Immune-mediated necrotizing myopathy associated with statins: history and recent developments

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Purpose of review
The use of statins has increased exponentially over the last 2 decades. Consequently, side effects have also increased, with muscle-related side effects commonly reported.

Recent findings
Although once thought to be only associated with self-limited direct myotoxicity, statins have recently been described in association with an autoimmune myopathy in association with antibodies directed against 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the rate limiting enzyme in cholesterol synthesis and the pharmacologic target of statins. Since this discovery, various cohorts have been identified worldwide and highlight both similarities and differences among them.

Summary
Recent studies from different fields have revealed diverse aspects of anti-HMGCR-associated immune-mediated necrotizing myopathy (IMNM). HMGCR IMNM is a unique autoimmune disease characterized by a well defined environmental trigger (statins) and a strong association with a genetic risk factor (Human leukocyte antigen D related B 1*11:01). New diagnostic modalities have been established to confirm the presence of anti-HMGCR antibody and confirm the diagnosis of HMGCR IMNM. Clinical studies have shown that disease severity, as measured by muscle strength, as well as the rate of response to treatment have been associated with age at disease onset. Furthermore, a case series supported that intravenous immunoglobulin administration, perhaps even as monotherapy, may be a beneficial therapeutic intervention for selected patients.

Keywords
anti-3-hydroxy-3-methylglutaryl-CoA reductase, myopathy, stains, statin myopathy, statin toxicity

INTRODUCTION

The idiopathic inflammatory myopathies (IIMs) are a diverse group of autoimmune disorders affecting mainly the skeletal muscles. Typically, patients with IIM experience progressively worsening proximal muscle weakness, and present with elevated muscle enzymes, distinctive electromyography (EMG) abnormalities, characteristic muscle biopsy findings and myositis-specific antibodies. Since 1975, many classification criteria for diagnosis of IIM have been proposed, but the Bohan and Peter [1,2] criteria still remain the most commonly used in clinical practice and research. Nevertheless, emerging data, including the identification of novel myositis-specific antibodies [3], advancement in immunopathologic fields and new insights into the immune-mediated mechanisms involved in the autoimmune processes, emphasize the need to introduce new classification criteria for this heterogeneous group of autoimmune muscle diseases.

In 2004, the Muscle Study Group/European Neuro Muscular Centre (ENMC) classified the IIMs, based predominately on muscle biopsy features, into polymyositis, dermatomyositis, inclusion body myositis, nonspecific myositis and immune-mediated necrotizing myopathy (IMNM) [4]. IMNM was defined by the presence of muscle cell necrosis and degeneration along with a lack of significant inflammatory infiltrates (Table 1). The ENMC criteria introduced a new comprehensive list of exclusion criteria, such as indications of muscular dystrophy

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KEY POINTS

- Anti-HMGCR-associated IMNM. HMGCR IMNM is a distinct autoimmune muscle disease characterized by a well defined environmental trigger (statins) and a strong genetic association (HLA DRB1*11:01).
- New diagnostic modalities have been developed to confirm the presence of anti-HMGCR antibody and establish the diagnosis of HMGCR IMNM. Some are now commercially available.
- Whether anti-HMGCR antibodies play a pathogenic role in the disease process is still unclear.
- Disease severity, as measured by muscle strength, as well as the rate of response to treatment have been associated with age at disease onset.
- There are no guidelines for therapy; however, at least some small studies suggest that intravenous immunoglobulin may be beneficial, even as monotherapy.

or perifascicular atrophy, to better differentiate and subclassify patients with this type of myositis. In this review, we intend to summarize and present the recent data regarding the clinical picture, immunopathology and therapeutic options in the field of the statin-associated IMNM.

STATINS

In early 1970s, clinical studies were starting to convey the contribution of cholesterol to atherosclerosis and, therefore, led to the need of new drug development. In 1976, Japanese biochemist Akira Endo was able to isolate three compounds from the fungus species *Penicillium citrinum*, which were able to impede cholesterol synthesis in a mouse liver enzyme system by blocking the 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) enzyme [5]. Two years later, the first medication in its class of statins, Mevacor (Lovastatin; Merck, Rockville, MD, USA), was marketed, which was isolated from *Aspergillus terreus*. As of today, seven different statins are available in the US market, and they have proved to be some of the most widely used and profitable medications in recent years.

