

# Statin-Associated Autoimmune Myopathy: Current Perspectives

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Eleni Tiniakou 

Johns Hopkins University School of  
Medicine, Department of Medicine,  
Division of Rheumatology, Baltimore,  
MD, USA

**Abstract::** Although generally well tolerated, statin users frequently report muscle-related side effects, ranging from self-limiting myalgias to rhabdomyolysis or the rare clinical entity of statin-associated immune-mediated necrotizing myopathy (IMNM). Statin-associated IMNM is based on the development of autoantibodies against 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the rate-limiting enzyme in cholesterol synthesis and the pharmacologic target of statins, and leads to a necrotizing myopathy requiring immunosuppressive therapy. This review attempts to recapitulate the diverse aspects of anti-HMGCR IMNM, including clinical presentation, diagnostic modalities, genetic risk associations, therapeutic options and potential pathogenic pathways.

**Keywords:** statins, myopathy, statin toxicity, statin myopathy, anti-HMGCR

## Introduction

Cardiovascular disease (CVD) is the leading cause of death in most developed countries, and a large proportion could be prevented by modifying existing metabolic risk factors, like dyslipidemia.<sup>1,2</sup> Therefore, lipid-lowering strategies are one of the cornerstones of primary and secondary prevention of CVD. Statins are the most significant drug of the cholesterol-lowering armamentarium by inhibiting the enzyme hydroxyl-methyl-glutaryl-Co-A reductase (HMGCR), the rate-limiting step in cholesterol synthesis.<sup>3</sup>

Although generally well tolerated, statin users frequently report muscle-related side effects, ranging from self-limiting myalgias to rhabdomyolysis or the rare entity of statin-associated immune-mediated necrotizing myopathy (IMNM).<sup>4</sup> Based on recently published guidelines for the management of cholesterol by the American College of Cardiology and the American Heart Association (ACC-AHA), approximately 9 out of 10 men and more than half of the women age between 60 and 75 years should be on cholesterol lower medications, namely statins.<sup>5,6</sup> Therefore, given the projected increase of statin use, we expect similarly an exponential rise even in the rarest side effects.

Statin-associated IMNM is a recently described entity based on the development of autoantibodies against the enzyme HMGCR, and leads to a necrotizing myopathy requiring immunosuppressive therapy.<sup>7</sup> In this review, we recapitulate the definition, clinical picture, pathophysiology and therapeutic options of the anti-HMGCR myopathy.

## Statin Myopathy

Half of the side effects of statins are related to muscle complaints. The majority of the complaints include nonspecific benign symptoms, and 7–25% will develop

Correspondence: Eleni Tiniakou  
Johns Hopkins University School of  
Medicine, 5200 Eastern Avenue, Mason  
Lord, Center Tower, Baltimore, MD  
21224, USA  
Tel +1 410 550-6962  
Email etiniak1@jhmi.edu

a documented muscle event.<sup>4,8-10</sup> These include myalgia, myopathy, myositis (including INMN), myonecrosis or rhabdomyolysis.<sup>11</sup> While all events could co-exist, it is important to establish a non-ambiguous terminology and note the differences, as the nomenclature will define further management and work up.

Myalgia is muscle aches without the presence of any objective muscle damage, like elevated CPK. Statin-associated myopathy is a broad term and is defined by the presence of muscle weakness. When there is additionally evidence of muscle inflammation (as defined by elevated CPK, muscle edema on MRI imaging studies or muscle biopsy), we can use the term myositis. Lastly, elevation of CPK more than 10 times the upper limit of normal (ULN) can be named myonecrosis and rhabdomyolysis when there is evidence of myoglobulinuria or renal failure.<sup>11</sup>

Statins can cause myopathy/myositis either as a noninflammatory, toxic effect<sup>12</sup> or as a trigger of an autoimmune process have quite similar initial presentation. The difference between the two conditions though is the effect that has the discontinuation of the offending toxic agent (Table 1). While in the first case, the weakness resolves within weeks or months, in the latter case, the statins have triggered a self-sustained inflammatory cycle requiring the addition of immunosuppression in order to reverse the myopathy, as we see in idiopathic inflammatory myopathies (IIM).

