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Review article

Statin induced necrotizing autoimmune myopathy

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ABSTRACT

Statin induced necrotizing autoimmune myopathy (SINAM) is a recently characterized entity belonging to the spectrum of statin myotoxicity. It is a more severe form, and is usually associated with significant proximal muscle weakness, strikingly elevated creatine kinase levels and persistent symptoms despite statin discontinuation. The characteristic pathological finding is a marked muscle fiber necrosis with minimal or no inflammation on muscle biopsy. SINAM is an autoimmune disorder associated with an antibody against 3-hydroxy-3-methyglutaryl-coenzyme A reductase (HMGCR), and the antibody titer is a useful marker for assessing treatment response. However, anti-HMGCR positive myopathies are also caused by unknown etiologies other than statin exposure, especially in the younger population. SINAM should be promptly recognized as immunosuppressive therapy can improve its clinical outcome significantly. Further research is needed to elucidate its pathogenesis and provide evidence based guidelines for management.

Contents

1. Introduction

Statins are a class of medications that are widely prescribed for the prevention of cerebrovascular and cardiovascular diseases. An estimated 25 million patients take statin class medications worldwide [1]. Statins are safe in majority of patients, but side effects limit their usage, resulting in discontinuation in 5 to 20% of patients [2]. Among these, muscle-related adverse events are the most common [3].

The clinical spectrum of statin-induced myotoxicity varies greatly from asymptomatic elevation of creatine kinase (CK) to muscle pain, muscle weakness, biopsy proven myositis and rhabdomyolysis. More recently, a rare but unique entity named statin induced necrotizing autoimmune myopathy (SINAM) was characterized [4–7]. This review aims at consolidating the latest development on SINAM, with a focus on its pathogenesis, clinical features and treatment strategies.

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2. Classification of statin-induced myotoxicity

Based on pathogenesis, statin associated myotoxicity can be classified into toxic and autoimmune forms. Until recently, statin induced myotoxicity, if not otherwise specified, referred to the non-autoimmune and often self-limited adverse events related to muscle. In an effort to unify the terminology, the Phenotype Standardization Project recently convened an international expert workshop on statin induced myotoxicity to agree upon the definitions for a variety of statin related myotoxicity. The proposed definitions, categories and their incidences are outlined in Table 1 [8]. Among self-limited statin myopathies, asymptomatic CK elevation and myalgia without CK elevation are the most commonly occurring, while rhabdomyolysis is the least frequent but the most serious entity, characterized by significant CK elevation and often release of myoglobin into the blood stream.

Most self-limited statin myotoxicity occurs within first 12 weeks of statin exposure [9]. From the Prediction of Muscular Risk in Observational Conditions (PRIMO) study, the median time to onset of muscle symptoms was 1 month after statin initiation, although 15% patients developed symptoms 6 months later [3]. Myalgias in statin myopathy were mostly localized to the thighs and calves, and generalized myalgias occurred in approximately 25% of patients [3].

Except for the rare fatal cases of acute rhabdomyolysis, statin induced muscle symptoms usually resolve upon cessation of offending medication. One study reported that myalgias took an average of 2.3 months to dissipate, with a range of 1 week to 14 months. Approximately half of patients who developed side effects on one statin tolerated a different statin without recurrence of similar symptoms [10].

The underlying mechanisms for self-limited statin myotoxicity have not been fully understood. Several mechanisms were suggested, including isoprenoid depletion, decreased sarcolemmal membrane cholesterol, inhibition of ubiquinone or coenzyme Q10 synthesis or disturbed calcium metabolism. The muscle pathological findings are non-specific, often with observations of muscle fiber necrosis, degeneration, and phagocytic infiltration. In some cases, lipid filled vacuoles and ragged red fibers were observed [11,12].

Risk factors for self-limited statin myotoxicity include age above 65 years, Asian descent, heavy exercise, low body mass index, excess alcohol consumption, vitamin D deficiency, diabetes mellitus, thyroid dysfunction, renal or liver disease, and exposure to other interacting drugs [3,13–15]. Presence of a single nucleotide polymorphism rs4363657 in the SLCO1B1 gene is strongly associated with the occurrence of statin myotoxicity [16].

