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Review on Statins Stimulating Rhabdomyolysis

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ABSTRACT: This review aims to explore the mechanism, pathophysiology, and management of statin-induced rhabdomyolysis. Statins are among the most commonly prescribed medications for the prevention of cardiovascular disease due to their efficacy in lowering LDL cholesterol. While generally well tolerated, a rare but potentially severe adverse effect, such as statin-associated muscle symptoms (myalgia, myositis, rhabdomyolysis, and statin-induced necrotizing autoimmune myopathy), is higher risk for patient age groups above 80 years, acute coronary syndrome, stroke, liver cirrhosis, and hypercholesterolemia. The risk can be reduced by different type of statins and reduced dose of statins. Statins inhibit HMG-CoA reductase, which also decreases the levels of prenylated protein (geranylgeranyl-pyrophosphate, farnesyl -pyrophosphate), coenzymeQ10, mitochondrial dysfunction leading to muscle cell damage and increased level of myoglobulin release in blood stream which ultimately increase CK level causing renal shutdown and muscle cell damage alters potassium level which leads to arrhythmia increasing the risk of fatality. Diagnosed by elevated creatine kinase, transaminase, and myoglobinuria. The futuristic approach of this article is to shed light on the need to reduce the risk of rhabdomyolysis by dose adjustment and altering pharmacokinetics.

KEYWORDS: Statin-Induced Rhabdomyolysis, HMG-CoA Reductase Inhibitors, Muscle Toxicity Mechanisms, Creatine Kinase Elevation, Risk Mitigation Strategies.

INTRODUCTION

Statins are selective competitive inhibitors of β-hydroxy β-methylglutaryl-CoA reductase which converts HMG-CoA to mevalonate in cholesterol biosynthesis and also regulates the LDL receptor and promote intake of LDL by hepatocytes there by reducing the risk of cardiovascular disorders.

PHARMACOKINETICS:

Statins are lipid lowering agents which have two form active acidic and inactive lactone form.1 Lactone forms are highly lipophilic and crosses the cell membrane through passive diffusion and acidic forms are hydrophilic which crosses the cell membrane through active transport. The prodrug of statin are in the form of lactone and active drug are in the form of acid.2

HYDROPHILIC STATINS: Pravastatin, Rosuvastatin.

LIPOPHILIC STATINS: Atorvastatin, Fluvastatin, Pitavastatin, Simvastatin, Lovastatin.

Lipophilic statins are orally well absorbed than hydrophilic statins. Metabolised by CYP450 enzymes present in liver by oxidation, glucoridination, lactonation. Statins acts as substrates for P-glycoprotein and CYP450 family specifically for CYP3A4 enzyme.3

Statins are transported to hepatocytes via a solute carrier transporter primarily by organic anion transporting polypeptide [OATP1B1]. Lipophilic statins are widely distributed and has high affinity for plasma protein binding and excreted through urine in unchanged form.4

PATHOPHYSIOLOGY

MECHANISM OF STATIN INDUCED RHABDOMYOLYSIS

1. INHIBITION OF PROTEIN PRENYLATION

In the biosynthesis of cholesterol, the steps involved are conversion of AcetylCoA to AcetoacetylCoA. AcetoacetylCoA to HMGCoA, HMGCoA to Mevalonate, Mevalonate to Isopentyl pyrophosphate. Isopentyl pyrophosphate to Geranyl pyrophosphate and Farnesyl pyrophosphate resulting in the synthesis of cholesterol.

Due to the use of statins, inhibition of mevalonate occurs which results in the inhibition of prenylated protein in the synthesis of cholesterol.

For the process of isoprenylation there are proteins required which particularly includes small GTP binding protein such as Rab, Ras and Rho proteins.5

These proteins perform various functions such as,

- Rab - vesicle trafficking
- Ras - Activator for G-protein receptor and tyrosine kinase pathway.
- Rho - Modulate cytoskeleton formation and adhesion

There are four prenyltransferases which are responsible for catalysation of protein prenylation. They are fasrnesyltransferase [FTase] and geranylgeranyltransferase types I,II,III [GGTase -I,II,III].6

The site of protein prenylation is cytosol. In FTase and GGTase -I prenylation takes place through the binding of isoprenoid substrate to the active site followed by other

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protein substrate forming the prenylated product.