## Statin-Associated IMNM

IIM are a heterogeneous group of systemic autoimmune syndromes resulting from injury of the skeletal muscles. Patients with IIM exhibit a wide variety of phenotypes and several classification criteria have developed in an effort to

divide them in groups with similar patterns. IIM are first defined by Bohan and Peter as polymyositis (PM) or dermatomyositis (DM), based on the presence of symmetric proximal muscle weakness, elevated muscle enzymes, characteristic electromyography (EMG) abnormalities, typical muscle biopsy findings and/or distinguishing skin rash.<sup>13,14</sup> However, over the last 40 years, the detection of distinct histological patterns and identification of novel myositis specific antibodies (MSA)<sup>15</sup> have exposed the complexity of IIM. Moreover, the different types of IIM can differ based on their muscle biopsy features, defined a new separate category: the immune-mediated necrotizing myopathy (IMNM).<sup>16</sup> The diagnosis of IMNM is restricted by the presence of muscle cell necrosis and degeneration, with sparse inflammatory infiltrates. Further subclassification based on MSA has divided IMNM into three homogeneous entities: anti-HMGCR myopathy, anti-SRP myopathy and antibody-negative IMNM.<sup>17</sup>

## Anti-HMGCR Autoantibody

The first report associating statins with the development of an autoimmune myopathy requiring immunosuppressive treatment was published in 1994 and followed by several others.<sup>18-26</sup> The first case series suggesting the presence of a statin-associated necrotizing myopathy of an autoimmune nature was published in 2004.<sup>27</sup> Later on, Needham et al described eight patients with muscle biopsies consistent with necrotizing myositis and evidence of MHC-I upregulation, while they exhibited improvement with the initiation of immunosuppression, all pointing towards an autoimmune process.<sup>28</sup> Additional reports

**Table 1** Differential Between Self-Limited Statin Myopathy and Statin-Associated Immune-Mediated Necrotizing Myopathy

	Self-Limited Statin Myopathy	Statin-Associated IMNM
Frequency	7–29% of statin users	2/million/year
Myalgias	Common	Common
Proximal muscle weakness	Uncommon	Common
CK values (IU/L)	Normal or elevated; >100fold in rhabdomyolysis	>1,000
Genetic risk factor	SNP in <i>SLC01B1</i>	<i>DRB1*11:01</i>
Prognosis	Resolution after discontinuation of statins	Progressively worse
HMGCR autoantibody	Absent	Present
EMG	May show irritable myopathy	Irritable myopathy
Muscle MRI	May show muscle edema	Muscle edema
Muscle biopsy	Variable	Necrosis, degeneration and regeneration
Treatment	Withdraw statins	Withdraw statins; immunosuppression

**Abbreviations:** IMNM, immune mediated necrotizing myopathy; CK, creatine kinase; SNP, single nucleotide polymorphism; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; EMG, electromyogram.

were published in support of this theory,<sup>29</sup> but it was not until 2010 when Christopher-Stine et al described a novel autoantibody against 100-kD and 200-kD proteins when screening patients with biopsy proven necrotizing myopathy.<sup>30</sup> These patients had proximal muscle weakness, muscle edema on MRI, irritable myopathy on EMG and highly elevated CK levels (mean 10,333 IU/L; range 3052–24,714). Importantly, 83.3% of these patients above the age of 50 years old were on a statin, compared to 25% in DM and 36.8% in PM, implying a correlation with statin exposure. It was subsequently verified that this novel autoantibody was indeed recognizing HMGCR enzyme, which is a 100-kDa protein forming 200-kD dimers as well.<sup>31</sup>

Anti-HMGCR autoantibodies are highly specific for this type of autoimmune myopathy, and they are not associated per se with hyperlipidemia, self-limiting side effects from statins or genetic muscle disease. Almost 2,000 patients of the community-based Atherosclerosis Risk in Communities (ARIC) Study and 98 French Canadian subjects with familial hypercholesterolemia were screened for the presence of anti-HMGCR antibodies and none of them were positive.<sup>32</sup> Subsequently, two different studies of patients with history of statin intolerance (101 patients and 79 patients) were negative for these antibodies, and in all cases the muscle-related side effects were self-limited after cessation of the drug.<sup>33,34</sup> Similarly, anti-HMGCR antibodies were not detected in patients with documented muscle dystrophy.<sup>35</sup> Therefore, anti-HMGCR antibodies can be used to define anti-HMGCR IMNM and differentiate from the self-limited toxic effect of statins.

