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Atorvastatin-induced necrotizing autoimmune myositis

An emerging dominant entity in patients with autoimmune myositis presenting with a pure polymyositis phenotype

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Abstract

The general aim of this study was to evaluate the disease spectrum in patients presenting with a pure polymyositis (pPM) phenotype. Specific objectives were to characterize clinical features, autoantibodies (aAbs), and membrane attack complex (MAC) in muscle biopsies of patients with treatment-responsive, statin-exposed necrotizing autoimmune myositis (NAM). Patients from the Centre hospitalier de l'Université de Montréal autoimmune myositis (AIM) Cohort with a pPM phenotype, response to immunosuppression, and follow-up ≥3 years were included. Of 17 consecutive patients with pPM, 14 patients had a NAM, of whom 12 were previously exposed to atorvastatin (mean 38.8 months). These 12 patients were therefore suspected of atorvastatin-induced AIM (atorAIM) and selected for study. All had aAbs to 3-hydroxy-3-methylglutaryl coenzyme A reductase, and none had overlap aAbs, aAbs to signal recognition particle, or cancer. Three stages of myopathy were recognized: stage 1 (isolated serum creatine kinase [CK] elevation), stage 2 (CK elevation, normal strength, and abnormal electromyogram [EMG]), and stage 3 (CK elevation, proximal weakness, and abnormal EMG). At diagnosis, 10/12 (83%) patients had stage 3 myopathy (mean CK elevation: 7247 U/L). The presenting mode was stage 1 in 6 patients (50%) (mean CK elevation: 1540 U/L), all of whom progressed to stage 3 (mean delay: 37 months) despite atorvastatin discontinuation. MAC deposition was observed in all muscle biopsies (isolated sarcolemmal deposition on non-necrotic fibers, isolated granular deposition on endomysial capillaries, or mixed pattern). Oral corticosteroids alone failed to normalize CKs and induce remission. Ten patients (83%) received intravenous immune globulin (IVIG) as part of an induction regimen. Of 10 patients with ≥1 year remission on stable maintenance therapy, IVIG was needed in 50%, either with methotrexate (MTX) monotherapy or combination immunosuppression. In the remaining patients, MTX monotherapy or combination therapy maintained remission without IVIG. AtorAIM emerged as the dominant entity in patients with a pPM phenotype and treatment-responsive myopathy. Isolated CK elevation was the mode of presentation of atorAIM. The new onset of isolated CK elevation on atorvastatin and persistent CK elevation on statin discontinuation should raise early suspicion for atorAIM. Statin-induced AIM should be included in the differential diagnosis of asymptomatic hyperCKemia. Three patterns of MAC deposition, while nonpathognomonic, were pathological clues to atorAIM. AtorAIM was uniformly corticosteroid resistant but responsive to IVIG as induction and maintenance therapy.

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Dr Yves Robitaille is deceased.

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Abbreviations: aAbs = autoantibodies, AIM = autoimmune myositis, ANA = antinuclear antibodies, anti-HMGCR = aAbs to 3-hydroxy-3-methylglutaryl coenzyme A reductase, anti-SRP = aAbs to signal recognition particle, atorAIM = atorvastatin-induced AIM, AZA = azathioprine, CHUM = Centre hospitalier de l'Université de Montréal, CK = creatine kinase, DM = dermatomyositis, EMG = electromyogram, IMNM = immune-mediated necrotizing myopathy, IVIG = intravenous immunoglobulins, MAC = membrane attack complex, MHC-I = major histocompatibility complex class I, MMF = mycophenolate mofetil, MRI = magnetic resonance imaging, NAM = necrotizing AIM, PM = polymyositis, SD = standard deviation.

Keywords: anti-HMGCR autoantibodies, atorvastatin, autoimmune myositis, necrotizing autoimmune myopathy, polymyositis, statin

1. Introduction

The spectrum and classification of autoimmune myositis (AIM) is evolving rapidly. The existence of the polymyositis (PM) entity as defined by Bohan and Peter[1] has been challenged. A recent clinicoserological classification of 100 consecutive French Canadians with AIM found that overlap myositis and pure dermatomyositis (DM) were the dominant entities, whereas pure PM emerged as an uncommon entity.[2] Furthermore, the original pathological definition of an endomysial mononuclear cell infiltrate with invasion of non-necrotic fibers is actually strongly suggestive of inclusion-body myositis rather than PM.[3] The current clinical definition of PM is therefore a phenotype of muscle disease at high risk for mimicry with other myopathies.[4]

Recently, new pathological descriptions of immune myopathy were suggested, including necrotizing AIM (NAM), which is synonymous with immune-mediated necrotizing myopathy (IMNM) and is now recognized as an entity distinct from PM.[5,6] NAM is associated in particular with autoantibodies (aAbs) to signal recognition particle (anti-SRP), cancer, and with a novel aAb, aAbs to 3-hydroxy-3-methylglutaryl coenzyme A reductase (anti-HMGCR) linked most often to statin exposure.[5,6] Identification of NAM, therefore, further expands the differential diagnosis of pure PM.

