

Statins and Immune-Mediated Necrotizing Myopathy

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Abstract

Statins are a well-recognized cause of a variety of skeletal myopathic effects, which generally resolve when discontinuing the treatment. Among autoimmune manifestations associated with statins, there is immune-mediated necrotizing myopathy (IMNM).

The present article summarizes the main features of statin-related IMNM, describing diagnosis, classification, epidemiology, treatment, and the main autoantibodies detected.

Although it is impossible to define the precise number, it is evident that more than 550 statin-related IMNM cases have been described in the literature. Among IMNM, two forms must be distinguished: with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) and with anti-signal recognition particle (SRP) antibodies. The differential diagnosis should be made between the IMNM and self-limited statin-related myopathy, drug-induced rhabdomyolysis, and nonautoimmune myopathies.

Patients who have failed to normalize high creatine phosphokinase (CPK) after statin withdrawal should be tested for anti-HMGCR antibodies and, if these are positive, undergo muscle biopsy to confirm the diagnosis of IMNM. Pharmacological therapy of IMNM, not yet based on evidence, involves the use of high-dose corticosteroids, immunosuppressant drugs used alone or in combination, intravenous immunoglobulins (IVIg) or plasmapheresis.

Keywords: Hydroxymethylglutaryl-CoA Reductase Inhibitors; Dermatomyositis; Polymyositis; Immune-mediated necrotizing myopathy; Anti-HMGCR antibodies

Statine e miopatia necrotizzante immuno-mediata

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STATINS

Statins are among the most widely prescribed drugs. They helped increase the survival rate in patients affected by cardiovascular disease.

Millions of prescriptions are written annually for this class of drugs. Therefore, it is of the utmost importance to closely monitor patients for adverse and even life-threatening side effects.

The most common side effects of statins include the development of toxic myopathies, which usually resolve after drug removal (about 2-20% of patients treated with statins [1]). The risk of statin myopathy and/

or increased creatine phosphokinase (CPK) is dose-dependent.

Statin-related muscle side effects have recently been systematically classified [2]: as SRM 6 class it is possible to find the rarest among muscle side effects, those concerning autoimmune phenomena (Table I).

In fact, recently, immune-mediated necrotizing myopathy (IMNM) has been found to be sometimes associated with statin use.

In addition, exposure to statins was reported in some cases of inflammatory myopathies such as polymyositis (PM) and dermatomyositis (DM). The association of statins and PM or DM is sustained by some authors, and criticized by others, who believe that these cases could be IMNM.

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Table 1. *Statin-related myotoxicity phenotype classification. Modified with permission to reuse from [2]*

CPK = creatin phosphokinase; HMGCR = 3-hydroxy-3-methylglutaryl-coenzyme A reductase; SRM = statin-related myotoxicity; ULN = upper limit of normal

SRM Classification	Phenotype	Definition	Incidence
SRM 0	CPK elevation < 4 x ULN	No muscle symptoms	1.5-26%
SRM 1	Myalgia, tolerable	Muscle symptoms without CPK elevation	0.3-33%
SRM 2	Myalgia, intolerable	Muscle symptoms, CPK < 4 x ULN, complete resolution on dechallenge	0.2-2/1000
SRM 3	Myopathy	CPK elevation > 4 x ULN with or without muscle symptoms, complete resolution on dechallenge	5/100,000 patient-years
SRM 4	Severe myopathy	CPK elevation > 10 x ULN < 50 x ULN, muscle symptoms, complete resolution on dechallenge	0.11%
SRM 5	Rhabdomyolysis	CPK elevation > 10 x ULN with evidence of renal impairment + muscle symptoms or CPK > 50 x ULN	0.1-8.4 /100,000 patient-years
SRM 6	Autoimmune-mediated necrotizing myositis	HMGCR antibodies, HMGCR expression in muscle biopsy, incomplete resolution on dechallenge	~2/million per year

CLASSIFICATION AND DIAGNOSTIC CRITERIA

In 2003, in the Netherlands the category of immune-mediated necrotizing myopathy (IMNM) was introduced for the first time by the European Neuromuscular Centre Workshop [3].

In 2017, the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) defined the classification criteria of inflammatory myopathies (IIMs) [4].

In the same year an integrated classification of inflammatory myopathies, authored by Allenbach and colleagues [5], was published. Unlike the EULAR classification, the difference between PM, a very uncommon isolated disease, and IMNM was well defined.