The use of statins has increased exponentially over the last 2 decades. In 2013, the American College of Cardiology and the American Heart Association published new guidelines for the management of cholesterol [6] based on elevated LDL cholesterol level, the presence of diabetes or the predicted risk of a cardiovascular event. When these guidelines are used to estimate the number of persons in the United States who would be eligible for statin therapy, the number reaches 56 million Americans between the ages of 40 and 75 years [7], accounting for almost one-fifth of the population. Particularly amongst adults between 60 and 75 years, 87.4% of men and 53.6% of women are now advised to be on cholesterol-lowering medications. Consequently, we expect to see a substantial increase in the consumption of statins and their side effects thereof.

STATIN TOXICITY

At least half of the documented statin-associated side effects are related to muscle complaints [8,9]. Various studies have reported that 7–29% of people on statins can develop nonspecific myalgias and weakness [10,11]. As defined by the European Atherosclerosis Consensus Panel, the spectrum of muscle-related events includes a broad range of manifestations, encompassing asymptomatic elevation of creatine kinase, myalgias, rhabdomyolysis, up to myositis or myopathy [12].

There have been many attempts to explain the multitude of myotoxic effects of statins. Inhibition of HMGCR not only decreases the synthesis of cholesterol, which is essential for the maintenance of the cell membrane, but can also have effects on other metabolic pathways, like Coenzyme Q_{10} production and mitochondrial function. Other theories evoked include also individual variations in hepatic uptake of drugs, deficiencies in cell membrane repair or impaired sarcoplasmic reticulum calcium cycling [13,14].

PROTOTYPIC PATIENT

A 59-year-old woman, with history of longstanding diabetes, hypertension and hypercholesterolemia, was started on high-intensity statin (atorvastatin 80 mg) in fashion with the appropriate guidelines. A month later, she noticed that she required help to get out of the car and progressively could not even get up from a chair. When her creatine phosphokinase was checked 8 months later, it was above 17 000. She was diagnosed with statin-induced rhabdomyolysis, and the presumed offender was stopped. Six months later, she continued to complain of muscle weakness. Her EMG was consistent with irritable myopathy, and her muscle biopsy showed necrotizing myopathy with lack of inflammatory infiltrate. Examples like the aforementioned patient, although rare, cultivated the impression that statins were potentially associated with the development of autoimmune muscle disease.

Table 1. European Neuro Muscular Centre diagnostic criteria for immune-mediated necrotizing myopathy [4]

Clinical criteria	
	Inclusion
	Onset over 18 years
	Subacute or insidious onset
	Pattern of weakness
	Symmetric proximal > distal
	Neck flexor > neck extensor
	Exclusion
	Clinical features of IBM
	Ocular weakness, isolated dysarthria, neck extensor > neck flexor weakness
	Toxic myopathy, active endocrinopathy, amyloidosis, family history of muscular dystrophy or proximal motor neuropathies
Elevated CK	
Other laboratory criteria (1 of 3)	
	Electromyography (EMG)
	MRI
	Myositis-specific antibodies
Muscle biopsy criteria	
	Inclusion
	Many necrotic muscle fibers as the predominant abnormal histological feature
	Inflammatory cells are sparse or only slight perivascular
	Perimysial infiltrate is not evident
	MAC deposition on small blood vessels or pipestem capillaries on EM may be seen
	Tubuloreticular inclusions in endothelial cells are uncommon or not evident
	Exclusion
	Endomysial inflammatory cell infiltrate (T cells) surrounding and invading nonnecrotic muscle fibers
	Endomysial CD8+ T cells surrounding, but not definitely invading nonnecrotic muscle fibers, or ubiquitous MHC-1 expression
	Perifascicular atrophy
	MAC depositions on small blood vessels, or reduced capillary density, or tubuloreticular inclusions in endothelial cells on EM, or MHC-1 expression of perifascicular fibers
	Perivascular, perimysial inflammatory cell infiltrate
	Scattered endomysial CD8 þ T cells infiltrate that does not clearly surround or invade muscle fibers
	Rimmed vacuoles, ragged red fibers, cytochrome oxidase-negative fibers that would suggest IBM
	MAC deposition on the sarcolemma of nonnecrotic fibers and other indications of muscular dystrophies with immunopathology

CK, creatine kinase; EM, electron microscopy; IBM, inclusion body myositis; MAC, membrane attack complex; MHC, major histocompatibility complex.

