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Statin-induced necrotizing myositis – A discrete autoimmune entity within the "statin-induced myopathy spectrum"

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Abstract

Statin-induced necrotizing myositis is increasingly being recognised as part of the "statin-induced myopathy spectrum". As in other immune-mediated necrotizing myopathies, statin-induced myositis is characterised by proximal muscle weakness with marked serum creatine kinase elevations and histological evidence of myonecrosis, and with little or no inflammatory cell infiltration. Unlike other necrotizing myopathies, statin-induced myopathy is associated with the presence of autoantibodies directed against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (the enzyme target of statin therapies), and with HLA-DRB1*11. This article summarises the clinical presentation, investigations and management of this rare, but serious complication of statin therapy.

Keywords

Statin; Myositis; Antibody; Necrotizing; HMGCR; 200/100 kDa

1. Introduction

Since their introduction over 20 years ago, statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) have become one of the most widely prescribed medications, with atorvastatin becoming the bestselling drug in history in 2003(1), with worldwide sales worth $12.4 billion in 2008. Statins have proven efficacy in reducing cardiovascular risk and are

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usually well tolerated. However, it has become apparent that skeletal muscle-related side effects associated with statin use are a greater problem than was initially understood from their original licensing trials. In addition to the relatively common self-limiting episodes of statin-induced myalgias, a statin-induced necrotizing myositis is increasingly being recognised. In 2010, an autoantibody to a 200/100kDa protein complex was also first described, which was found to be strongly associated with statin-induced necrotizing myositis(2). This antibody was subsequently identified as being directed against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), the enzyme target of statins, and thus suggesting an intriguing pathogenic link with statin use. This review article summarises the recent evidence and understanding of this rare, but significant complication of statin therapy.

2. The Range of the “Statin-Induced Myopathy Spectrum”

In the original clinical trials of statins, myalgias and/or myopathic problems were not identified as common adverse events, with only 1-5% of participants reporting muscle-related side effects in both intervention and placebo groups(3,4). However, subsequent observational studies have estimated a higher incidence of muscle complaints, ranging between 9-20%(5-7), highlighting the discrepancy between clinical trials with restrictive inclusion criteria and ‘real-life’ experience in patients with potential co-existent risk factors. It has also become apparent that muscle symptoms related to statin use range widely, from the relatively commonly reported non-specific myalgias through the recently described necrotizing myositis to the rare but sometimes fulminant rhabdomyolysis. In 2010, the antibody to the 200/100 kDa protein complex (anti-HMGCR) was identified in some cases of necrotizing myositis, and most of these patients were subsequently found to be statin users (2), giving rise to what is now appreciated as the discrete entity of statin-induced necrotizing myositis. Although usually present in usually small numbers, the inflammatory cell infiltrates found histologically in muscle tissues, and the presence of anti-HMGCR pointed to the likely autoimmune nature of this form of myositis. Part of the challenge in accurately assessing the impact of statin-related myopathy has been identifying a coherent definition for this problem. With the wide range of muscle symptoms associated with statin use, it has proved challenging to delineate diagnostic boundaries. However, it is clear that “statin-induced myopathy” encompasses a spectrum of muscle problems with varying severity and likely differential pathophysiologies.

Classification

Although no internationally agreed criteria exist for statin-induced myopathy, the American College of Cardiology (ACC), the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) definitions and terminology(8) are the most widely used and to define the known types of differing statin-induced muscle problems and pathologies, and which should perhaps be best termed the “statin-induced myopathy spectrum”, as set out below:

- Statin-induced myalgia: muscle symptoms without creatine kinase (CK) elevations.

- Statin-induced myositis: muscle symptoms with CK elevations.
- Statin-induced rhabdomyolysis: muscle symptoms with marked CK elevations (over 10 times the upper limit of normal with an elevated creatinine count and the occasional presence of brown urine (myoglobinuria).

In patients with myalgias and only mild CK elevations muscle biopsy specimens would likely show no myonecrosis or inflammatory cell infiltrates, so it is unclear whether statin-induced myositis (as per the above classification) and the more recently described statin-induced necrotizing myositis are the same entity, though clearly they both form part of the statin-induced myopathy spectrum.

