THE SELF-LIMITING NATURE OF STATIN-INDUCED RHABDOMYOLYSIS

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لقد أصبحت الستاتنز في مقدمه العلاجات لزياده الدهون، والذبحه الصدريه، والسكته الدماغيه.
وقد تسبب هذه الأدويه إعتلال العضلات. وفي أغلب الحالات يكون هذا الإعتلال محدود وبحاجه فقط الى علاجات مسانده . يصف هذا التقرير حالتين من إ عتلال العضلات بسبب الستاتنزمع التركيز على التعريف ،عوامل الخطوره ، الصفات السريريه، و طبيعه الإعتلال المحدوده.

الكلمات المفتاح: الستاتنز، إعتلال العضلات

Statins have come to the forefront of treatments for hyperlipidemias, coronary artery diseases and strokes. They have been shown to cause myotoxicity and rhabdomyolysis. In most cases, rhabdomyolysis is self-limiting and needs supportive therapy. Two cases of statin-induced rhabdomyolysis are reported emphasizing the definition, risk factors, clinical features and the self-limiting nature of the disorder.

***Key Words**: Statins, myopathy, rhabdomyolysis.*

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INTRODUCTION

Statin drugs, the main lipid lowering agents now widely used in the treatment and prevention of cardiovascular and cerebrovascular ischemic events, act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase.[1] Currently, available statins include Cerivastatin, Simvastatin, Fluvastatin, Atorvastatin, Lovastatin, Pitavastatin, Rosuvastatin and Pravastatin (Table 1).[2] The main complaints experienced by patients on statin therapy are myopathic symptoms such as fatigue, myalgia and rhabdomyolysis. Others relate to hepatic or neuropathic complications.[3] The statin-induced myopathy is self-limiting and does not require extensive investigations or therapy as opposed to other forms of myopathy.[4] It usually improves on cessation of statins and administration of supportive therapies. We report two patients with statin–induced myopathy and review the current literature.

CASE 1

A 37-year-old nurse had new onset partial seizures with secondary generalization due to convexity meningioma. She was started on carbamazipine without recurrence of seizure. She was noted to have incidental hyperlipidemia (cholesterol 412mg/dl, LDL 337, HDL 19). She developed fatigue myalgia and proximal muscle weakness with an elevated serum creatine kinase (CK) of 23,950 iu/ml (>10times serum CK level) three months after starting Atorvastatin 40 mg per day. The CK returned to normal values within two weeks of stopping her Atorvastatin. She became free of symptoms and was off the statin therapy.

CASE 2

A 75-year-old lady with Parkinson's disease controlled on anti-parkinsonian medication (Stalevo, Trihexaphenidl, Bromocriptine, Selegline and vitamin E) for more than five years who had been on Atorvastatin 10 mg per day for two years because of hypercholesterolemia (cholesterol 252 mg/dl, LDL 157, HDL 38) presented to the emergency room with nausea, myalgia and weakness: Serum CK 25,000 iu/ml (>10 times elevation) and no myoglobinuria. Atorvastatin was stopped and supportive therapy

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***Table 1**: The statins available for the therapy of hypercholesterolemia*

Name	Year	Formulation	Dose	t ½ (hr)	Metabolism	Solubility	Protein binding %	Manufacturer
Lovostatin (Mevacor, Altoprev)	1987	10/20/40/60 mg per tab	20-80 mg/day	2.9	Hepatic	Lipophilic	<95	MERCK
Pravastatin (Pravachol)	1991	10/20/40/80 mg per tab	10-80 mg/day	1-3-2.8	Hepatic	Hydrophilic	40-55	Bristol-Myers-Squibb
Atorvastatin (Lipitor)	1999	10/20/40 mg per tab	10-80 mg/day	15-30	Hepatic	Lipophilic / Hydrophilic	80-90	Parke-Davis
Fluvastatin (Lescol)	1999	80 mg per tab	20-80 mg/day	0.5-2.3	Hepatic	Hydrophilic	>99	Novartis
Cerivastatin* (Baycol, Lipobay)	1999	0.3/0.4/0.8 mg per tab	0.3 mg 0.4 mg	2.1-3.1	Hepatic	Lipophilic	>99	Bayer
Simvastatin (Zocor)	2000	5/10/20/40 mg per tab	10-80 mg/day	2-3	Hepatic	Lipophilic	>95	MERCK
Rosuvastatin (Crestor)	2003	5/10/20/40 mg per tab	5-40 mg/day	19	Hepatic	Hydrophilic	88	AstraZeneca
Pitavastatin (Livalo)	2003	1/2 mg per tab	1-4 mg/day	11	Hepatic	Lipophilic	96	Kowa