The deposition of membrane attack complex components (MAC) was originally described in DM, with localization of MAC on endomysial capillaries.[7] More recently, sarcolemmal deposition of MAC was reported in other myopathies, including NAM associated with anti-SRP and anti-HMGCR.[8,9] Interestingly, sarcolemmal MAC deposition detected on muscle biopsies was considered an exclusion criterion for PM at the 119th European Neuromuscular Center international workshop.[10]

In light of these observations, the objective of the present study was to further characterize the disease spectrum in patients presenting with an apparent pure PM phenotype. Specifically, clinical features, serum aAbs, and MAC in muscle biopsies of patients with statin-exposed, treatment-responsive NAM were evaluated.

2. Patients and methods

2.1. Patients

A patient cohort with a diagnosis of AIM between 2005 and 2014 was longitudinally followed at Centre Hospitalier de l'Université de Montréal (CHUM) and Hôpital du Sacré-Coeur in Montreal, Quebec, Canada. All patients fulfilled 7 inclusion criteria. First, patients were 18 years or older at the time of myositis diagnosis. Second, the presence of a myopathy was defined by elevated serum creatine kinase (CK) plus at least one of the following: proximal muscle weakness, an abnormal electromyogram (EMG), and/or an abnormal muscle biopsy. If CKs were normal, the presence of a myopathy was defined as an abnormal magnetic resonance imaging (MRI) of the thigh muscles. Third, patients had to present with a pure PM clinicoserological phenotype, that is, absence of DM rash, overlap connective tissue disease features, and overlap aAbs, as described.[2] Fourth, serum had to be available for further analysis. Fifth, at least 1 skeletal muscle biopsy had to be available. Sixth, follow-up of at least 3 years from the initial CK elevation to last visit was required. The last inclusion criterion was a documented clinical response to immunosuppressive treatment (as established by expert opinion) or clear improvement on statin discontinuation. The rationale for excluding treatment-refractory patients is that the PM phenotype and refractory PM are at high risk for AIM mimickers, such as muscular dystrophies.

2.2. Data collection

Data on history, physical findings, and investigations were collected by retrospective medical record review using a standardized protocol. Data collection was focused on demographics, myopathic features, chronology of events preceding diagnosis (statin use, CKs, and clinical manifestations), treatment strategies (induction vs maintenance) and muscle pathological characteristics. This study was in compliance with the Declaration of Helsinki. Patients provided written informed consent for clinical data and serum collection. Biobank and clinical data collection procedures were approved by the CHUM Ethical Review Board.

2.3. Definitions

(1) *Pure PM clinicoserological phenotype:* absence of DM rash, overlap features, and overlap aAbs.[2,11]
(2) *NAM* is synonymous with IMNM or necrotizing myopathy.[5,6] Three individual subsets are recognized: anti-SRP-related NAM, anti-HMGCR-related NAM, and paraneoplastic NAM. In the present study, the pathological features on muscle biopsy necessary for an AIM to be classified as NAM were the absence of significant inflammation and the presence of necrosis and/or regenerating fibers.
(3) *Overlap connective tissue disease* features were as described[2,11]: polyarthritis, Raynaud phenomenon, sclerodactyly, scleroderma proximal to metacarpophalangeal joints, systemic sclerosis-type calcinosis in the fingers, lower esophageal, and/or small bowel hypomotility, carbon monoxide lung diffusing capacity <70% of the normal predicted value, interstitial lung disease on chest radiogram and/or computerized tomography scan, discoid lupus, antinative deoxyribonucleic acid antibodies plus hypocomplementemia, 4 or more of 11 American College of Rheumatology criteria for systemic lupus erythematosus,[12] and antiphospholipid syndrome.

(4) *Overlap aAbs* included aAbs to Jo-1 and all other synthetases, scleroderma-associated, as well as scleroderma-specific aAbs and anti-nup aAbs.[2,11,13]
(5) *Abnormal EMG*: presence of myopathic abnormalities, with or without fibrillations or complex repetitive discharges.[1]
(6) *Atorvastatin-induced AIM* (atorAIM) is an AIM induced by atorvastatin exposure.
(7) Definitions for assessment of *atorAIM treatment* were described as follows[2]:
- *Adequate initial corticosteroid therapy*: a daily prednisone dose of at least 40 mg during at least 1 month, followed by a steroid taper that was neither too rapid (based on clinical judgment) nor done in alternate-day fashion;
- *Induction*: therapeutic strategy to induce remission;
- *Maintenance*: after induction, therapeutic strategy to maintain remission; *remission*: sustained serum CK levels below 500 U/L with improved proximal muscle strength; *corticosteroid resistance*, or *refractory myositis* (as opposed to responsive myositis): myositis where adequate initial corticosteroid therapy failed to induce remission;
- *Responsive myositis*: decreasing serum CK to normal or below 500 U/L with improving proximal muscle strength.