In view of the autoantibody association in statin-induced necrotizing myopathy, this should likely be classified as an immune-mediated necrotizing myopathy. Other immune-mediated necrotizing myopathies include those associated with the presence of antibodies directed against the signal recognition peptide (anti-SRP) and paraneoplastic necrotizing myositis. Clinical features of anti-SRP positive and paraneoplastic associated necrotizing myopathies are similar to statin-induced autoimmune myositis, and include significantly elevated serum CK levels (usually >3000 IU), rapid onset of symptoms with weakness and dysphagia due to a severe myopathy (9-11). A range of cancers are associated with paraneoplastic necrotizing autoimmune myositis including gastrointestinal, pancreatic and gallbladder adenocarcinoma, small cell and non-small cell lung, breast, prostate and transitional cell cancers and myeloma(11-15). As with statin-induced autoimmune myositis, other organ systems do not appear to be affected in paraneoplastic cases, so pulmonary fibrosis, skin manifestations and arthralgias/arthritis do not occur (16).

In view of the severity of symptoms and pathological findings in statin-induced autoimmune myositis, it may be that this is a clinical entity distinct to the other statin myopathies, though it remains a possibility that statin-induced myositis, as classified above, and statin-induced autoimmune myositis, as recently described and set out here, are mild and severe ends of a single statin-induced myositis spectrum. Alternatively these two statin-induced myositis problems are discrete entities. As such, it may be appropriate that statin-induced autoimmune myositis should be classified according to the criteria for adult dermatomyositis (DM) and polymyositis (PM) (17,18), which include symmetrical muscle weakness, proximal muscle involvement and elevated serum CK levels. Given that, to date, the anti-HMGCR autoantibody has not been described in myopathies other than statin-induced autoimmune myositis, it may be that the detection of this autoimmune myositis - specific autoantibody would now allow for the classification of statin-induced autoimmune myositis as a distinct inflammatory myopathy subset, though clearly not an idiopathic one.

A number of factors have been identified that appear associated with increased risk for the commoner statin-induced myalgia and non-autoimmune myositis problems. These can be broadly classified into exogenous and endogenous risk factors. Examples of exogenous risk factors include drugs that are metabolised by the various hepatic cytochrome P450 pathways (such as ciclosporine, amiodarone, warfarin, colchicine, fibrates etc.), alcohol excess, heavy exercise and consumption of grapefruit juice in excess of 1 litre per day. Endogenous factors include advanced age (>65 years), low body mass, thyroid dysfunction, metabolic disorders

as well as multisystem disease (e.g. renal or hepatic dysfunction) (19). However, although these factors have been associated with statin-induced myopathy, their association with statin-induced autoimmune myositis remains unclear.

Epidemiology

Autoimmune myositis is rare, with an estimated prevalence of 22 in 100,000 (20) and statin-induced autoimmune myositis is rarer still, with a prevalence of 1 in 100,000 (21). There is less of a female preponderance in statin-induced autoimmune myositis (20), and onset appears to be more common after the age of 50(2). Those patients who present at younger age of onset of symptoms appear to represent a slightly different subgroup of patients, where despite clinically having symptoms in keeping with a diagnosis of statin-induced autoimmune myositis and the presence of HMGCR antibodies, a history of statin exposure is sometimes lacking. In contrast to those patients with a history of statin exposure, this subset is often of African American descent, possess a higher serum CK level and respond less well to treatment(21).

Diagnosis—Due to the rarity of the condition, diagnosing statin-induced autoimmune myositis can be challenging, and exclusion of more common medical conditions is essential. The identification of autoantibodies is helpful in making a diagnosis, but not all centres will have ready access to the appropriate ELISA kit or have facilities for immunoprecipitation, and due to a low positive predictive value, the presence of the anti-HMGCR autoantibody alone does not make the diagnosis. To further complicate matters, anti-HMGCR may also be identified in those individuals not exposed to statins, who present with a similar clinical phenotype. However, a diagnosis of statin-induced autoimmune myositis can be considered likely in those statin-exposed patients who present with myalgias, muscle weakness, and elevated CK levels that test positive for anti-HMGCR antibodies (22).

3. Clinical Presentation

As with all complex medical conditions, a comprehensive clinical history is essential in establishing a diagnosis of statin-induced autoimmune myositis. The time of onset of symptoms can be difficult to exactly ascertain, as non-specific myalgias may have started insidiously some time before medical advice was sought, emphasising the issue of recall bias when taking a history, and should not be underestimated. Due to the relative frequency of the more benign statin-induced myalgias, primary care physicians may have tried withdrawing or trialling a number of different statins before making a referral to a specialist service. This can make establishing a culprit statin ever more challenging and make it difficult to identify the true time of onset of disease. No one particular statin has been implicated in causing statin-induced autoimmune myositis. Nonetheless, establishing which statin may be the causative agent may be important in the longer-term management of the condition, to avoid future re-exposure without excluding a whole class of medications.

