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Post-marketing surveillance of Atorvastatin and Rosuvastatin- A descriptive analysis of Musculoskeletal adverse effects from Eudravigilance Database

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ABSTRACT

Introduction- Statins are drugs frequently prescribed in patients suffering from dyslipidaemia and, even, in patients with coronary artery disease, diabetes mellitus, stroke, blood hypertension, and chronic kidney disease with or without dyslipidaemia. Statins are molecules of fungal origin that, by inhibiting the hydroxymethylglutaryl-CoA (HMG-CoA) reductase enzyme, a key step in the sterol biosynthetic pathway, became powerful cholesterol-lowering medications.

Areas Covered- In this review article, the post marketing surveillance of atorvastatin and rosuvastatin are discussed based on the analysis of electronic reports containing suspected adverse reactions associated with statins, submitted to Eudravigilance (EV), up to February 2024.

Expert opinion- Muscle soreness and other musculoskeletal adverse effects that have not been previously linked to statin use have been observed in a worrying pattern by the post-marketing surveillance of Atorvastatin and Rosuvastatin. The number of complaints of muscular pain associated with statin use was sufficient in the Eudravigilance database as of February 2024. Larger, more varied patient populations, longer follow-up times, and standardised reporting and data collection techniques are some of the technical, technological, and methodological constraints. Future developments in this area can include investigating substitute treatments for hyperlipidemia and creating novel statin formulations with less side effects.

Key words –Adverse Effects, Eudravigilance-Database, Musculoskeletal Disorder, Post Marketing Surveillance, Statins

ARTICLE HIGHLIGHTS

- Statins inhibit HMG-CoA reductase, reducing cholesterol production and increasing LDL receptor expression, leading to significant reductions in LDL-cholesterol levels.
- Structural and pharmacokinetic differences between statins, such as lipophilicity and CYP450 metabolism, contribute to variations in their clinical effects and adverse event profiles.
- Statin-associated adverse effects include hepatotoxicity, myopathy, rhabdomyolysis, and increased risk of diabetes, with the elderly population being more susceptible.
- The mechanisms underlying statin-induced hepatotoxicity and muscle-related adverse effects likely involve inhibition of CYP450 enzymes and alterations in the mevalonate pathway.
- While statin therapy has a generally favourable safety profile in children, careful monitoring is still recommended due to the potential for adverse effects.

INTRODUCTION

Statin medications are the inhibitors of the hydroxymethylglutaryl-CoA (HMGCoA) reductase enzyme and function by inhibiting the crucial step in the sterol biosynthetic pathway, besides its strong cholesterol-lowering mechanism, Statin medications are also a potent contributor in the prevention of various cardiovascular diseases [1]. The clinical studies report that statin therapies contribute significantly to microbiological research to identify a novel antimicrobial activity [2]. In conclusion with the previous researches on the safety and efficacy profiles of the statins, the drugs belonging to this class are currently the most appropriate alternative for the treatment of disorders like hyperlipidemia and other heart related risk in patients with a baseline level of bad cholesterol in the plasma.

Mechanism of Action of Statins

The primary and most significant rate-limiting enzyme in the mevalonate system, HMG-CoA reductase, is competitively inhibited by statins. Inhibition of this site impedes the conversion of HMG-CoA to mevalonic acid by blocking substrate entrance. Due to the liver producing less cholesterol as a result, there is an increase in the production of microsomal HMG-CoA reductase and the expression of the LDL receptor on tissue surfaces. This facilitates increased removal of LDL-c by the blood, resulting in a 20% to 55% reduction in the amount of LDL-c in circulation [3]. Both LDL-c and cardiovascular morbidity and death can be decreased with statins. Additionally, they might have pleiotropic effects unconnected to fats. The aforementioned benefits encompass improved endothelial function, stabilisation of atherosclerotic plaque, impacts on bone metabolism, immunomodulatory, antithrombotic, and anti-inflammatory characteristics [4].