ANTI-3-HYDROXY-3-METHYLGLUTARYL-COA REDUCTASE AUTOANTIBODY

The muscle-related adverse effects of statins usually resolve within weeks to months after cessation of statins, as they are thought to be due to a noninflammatory, toxic effect [15]. However, some patients would develop persistent myositis and eventually meet the diagnosis of polymyositis, as per Bohan and Peter criteria [16,17]. In the late 2000s, the hypothesis of statins triggering an autoimmune reaction was emerging, quite revolutionary in the concept that a medication can lead to a pure autoimmune development [18].

Still, it was not until 2010, when a new antibody targeted against HMGCR, the pharmacologic target of statins, was described and was able to explain the persistent muscle symptoms [19]. Out of 454 patients of the Johns Hopkins Cohort who were screened, 26 patients were found to have predominant necrosis on muscle biopsy and no known antibody. Sixteen of those were able to immunoprecipitate 200/100 kDa proteins when their sera were assessed using HeLa lysates. These patients had proximal muscle weakness, muscle edema on MRI, irritable myopathy on EMG and elevated creatine kinase levels (mean 10 333 IU/l; range 3052–24 714). When the clinical characteristics of these patients were analyzed, it was detected that 83.3% of those above the age of 50 years old were on a statin, compared with 25% in dermatomyositis and 36.8% in polymyositis. That observation led to further investigation of a potential relationship between drug exposure and this newly found autoantibody. Initially, it was established that statins were able to upregulate the expression of the 200/100-kDa autoantigen in muscle fiber cultures [20]. That could mean that the target autoantigen could be any of the 19 enzymes involved in the mevalonate pathway. As HMGCR is a 97-kDa protein, it stood to reason that it would be the first one to screen. Indeed, the recognition that the novel autoantibody recognized the HMGCR, led to the formation of a new subgroup of IIM known as anti-HMGCR associated IMNM. The 200-kDa protein has not been identified to date but thought to potentially be a dimer.

To test the diagnostic utility of this new antibody, 1966 participants of a community-based Atherosclerosis Risk in Communities Study and 98 French Canadian patients with familial hypercholesterolemia were screened for the presence of anti-HMGCR antibodies. None of those patients were found to be positive for these autoantibodies, although a significant portion of those were exposed to a statin. Therefore, anti-HMGCR could be used as a discriminating factor between self-resolved toxic myopathy and IMNM, which requires immunosuppressive treatment [21]. This was also verified at a consequent study amongst 101 patients with severe self-limited statin intolerance and proved that self-limiting symptoms are not associated with autoantibody formation [22]. In addition, when 47 patients with an inherited muscle disease were screened, none of those were found to be positive for anti-HMGCR, suggesting once again that these antibodies are highly specific [23]. Contrariwise, when eight refractory patients had whole exome sequencing of their DNA, no pathogenic mutations in dystrophy genes were discovered [24▪].

IMMUNOFLUORESCENCE PATTERN

The commonly used diagnostic method for anti-HMGCR antibodies has been an ELISA, which sensitivity has been verified when compared with the gold standard procedure of immunoprecipitation assay. A new screening method based on immunofluorescence pattern has recently been suggested, in which the antibodies create a centrolobular distribution amongst stained rat hepatocytes [25▪]. This observed pattern was unique for anti-HMGCR antibodies and can be used as an initial screening test, as it is relatively inexpensive.

MUSCLE BIOPSY FINDINGS

As mentioned previously, the anti-HMGCR autoantibody was discovered on the basis of observations based on patients with IMNM. All consecutive patients of the Johns Hopkins Cohort were screened for anti-HMGCR, and muscle biopsies from 18 patients were available for review [26]. The majority of those patients were exposed to statins (16/18 or 88.9%). The data confirmed the predominance of myofiber degeneration and infiltrating macrophages of the M2 phenotype, known to contribute to muscle regeneration and repair. Major histocompatibility complex class I was found to be upregulated in the majority of the biopsies, consistent with IIM. However, 20–30% of them had also collections of inflammatory cells, 50% of which were identified as scattered T cells (CD4+ and CD8+). The above results were also confirmed at a European and another US cohort, with the only difference that the exposure to statins was significantly lower [27,28].