2.4. Serum autoantibodies

Coded serum samples were biobanked at −80 °C, and all studies for aAbs were done without knowledge of clinical data or diagnosis. Antinuclear antibodies (ANA) were determined by indirect immunofluorescence on HEp-2 cells at 1:40 serum screening dilution (Antibodies Inc.; Davis, CA).[14]

Anti-HMGCR were detected by addressable laser bead immunoassay (ALBIA) using purified human recombinant HMGCR (Sigma Aldrich; St. Louis, MO: Catalogue #H7309) and performed on the Luminex 200 platform (MJF, Mitogen Advanced Diagnostics Laboratory; Calgary, AB, Canada). Control positive sera containing anti-HMGCR used to establish the ALBIA were kindly provided by Andrew Mammen, MD (Johns Hopkins University, Baltimore, MD). Briefly, the cutoff values for the anti-HMGCR assay were validated by testing serum samples from 45 apparently healthy adults, 45 adults with osteoarthritis of age >60 years, 50 hemodialysis patients on statin therapy (with chronic renal insufficiency secondary to diabetic or hypertensive nephropathy), 45 patients with rheumatoid arthritis and positive anti-cyclic citrullinated peptide aAbs, 45 patients with systemic lupus erythematosus, and 100 French Canadian patients with AIM.[2] Cutoff values were set as follows: normal range, <250 mean fluorescence units (MFU); low positive, 251 to 500 MFU; moderate positive, 501 to 999 MFU; and high positive, >1000 MFU.

2.5. Protein A–assisted immunoprecipitation

Sera were analyzed for aAbs by protein A–assisted immunoprecipitation, both for nucleic acid analysis (ribonucleic acid silver stain) and for proteins (metabolically labeled with ^{35}S-methionine), along with double immunodiffusion (INT).[15–17] These immunoassays detect anti-SRP, all of the described antisynthetases (Jo-1, PL-7, PL-12, OJ, EJ, KS, Tyr, and Zo), anti-PM-Scl, anti-SumoAE, anti-RNA polymerase III, anti-Th/To, anti-U2RNP, anti-U3RNP, anti-U5RNP, anti-Mi-2, anti-p155/140, and anti-MJ. Immunoprecipitation of anti-p155/140 and anti-MJ was confirmed by an immunoblotting method.

2.6. Pathology

Seventeen skeletal muscle biopsies were performed on the 12 index patients and were analyzed by 2 myopathologists (JF and YR). The following pathological features on muscle biopsy were evaluated: presence and location of mononuclear cell inflammation; muscle fiber size, for the presence of perifascicular atrophy, hypertrophy, and muscle fiber size variation; muscle fiber pathologic features of focal invasion of non-necrotic fibers by lymphocytes, necrosis, regeneration, and presence of mitochondrial changes; presence of macrophages, by acid phosphatase staining and anti-CD68 testing; major histocompatibility complex class I (MHC-I) expression on muscle fibers; MHC-I expression on capillaries, to assess capillary loss; and presence and location of MAC (C5b-9) deposition. MAC was detected by immunocytochemistry using a mouse monoclonal anti-human C5b-9 antibody (code no. M0777, DakoCytomation; Glostrup, Denmark).

2.7. Statistical analysis

The Wilcoxon rank-sum test was used for comparison of serum CK group means (Prism 6.0 software, GraphPad Software Inc.; San Diego, CA).

3. Results

Between 2005 and 2014, we identified 17 consecutive patients followed for at least 3 years with an AIM associated with a pure PM clinicoserological phenotype (Fig. 1). All patients were followed by a rheumatologist with expertise in AIM, either as the primary treating physician or as part of a multidisciplinary team.

Of these 17 patients, 3 patients were excluded because of prominent inflammatory infiltrates on muscle biopsy (Fig. 1). One patient had an HIV infection and endomysial inflammation (not tested for anti-SRP and anti-HMGCR). The second patient (negative for anti-SRP and anti-HMGCR) had endomysial inflammation without other pathological features of inclusion body myositis, whereas the last patient (negative for anti-SRP, not tested for anti-HMGCR) had significant perimysial and perivascular inflammation. The remaining 14 patients had necrosis and/or regeneration on muscle biopsy consistent with NAM. None had positive anti-SRP or cancer-associated NAM. Of these 14 patients, 12 had previously been exposed to a statin and 2 had not (of the latter 2 patients, 1 was anti-HMGCR-positive and 1 was negative). The statin used was atorvastatin in all patients, and they were therefore suspected of atorAIM (Fig. 1). This dominant patient subset with atorAIM, representing 70.6% (n = 12/17) of the cohort, is the focus of the present study.

3.1. Demographics, statin use, and myopathic symptoms of atorAIM

The demographics and myopathic symptoms of these 12 patients are shown in Table 1. There were 6 women and 6 men with a mean age of 66 years (range 43–81 years) at diagnosis. Two patients received atorvastatin for isolated hypercholesterolemia, whereas most patients had either type 2 diabetes mellitus (75%) and/or atherosclerotic disease (50%). The highest daily atorvastatin dose was 20 mg in 6 patients, 40 mg in 5 patients, and 80 mg in 1 patient. The mean duration of atorvastatin therapy before first CK elevation was 38.8 months (range 15–84 months). The