Structural Characteristics and Pharmacokinetics of Statins

The active component of statins, modified 3,5-dihydroxyglutaric acid, is structurally comparable to the body's natural substrate, HMG-CoA, and the mevaldyl CoA transition state intermediate. The 3R,5R structure of the statin is required for the stereoselective process by which this active site binds to and inhibits HMG-CoA reductase activity. The active moiety of a statin can have one or more of the following attached: a partially reduced naphthalene (lovastatin, simvastatin, pravastatin), a pyrrole (atorvastatin), an indole (fluvastatin), a pyrimidine (rosuvastatin), a pyridine (cerivastatin), or a quinoline (pitavastatin). This leads to the molecular and clinical variations among statins. The pharmacological properties and solubility of the statin are determined by the substituents within the ring. The presence of nonpolar substituents causes lipophilicity (atorvastatin, lovastatin, fluvastatin, pitavastatin,

simvastatin, and cerivastatin), whereas hydrophilicity (pravastatin and rosuvastatin) is caused by the similar extra polar substituents in addition to the active site [5,6]
The differing pharmacokinetic characteristics of statins are partly due to their lipophilicity and route of administration. When simvastatin and lovastatin are given, their lactone forms become inactive and the body converts them to their active forms. On the other hand, atorvastatin, fluvastatin, pravastatin, rosuvastatin, and pitavastatin are administered in the active acid form. Hydrophilic statins must be taken into the liver through a carrier, but lipophilic statins can passively diffuse through the cell membrane and so lower hepatoselectivity because they can also diffuse into other tissues. Lipophilic statins are frequently removed via oxidative biotransformation, whereas water-soluble statins are eliminated unchanged. CYP2C9 is primarily in charge of fluvastatin metabolism, whereas CYP3A4 mostly metabolises atorvastatin, lovastatin, and simvastatin. Moreover, each and every statin serves as a substrate for many membrane transporters [6-8]

Metabolism and Excretion of Statins
Various drugs that belong to the class of statins are converted from active to inactive form by the CYP450 family of enzymes although the Cytochrome P450 is responsible to metabolise numerous classes of drugs, a few drugs like Atorvastatin, Lovastatin, and Simvastatin are metabolized by the enzymes of CYP450 [9]. A study has found evidence regarding the active metabolite of atorvastatin and many other drugs that belonged to the same class. These metabolites are 2-hydroxy and 4-hydroxy-atorvastatin acid, apart from this a proportion of circulating inhibitory activity of drugs like lovastatin and simvastatin were additionally discovered, that were attributable to their active metabolites [10]. Just like atorvastatin, for simvastatin, the β-hydroxy acid and its 6′-hydroxy, 6′-hydroxymethyl, and 6′-exomethylene derivatives were found to be the major active metabolites [11,12]. Unlike Fluvastatin that was observed to be metabolized by the Cytochrome P2C9 isoenzyme, various other drugs that belonged to statins class like pitavastatin, pravastatin, and rosuvastatin had not shown any reliable evidence to undergo substantial metabolism by CYP450 pathways [13,14]. The researchers have also noted that the interaction between statins metabolised by CYP450 may increase the incidence of muscle toxicity. and the drugs that inhibited the activity of CYP450 particularly the CYP3A4 isoforms. The interactions, nevertheless resulted in the accumulation of statin drugs in plasma that significantly resulted in increased risk of adverse effects and toxicities [15-17]. The bile plays a prominent aspect in the elimination of the majority of statins that are converted into the inactive form by the liver, considering the precautionary aspects in patients who have a hepatotoxicity history. The studies supported the evidence of precautionary administration of therapy in subjects with hepatic dysfunction which was proved to be concerning issue for statin-induced myopathy. The pravastatin considered to be eliminated by the liver and kidney mostly in the unchanged form [18-20]. It was also observed that the pharmacokinetic profile of pravastatin was altered due to the hepatic dysfunction in a patient, However, the un-noticeable alteration in Absorption, Distribution, Metabolism and Elimination (ADME) profile of drugs like rosuvastatin with the patients who had a moderate hepatic impairment and it was eliminated in an unchanged form by both liver and kidneys [21-23]