*Voluntarily withdrawn from market by manufacturer.

administered. Over the ensuing four weeks she returned to her baseline full function, with normal serum CK.

DISCUSSION

The most widely used current definition of statin-induced myopathy includes the following: myopathy, a general term for any muscle disease; myalgia, muscle symptoms without CK elevation; myositis, myalgia with elevation of CK and rhabdomyolysis muscle symptoms with more than 10-fold elevation of serum CK.[5] Although this definition is still widely used, it has recently been modified.[7] It is clear from these definitions that both our patients had rhabdomyolysis.

The occurrence of myopathic symptoms in patients taking statins is probably under-reported and may be as much as 5% or more.[8] On the other hand, myositis and rhabdomyolysis are less common with a reported incidence of 97 and 4.4 per 100,000 patient years respectively. Rhabdomyolysis is associated with 0.3 per 100,000 patient years mortality rate.[9] Most of these patients suffer from other underlying systemic diseases.[10] Although any one of the statins can cause myotoxicity in a dose dependent pattern, it is more likely to be seen in its lipophilic rather than the hydrophilic forms[11] and the risk factors are illustrated in Table 2.[12] It is noteworthy that both patients presented with statin-induced rhabdomyolysis and also had identifiable risk factors of gender and concomitant drug use as reported in the literature.[8,10-12] The temporal relationship between statin therapy and myopathic symptoms is not clear. It usually starts within the first month but may be delayed for as long as four years.[13] This temporal variability was similarly seen in our patients, one of which had the onset of symptoms within one month and the other, two years after starting statin therapy. The diagnosis of statin myotoxicity is based mainly on the constellation of myopathic findings since

***Table 2:** Risk factors for statin-induced myopathy*

Age
Female gender
Small body mass index
Physical exercises
Coexisting medical illness
Hepatic disease
Renal disease
Diabetes mellitus
Hypothyroidism
Pre-existing muscle disease
Concomitant medications
Fibrates (Fimfibrozil)
Vitamin K antagonists (Warfarin)
Macrolide antibiotics (Azithromycin)
Azole antifungals (Itaconazole)
HIV protease inhibitors
Verapamil
Amiodarone
Alcohol
Surgery

specific morphologic markers are lacking on muscle biopsy, which is seldom needed to confirm the diagnosis.[14]

Several mechanisms have been proposed to explain the statin-induced myotoxicity.[15] The most common explanation invokes the deficiency of one of the three products in the HMG-CoA reductase pathway:[16] impaired cholesterol synthesis with secondary membrane hyper-excitability; deficiency of relevant compounds like mevalonate and ubiquinone (CoQ10) leading to mitochondrial dysfunction; or prenylated protein causing altered intracellular messaging which induce vacuolation of the myofibers, degeneration and eventually apoptosis.

It has been suggested that baseline and follow-up CK measurements are not required but are useful in high risk patients or patients with nonspecific symptoms, as well as to confirm the diagnosis and assess severity of muscle damage.[6,16] Persistent CK elevation should prompt discontinuation of statins in the absence of other causes, and elevation more than 10 times normal value indicates rhabdomyolysis and such patients need hospital admission and administration of supportive therapies. Other forms of statins could be used after recovery is achieved.[17] The role of CoQ10 supplements is not clear as some case reports describe some improvement with CoQ10 supplements, others have not.[18]

Our cases document the occurrence of myopathic symptoms in individuals on statin therapy and highlight the self-limiting non-fatal nature of rhabdomyolysis after stopping the agent and managing potential risk factors for statin-induced myopathy. These findings suggest the need for increased clinical awareness of statin-induced myopathy. Also, physicians need to advise their patients on the use of statins and alert them of potential side effects.

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