Anti-HMGCR autoantibodies can be used not only for diagnosis, but also as a marker of disease activity. The titers of the antibody are strongly associated with CK levels and inversely associated with muscle strength.<sup>36</sup> However, since CK is a less expensive test, there is no need to longitudinally monitor the anti-HMGCR levels unless for research purposes. Interestingly, the anti-HMGCR titers always remain positive even when the CPK normalizes and the disease is quiescent.<sup>36</sup>

## Detection Methods of Anti-HMGCR Autoantibody

Detection of the anti-HMGCR autoantibodies in the clinical setting is based on a commercially available ELISA. The sensitivity and specificity of the ELISA are 94.4% and 99.3%, respectively.<sup>32</sup> While this ELISA has very high

negative predictive value, meaning that a negative result makes it unlikely that the patient does have anti-HMGCR IMNM, the opposite is not true. The positive predictive value of the HMGCR ELISA would be only 0.910 in a specialty clinic, where the pre-test probability is higher, and 0.001 in an unselected population, with a false-positive rate of 10.5%.<sup>32</sup> The gold standard for anti-HMGCR detection remains immunoprecipitation, which is only feasible in a research laboratory. Therefore, testing should be reserved only for cases with severe myopathy (highly elevated CPK and/or severe muscle weakness) persisting more than 6 weeks after cessation of statins.<sup>7</sup>

Alternate screening methods have been investigated, like addressable laser bead immunoassay (ALBIA), chemiluminescence or immunoblot.<sup>37–39</sup> Investigation into the immunofluorescence pattern the anti-HMGCR antibodies are creating, has led to the suggestion of using IF as an initial screening method. Anti-HMGCR autoantibodies exhibit a finely granular cytoplasmic pattern with perinuclear reinforcement in HEp2-cells,<sup>38,39</sup> and produce a centrolobular distribution on rat hepatocytes.<sup>40</sup> Positivity is observed in 30–61% of anti-HMGCR positive patients for HEp2-cells<sup>30,37</sup> and 91% of cases for the rat hepatocytes.<sup>40</sup> Albeit the pattern is visible in a small percentage of cells (10%),<sup>40</sup> which could reflect a heterogeneous expression of HMGCR in the cell lines.

## Association with Statin Exposure

The first description of anti-HMGCR myopathy was based on the Johns Hopkins cohort in 2010 and reported a mean age of patients 55 years (52.4–57.6) and 75% exposure to statins.<sup>30</sup> While the use of statins was overwhelming, there were still 25% of patients with similar clinical and laboratory characteristics that were statin naïve. As these patients demonstrated higher levels of CK, more severe muscle weakness and required more intense immunotherapy, it was initially thought that statin exposure was a marker for milder disease.<sup>41</sup> Long term follow-up demonstrated that it was actually the age at disease onset that determined the prognosis, with younger patients having more recalcitrant disease regardless of statin use (although they were less likely to have been exposed to statins).<sup>36</sup>

Since then, different cohorts in diverse geographic locations have reported various percentages of statin use (Table 2). When trying to interpret the different reports however, it is important to note the mean age of the relevant cohort, since statin use is associated with increasing age. Moreover, there is always the question if the

**Table 2** Demographic Characteristics and Statin Exposure of Patients with Anti-HMGCR+ Myopathy Across Different Studies