Adverse effects of statins
As per the studies conducted previously, statins were associated with developing abnormalities in serum transaminase levels which also resulted in hepatotoxicity [24]. Apart from this, the researchers, after-marketing surveillance revealed that atorvastatin administration was mostly associated with both fatal and non-fatal liver failure incidents [25]. The activity of the immune system against the hepatic cells that significantly resulted in autoimmune hepatitis [26]. As per the management of the hepatic abnormalities was concerned, it was noted that there was an

improvement in the serum transaminase level upon the tapering of the dose and discontinuation of the drugs. Also, it was observed that there was a resolve in mild elevation with adherence to the drug [27]. The histological and biochemical abnormalities related to the liver that persisted for a considerable time have also been communicated under the observation of a limited studies with no appropriate status in relief in adverse effects [28]. The mechanism of hepatotoxic adverse effects is unclear, although the studies conducted in the past suggested that the inhibition of the CYP450 enzymes led to the increased plasma concentration of statin drugs that led to immune-mediated responses [29]. As there were shreds of evidence for the inhibition of CYP450 enzymes few studies have also observed that the alteration in the hepatocyte membrane which provided a basis for various lipid components, led to the increased leakage and permeability of liver enzymes [30]. As per the onset of reaction is concerned according to a few studies, the adverse effects of some statin drugs occurred within the three months of administration of the dosage regimen [31]. Few studies have also observed that various statin drugs like atorvastatin showed its adversity within 1 month. The adverse effects mainly composed of hepatotoxicity which had chances to occur even after 8 to 10 years of initiation [32]. Since the above adverse effects were primarily related to liver toxicity or hepatotoxicity, there were further negative consequences identified. as per the few conducted researches that were related to muscular issues, it was observed, according to a few studies that statins associated muscle symptoms like myalgia and myopathy were observed that were generally without significant elevation in creatine kinase levels. Various other serious complications like rhabdomyolysis and myoglobinuria were also observed apart from this, few studies certainly observed the presence of antibodies against the Hydroxymethylglutaryl Co-A that resulted in adverse effects like Immune-mediated necrotizing Myopathy [33-36]. The mechanism of adverse effect was reported to be quite uncertain in the case of muscle-related effects, yet it was later brought into consideration that there was an alteration in the electrical and chemical characteristics of the sarcolemmarelated calcium ion flux and the affected change in the mevalonate pathway, played a significant role. It was also observed that conditions like rhabdomyolysis and myopathy were relatively due to the active circulation of the active statin drug, whereas other abnormal conditions like immune-mediated necrotizing myopathy were considered to be an immune-mediated effect that was due to the formation of antibodies against the Hydroxymethylglutaryl-Co-A reductase [37-40]. As per the onset of occurrence of statins-associated muscle-related adverse effects is concerned, some evidence supported the delayed occurrence of the effects. Most probably a few months to the end of the first year of the drug use. It was also evident that the muscle-related adverse effects were more actively reported when the same statin drug was re-introduced to the patient along with a concomitant medication and the immune-mediated reactions were possibly noted after a few years of drug administration [41,42]. Several observations related to the adverse effects of statin therapies as reviewed through various meta-analyses on observational and Randomized controlled clinical trials (RCTs) showed that statins developed diabetes and muscle disorders that were somehow unique and non-cardiovascular disease-related. A thorough assessment and in-depth discussion of the meta-analyses of observational studies and RCTs were provided by the American Heart Association, which corroborated the aforementioned evidence of adverse effects and other drug related problems [43,44]. As per the studies conducted by Preiss et al, subjects who were administered with the statin therapies had a greater incidence of acquiring diabetes, especially in patients who received a moderate to strong dose of therapy; however, the risk of developing diabetes was not as great in individuals who had a mild dose of therapy. It was evident from the study that statins appeared to generate a higher risk of diabetes [45]. A study conducted previously supported that the geriatric population who were obese and had a elevated plasma concentration of LDL level, were more prone to develop diabetes and other cardiovascular disorders. Mechanism by which statin therapy is involved in the causing diabetes was observed

through a study and the polymorphism was found to exist in the HydroxymethylglutarylCoA reductase gene resulted in its impaired activity that significantly resulted in weight gain with a drop in insulin levels and elevated levels of glucose in plasma [46,47]. A study observed and stated a fact that was to be considered while administering the patients receiving statin therapies, was that the subjects who were at a higher risk of developing diabetes had to get their vitals monitored and their HbA1c levels had to be checked, it was believed as per the studies that the increase in plasma sugar level would result in risk of complications in the future, thus in contrary statins proved to show their effectiveness to reduce the cause of morbidity and mortality by relieving the occurrence of various cardiovascular diseases at a short time interval hence the study also justified the risk and benefit ratio of statin therapies by outweighing the risk of increased plasma sugar levels [48]. The cognitive dysfunctions were also examined by some studies that conducted an RCT, and it was noted that the geriatric patients, who were administered pravastatin and a placebo, showed no cognitive impairment, similarly, patients who received simvastatin and a placebo showed no evidence of cognitive dysfunction [49-51]