Onset of symptoms can be variable, and non-specific myalgic symptoms may manifest some time before myonecrosis leads to significant loss of muscle power and clinical signs of weakness. Statin-induced autoimmune myositis tends to have an aggressive phenotype, with significant myonecrosis, an irritable pattern on electromyographic testing and higher serum

CK levels than one would normally associate with IIM. Despite this, early in the condition, patients have a remarkable paucity of symptoms until CK levels exceed several of 1000s (2). Muscle pain may be a feature although it is not usually sufficiently severe as to require analgesia. In keeping with the IIM, proximal muscles tend to be more severely affected. Distal muscle involvement, such as the deep flexors of fingers and deep extensors of the foot are more commonly seen in inclusion body myositis and neurodegenerative condition such as amyotrophic lateral sclerosis or Charcot-Marie-Tooth disease.

It is not yet clear if length or dose of statin exposure is related to the severity of the condition; as the diagnosis of statin-induced autoimmune myositis is made almost exclusively in tertiary centres. It seems likely that most patients will have had at least a few months of statin exposure prior to a formal diagnosis. Unlike other autoimmune myopathies, there does not appear to be extra-muscular organ involvement, such as that affecting the lungs or skin (23).

Given the discordance between the high prevalence of statin use in the general population, and the relative rarity of statin-induced autoimmune myositis, an exposure history alone is not adequate to make a diagnosis, so that exclusion of more common myopathies that may be mimicked by statin use should be undertaken. Therefore, enquiry about alcohol history, family history of hereditary muscle or metabolic disorders, endocrine disorders and infectious/tropical diseases is important(19). A comprehensive family history will also help identify possible genetic traits and a full drug history in addition to statin use will identify any other drugs that may be myotoxic (e.g. chemotherapeutic agents, anti-nucleoside analogues, bisphosphonates etc.)(24). A full drug history of supplements or herbal remedies taken by the patients is also essential, as natural lovastatin is found in red yeast rice extract. Drugs which interfere in the hepatic cytochrome P450 pathway, and consumption of grapefruit juice of in excess of 1 litre per day has been associated with non-autoimmune statin related myopathy(19), although an association with statin-induced necrotizing autoimmune myopathy is yet to be established.

5. Examination

As with the history, clinical examination of a patient suspected of having statin-induced autoimmune myositis should be focussed on excluding more common pathologies. Thus, examination of muscle power should identify the location or pattern of muscle weakness, which in statin-induced autoimmune myositis tends to be proximal and symmetrical in distribution, with distal muscle weakness more common in neurodegenerative conditions and inclusion body myositis, and asymmetric muscle weakness often indicative of neuropathic conditions. Early muscle atrophy and fasciculation are not associated with statin-induced autoimmune myositis, so their presence may indicate a chronic degenerative aetiology. As mentioned previously skin involvement is not typically associated with statin-induced autoimmune myositis, and signs such as calcinosis, Gottron’s papules, shawl/V-sign would point more to a diagnosis of DM. Indeed, out of the 16 patients reported as having anti-HMGCR antibodies by Christopher-Stine *et al* (2), none had features in keeping with DM.

Exclusion of possible endocrine abnormalities such as acromegaly, Cushing's and Addison's disease, as well as thyroid dysfunction should be undertaken. Metabolic disorders can be unveiled by the use of statins, so physician should be alert to signs of metabolic disorders, particularly McArdle's disease, carnitine palmitoyltransferase II deficiency, or myoadenylate deaminase deficiency, which may be present.

6. General Investigations

Due to the predominance of myonecrosis in statin-induced autoimmune myositis, creatinine kinase (CK) levels are usually significantly elevated, and often in excess of 10,000 IU/L. The exact cause of such marked CK elevations is unclear, but may be due to complement-mediated disruption of the sarcolemmal membrane(2). Due to potential renal dysfunction, in addition to serum CK monitoring, close attention should be paid to renal function, both biochemically and with urinalysis, to identify any renal compromise or myoglobinuria. In a fashion similar to that in IIM, inflammatory markers are usually not significantly elevated in statin-induced autoimmune myositis, despite the marked CK elevations, and so do not provide an accurate indicator of muscle damage or disease activity.

Electromyography (EMG) usually demonstrates an irritable myopathy pattern in similar to that seen in other inflammatory myopathies (25), so this is not specific for statin-induced autoimmune myositis.

