eliminate grapefruit from your diet, ask your doctor about how much grapefruit you can have.

Some drugs that may interact with statins and increase your risk of side effects include:

- Amiodarone (Cordarone, Pacerone), a medication for irregular heart rhythms
- Gemfibrozil (Lopid), another variety of cholesterol drug
- HIV treatments called protease inhibitors such as saquinavir (Invirase) and ritonavir (Norvir)
- Some antibiotics and antifungal medications, such as clarithromycin and itraconazole (Onmel, Sporanox)

- Some immunosuppressant medications, such as cyclosporine (Gengraf, Neoral, Sandimmune)

Many drugs may interact with statins, so be sure your doctor is aware of all the medicines you take when being prescribed with statins [50].

CONCLUSION

Statin treatment has been appeared to decrease major vascular occasions and vascular mortality in a wide scope of people however, there is vulnerability about its viability and security among more seasoned individuals. We attempted a meta-investigation of information from all huge statin preliminaries to think about the impacts of statin treatment. Statins are a class of medications regularly recommended by specialists to help lower cholesterol levels in the blood. By bringing down the levels, they help avoid coronary failures and stroke. Studies demonstrate that, in specific individuals, statins diminish the danger of respiratory failure, stroke, and even demise from coronary illness by about 25% to 35%. Concentrates likewise demonstrate that statins can diminish the odds of repetitive strokes or cardiovascular failures by about 40%. Statin medications work by hindering the activity of the liver catalyst that is in charge of delivering cholesterol. An excessive amount of cholesterol in the blood can cause a development of plaque on the dividers of the supply routes.

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