Study	Country	No of HMGCR + Patients	No of Screened Patients	Statin-Exposed Patients % (No)	Mean Age at Disease Onset in Years (range)	Females % (No)
Christopher-Stein et al, 2010 <sup>30</sup>	USA	16	26	63% (11/16)	54	63% (10/16)
Mammen et al, 2011 <sup>31</sup>	USA	45	750	66.6% (30/45)	52+/-16	57.8% (26/45)
Werner et al, 2012 <sup>41</sup>	USA	55	1006	72.7% (40/55)	-	
Allenbach et al, 2014 <sup>47</sup>	France	45	206	44% (20/45)	48.9±21.9	73.3% (33/45)
Ramanathan et al, 2015 <sup>44</sup>	Australia	6	-	100% (6/6)	70 (60–77)	50% (3/6)
Limaye et al, 2015 <sup>43</sup>	Australia	19	207	94% (16/17)	70 (55–89)	42% (8/19)
Klein et al, 2015 <sup>45</sup>	UK	15	217	100% (15/15)	67 (55–76)	64% (7/11)
Ge et al, 2015 <sup>48</sup>	China	22	405	15% (3/20)	-	73% (16/22)
Watanabe et al, 2015 <sup>51</sup>	Japan	8	460	37.5% (3/8)	65.5 (49–79)	37.5% (3/8)
Alshehri et al, 2015 <sup>42</sup>	USA	49	49	38% (19/49)	50 (12–83)	67% (33/49)
Alvarado-Cardenas et al, 2016 <sup>40</sup>	Spain	23	0	14 (6 patients missing data)	63 (52–82)	-
Kennedy et al, 2016 <sup>46</sup>	New Zealand	8	425	75% (2/8)	67.8 (56–81)	50% (4/8)
Kadoya et al, 2016 <sup>50</sup>	Japan	33	621	21% (7/33)	59 ± 15	70% (23/33)
Musset et al, 2016 <sup>38</sup>	Belgium, Canada, China, Czech Republic, France, Hungary, Italy, Japan, Mexico	62	1906	52% (31/60)	62.5 (58.0–67.0)	-
Watanabe et al, 2016 <sup>49</sup>	Japan	46	460	18% (8/45)	56.4 ± 16.1	69% (31/45)
Allenbach et al, 2016 <sup>56</sup>	France	52	-	46.1% (24/52)	50±22	73.1% (38/52)
Tiniakou et al, 2017 <sup>36</sup>	USA	104	1947	75% (78/104)	55.0 (52.4, 57.6)	59% (61/104)
Kishi et al, 2017 <sup>57</sup>	USA	5	440	0% (0/5)	8.1 (7.1–12.0)	60% (3/5)
Liang et al, 2017 <sup>54</sup>	Japan	9	62	0% (0/9)	7.2 (0.8–13)	56% (5/9)
Tansley et al, 2017 <sup>58</sup>	UK	4	381	0% (0/4)	9.25 (4–13)	75% (3/4)
Waters et al, 2017 <sup>76</sup>	Australia	8	14	100% (8/8)	65 (46–79)	-
Liang et al, 2017 <sup>54</sup>	Japan, Taiwan	9	62	0% (0/9)	(0.8–13)	-
Jiao et al, 2018 <sup>52</sup>	China	21	98	0% (0/21)	35.3 (6–67)	66.7% (14/21)
Aggarwal et al, 2019 <sup>53</sup>	USA	23	48	48% (23/48)	64.6 (55.1–73.4)	60.9% (14/23)
Meyer et al, 2020 <sup>55</sup>	Canada	55	-	100% (55/55)	67.7 (44–86.1)	45.5% (25/55)

patient has been exposed to statins from an alternate, non-documented source, although this has not been proved and remains a hypothesis. A study from the central US described anti-HMGCR IMNM in patients with mean age 50 years old and only 38% reported use of statins (18/47).<sup>42</sup> Two cohorts from Australia, with mean age of 70 years old, reported 94–100% of patients exposed to statins.<sup>43,44</sup> Similarly, a Czech cohort described 100% statin exposure in their patients with mean age 67 years old,<sup>45</sup> and a New Zealand cohort with mean age 76.8 years old reported 75% statin use.<sup>46</sup> However, cohorts from France, China, Japan and the USA acknowledged having a much lower statin exposure (44%, 0–15%, 18–37.5% and 38%, respectively).<sup>42,47–51</sup> All of them had a mean age around 50 years old (48.9, 50 and 56.4 years old for the French, US and Japanese cohort, while only 5/22 Chinese patients were over 50 years old and the other Chinese cohort had a mean age of 35).<sup>47,48,51,52</sup> Lastly, when cohorts from nine different countries, including China and France, were combined, there continues to be a statistically significant percentage of statin users (52 out of 91).<sup>38</sup>