Safety profile in the geriatric population

To study the safety and efficacy of statin therapy in elderly patients, RCT was performed in the geriatric population to notice the comparison of the effects of various cholesterol-lowering drugs. The research that was conducted on the geriatric population, included almost two lakh individuals with age more than 70 years of age, and it was noted that there were very minute proportions of risk reductions in severe cardiovascular diseases. Yet when the study ruled out those individuals who had major comorbidities like impaired renal functions or severe heart diseases, it was observed that there were still very minimal proportions of risk reductions in morbidity and mortality. The reason for this decreased proportion of risk reduction was observed to be the altered pharmacokinetic and pharmacodynamic parameters, drug interactions, and polypharmacy. As far as the safety profile of statins was concerned, there was no evidence of increased incidences of muscle-related adverse effects when a meta-analysis was performed on the geriatric subjects of age 60 years and above. Nevertheless, when diabetes was considered a risk factor associated with statin therapy, it was indicated that the statins induced much higher chances of inducing diabetes in the geriatric population. That nevertheless indicated the active scrutiny of the hyperglycaemic individuals treated with statins [52].

Safety Profile in Children

Although treatment of hyperlipidaemia was considered an effective choice in children from age 7 to 10 years, the livelihood modification at the early possible age initiated the control of congenital abnormalities in cholesterol levels in children as per the EAS/ESC guidelines. An analysis showed that the young subjects, typically the teenagers who were assessed with a family history of hyperlipidaemia. It was also noted that there were no significant risks of developing statins-related adverse effects in both, the offsprings and their guardian fellows who also had a family history of hyperlipidaemia. When the safety point of view, few subjects discontinued statins due to the adverse effects yet those adverse effects were not very severe or there was no known evidence of rhabdomyolysis noted [53]

1. Body:

In this review article, the post marketing surveillance of statins i.e. the safety-profile and adverse effects are discussedbased on the analysis of electronic reports containing suspected adverse reactions associated with statins, submitted to EudraVigilance (EV) database. Data were extracted from the adrreports.eu portal, the European Database of suspected adverse drug reaction reports [54].Spontaneous adverse reactions were reported in the EV database by both EEA and non-EEA regulators, marketing authorization holders, health professionals or patients [55].The regulations for data protection were not necessary, and the present study did not

involve the approval of the ethics board because the analysis included non-identifiable persons. Moreover, the data extracted from ICSRs did not contain personal information [56].
The tables below represent the information extracted from the database about the adverse reactions occurring from atorvastatin and rosuvastatin, based on the geographic origin, age and sex, reporters' group and the outcome of the reactions

Table 1: No. of individual cases identified in atorvastatin and rosuvastatin by reporter group

Reporter Group	Number of individual cases	
	Rosuvastatin	Atorvastatin
Healthcare Professional	9940	16,726
Non-Healthcare Professional	2795	4,758
Not Specified	5	140
Total	12740	21,624

Table 2: No. of individual cases identified in atorvastatin and rosuvastatin by outcome of event

Outcome	Number of individual cases	
	Rosuvastatin	Atorvastatin
Fatal	90	233
Not Recovered/Not Resolved	1926	3,625
Not Specified	419	459
Recovered/Resolved	4973	7,624
Recovered/Resolved with Sequelae	165	290
Recovering/Resolving	1747	3,796
Unknown	4111	6,983
Total	12740	21,624

Table 3: No. of individual cases identified in atorvastatin by age group and gender

Age Group\Sex	Female	Male	Not Specified	Total
Not Specified	1698	1703	632	4033
0-1 Month	1	1	0	2
2 Months - 2 Years	6	2	1	9
3-11 Years	5	8	0	13
12-17 Years	6	13	1	20
18-64 Years	3923	4722	74	8719
65-85 Years	4179	4046	95	8320
More than 85 Years	259	244	5	508
Total	10077	10739	808	21624