In September 2018, Selva-O’Callaghan and colleagues published on *Lancet Neurology* a new classification of inflammatory myopathies in the adult based on the clinical characteristics of the main clinical and phenotype-specific autoantibody groups [6]. Five main types of IIM are recognized:

- Dermatomyositis (with autoantibodies against Mi2, NXP2, TIF1, SAE, MDA5 or no autoantibodies detected), affecting mainly skin and muscle;
- Immune-mediated necrotizing myopathy (with autoantibodies against SRP, HMGCR or no autoantibodies detected), affecting mainly muscle in a severe manner;
- Sporadic inclusion-body myositis, affecting muscle severely;
- Overlap myositis (including antisynthetase syndrome, where autoantibodies against Jo1, PL7, and PL12 may be detected, and three other forms, with autoantibodies against Pm/Scl, Ku, and U1RNP), affecting mainly muscle and lung; and
- Polymyositis, with heterogeneous clinical features.

Many patients previously classified as having PM could now be considered to have antisynthetase syndrome without a rash, IMNM or sporadic inclusion-body myositis: the condition remains a diagnosis of exclusion.

Abbreviations of Autoantibodies

HMGCR	3-hydroxy-3-methylglutaryl-coenzyme A reductase
Jo1	histidyl-tRNA synthetase
MDA5	melanoma differentiation-associated gene 5
NXP2	nuclear matrix protein 2
PL7	threonyl-tRNA synthetase
PL12	alanyl-tRNA synthetase
Pm/Scl	anti-polymyositis-scleromyositis
SAE	small ubiquitin-like modifier activating enzyme
SRP	signal recognition particle
TIF1	transcription intermediary factor 1
U1RNP	U1 ribonucleoprotein

Muscle symptoms	Subacute, progressive, symmetrical, proximal muscle weakness (especially posterior thigh, medial thigh, and gluteal compartments)
CK	Increased (6000-10,000; range: 1000-50,000) and persistent despite statins discontinuation
EMG	Myogenic pattern (usually with spontaneous activity in the form of fibrillations and positive sharp waves)
MRI	Muscle edema, extensive necrosis, atrophy, fatty replacement, fascial edema, minimal or absent inflammation T1 hyperintensity especially in posterior thigh; STIR signal is increased and may be asymmetric
Risk factors	Statin drugs or supplements
Specific immunogenetic background	Adult: HLA-DRB1*11:01 allele Children: HLA-DRB1*07:01 allele
Muscle biopsy	Necrotizing myopathy Granular complement C5b-9 (MAC) deposition on the sarcolemma of myofibers Faint sarcolemmal MHC-I expression in non-necrotic/non-regenerating fibers
Therapy	Sensitive to prolonged therapy with corticosteroids + immunosuppressants, IVIg

Table II. Diagnostic criteria for statin-induced immune-mediated necrotizing myopathy (IMNM) or statin-induced necrotizing autoimmune myopathy (SINAM). Modified from [14-17]

CK = creatine kinase;
EMG = electromyography;
HMGCR = 3-hydroxy-3-methylglutaryl-coenzyme A reductase;
IVIg = intravenous immunoglobulin;
MAC = membranolytic attack complex;
MHC = major histocompatibility complex class I antigen;
MRI = magnetic resonance imaging;
STIR = short-tau inversion recovery sequences in MRI

Besides clinical criteria, magnetic resonance imaging (MRI) [3,7] can be useful to make the right diagnosis.

Statins have also been implicated in other autoimmune diseases, such as interstitial lung disease, myasthenia gravis, systemic lupus erythematosus, cutaneous lupus, vasculitis, autoimmune hepatitis, and lichen planus pemphigoides [8-10].

Several cases appeared in recent years in literature related to necrotizing myopathies associated with statins and with the coexistence of autoimmune phenomena [8,11].

In the list of rare diseases of Orphanet [12], immune-mediated necrotizing myopathy appears at n.206569 and has several synonyms: anti-HMG-CoA myopathy, anti-SRP myopathy, autoimmune necrotizing myositis, IMNM, immune myopathy with myocyte necrosis, and necrotizing autoimmune myopathy (NAM).

The possible causes for the onset of IMNM are: statins, connective tissue diseases, or cancer.

Until June 2018, the presence of 300 cases of IMNM overall was reported in Orphanet list [12], instead until February 2018 a French communication cited 390 cases in adults and 20 pediatric cases [13].