## Clinical Presentation

Patients with anti-HMGCR IMNM commonly present with subacute onset, progressive, symmetric proximal muscle weakness with significantly elevated CK levels that persists for months after discontinuation of statins. CK usually ranges in the thousands with values rarely below 1,000. Patients could exhibit myalgias and dysphagia, although this is present in less than one-third of the patients. Extramuscular manifestations, like arthritis or lung involvement, are similarly quite infrequent and if present, they should alert for further work up to rule out other causes of IIM.<sup>36,44,45,47,49,53–55</sup> Skin rash, similar to dermatomyositis, can be present in up to 60% in some cohorts,<sup>30,36,50,51,54,56–58</sup> although the exact skin pathology is not known. In these cases, the patients are still classified as having anti-HMGCR myositis with a DM-like rash.<sup>59</sup>

## Atypical Clinical Presentation

While the vast majority of patients present with symmetrical, proximal muscle weakness, a small percentage may exhibit atypical features, like asymmetry, scapular winging, disease onset is at a very young age and no report of statin exposure. In these cases, it might be challenging to differentiate from alternate diagnosis, like limb-girdle muscle dystrophy (LGMD), especially given the fact that

in 40–60% of LGMD cases no genetic abnormality is detected.<sup>60</sup> Anti-HMGCR antibodies have not been detected in cases of genetically confirmed inherited muscle diseases,<sup>35</sup> and inversely, patients with recalcitrant anti-HMGCR myopathy undergoing whole-exome sequencing did not reveal any concomitant pathogenic mutation.<sup>36</sup> On the other hand though, there have been reported cases of pediatric and young adult patients misdiagnosed as having LGMD, thus avoiding immunosuppression.<sup>42,54,57,61–64</sup> Therefore, anti-HMGCR autoantibody is recommended to be used as an evaluation tool in cases of suspected LGMD notwithstanding the lack of statin exposure.

## Muscle Biopsy Findings

The muscle biopsy findings in anti-HMGCR IMNM are characteristic of a necrotizing myopathy. The predominant feature is necrotic muscle fibers and regenerating fibers with sparse inflammatory infiltrates. Additionally, there can be membrane attack complex deposition on small blood vessels and membrane of few non-necrotic muscle fibers, as well as major histocompatibility complex (MHC) class I upregulation. However, up to one-third of the biopsies can have evidence of inflammatory cell infiltration, 50% of which were identified as scattered T cells (CD4+ and CD8+). These findings are similar regardless of age, statin exposure or geographic location of the patients.<sup>42,47,55,65,66</sup>

What needs attention is that the self-limited toxic effect of statins can also cause necrosis, regeneration and/or inflammation. However, immune findings like MHC class I upregulation in mature muscle fibers are absent. In cases where these findings are mild, however, it might be hard to interpret the pathologic findings. Therefore, it is preferable to defer the muscle biopsy for at least 4–6 weeks after statin cessation in order to avoid this conundrum, especially in cases when anti-HMGCR testing is not available for diagnosis.

## Genetic Risk Factors

HMGCR INMN has one of the strongest associations with HLA class II allele risk factor within autoimmune diseases. The HLA allele *DRB1\*11:01* has an odds ratio of 24.5 in Caucasians and 56.5 in African Americans.<sup>67</sup> The above association has been confirmed by additional cohorts from Australia, Japan and Europe as well.<sup>43,68,69</sup> Remarkably, a second HLA class II allele, *DRB1\*07:01*, has been identified as an immunogenetic risk factor in a pediatric cohort, suggesting a different trigger or



pathogenetic mechanism.<sup>57</sup> Despite this significant association, these alleles are quite frequent in the general population (7–26% of the control population), therefore, not a useful clinical tool for diagnosis.<sup>57,67</sup>