The GGTase-II requires Rab for catalysing prenylated proteins. After completion of protein prenylation the proteins are transferred to endoplasmic reticulum and attaches to cysteine.7

Statins delay the prenylation which causes the activation of caspase3 resulting in apoptosis.

This mechanism is unclear. These results are based on trials performed in skeletal myofibers of rat flexor digitorium brevis.

2. DEFICIENCY OF Co-ENZYME Q10

Co-enzymes Q10 is a co factor in mitochondrial energy metabolism. Statins reduces the levels of Q10 in skeletal muscle which affects the electron transport chain and calcium homeostasis. It also activates caspase activation which leads to apoptosis.

3.MITOCHONDRIAL DYSFUNCTION:

Statin disturbs CPT-2[carnitine palmitoyltransferase-II] mRNA along with CPT-I which is responsible for the oxidation of long chain fatty acids in mitochondria. Due to this SAMS [statin associated muscle symptoms] develops however which are not seen in all patients. This pathway generates ATP which is utilised by skeletal muscle. Although CPT2 is far away from the inhibition of HMG-CoA but it is assumed as effects of statin and mutation in mRNA of CTP2 acts as additive effect resulting in reduction of ATP production. More evidence and repots are needed to support this theory.

CASE REPORT: EVIDENCES

CASE 1:

A 74-year-old male patient was admitted with complaints of progressive swelling all over the body associated with pain and stiffness in the limbs for 2 weeks. He had history of oliguria and constipation for 4 days. His past medical history included hypertension, acid peptic disease, and cholecystectomy. Ongoing medications were amlodipine, Olmesartan hydrochlorothiazide, and pantoprazole. Atorvastatin 20 mg was added 15 days prior to his symptom onset. There was no other significant history.On examination, he had tachypnea, tachycardia, and high blood pressure. Nonpitting subcutaneous edema with severe muscle tightness and rigidity was noted. Reflexes were suppressed. Other systems were unremarkable.8

LAB INVESTIGATIONS:

On admission,

PARAMETERS	**RESULTS**
Haemoglobin	14.3 g/dl

Total leukocyte count	22400/mm3
Platelet	2.28 lakhs/mm3
Creatinine	1.13 mg/dl
Blood urea nitrogen	12.5 mg/dl
Bilirubin	1.1 mg/dl
SGOT/SGPT	2688/468 U/L
Creatinine phosphokinase (CPK)	192,000 U/L
Thyroid-stimulating hormone	70.5 mIU/L
Urine colour	High coloured (contains proteins and RBC)
Urine myoglobin	Positive

DIAGNOSIS:

On the basis of history collection, lab investigations, the patient was diagnosed with atorvastatin induced rhabdomyolysis with underlying hypothyroidism. Magnetic resonance imaging was done which showed diffuse swelling and abnormal signal involving almost all muscles of both lower limbs.

CASE 2:

A 73-year-old woman with a history of hypertension, hypothyroidism, mesenteric vein thrombosis, depression and hyperlipidaemia on statins for >9 years admitted with new-onset leg weakness, falls and dark-coloured urine. She reported that her legs felt like 'jello' and unable to support her body weight. She had also noticed reduced urine output with dark-coloured urine. Home medications included simvastatin that she had been taking for the last 9 years, antidepressants like sertraline, bupropion and aripiprazole that was restarted 6 months ago. The patient however endorsed some trouble swallowing and back pain.8

LAB INVESTIGATION:

Creatinine phosphokinase (CPK)	12 896 U/L

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Aspartate transaminase (AST)	420 U/L
Alanine transaminase	95 U/L
Urine colour	Cloudy urine with 0-2 RBCs
Aldolase	45.9 U/L

DIAGNOSIS:

Based on the elevated aldolase level, the patient was diagnosed with statin-induced rhabdomyolysis.