Incidence of statin-related IMNM was estimated to be 2-3 new cases in every 100,000 patients exposed to statins, with age at onset ranging from adulthood to elderly [14].

Immune-mediated necrotizing myopathy is a serious muscle complication that may be associated with statin use and has recently been described. It has been defined

after the discovery of anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies (anti-HMGCR). The characteristics of statin-related IMNM are described in Table II.

The positivity of anti-HMGCR antibodies defines the IMNM associated to them as "SINAM": statin-induced necrotizing autoimmune myopathy.

EPIDEMIOLOGY

I have recently described the clinical case [18] of an elderly woman with clinical manifestations suggestive for dermatomyositis/polymyositis: fatigue and progressive weakness for proximal deficit in the lower limbs, heliotrope rash on the face, erythema at the neck, back, and thighs, increase in CPK (peak 5968 IU/l) that did not regress with cortisone therapy, antinuclear antibody titer of 1:640 (fine speckled pattern), anti-Jo-1 negative, irritative proximal myopathy to EMG, muscle edema to the MRI of the pelvis and lower limbs. The patient had been taking statins for at least 12 years (pravastatin, then rosuvastatin).

This report, unfortunately not supported by the test for anti-HMGCR antibodies, has many similarities with the limited number of international case series [19-31] and with individual case reports described both before [32-40] and after the use of anti-HMGCR [41-66].

In Italy, there are only nine cases in reports [67-71] of probable IMNM. There are also

5 cases anti-HMGCR positive included in two large international case series [20,72].

In a European registry of 11 countries, 105 cases of IMNM are included in 3067 patients with myositis [72].

A comprehensive systematic review of 100 published case reports and case series of patients with statin-associated autoimmune myopathy was written last year by American Authors [73].

The communications presented in 2018 relate so far to New Zealand [30] with the description of 4 cases: 2 males + 2 females, age 59-77 years, long-term exposure to atorvastatin, CPK peak between 4.200 and 21.856 $\mu\text{mol/l}$, high titer anti-HMGCR, myositis-associated autoantibodies (MAA) and myositis-specific autoantibodies (MSA) negative. Electromyography (EMG) reported myopathic changes, while MRI showed extensive muscle edema. Biopsy demonstrated the presence of prominent fiber necrosis with infiltrating macrophages. The patients were given therapies with corticosteroids, methotrexate, and intravenous immunoglobulin (IVIg). A previous clinical series of 8 patients was described in 2016 [74], giving an overall incidence in New Zealand of 1.7/million/year although it has been estimated at 2 million/year in a US population.

Two additional cases in the USA [75,76], one in Brazil [77], four cases in UK [78,79] and five cases in France [80] have been so far described in the literature in 2018.

The statin mainly implicated in the IMNM was usually high dose atorvastatin, followed by simvastatin, pravastatin, and fluvastatin. Rosuvastatin has been described in only 13 cases [19,22-24,41,61,81-84].

The high risk of neoplasia in autoimmune necrotizing myopathies has been reported [85].

Increasingly frequent, even if anecdotal, are the reports of the positivity of anti-HMGCR in paraneoplastic necrotizing myopathy [77], especially in the Japanese population [83,86-88]: prevalence rates of cancer association (detected within 3 years of anti-HMGCR myopathy diagnosis) ranges from 4% to 36% and no specific type of cancer was observed [86].

AUTOANTIBODIES

There are two forms of IMNM respectively associated with positive anti-SRP and anti-HMGCR antibodies. These two

antibodies were positive in 2/3 of cases of autoimmune necrotizing myopathy.

The detection of these antibodies associated with thigh MRI defines the two subtypes that have different systemic and anatomical involvement, while muscle biopsy instead provides an identical result [7,89,90].

Anti-HMGCR

In 2010 Cristopher-Stine and colleagues [91] found in the sera of patients with necrotizing myopathy of unknown etiology the presence of a pair of immunoprecipitates of molecular weight 200 and 100 kDa, not corresponding to those already known in the myositis. The autoantigens of these antibodies came from 3-hydroxy-3-methylglutaryl-coenzyme A reductase with muscle expression. This autoantibody, directed against the pharmacologic target of statins, were termed "anti-HMGCR" [92-96].