## Disease Prognosis

Based on a longitudinal analysis of the Johns Hopkins cohort including 104 patients followed for approximately 3 years, the age at disease onset was identified as the most important prognostic factor. Every 10 additional years at disease onset was associated with additional 2.2 points in muscle strength. That means that while the majority of patients above 60 years old recovered full strength (85%) within 4 years, this was true for less than half of patients below 52 years old.<sup>36</sup> Importantly, statin exposure was not found to be the determining factor for disease progress. Similarly, a Chinese cohort of 21 patients, who were all statin-naïve, verified that the younger patients had a worse prognosis.<sup>52</sup> Longitudinal analysis of a Canadian cohort of 55 patients showed that early intervention leads to more efficacious treatment and maintained remission.<sup>55</sup> These longitudinal studies emphasize that our efforts should focus on early diagnosis and aggressive treatment especially of the younger population.

## Cancer Association

Several studies have investigated the relationship of anti-HMGCR IMNM with malignancy and the results are ambivalent depending on the geographic location. No statistical association with cancer has been found in Australian, Canadian or US cohorts, with the majority of patients reporting statin exposure.<sup>36,43,53,55</sup> On the other end, cohorts from France and Japan revealed a significant percentage of patients developing cancer.<sup>56,68</sup> Interestingly, 12/33 of anti-HMGCR+ Japanese patients were identified to have synchronous cancer (92% within one year of the myositis diagnosis) and 33% statin exposure, implying that in these cases cancer could have been the trigger for the myositis.<sup>50</sup> Therefore, besides the age-appropriate cancer screening, a rigorous work up could potentially be reserved for patients descending from specific regions.

## Therapy

The majority of the patients with anti-HMGCR myopathy is statin associated, at least according to the US experience. Rechallenge with statins has led to worsening of the disease,<sup>28,44,70</sup> so statins are contraindicated in these

patients. It is recommended that it is documented in the patient's chart of having drug hypersensitivity to statins or including them into their "allergy list", so future rechallenge will be avoided. Although there is no available data for anti-HMGCR positive patients without history of statin exposure, we would recommend avoidance of the class in these cases as well. Therefore, the first step in management includes discontinuation of statins.

The vast majority of patients with anti-HMGCR myopathy will require aggressive immunosuppression. As there are no controlled studies, the treatment regimen for each patient depends on disease severity and physician preference. Prednisone is regarded commonly as a first-line agent along with the addition of a steroid-sparing agent, like methotrexate, mycophenolate, azathioprine, intravenous immunoglobulin (IVIG) or rituximab. Methotrexate or IVIG seem to be the agent of choice after prednisone for most cohorts,<sup>36,44,47,53</sup> and specifically IVIG can be successfully employed for refractory cases. Cases report has also pointed out potential benefit of cyclosporine as well in recalcitrant disease.<sup>71</sup> Based on this experience, the 224th European NeuroMuscular Center (ENMC) International Workshop on necrotizing myopathies suggested the concurrent initiation of steroids and methotrexate, adding IVIG in severe cases at disease onset or within 6 months if response has been inadequate. Initial series of 3 patients with anti-HMGCR myositis, who could not tolerate steroids, confirmed efficacy of IVIG monotherapy as initial treatment.<sup>17</sup> Especially in cases where symptoms are relatively mild, steroids could be avoided,<sup>53,55</sup> and if IVIG is combined with any steroid-sparing agent, remission could be achieved faster.<sup>55</sup> Lastly, Rituximab can be reserved as a fourth-line agent.<sup>17</sup> Experience with rituximab is limited; there are few reports utilizing it as a rescue therapy for refractory cases,<sup>66,72</sup> but with limited benefit. The reason for that could be irreversible widespread muscle atrophy establishing at later stages of the disease. In conclusion, given the association of severity with onset of disease at a young age,<sup>36</sup> one could argue that aggressive therapy (IVIG, steroid-sparing agent, with or without steroids) should be considered especially for younger patients and can be tailored for the older patients based on their comorbidities and severity of muscle weakness.