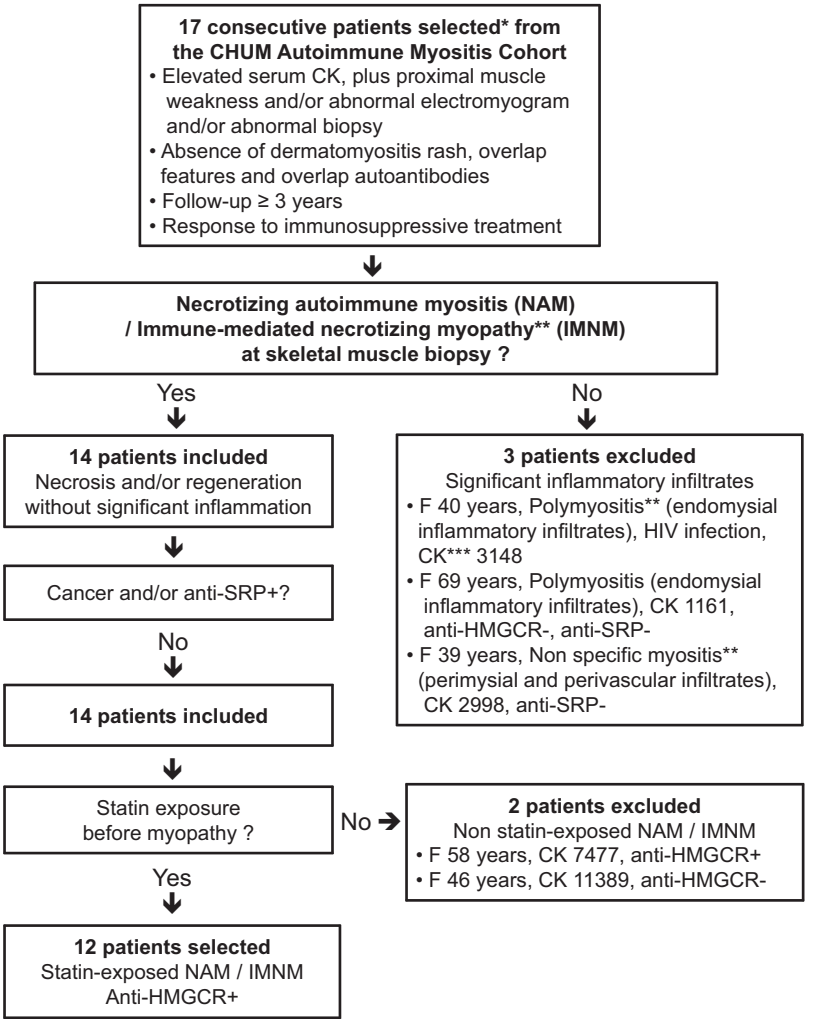

Figure 1. Flow diagram showing how patients with statin-exposed necrotizing autoimmune myositis/immune-mediated necrotizing myopathy were identified. *As described in Section 2. †As defined in Ref. [10]. ‡Serum creatine kinase at diagnosis, U/L. F = female, M = male.

mean interval between atorvastatin initiation and the diagnosis of atorAIM was 59.3 months (range 17–127 months).

In all patients, suspicion of atorAIM eventually led to discontinuation of atorvastatin. The mean interval between atorvastatin discontinuation and the diagnosis of atorAIM was 17.8 months (range 0–79 months). Specifically, 4 out of 12 patients discontinued atorvastatin either at diagnosis (n = 2) or within 3 months of diagnosis (n = 2). Interestingly, the remaining 8 (67%) patients had discontinued atorvastatin for a mean of 26 months (range 8–79 months) at the time the diagnosis of atorAIM was made.

Myalgias were noted in 8 patients (67%) before diagnosis of atorAIM. In 4 of these 8 patients (50%), myalgias occurred within 4 months of the diagnosis of atorAIM, whereas in the other 4 patients myalgias were present during 12 to 50 months before diagnosis. Nine (75%) patients reported subjective proximal skeletal muscle weakness on average within 12 months of diagnosis. Objective moderate oropharyngeal dysphagia was present in 3 patients (25%). Patients 2, 8, and 9 had dysphagia respectively for 12, 3, and 1 month(s) before the diagnosis of atorAIM. In all patients, dysphagia resolved within a year of treatment of atorAIM.

3.2. Staging and chronology of myopathic features leading to atorAIM diagnosis

Three distinctive and dynamic clinical stages of myopathy were recognized:

- Stage 1: serum CK elevation, normal muscle strength, and normal EMG.
- Stage 2: CK elevation, normal muscle strength, and abnormal EMG.
- Stage 3: CK elevation, proximal muscle weakness, and abnormal EMG.

At *diagnosis*, 10 out of 12 patients (83%) had stage 3 myopathy (mean CK elevation: 7661 U/L), whereas the remaining 2 patients had stage 1 myopathy (Table 1). However, examination *at presentation* revealed a markedly different staging distribution. Thus, whereas 5 of 12 (42%) patients presented in stage 3 myopathy, 6 of 12 patients (50%) presented

with stage 1 myopathy (mean CK elevation: 1540 U/L) and a single patient (patient 1) presented in stage 2. Four of the 6 patients (67%) with stage 1 myopathy later progressed to stage 3 myopathy after a mean delay of 38 months (range 14–95 months) despite atorvastatin discontinuation, whereas the remaining 2 patients remained in stage 1 (Table 1).

The chronology of dynamic events leading to diagnosis in patients presenting in stage 1 myopathy is shown in Table 2, whereas patients presenting in stage 2 or 3 are shown in Table 3. In these tables, the time of atorAIM diagnosis and treatment initiation is identified as T0.