6.1. Autoantibodies

In 2010, Christopher-Stine *et al*(2) identified a novel autoantibody to a 200/100 kDa protein complex in 16 of 25 patients who presented with necrotizing myopathy in whom no other specific antibody or clinical diagnosis had been identified. There was a significant association with prior statin exposure, where 63% of patients with the autoantibody had a prior exposure to statins compared with 15.2% DM ($p = <0.05$) and 18.4% PM ($p = <0.05$) and 35.5% of IBM ($p=0.08$) patients who had a prior exposure. The anti-200/100kDa positive group were younger than the other myositis subgroups, but when the analysis only included patients over 50 years of age, there was an even greater association between prior statin exposure and the presence of the autoantibody, compared with the three traditional IIM subsets.

Further work by Mammen *et al* (21) has identified the autoantigen target of the 100 kDa component of the anti-200/100 autoantigen to be HMGCR, the therapeutic target of statins. In an analysis of 750 patients at the Johns Hopkins Myositis Centre, 45 patients with the anti-200/100 autoantibody were identified, and among those patients aged over 50 years old, 92.3% had been exposed to statins. In 2012, the validity of an ELISA to detect this autoantibody was demonstrated (26), and has enabled screening without initial expensive and time consuming immunoprecipitation. The ELISA assay has a sensitivity and specificity of 94.4% and 99.3% respectively, although a low positive predictive value of 0.001 in an unselected population means that confirmatory immunoprecipitation test may still be still necessary. However, the negative predictive value in an unselected population is >0.999, meaning that a negative ELISA result almost entirely excludes the likely presence of this strategically important autoantibody.

Recent work by Werner *et al* (27) has demonstrated that initial levels of anti-HMGCR correlate with serum CK levels and clinical severity in patients with statin-induced autoimmune disease, and subsequent treatment-induced clinical improvements are matched by falling titres of this antibody.

6.2. Muscle biopsy

Muscle biopsies in anti-HMGCR positive patients have a predominant myofibre necrosis pattern. Interestingly, despite this extensive myonecrosis, there appears to be less inflammation and lymphocytic infiltration when compared with biopsies from traditional PM and DM patients. There is generally an absence of CD8+ T cells invading muscle fibres, although their presence does not exclude a diagnosis of statin-induced autoimmune myositis (25). In addition to this lack of lymphocyte infiltration, a dominant macrophage population and an abundant myophagocytosis is often present (28).

Endomysial and perimysial inflammatory infiltrates have been noted in up to 30% of muscle biopsies from patients with anti-HMGCR autoantibodies, but the degree of inflammation is typically milder, with no significant denervation, amyloid deposition or abnormal glycogen accumulation which may be seen in IBM and glycogen storage disorders(2). Interestingly, expression of HMGCR protein has been noted to be significantly up-regulated in regenerating muscle tissue from patients with statin-induced necrotizing myositis (23). Strong MHC class 1 staining was identified on muscle biopsies in about half of patients with anti-HMGCR antibodies in a series of patients from Johns Hopkins(2). Other case series have identified MHC class 1 staining to be up regulated in the majority of cases of presumed statin-induced autoimmune myositis(29,30). However, as these case series were described prior to the identification of the anti-HMGCR antibody, it is difficult to compare results across these studies. Nevertheless, MHC class 1 staining is a helpful pointer towards immune mediated myopathies, as such staining is only rarely noted in metabolic or genetic muscle disorders(31). Sarcolemmal MHC class 1 staining appears to be particularly specific to statin-induced autoimmune myositis, and in sharp contrast to other IIM(28,29). This can be particularly helpful, as some non-inflammatory muscle disorders such as dysferlinopathies and facioscapulohumeral muscular dystrophies can demonstrate inflammation in muscle biopsy specimens(31).

6.3. Genetics

As with previous genetic association studies relating to IIM, a strong correlation with the Human Leukocyte Antigen (HLA) class II region is noted, particularly, HLA-DR11 in both white and African American patients compared with healthy controls (70% vs 17%, $p = 1.2 \times 10^{-6}$, odds ratio [OR] 10.4, 95% confidence interval [CI] 3.6-31.4 and 88% vs 21%, $p = 0.0002$, OR = 26.4, 95% CI = 3.1-590.3 respectively), with high resolution mapping showing that 95% with DR11 had DRB1*11:01. Conversely, HLA-DQA1 and HLA-DQB6 alleles were decreased in frequency in white anti-HMGCR positive patients compared with healthy controls (25% vs 64%, $p = 5.5 \times 10^{-4}$ and 0% vs 45%, $p = 2.1 \times 10^{-5}$, respectively) (26). Other genetic associations have been identified between non-autoimmune statin-induced myopathy and myalgia. Polymorphisms in the SLCO1B1 gene, which codes for the OATP1B1 which regulates the hepatic uptake of statins has been noted to be associated with

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statin-induced myopathies(32), although to date no association has been noted to date with the necrotizing autoimmune myositis seen in anti-HMGCR positive patients.