Given the rarity of infiltrating T cells, the presence of membrane attack complex depositions on nonnecrotic muscle fibers and association of antibody titers with disease severity, the authors hypothesized on the interaction of autoantibodies and complement cascade as the main pathogenetic

pathway for anti-HMGCR IMNM [26]. Concurring to the idea aforementioned, culture of muscle fibers with anti-HMGCR antibodies in an in-vitro system induced muscle fiber atrophy and decreased myofiber fusion [29▪▪]. The above outcome implicates the autoantibodies as being pathogenic, rather than an epiphenomenon of an autoimmune process. However, further studies need to be conducted to confirm the results *in vivo* as well.

CLINICAL CHARACTERISTICS/STATIN EXPOSURE

The typical clinical picture of anti-HMGCR IMNM involves a patient with proximal muscle weakness and significantly elevated creatine kinase levels. Although proximal muscle weakness is commonly uniform between the patients with anti-HMGCR+ IMNM, extramuscular manifestations are relatively rare. These can include dysphagia, skin or lung involvement [19,24▪,27,30,31].

However, there are differences depending on the origin of the described cohort. Many anti-HMGCR myositis cohorts have been reported worldwide (Table 2). The Johns Hopkins cohort reported mean age of patients 55 years (52.4–57.6), with female (59%) and white (72%) predominance, and elevated creatine kinase of 2812 IU/l (1399–6821 IU/l). The majority of those had a prior history of statin exposure (75%) [24▪]. In juxtaposition, a cohort from central United States described anti-HMGCR IMNM in patients with mean age 50 years old, 67% women, 76% whites and only 38% reported use of statins (18/47) [28]. In a study from Australia, the mean age of the typical patient was 70 years old (55–89 years), male (61%) and 84% exposed to statins (16 out of 19) [32]. When assessing a single-center cohort from the Czech Republic, 36% of them were men, mean age of 55 years old, and all of them admitted use of statins (15 out of 15, 100%) [33]. Similarly, eight patients were described in New Zealand with mean age 67.8 years and 75% exposure to statins [34]. At the same time, France, China and Japan documented to have a much lower statin exposure. The French Myositis Network reported 45 anti-HMGCR+ patients, of whom 73% were women, with a mean age of 48.9, and only in 44%, there was an association with statins [27]. The study from China identified only 15% prevalence of statin exposure in anti-HMGCR positive patients. However, only five out of the 22 patients were over the age of 50 years old [30]. In Japan, the mean age of anti-HMGCR+ patients was 56.4 and only 18% (eight out of 48) had ever been on a statin [31].

Lastly, collaborative work comprising nine different countries, including China and France, reported a mean age of 62.5 (58.0–67.0) with a statistically significant ratio of increased statin users amongst the patients with anti-HMGCR myopathy (52 out of 91) [39▪]. The difference in statin exposure is probably associated with the mean age of the relevant cohort, as statin prevalence is associated with increasing age.

GENETIC RISK FACTORS

HMGCR INMN is additionally unique, as it has one of the strongest associations between an immunogenetic risk factor and autoimmune disease. The class II human leukocyte antigen (HLA) allele D related B (DRB)1*11:01 has an odds ratio (OR) of 24.5 in whites and 56.5 in blacks [44]. The above finding has been verified in different cohorts from Australia and Japan as well [32,45]. Interestingly enough, a recent study based on a pediatric cohort from the United States showed an association with DRB1*07:01 [41▪]. That implies that there is probably a different mechanism causing autoimmunity between children and adults that does not involve statin exposure and most likely involve different epitope recognition.

TITERS AND STRENGTH AND AGE

At an initial study in 2012, the titer of anti-HMGCR antibodies was associated with creatine kinase and inversely correlated with muscle strength but only for statin exposed patients. Although autoantibody titers and creatine kinase levels decreased over time with treatment in statin exposed patients, on the other hand, statin naïve patients were quite resistant, implying reasonably a different pathogenetic process [35]. However, a follow-up analysis of the same cohort showed that a history of statin exposure was not independently associated with the severity and the improvement rate, as measured by increase in muscle strength. Instead, age at disease onset associated with severity; interestingly and somewhat counterintuitively, patients who were older at disease onset were usually stronger and were found to improve faster than younger patients [24▪].

DIABETES

Type 2 diabetes mellitus has been associated with anti-HMGCR myopathy at the Johns Hopkins cohort (OR: 15.6, $P=0.006$) [46▪], although this relationship was not maintained in the Australian cohort, when controlling for sex and statin use [32].