In Table 2, taking patient 3 as an example, it can be seen that the serum CK level was normal (86 U/L) at the time of atorvastatin initiation 41 months before diagnosis of atorAIM. An isolated CK elevation (1454 U/L, i.e., stage 1 myopathy) was noted 26 months before diagnosis of atorAIM, leading to statin discontinuation 3 months later. After atorvastatin discontinuation, CK levels which had initially decreased by 60% (from 1680 to 702 U/L) later fluctuated in the abnormal range until T0, where they reached 8300 U/L. At that time, the patient had developed proximal muscle weakness and an abnormal EMG and was therefore in stage 3 myopathy. Similarly, patient 2 had an improved yet persistent CK elevation following atorvastatin discontinuation and was diagnosed 79 months later with a stage 3 myopathy.

Overall, in patients presenting with stage 1 myopathy, statin discontinuation led either to initial 45% to 90% CK lowering (but never to normal levels) with subsequent elevation rebound, or persistent CK elevation eventually leading to diagnosis of atorAIM (Table 2). Thus, CK levels never completely normalized following statin discontinuation.

In Table 3, taking patient 1 as an example, the serum CK level was normal (135 U/L) at the time of atorvastatin initiation 51 months before diagnosis of atorAIM. However, 11 months before diagnosis, CK was elevated (5613 U/L), and an EMG was myopathic despite normal muscle strength (i.e., stage 2 myopathy), leading to statin discontinuation. Nevertheless, patient 1 progressed 11 months later to stage 3 myopathy. Overall, Table 3 shows that discontinuation of atorvastatin before T0 was followed either by CK stabilization, CK lowering with subsequent elevation rebound, or persistent CK elevation (Table 3). Thus, as in the case of stage 1 myopathy, CK levels never normalized following statin discontinuation in patients presenting in stage 2 or 3.

At the time of first documented CK elevation, CK levels were significantly higher in patients presenting in stage 2 or 3 myopathy versus those in stage 1 myopathy (mean 5834 standard deviation (SD) 3652 U/L vs 1539 SD 1386 U/L, $P=0.015$ by Wilcoxon rank-sum test). Similarly, CK levels were greater at the time of statin discontinuation in patients presenting in stage 2 or 3 versus those in stage 1 (mean 6070 SD 3279 U/L vs 2267 SD 1111 U/L, $P=0.016$). However, when compared at T0, CK levels were similar between the 2 groups (mean 8173 SD 3763 U/L vs 5911 SD 3834 U/L, $P=0.48$). The highest CK level observed in stage 3 myopathy was 11,755 U/L.

EMG testing was abnormal at any time in 9 patients. At diagnosis, EMG testing showed an abnormal myopathy of the lower extremities in 7 patients and was normal in patient 7. Patients 1 and 2 had an abnormal EMG testing 11 and 8 months before diagnosis, respectively (Table 1). Two additional patients (patients 3 and 10) had a normal EMG done, respectively, 20 and 48 months before diagnosis.

Table 1

Demographics, myopathic features, and staging of 12 patients with atorvastatin necrotizing autoimmune myositis.

	Patients											
	1	2	3	4	5	6	7	8	9	10	11	12
Demographics												
Sex	M	F	M	F	F	M	F	M	F	M	M	F
Age at diagnosis, y	43	73	66	59	68	81	57	70	74	80	69	53
Type 2 diabetes	+	+	+	+	+	−	−	−	+	+	+	+
Coronary or peripheral artery disease	−	+	−	−	+	+	−	−	+	−	−	+
Highest atorvastatin dose, mg	40	20	40	20	80	40	20	20	40	20	40	20
Statin therapy duration before initial CK elevation, mo	40	32	15	84	29	19	62	17	17	59	36	56
Myopathic features												
Myalgias	−	+	+	+	+	+	−	−	+	+	−	+
Time from onset to diagnosis*, mo	N/A	−44	−26	−4	−12	−4	N/A	N/A	−1	−50	N/A	−1
Subjective weakness	+	+	+	+	+	+	−	+	+	−	−	+
Time from onset to diagnosis, mo	−14	−44	−26	−4	−12	−4	N/A	−6	−1	N/A	N/A	−1
Objective oropharyngeal dysphagia	−	+	−	−	−	−	−	+	+	−	−	−
Time from onset to diagnosis, mo	N/A	−12	N/A	N/A	N/A	N/A	N/A	−3	−1	N/A	N/A	N/A
Abnormal EMG leading to diagnosis	+	+	−	+	+	+	−	+	+	−	+	+
Time from test to diagnosis, mo	−11	−8	−20	−1	0	0	−2	0	0	−48	0	0
Abnormal MRI leading to diagnosis	+	ND	−	ND	+	ND	−	+	ND	−	+	ND
Time from test to diagnosis, mo	−9	ND	−12	ND	0	ND	0	0	ND	−40	0	ND
CK level at diagnosis, U/L†	11,590	2770	8300	4682	2267	10,465	6660	11,755	10,048	3687	4750	9987
Stage of myopathy at presentation	2	1	1	3	3	3	1	1	3	1	1	3
Stage of myopathy at diagnosis	3	3	3	3	3	3	1	3	3	1	3	3
Follow-up												
Duration of follow-up since diagnosis, mo	62	45	76	75	90	78	86	113	73	0	40	52
CK level at last follow-up, U/L	403	213	193	82	37	484	400	55	77	1232	156	3034
Normal (or near-normal) strength at last follow-up	+	−	+	+	−	+	+	+	+	+	−	−

"−" = absent, "+" = present, CK = creatine kinase, EMG = electromyography, F = female, M = male, mg = milligrams, MRI = magnetic resonance imaging, N/A = not applicable, ND = not done, U/L = units per liter.