7. Pathogenesis

Despite recent advances, the pathogenesis of statin-induced autoimmune myositis remains unclear. Statin exposure up-regulates HMGCR in statin exposed muscle(21) and the presence of an autoantibody to HMGCR suggests that statin exposure may play a direct pathological role in the development of this condition. HMGCR is constitutively expressed at a low level by mature muscle cells, however, expression is markedly up regulated in regenerating muscle, suggesting a possible stimulus for a perpetuated antigen driven immune response in recovering muscle tissue(25). As with all inflammatory myopathies, it is not clear whether antibodies play a directly pathogenic role, or if they are biomarkers of other processes. The association with HLA-DRB1*11*01 suggests that there may be a group of individuals who are more susceptible to developing this condition on exposure to statins. It remains to be elucidated whether statin exposure alone in genetically susceptible individuals is sufficient to induce myositis, or whether further triggers or susceptibilities are required.

8. Management

Exposure

Due to the rarity of statin-induced autoimmune myositis, treatment is usually managed by a specialist centre with expertise in managing IIM. Treatment firstly involves the discontinuation of the offending statin, which often results in the resolution of the myopathic process. However in some instances, despite statin discontinuation, inflammation and muscle necrosis can become self-sustaining, suggesting that the statin can somehow trigger an autoimmune process independent of the medication itself.

Immunosuppression—When required, immunosuppression is usually initially given in the form of corticosteroids, followed by longer-term systemic immunosuppression. The condition tends to respond favourably to treatment, with improvement in muscle strength and reduction of CK. Due to the rarity of statin-induced autoimmune myositis, specialist experience usually guides the choice of immunosuppression, although methotrexate, azathioprine and mycophenolate are probably the most commonly used. Rituximab has also been used in some cases (29,33). Antibody levels appear to correlate with disease activity(27), although even in those patients with clinical remission, anti-HMGCR levels do not appear to return to within the normal range. Tapering of medication can be undertaken, although withdrawal of medication sometimes leads to a resurgence of the condition, even in the absence of statin re-exposure.

Additional treatments, such as coenzyme Q and vitamin D supplementation have been tried in non-autoimmune statin related myalgia, although their efficacy has not been validated in the studies that have been undertaken to date. Some reports suggest that hydrophilic statins may be less likely to precipitate non-immune statin related symptoms (19) although there are no studies to date involving patients with statin-induced autoimmune myositis.

Longer-term management of hypercholesterolemia remains a challenge in patients who have suffered with statin-induced autoimmune myositis. It is unknown if the condition is induced by a class effect of statins or individual drug susceptibilities. As such, alternative strategies, such as lifestyle modifications (smoking cessation, weight loss, dietary modification) and blood pressure management should be undertaken. Fibrates are occasionally used, although their long-term benefits remain considerably less validated in comparison to statins and have also been identified as causing myopathy themselves (19).

Non-pharmacologic treatment

As with all inflammatory myopathies, a multidisciplinary approach is essential. Comprehensive specialist physiotherapy undertaken by those with experience of managing these complex patients is essential, as is accurate serial documentation of muscle strength to guide longer-term therapy.

6. Conclusions

Statin-induced autoimmune myositis remains a rare (and likely new) subset of the statin-induced myopathy spectrum. As such, presentation, response to treatment and long-term prognosis remain incompletely defined and the evidence base for best-practice treatment is lacking. It is clear that statins act as an environmental trigger to induce a complex autoimmune disease in some of those with the genetic susceptibilities described. As the number of cases identified increases, and with the use of commercially available ELISAs, that it will become more feasible to more fully investigate the phenotype of the condition and its natural history. With a greater understanding of this condition, it may also be possible in the future to stratify an individual's risk for developing this complication prior to statin exposure and prevent unnecessary morbidity and mortality.

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Take Home Points

- Statin-induced autoimmune myositis is a rare necrotizing myositis characterised by high serum CK levels and limited or absent inflammation on muscle biopsy.
- Exclusion of more common endocrine, genetic and metabolic myopathies is essential.
- Anti-HMGCR antibodies are associated with the condition and can be diagnostic in the setting of an appropriate clinical history.
- Extra-muscular organ involvement is uncommon.
- Immunosuppression may be required in some patients to ameliorate symptoms.
- Statin-induced autoimmune myositis usually responds well to immunosuppression, if required.