Table 4: No. of individual cases identified for rosuvastatin by age group and gender

Age Group\Sex	Female	Male	Not Specified	Total
Not Specified	2499	2762	1218	6479
0-1 Month	1	7	1	9
2 Months - 2 Years	6	7	0	13
3-11 Years	9	10	0	19
12-17 Years	25	9	0	34
18-64 Years	5704	6800	110	12614
65-85 Years	6061	5331	83	11475

More than 85 Years	471	347	3	821
Total	14776	15273	1415	31464

CONCLUSION

Musculoskeletal and connective tissue disorder that were reported with the administration of statins like atorvastatin and rosuvastatin were analysed in this article, yet it has been observed that, the number of reactions reported were more in case of rosuvastatin than atorvastatin, for both the statin medications the 18-64 years of age group was most affected and the majority reporting groups were the healthcare professionals. The recovery outcome was higher in case of atorvastatin yet the fatality outcome with atorvastatin was also more as compared to rosuvastatin

Expert Opinion [57]

A troubling pattern of musculoskeletal side effects, particularly muscular soreness, that has not been previously linked to statin therapy has been identified by the post-marketing surveillance of Atorvastatin and Rosuvastatin. As of January 2016, 165 reports of statin-related muscular discomfort were found in the Eudravigilance database; 11 of these cases were directly connected to the use of Atorvastatin and Rosuvastatin without any other pertinent co-medication, co-morbidity, or recent intense activity. This implies that there might be a connection between taking these statins and experiencing muscle soreness.

Effect on clinical practice and real-world outcomes: The correlation between muscular soreness and statin use may have a major influence on treatment protocols, drug usage, and diagnosis in the real world. A contraction-induced injury, muscular soreness is usually categorised as a strain (grade I), partial tear (grade II), or total tear (grade III) and is mostly caused by strong eccentric contractions or overstretching of the muscle. The development of muscular soreness in patients on Rosuvastatin and Atorvastatin may necessitate modifications to recommended treatment plans, including more attention to side effects related to the musculoskeletal system. However, a lack of knowledge and comprehension of the connection between statin use and muscular discomfort may make it more difficult to incorporate these modifications into clinical practice.

Important areas for development and constraints: In addition to identifying risk factors and potential preventative interventions, more research is required to better understand the mechanisms behind the relationship between statin use and muscle soreness. The requirement for bigger, more diverse patient populations, longer follow-up periods, and standardised reporting and data gathering procedures are some examples of the technical, technological, and methodological restrictions. Further research is also hampered by the lack of a clear endpoint in the investigation of the negative effects of statin use on the musculoskeletal system.

Prospect for additional study: There is a great deal of room for additional research in this field, with the goal of discovering new risk factors, creating prevention strategies, and refining treatment protocols for patients taking rosuvastatin and atorvastatin. Prioritising patient safety and wellbeing while approaching this study is crucial, as is being aware of its limitations and difficulties.

Discipline's future: Research into the musculoskeletal side effects of using rosuvastatin and atorvastatin, as well as ongoing post-marketing surveillance, are key components of this discipline. Still, it's vital to take into account other interesting directions for this field of study, like creating novel statin formulations with fewer side effects related to the musculoskeletal system.

Field evolution: Over the course of the next five to ten years, it is anticipated that the field will change due to the creation of new treatment protocols and prevention measures as well as a better knowledge of the mechanisms underlying the link between statin use and muscular pain.

It's also feasible, though, that the field will move in the direction of novel statin formulations with less side effects related to the musculoskeletal system or towards alternate treatments for hyperlipidemia.

Abbreviations
ADME: Absorption, Distribution, Metabolism, and Excretion
ADR: Adverse Drug Reaction
AMA: American Medical Association
ATP: Adenosine Triphosphate
BMI: Body Mass Index
CYP450: Cytochrome P450
DNA: Deoxyribonucleic Acid
EEA: European Economic Area
EV: EudraVigilance
FDA: Food and Drug Administration
HbA1c: Hemoglobin A1c
HDL: High-Density Lipoprotein
HMGCoA: Hydroxymethylglutaryl-CoA
ICSRs: Individual Case Safety Reports
LDL: Low-Density Lipoprotein
RCTs: Randomized Controlled Trials
RNA: Ribonucleic Acid

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