* Of atorvastatin necrotizing autoimmune myopathy.

† Normal serum CK level 30 to 213 U/L.

Table 2

Chronology of events leading to diagnosis of atorvastatin autoimmune myositis in 12 patients presenting in stage 1 myopathy.

Patients presenting in stage 1 myopathy	Statin initiation	First CK elevation	Statin discontinuation	CK evolution after statin discontinuation		Diagnosis and treatment initiation (T0)
Patient 2						
Timing from T0, mo	−127	−95	−79	−69		0
CK level, U/L*	Unknown	582	1188	519		2770
Stage of myopathy	N/A	1	1	1		3
CK dynamics				↓	↑	
Patient 3						
Timing from T0, mo	−41	−26	−23	−18		0
CK level, U/L	86	1454	1680	702		8300
Stage of myopathy	N/A	1	1	1		3
CK dynamics				↓	↑	
Patient 7						
Timing from T0, mo	−84	−22	−12			0
CK level, U/L	Unknown	238	1501			6660
Stage of myopathy	N/A	1	1			1
CK dynamics				↑		
Patient 8						
Timing from T0, mo	−34	−17	−14			0
CK level, U/L	Unknown	500	1904			11,755
Stage of myopathy	N/A	1	1			3
CK dynamics				↑		
Patient 10						
Timing from T0, mo	−108	−49	−48	−34		0
CK level, U/L	Unknown	2925	3793	429		1232
Stage of myopathy	N/A	1	1	1		1
CK dynamics				↓	↑	
Patient 11						
Timing from T0, mo	−50	−14	−14	−8		0
CK level, U/L	85	3539	3539	1994		4750
Stage of myopathy	N/A	1	1	1		3
CK dynamics				↓	↑	

"↑" = higher, "↓" = lower, CK = creatine kinase, N/A = not applicable.
* Normal serum CK level 30 to 213 U/L.

MRI of the thigh muscles was abnormal in 4 of 7 patients tested: either significant short tau inversion recovery inflammation (i.e., muscle edema) or T1 atrophy and fat replacement was noted (Table 1).

3.3. Treatment of atorAIM: induction therapy

All but one of the patients (92%) were treated with corticosteroids. In the 9 (75%) patients treated with adequate oral corticosteroids alone as induction therapy, this approach was unable to normalize CKs and induce remission of the myopathy (Table 4). Weekly intravenous pulse methylprednisolone (500 mg) was also attempted in 5 patients (42%). However, because of the corticoresistance of atorAIM, intravenous immunoglobulins (IVIG) were used as second-line agent in 8 patients (67%). AtorAIM was notably responsive to IVIG as part of induction therapy.

Four patients did not need pulse methylprednisolone or IVIG therapy as induction therapy (Table 4). Of these, 2 patients were treated in stage 3 myopathy (patients 6 and 11) and 2 patients were treated in stage 1 myopathy (patients 7 and 10). Patient 6 responded, albeit slowly, to the combination of oral prednisone and methotrexate (MTX) as induction therapy, while patient 11 responded rapidly to the same induction therapy but subsequently needed IVIG as maintenance therapy in order to taper corticosteroids. Patient 7 responded slowly over 17 months to a combination of oral corticosteroids and MTX and never developed stage 3 myopathy with overt weakness. Finally, patient 10 was diagnosed in stage 1 myopathy, while previous statin discontinuation had initially substantially lowered his serum CK levels from 3793 to 429 U/L, this was followed by rebound CK elevation to 1232 U/L as shown in Table 2, and he was started on MTX monotherapy shortly before the end of follow-up.

3.4. Treatment of atorAIM: maintenance therapy

Of 10 patients with evaluable maintenance therapy (defined as a remission of at least 1 year on stable maintenance therapy), IVIG was needed in 5 patients (50%), either with MTX monotherapy (n = 3) or with combination immunosuppression (n = 2) (Table 5). In the remaining 5 patients, MTX monotherapy (n = 3) and combination therapy (n = 2) maintained remission without IVIG. Patient 3 successfully stopped IVIG therapy after 2 years, patient 2 is being slowly tapered off IVIG therapy, but 3 patients are still on IVIG therapy because of unsuccessful attempts at discontinuation.

Combination of at least 2 drugs, including MTX, either with IVIG, azathioprine (AZA), or mycophenolate mofetil (MMF), was needed in 7 patients (70%) with atorAIM. This myopathy proved to be particularly refractory to treatment. For example, 4 unsuccessful combination therapies were attempted in patient 1

Table 3

Chronology of events leading to diagnosis of atorvastatin autoimmune myositis in 12 patients presenting in stage 2 or 3 myopathy.