Although the bulk of patients requires treatment, there is a small percentage that do not exhibit any weakness. The Johns Hopkins cohort reported approximately 4% (4 out of 104) of their patients did not require treatment due to mild

symptoms,<sup>36</sup> and 3 out of 45 patients of a cohort in France showed improvement of their symptoms after discontinuation of statins.<sup>47</sup> However, recently published experience from Canada argues that all patients might benefit from treatment; 22/55 (40%) of their cohort did not have any weakness at diagnosis, but 13 of them eventually developed weakness within a median time of 21.6 months (7.0–95.0) and it was more difficult to control the disease at that stage.<sup>55</sup> This is a retrospective study, but demonstrates the need for well-designed clinical trials to answer these questions, especially given our ability to identify patients at an early stage with the use of antibodies.

It still remains the question how to manage hyperlipidemia in these patients, since statins are considered an aggravating factor for the disease. Lipid-lowering medications that avoid the mevalonate pathway, like fenofibrate or ezetimibe, are encouraged starting on a lower and intermittent dosing until it is confirmed they do not cause any side effects. The newer biologic agents proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which act by increasing the cellular uptake of low-density lipoprotein (LDL), were shown to be safe in patients with anti-HMGCR myopathy and, interestingly enough, allowed 2 patients to decrease their immunosuppression.<sup>73</sup> As PCSK9 inhibitors cause downregulation of HMGCR, it is postulated that the spontaneous clinical improvement could be due to decrease of the autoantigen.

## Pathogenesis

The pathogenesis of anti-HMGCR myopathy is still under investigation and there are several critical questions that need to be answered. First of all, which is the exact role of statins? Beginning mid-1990s, case reports of autoimmune myopathy following statin use began to emerge.<sup>27,28</sup> That led to the hypothesis that statins were associated with this autoimmune process, which was further supported by the finding of a new antibody that was binding actually to HMGCR, the pharmacologic target of statins, and the fact that the majority of patients with this autoantibody were indeed exposed to statins.<sup>36,43–46,55</sup> Statins could participate in the initiation of autoimmunity by (1) increasing the expression and availability of the autoantigen HMGCR, and (2) binding to HMGCR causing conformational changes to the protein and alternate processing by antigen presenting cells, leading to immunogenic HMGCR peptides through certain HLA proteins (DRB1\*11:01). The counterargument for this hypothesis is that there is a significant percentage of patients never been exposed to statins.<sup>47,48,50,51</sup> This could be explained by exposure to statins through diet or it

could be that there is a different pathogenic mechanism for these patients. Nevertheless, clinical experience shows worsening of this type of myositis after rechallenging with statins,<sup>28,44,70</sup> so the term utilized to describe this entity continues to be statin-associated myopathy.

The second question relates to the role of the anti-HMGCR antibodies. The correlation of the antibody titer with CK and inverse correlation with muscle strength<sup>36</sup> was the first indication that these antibodies could be pathogenic. The deposition of membrane attack complex on the surface of muscle fibers, addition of anti-HMGCR antibodies in muscle cultures causing atrophy<sup>74</sup> and passive transfer of these antibodies in mice causing muscle weakness support their pathogenic role.<sup>75</sup> However, the persistence of anti-HMGCR antibodies even in patients with normal muscle strength, and limited efficiency of plasmapheresis and/or rituximab treatments, continue to be persistent queries in the clinical praxis requiring further studies.

## Conclusion

The diagnosis of anti-HMGCR IMNM is based on the detection of antibodies against HMGCR. It is a unique clinical entity in the sense that it is associated with an environmental trigger (statins) and has a strong genetic background (HLA-DRB1\*11:01). While investigative work up ought to be reserved only for persistent cases of muscle weakness and/or hyperCKemia after discontinuation of statins, clinical suspicion should be high even in cases of no apparent statin exposure. Increasing data support a pathogenic role of the antibodies, which can lead to the identification of novel therapeutic targets. There are still outstanding questions regarding the epidemiology, pathogenesis and treatment of statin-associated IMNM, which future studies aspire to answer.

## Disclosure

The author reports no conflicts of interest in this work.

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