Table 2. Clinical and laboratory characteristics of HMGCR+patients across different study populations

Reference	Country	No of HMGCR+ patients	No of screened patients	Statin exposed patients [% (no)]	Mean age at disease onset in years (range)	Females [% (no)]	Screening/ verification of anti-HMGCR antibodies	Mean CPK [IU/l (range)]	Dysphagia [% (no)]	Myalgia [% (no)]	Cancer [% (no)]	Skin rash [% (no)]	ILD [% (no)]	Arthralgia [% (no)]	IMNM [% (no)]	DRB 1*11:01 [% (no)]
Christopher-Stine *et al.* [19]	USA	16	26	63% (11/16)	54	63% (10/16)	ELISA/IP	10 333 (3052–24 714)	63% (11/16)	75% (12/16)	13% (3/16)	44% (7/16)	0% (0/16)	50% (8/16)	–	–
Mammen *et al.* [20]	USA	45	750	66.6% (30/45)	52 ± 16	57.8% (26/45)	ELISA/IP	9718 ± 7383	–	–	–	–	–	–	100% (40/40)	–
Werner *et al.* [35]	USA	55	1006	72.7% (40/55)	–		ELISA/IP	10 104 ± 6973	–	–	–	–	–	–	71.7% (38/53)	–
Allenbach *et al.* [27]	France	45	206	44% (20/45)	48.9 ± 21.9	73.3% (33/45)	ALBIA	6941 ± 8802	26.7% (12/45)	53.3% (24/45)	–	–	2.2% (1/45)	11.1% (5/45)	97.6% (42/43)	–
Ramanathan *et al.* [36]	Australia	6	–	100% (6/6)	70 (60–77)	50% (3/6)	ELISA	6126 (2700–16 200)	–	–	–	–	–	–	100% (6/6)	–
Limaye *et al.* [32]	Australia	19	207	94% (16/17)	70 (55–89)	42% (8/19)	ELISA/ immunoblot	–	–	–	26% (5/19)	–	–	–	9% (2/19)	90% (10/11)
Klein *et al.* [33]	Czech Republic	15	217	100% (15/15)	67 (55–76)[a]	64% (7/11)	ELISA	–	–	36% (4/11)	–	–	–	–	73% (11/15)	–
Ge *et al.* [30]	China	22	405	15% (3/20)	–	73% (16/22)	ELISA	2538.7 ± 3047.6	50% (10/20)	70% (14/20)	–	–	15% (3/20)	25% (5/20)	67% (8/12)	–
Watanabe *et al.* [37]	Japan	8	460	37.5% (3/8)	65.5 (49–79)	37.5% (3/8)	ELISA/IP	7737 (3028–10 452)	0% (0/8)	37.5% (3/8)	–	–	–	–	–	–
Alvarado-Cardenas *et al.* [25▪]	Spain	23	0	14 (6 patients missing data)	63 (52–82)		ELISA/i mmunoblot	6941 (2270–18 417) 50% (7/14)	–	50% (7/14)	–	–	–	–	–	83% (5/6)
Kennedy *et al.* [34]	New Zealand	8	425	75% (2/8)	67.8 (56–81)	50% (4/8)	ELISA	10 500 (4200–21 800)	–	–	–	–	–	–	–	–
Kadoya *et al.* [38▪]	Japan	33	621	21% (7/33)	59 ± 15	70% (23/33)	ELISA/ Western Blot	9767 ± 8131	24% (8/33)	42% (14/33)	36% (12/33)	15% (5/33)	3% (1/33)	6% (2/33)	–	–
Musset *et al.* [39▪]	Belgium, Canada, China, Chech Republic, France, Hungary, Italy, Japan, Mexico				62	1906	52% (31/60)	62.5 (58.0–67.0)	–	ELISA	–	–	–	–	–	–
–	74% (32/44)	–														
Watanabe *et al.* [31]	Japan	46	460	18% (8/45)	56.4 ± 16.1	69% (31/45)	ELISA/IP	6436 ± 4403	44% (20/45)	22% (10/45)	4% (2/45)	4% (2/45)	7% (3/45)	0% (0/45)	100% (45/45)	–
Allenbach *et al.* [40▪]	France	52	–	46.1% (24/52)	50 ± 22	73.1% (38/52)	ALBIA	7012 ± 5944	–	–	17% (9/52)	0% (0/52)	–	–	–	–
Tiniakou *et al.* [24▪]	USA	104	1947	75% (78/104)	55.0 (52.4, 57.6)	59% (61/104)	ELISA/IP	2812 (1399–6821)	27% (29/104)	–	6% (6/104)	5% (5/104)	4% (4/104)	–	77% (80/104)	–
Kishi *et al.* [41▪]	USA	5	440	0% (0/5)	8.1 (7.1–12.0)	60% (3/5)	ELISA/IP	–	60% (3/5)	40% (2/5)	–	60% (3/5)	0% (0/5)	100% (5/5)	40% (2/5)	0% (0/5)
Liang *et al.* [42]	Japan	9	62	0% (0/9)	7.2 (0.8–13)	56% (5/9)	ELISA	6553 (352–10 891)	–	22% (2/9)	–	22% (2/9)	0% (0/9)	–	100% (9/9)	–
Tansley *et al.* [43]	UK	4	381	0% (0/4)	9.25 (4–13)	75% (3/4)	ELISA/ Western Blot	15 500 (12 180–44 002)	–	–	–	50% (2/4)	–	–	0% (0/4)	–