Patients presenting in stage 2 or 3 myopathy	Statin initiation	First CK elevation	Statin discontinuation	CK evolution after statin discontinuation		Diagnosis and treatment initiation (T0)
Patient 1						
Timing from T0, mo	−51	−11	−11			0
CK level, U/L*	135	5613	5613			11,590
Stage of myopathy	N/A	2	2			3
CK dynamics				↑		
Patient 4						
Timing from T0, mo	−87	−3	−3			0
CK level, U/L	Unknown	4884	4884			4682
Stage of myopathy	N/A	3	3			3
CK dynamics				←→		
Patient 5						
Timing from T0, mo	−37	−12	−8	−2		0
CK level, U/L	55	680	2095	956		2267
Stage of myopathy	N/A	3	3	3		3
CK dynamics				↑	↓	
Patient 6						
Timing from T0, mo	−20	−1	−1			0
CK level, U/L	147	3793	3793			10,465
Stage of myopathy	N/A	3	3			3
CK dynamics				↑		
Patient 9						
Timing from T0, mo	−17	0	0			0
CK level, U/L	124	10,048	10,048			10,048
Stage of myopathy	N/A	3	3			3
CK dynamics				N/A		
Patient 12						
Timing from T0, mo	−56	0	0			0
CK level, U/L	Unknown	9987	9987			9987
Stage of myopathy	N/A	3	3			3
CK dynamics				N/A		

"←→" = stable, "↑" = higher, "↓" = lower, CK = creatine kinase, N/A = not applicable.
* Normal serum CK level 30 to 213 U/L.

before achieving remission with a combination of MMF, abatacept, and IVIG (Table 5). Similarly, patient 5 needed a combination of 4 drugs to maintain remission. This aggressive therapy combination strategy allowed complete tapering of corticosteroids in most patients (n = 9), while 3 patients remained on low-dose prednisone 5 mg daily. Patient 3, who was on combination MTX, AZA, and IVIG to induce corticosteroid-free remission and resolution of proximal weakness, then stopped IVIG successfully and then MTX, followed in the last year by AZA. The other patients on combination therapy could not be tapered off (Table 5).

3.5. Anti-HMGCR autoantibodies

Anti-HMGCR antibodies as determined by ALBIA were present in sera from all 12 patients (mean 4328.75 MFU, range 357.5–7095 MFU). Anti-HMGCR were highly positive in 10 patients, moderately positive (778.5 MFU) in patient 4, and low positive in patient 11 (357.5 MFU).

3.6. Other autoantibodies

By indirect immunofluorescence on HEp-2 cells, ANA were negative in 11 of 12 samples and weakly positive in a single sample (diffuse granular pattern, endpoint titer 1:80). None of the sera displayed cytoplasmic fluorescence.

Immunoprecipitation analysis, performed in sera from the 12 index patients, was negative for AIM aAbs, including for anti-SRP and the various anti-synthetases.

3.7. Muscle pathological characteristics of atorAIM

Skeletal muscle biopsy was performed in all 12 patients and was repeated in 5 patients (n = 17 biopsies). MAC (C5b-9) deposition was observed in all tested muscle biopsies (n = 14) (Table 6). Three patterns of MAC distribution were observed: isolated sarcolemmal deposition on non-necrotic fibers, isolated granular deposition on endomysial capillaries, and a mixed pattern.

Necrosis and regeneration without inflammation was seen in all biopsies except in a biopsy performed 12 months before diagnosis in patient 3 (Fig. 2). Interestingly, at that time, patient 3 was in stage 1 myopathy, and MAC deposition on endomysial capillaries was the only abnormal pathological finding. At diagnosis, myopathy had progressed to stage 3, and a repeat muscle biopsy revealed abundant necrosis and regeneration as well as MAC deposition on endomysial capillaries (Fig. 2, Table 6). No capillary loss was found in patients showing MAC deposition in endomysial capillaries.

Table 4

Treatment of atorvastatin autoimmune myositis in 12 patients—induction therapy.

Induction therapy	Myopathy stage at initiation of corticosteroid therapy	Induction with adequate corticosteroids*	Induction with pulse methylprednisolone	Induction with IVIG	Corticosteroid resistance*	Time to normal CK (or <500 U/L) on successful therapy, mo	Time to initiation of DMARDS, mo
Presentation with an objective myopathy on initial CK elevation, patients							
1	3	–	+	+	+	53	0
4	3	+	+	+	+	13	11
5	3	+	+	+	+	18	0
6	3	+	–	–	N/E	7	0
9	3	+	+	+	N/E	3	0
12	3	+	–	+	+	17	10
Presentation with an isolated CK elevation, patients							
2	3	–	–	+	N/E	5	0
3	3	+	+	+	+	18	2
7	1	+	–	–	N/E	17	0
8	3	+	–	+	N/E	4	0
10	1	–	–	–	N/E	N/E	0
11	3	+	–	–	N/E	4	0

"–" = absent, "+" = present, CK = creatine kinase, DMARDS = disease-modifying antirheumatic drugs, IVIG = intravenous immunoglobulins, N/E = data not evaluable.
* As defined in Section 2.3.

MHC-I expression on muscle fibers was noted in 8 (57%) of 14 tested biopsies. Thus, overall, MHC-I staining was absent in 43% of tested biopsies (n = 6/14). In stage 3 biopsies, MHC-I staining was absent in 27% of tested samples (n = 3/11), whereas in stage 1, it was absent in 2 out of 3 biopsies.