Anti-HMGCR autoantibodies were specific for statin-related IMNM: the prevalence of statin exposure was between 40% and 92% in patients with these antibodies [20,22,24,27,29,92,94-99], whereas they were found positive only in small proportion in inflammatory myopathies [20,24].

A 2015 Chinese study confirmed a low positivity (5.4%) of anti-HMGCR in patients with IIMs [81]. A multicenter international research, published in 2016, has shown, in addition to a low prevalence in polymyositis (4.4%) and in dermatomyositis (1.9%), a high presence of such antibodies (76.5%) in a population of elderly, aged > 50 years, with IMNM exposed to statins [81].

They were also found in 30-50% of subjects not exposed to statins.

In patients with HMGCR antibodies and autoimmune myopathy but without statin exposure, including children [13,22,100], other possible sources of statin exposure have been hypothesized in consumption of red yeast rice (*Monascus purpureus*, Monacolina K), *Pu-erh* tea (rich in *Aspergillus terreus*), food containing certain type of oyster mushrooms, and other molds and yeasts all natural sources of statins [1,101].

Pediatric anti-HMGCR positive cases were all negative for statin exposure [102] demonstrating that autoantibody may simply develop as an auto-immune reaction with an unknown trigger.

It is reported that in Asians the myopathy is not typically associated with statin use.

A specific immunogenetic background in children is HLA-DRB1*07:01 [103] unlike DRB1*11:01 allele in adults.

Tests for anti-HMGCR by ELISA, currently limited to a few centers, presented high sensitivity (94%) and high specificity (99%).

Autoantibody levels are correlated with both creatine kinase and the degree of proximal muscle weakness [22,92,95,98], to be considered a highly specific biomarker of disease.

HMGCR antibodies, although specific, do not appear to inhibit the target enzyme. This observation is consistent with the lack of specificity of the lipid profile [104].

The intake of atorvastatin and diabetes mellitus type 2 were the two most significant independent predictors for the onset of myopathy associated with anti-HMGCR [105,106].

Anti-HMGCR antibodies persist even after cessation of statin therapy [107] and despite clinical improvement following immunosuppressive therapy.

Anti-SRP

Anti-SRP patients are weaker than anti-HMGCR patients, suggesting that IMNM includes at least two distinct forms of myositis associated with these two autoantibodies.

In the anti-SRP positive IMNM, neurological symptoms and muscular involvement are present with limb and neck muscle weakness, dysphagia and respiratory failure, symptoms always present and more severe than the form with HMGCR positive [89,108].

MRI in anti-SRP subjects detects a more extensive muscle atrophy and a higher adipose substitution, compared to anti-HMGCR demonstrating that autoantibodies define precisely these two distinct clinical subgroups [59,109-111].

While anti-SRP and anti-HMGCR antibodies show a strong affinity for their antigenic target, affinity and clinical severity cannot be associated.

DIFFERENTIAL DIAGNOSIS

According to some Authors, the majority of patients with necrotizing myopathy with a history of statins before the discovery of anti-HMGCR were classified as polymyositis. The statin-triggered IMNM and polymyositis would therefore not be

two distinct entities, but part of the same pathophysiological spectrum also because they respond well to immunosuppressive treatment [19,112].

In addition, a genetic risk factor in adult subjects was established by the class II HLA allele DRB1*11: 01 [11]: it is strongly associated with the development of anti-HMGCR antibodies, even in patients without known exposure to statins.

In the IMNM, magnetic resonance detects a characteristic pattern of muscular abnormalities involving mainly hip rotators and glutei: IMNM have significantly more widespread muscle edema, atrophy, and fatty replacement compared with those with polymyositis (PM) and dermatomyositis (DM), unlike the fascial edema is more common and widespread in dermatomyositis [7].

In the differential diagnosis of necrotizing myopathy, rhabdomyolysis produced by drugs should be excluded, in particular those responsible for the neuroleptic malignant syndrome.

The list of drugs causing muscle necrosis is long [19,112,113], and cholesterol-lowering agents (statins, fibrates), the immunophilins cyclosporine and tacrolimus, nucleoside analogs (telbivudine and entecavir) and drugs causing neuroleptic malignant syndrome (NMS)[114-116] are among the more common ones.

In addition, alcohol intoxication (in binge drinking), cocaine and heroin are associated with muscle necrosis.

Snake venoms (rattlesnake and cobra) produce isolated muscle fiber necrosis and regeneration.