CASE 3:

A 77-year-old man presented to our attention complaining of weakness and myalgia of the lower limbs for about a month. His past medical history revealed ischemic heart disease in 2017, thyroidectomy, localised colorectal cancer resection 10years before, benign prostate hyperplasia, and abdominal aorta aneurysm. At the time of admission, medications include atorvastatin 40mg/day, aspirin 100mg/day, ramipril 2.5mg/day, levothyroxine 50µg/day and 75µg/day on alternate days, alfuzosin 10mg/day, and dutasteride 0.5mg/day. On examination, the patient showed good muscle tone according to his age in both upper and lower limbs. Lower limb weakness slightly progressed (gluteus muscles strength: 3/5, iliopsoas strength: 4/5).10

LAB INVESTIGATIONS:

Creatine phosphokinase (CK)	6978IU/L
Lactate dehydrogenase (LDH)	695IU/L
Alanine aminotransferase (ALT)	401IU/L

DIAGNOSIS:

An MRI scan of the lower limbs revealed bilateral intramuscular oedema with patchy distribution involving the gluteus muscle and iliopsoas muscle. Muscle biopsy highlighted the presence of necrosis with macrophages infiltration and thickening of connective tissue with mild inflammatory changes.

The patient was diagnosed with atorvastatin induced rhabdomyolysis.

CASE 4:

A 42-year-old female with a medical history of hypertension, obesity, and recently diagnosed hyperlipidemia (seven

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months ago) presented due to complaints of muscle aches, purpura on her left arm, progressive odynophagia, and tongue swelling for the past three weeks. Past surgical history was unremarkable, and family history was significant for type II diabetes mellitus in the mother. On presentation, the patient was hemodynamically stable with a heart rate of 92 beats per minute, temperature of 98 F, and blood pressure of 119/69 mmHg. The patient showed symptoms of proximal muscle weakness, including the ability to stand up from a chair using hands. Her home medications include semaglutide and newly started atorvastatin. She was started on atorvastatin 40 mg seven months ago. On examination, the rash was purpuric, and the patient was noted to have weakness in the proximal and distal muscles in the arms and legs and mild tongue swelling; the rest of the examination was unremarkable.11

LAB INVESTIGATIONS:

Red blood cell (RBC)	5.36 MIL/ul
Hemoglobin (Hb)	16.2 g/dl
Creatinine	0.5 mg/dl
ALT	721 unit/L
AST	1088 unit/L
CPK	20.000 unit/L

DIAGNOSIS:

The MRI scan showing multifocal areas of fairly symmetric appearing moderate intramuscular oedema scattered throughout the bilateral lower extremities. MRI findings were consistent with multifocal areas of bilateral myositis. The patient was diagnosed with statin-induced rhabdomyolysis.

EVALUATION:

The physical examination includes muscle weakness, muscle pain, muscle exertion worsens with exercise. Urine analysis reveal abnormalities in urine like myoglobinuria due to release of myoglobulin in urine and discoloured urine with red blood cells. Magnetic resonance imaging reveals about the intensity of inflammatory responses. The main feature of diagnosing rhabdomyolysis is elevated

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level of creatine phosphokinase and transaminase.12

TREATMENT FOR STATIN INDUCED RHABDOMYOLYSIS:

The statins are transported to the liver by organic anion transporting polypeptide 1B1, which is controlled by the gene SLCO1B1, so the drugs which causes mutation should be avoided. Longer half life statins such as atorvastatin should be given in reduced dose in intermittent alternative days. If no muscle symptoms seen, can continue statins. If statin associated muscle symptoms are identified, discontinuation of statin is recommended.13,14

Non Statin based therapies are recommended to patients who are statin intolerant, these drugs include,

- PCSK9 Inhibitors Alirocumab, Evolocumab (reduces the LDL-C level)
- Selective cholesterol absorption inhibitor Ezetimibe (inhibits NPC1L1 protein which helps in cholesterol transportation into the small intestine)
- Bile acid sequestrants Colesevelam , cholestyramine, colestipol
- If results in Immune mediated necrotizing myopathy (autoimmune disorder in which body's immune system mistakenly attacks the muscle fibres leads to necrosis and cell death) immunosuppressants like methotrexate, azathioprine can reduce the exacerbation.

CONCLUSION:

Although rhabdomyolysis happens to be a disease which is a rare condition but the risk intensity of rhabdomyolysis futuristically leading to immune mediated necrotizing myopathy has newly increased in incidence Therefore there is need for dose adjustment, and caution in the use of statins in patients, considering factors which alleviate the risk of rhabdomyolysis. The drugs which increase the plasma level of statins should be avoided in combination with statin therapy.

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