CPK, creatine phosphokinase; DRB, D related B; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; ILD, interstitial lung disease; IMNM, immune-mediated necrotizing myopathy.
[a]Octapharm for LCS disclosures.

CANCER

The association between inflammatory myopathy and cancer was initially described at the beginning of the twentieth century and has since been established in different cohorts [47]. Similarly, an association was investigated by Limaye *et al.* [32] but was not statistically significant. However, in the French cohort, anti-HMGCR-positive myositis patients were indeed found to have a modestly increased risk of malignancy (17.3%), with a mean age at the age of diagnosis of cancer of 67 ± 15 years, whereas the mean age at the diagnosis of myopathy was 50 ± 22 years [40▪]. That implies that the older the patient develops myopathy, the more likely it is to be diagnosed with myositis associated malignancy. Comparably, 36% of anti-HMGCR+ Japanese patients were identified to have synchronous cancer (92% within 1 year of the myositis diagnosis) and 33% of them had history of statins (four out of 12) [38▪]. The authors concluded that malignancy itself could be a trigger, rather than exclusively the statin, which could lead to the development of HMGCR+ myopathy. At the opposite end of the spectrum, no association with malignancy was found at the Johns Hopkins cohort, which comprises patients of older age and with a higher prevalence of statin use [24▪].

THERAPY

Self-limited statin-induced toxic myopathy generally resolves within few weeks to months after cessation of the medication. In the case of anti-HMGCR IMNM, however, statins are thought to trigger a perpetual autoimmune process. On rare occasions, patients have been reported to improve without the use of immunosuppression [24▪,27], but the majority of anti-HMGCR-positive patients require intensive treatment for control of their disease. Previous reports have indicated that patients often require at least two agents for remission of the disease, as established by improvement of the muscle strength [24▪,27,31], but one case series suggested that intravenous immunoglobulin (IVIG) monotherapy could be adequate for a specific subset of patients [48]. Given the recent association of severity of disease with age at disease onset [24▪], we would suggest tailoring the intensity of the treatment to the age of the patient.

CONCLUSION

Recent studies from different fields have revealed diverse aspects of the anti-HMGCR associated IMNM. HMGCR IMNM is a unique autoimmune disease characterized by a well defined environmental trigger (statins) and a strong association with a genetic risk factor (HLA DRB1*11 : 01). New diagnostic modalities have been developed to confirm the presence of anti-HMGCR antibody and establish the diagnosis of HMGCR IMNM. Whether anti-HMGCR antibodies play a pathogenic role in the disease process remains to be addressed. Clinical studies have shown that disease severity, as measured by muscle strength, as well as the rate of response to treatment have been associated with age at disease onset. Furthermore, a case series supported that IVIG administration may be a beneficial therapeutic intervention for selected patients.

Given the rarity of the disease, multicenter studies are required to recruit sufficient number of patients to study the clinical spectrum of the disease, to understand the immunopathologic mechanisms involved in disease pathogenesis, and to test additional therapeutic choices. The discovery of key molecular and biological pathways involved in the disease process could offer the opportunity to identify potential diagnostic and prognostic biomarkers and thus lead to innovative therapeutic targets.

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Conflicts of interest

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- ▪ of special interest
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