Nonautoimmune myopathies most frequently misdiagnosed as myositis in children include inherited dystrophy, due to relatively slow progression and myopathological similarity: dysferlinopathy (limb-girdle muscular dystrophy 2B—LGMD 2B), calpainopathy (LGMD 2A) and facio-scapulothoracic dystrophy (FSHD) [22,77,100,117,118].

In the adult the differential diagnosis must be made with sporadic inclusion body myositis (sIBM), hypothyroid myopathy and severe self-limited statin myopathy [119].

Regarding statin myotoxicity, the main epidemiological studies have shown that neither statin myalgia nor CPK levels < 5 times upper limit of normal (ULN) and without muscle weakness are associated with the presence of anti-HMGCR [97,98].

In all cases of severe myopathy, but self-limited by the discontinuation of the statin,

there was no positive finding for anti-HMGCR [120]. Therefore, in these cases such antibodies should not be tested.

In the self-limited statin-related myopathy a genomewide association study revealed a strong association with a single nucleotide polymorphism (SNP) rs4363657 located within the SLCO1B1 (solute carrier organic anion transporter family, member 1B1) gene on chromosome 12 [11,121].

TREATMENT

Pharmacological therapy of IMNM, not yet based on evidence, involves the use of high-dose corticosteroids and immunosuppressant drugs used alone or in combination: methotrexate, azathioprine, mycophenolate mofetil, rituximab, cyclophosphamide, etanercept (results about its use are conflicting), abatacept, tocilizumab, tacrolimus and cyclosporine. In addition, intravenous immunoglobulins (IVIg) or plasmapheresis may be

beneficial in case of severe manifestations of the disease [6].

In a lot of drugs, an initial induction therapy is required before maintenance therapy.

However, rigorous data from the literature are lacking: an international consensus regarding treatment recommendations for patients with anti-HMGCR and anti-SRP myopathies has recently been presented [17] for the use of steroids, methotrexate, IVIg and rituximab together with a review in 2018 [6] where the treatment of severe manifestations of the disease was described.

CONCLUSIONS

Even though it is a rare phenomenon (around 550 cases described in the literature), statins may cause an autoimmune disease called “statin-related immune-mediated necrotizing myopathy”. It is characterized by progressive rhabdomyolysis with intense

Practical Applications

- Patients taking high dose statins, over the age of 50, who develop myopathy with muscular asthenia associated with increased CPK > 5 times the upper limit are at risk of developing autoimmune necrotizing myopathy
- In subjects taking statins, testing for anti-HMGCR autoantibodies may help to discriminate between self-limited rhabdomyolysis and statin-associated autoimmune myopathy
- In myopathic patients positive for anti-HMGCR, especially in the elderly, it is necessary to verify the coexistence of neoplasia
- Patients who have failed to normalize high CPK (> 10 times the upper range of normal) after statin withdrawal and after cortisone therapy should be tested for anti-HMGCR antibodies and, if these are positive, undergo muscle biopsy to confirm the diagnosis of IMNM

Key Points

- Statin intolerance is the main reason for discontinuing therapy for hypercholesterolemia associated with or without cardiovascular disease
- Besides the known side effects on muscle, statins can cause autoimmune phenomena
- A rare but serious complication is progressive rhabdomyolysis with intense and widespread muscular impairment that does not respond to drug withdrawal
- This new entity, called statin-related IMNM, is associated with the presence of autoantibodies against 3-hydroxy-3-methyl-glutaryl-CoA reductase, a key enzyme in the synthesis of inhibited cholesterol by statins
- The diagnosis is addressed by the positivity of these antibodies and confirmed by muscle biopsy
- Exclusion of more common endocrine, genetic, and metabolic myopathies is essential
- Inflammatory myopathies are a very heterogeneous group of illnesses that can present with a very different clinical phenotype
- Drug therapy, not yet subject to guidelines, is challenging and requires, in addition to corticosteroids, immunosuppressive medications, and often immunoglobulins, and plasmapheresis
- The international literature has reported around 550 statin-associated IMNM

and widespread muscular impairment and doesn't respond to drug withdrawal. Autoantibodies against HMGCR may be detected. The diagnosis is challenging and the treatment, not yet regulated by guidelines,

is generally based on corticosteroids and immunosuppressants.

On the basis of the cases described and literature review some practical applications may be summarized.

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Conflicts of interests

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