Occurrence of self-limited statin myotoxicity is often related to the pharmacological properties of statins. Hydrophilic statins (rosuvastatin or pravastatin) are less likely to enter myocytes and therefore less myotoxic than lipophilic ones (lovastatin, simvastatin, fluvastatin, atorvastatin and pivastatin). The higher the dose of statin used, the more likely myotoxicity occurs. A meta-analysis of 4 large randomized trials showed an almost 10-fold increased risk of myopathy in patients on high dose statins (i.e. simvastatin or atorvastatin 80 mg/day) when compared with moderate doses [17].

3. Clinical features of SINAM

In 2007, Needham et al. published a case series of 8 patients who developed statin associated myopathy presenting with progressive weakness and high CK levels which persisted even after statin discontinuation. On pathology, significant muscle fiber necrosis was seen in 7 of 8 patients while mostly minimal endomysial inflammatory infiltrates were present in 3 cases. Despite a relative lack of inflammation on muscle biopsy, a few findings strongly supported the immune-mediated nature of this newly defined entity. A diffuse or multifocal up-regulation of MHC class I expression in non-necrotic muscle fibers was seen in all patients, and an up-regulation of MHC class II expression was also seen in 2 of 8 patients. The up-regulation of both MHC class molecules is characteristic of inflammatory myopathies including polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM) but rarely found in metabolic or inherited myopathies [18,19]. Additionally, 7 patients were treated with prednisone alone or in combination with methotrexate. All improved symptomatically and serologically within 2 months, and complete resolution of symptoms occurred within 9 months after treatment initiation [4]. Three years later, a second case series with similar clinical and pathological features of statin induced necrotizing myopathy was reported [5]. In this study, all 25 cases demonstrated symmetrical proximal weakness and elevated CK levels persisting for at least one month after statins were discontinued. In all cases, the predominant finding on muscle biopsy was myonecrosis without significant inflammation around non-necrotic fibers, and clinical improvements were observed following immunosuppressive treatment. These two studies provided strong evidence that statin usage may lead to development of a necrotizing autoimmune myopathy with unique features (Table 2).

Statin induced necrotizing autoimmune myopathy (SINAM) is usually characterized by a rapid onset of severe proximal weakness, and CK levels of typically over 6000 IU/L. Distal weakness and dysphagia may also occur [5]. SINAM can also start off by mimicking self-limited statin intolerance with myalgia and/or mild weakness, and severe symptoms may develop later [6]. From the Grable-Esposito et al. cohort, the average duration of statin exposure prior to symptomatic onset was 3 years (range of 2 months to 10 years) [5]. It is not yet clear if the severity of SINAM is related to the length or dose of statin exposure. Clinical symptoms may persist or even start after stopping the offending medication, although rare cases of spontaneous improvement following statin discontinuation were recently described [7]. The incidence of myalgia in SINAM is variable among different studies [4–6]. Extramuscular involvement including pulmonary fibrosis, skin manifestation and arthritis does not typically occur.

Multiple statins including simvastatin, lovastatin, pravastatin, fluvastatin and atorvastatin were associated with SINAM suggesting that this is a class rather than a specific statin effect [4–7]. Additionally, SINAM appears to have more consistent statin exposure when compared to other inflammatory myopathies including PM, DM and IBM in age adjusted incidence comparison [4,5]. SINAM typically occurs in the absence of all other known risk factors for self-limited statin

Table 1
Statin-related myotoxicity phenotype classification [8].

Classification	Phenotype	Definition	Incidence
SRM 0	CK elevation < 4 X ULN	No muscle symptoms	1.5–26%
SRM 1	Myalgia, tolerable	Muscle symptoms without CK elevation	0.3–33%
SRM 2	Myalgia, intolerable	Muscle symptoms, CK < 4 X ULN	0.1–1/1,000
SRM 3	Myopathy	CK 4 to 10 X ULN +/− muscle symptoms	5/100,000 Patient-years
SRM 4	Severe myopathy	CK 10 to 50 X ULN, muscle symptoms	0.11%
SRM 5	Rhabdomyolysis	CK > 10 X ULN with muscle symptoms and renal impairment; Or CK > 50 X ULN	0.1–8.4/100,000 Patient –years
SRM 6	Autoimmune-mediated necrotizing myositis	HMGCR antibodies, incomplete resolution upon discontinuation	~2/million per year

SRM statin-related myotoxicy, CK creatine kinase, ULN upper limit of normal.