4. Discussion

The objective of the present study was to further characterize the disease spectrum in patients presenting with a pure PM clinicoserological phenotype. Seventeen patients followed for at least 3 years with such a pure PM phenotype and treatment-responsive myopathy were identified. Of these patients, 82% (n = 14/17) had NAM on biopsy, of which 86% (n = 12/14) had previously been exposed to atorvastatin, leading to the diagnosis of atorAIM. Thus, atorAIM broadens the differential diagnosis of PM and, furthermore, emerges as a dominant entity in patients presenting with a pure PM phenotype.

Various investigators have described statin-induced AIM, most commonly related with atorvastatin use, and its place as a distinct subset of AIM can now be affirmed based on strong clinical, pathological, and serological arguments.[18–20] As several conclusions stem from the data presented herein, this study sheds light on the natural history of statin-induced AIM and further expands the spectrum of associated features.

First, *the distinct modes of presentation of atorAIM observed herein led to introduce the concept of staging of statin-induced AIM*, as 3 clinical stages were recognized: stage 1—serum CK elevation, normal muscle strength, and normal EMG; stage 2—serum CK elevation, normal muscle strength, and myopathic EMG; and stage 3—serum CK elevation, proximal muscle weakness, and myopathic EMG. Thus, at *diagnosis*, 83% of

Table 5

Treatment of atorvastatin autoimmune myositis in 12 patients - maintenance therapy.

Maintenance therapy	Maintenance therapy with IVIG	Maintenance with daily prednisone 5 mg	Unsuccessful maintenance therapy trial, n	Unsuccessful maintenance agents	Successful maintenance therapy
Presentation with an objective myopathy on initial CK elevation, patients					
1	+	–	4	*	MMF + ABA + IVIG
4	+	–	1	MTX	MTX + IVIG
5	+	+	1	MTX	MTX + MMF + IVIG + CS
6	–	–	0	N/A	MTX
9	–	–	0	N/A	MTX
12	–	+	0	N/A	N/E
Presentation with an isolated CK elevation, patients					
2	+	–	1	MTX	MTX + IVIG
3	–	–	1	MTX	MTX + AZA
7	–	–	0	N/A	MTX
8	–	–	0	N/A	MTX + AZA
10	–	–	0	N/A	N/E
11	+	+	0	N/A	MTX + IVIG + CS

"–" = absent, "+" = present, ABA = abatacept, AZA = azathioprine, CS = corticosteroids, CK = creatine kinase, ETA = etanercept, IVIG = intravenous immunoglobulins, MMF = mycophenolate mofetil, MTX = methotrexate, N/A = data not applicable, N/E = data not evaluable, RITUX = rituximab.
* MTX + MMF + IVIG, MTX + ETA + IVIG, MTX + RITUX + IVIG, MTX + AZA + IVIG.

Table 6

Pathologic characteristics at skeletal muscle biopsy in 12 patients with atorvastatin autoimmune myositis.

Patient biopsies	Patient characteristics at biopsy					Connective tissue	Muscle fiber pathologic features			Immunochemistry			
	Biopsy site	CK level at biopsy, U/L*	Timing of biopsy to diagnosis, mo	Stage of myopathy at diagnosis	Corticosteroid exposure at biopsy	Acid phosphatase staining	Variation in size	Necrosis	Regeneration	Class I MHC expression on fibers	Capillary loss	C5b-9 deposition on non-necrotic fibers	C5b-9 deposition on endomysial capillaries
1A	Quadriceps	4830	−5	3	−	+	+	+ (A)	+ (A)	−	−	+	+
1B	Deltoid	11,590	<1	3	+	+	+	+ (A)	+ (A)	ND	ND	−	+
2A	Quadriceps	2770	−4	3	−	+	+	+ (A)	+ (A)	+	−	+	+
2B	Deltoid	2372	0	3	−	+	+	+ (A)	+ (A)	+	−	+	+
3A	Quadriceps	1111	−12	1	−	ND	−	−	−	−	−	−	+
3B	Deltoid	1201	3	3	+	ND	+	+ (A)	+ (A)	+	−	−	+
4A	Deltoid	4682	0	3	−	+	−	+ (A)	+ (A)	+	−	+	−
4B	Deltoid	1999	9	3	−	−	+	+ (A)	+ (A)	+	−	+	−
5A	Quadriceps	2267	0	3	−	+	−	+ (A)	+ (A)	ND	ND	ND	ND
5B	Quadriceps	3151	12	3	+	+	+	+ (A)	+ (A)	ND	ND	ND	ND
6	Quadriceps	10,465	0	3	−	−	−	+ (R)	+ (R)	+	−	−	+
7	Quadriceps	6660	0	1	−	+	−	+ (A)	+ (A)	+	−	−	+
8	Quadriceps	11,755	<1	3	+	ND	Unknown	+ (R)	+ (R)	NEG	−	+	NEG
9	Deltoid	10,048	<1	3	+	+	+	+ (A)	+ (A)	+	−	ND	ND
10	Quadriceps	3687	−48	1	−	+	+	+ (R)	+ (R)	−	−	+	+
11	Quadriceps	4750	<1	3	+	−	+	+ (R)	+ (R)	−	−	−	+
12	Quadriceps	9987	0	3	−	+	+	+ (A)	+ (A)	−	−	+	−

"−" = absent, "+" = present, "<" = less than, A = abundant, CK = creatine kinase, MHC = major histocompatibility complex, ND = not done, R = rare.

*Normal serum CK level 30 to 213 U/L.

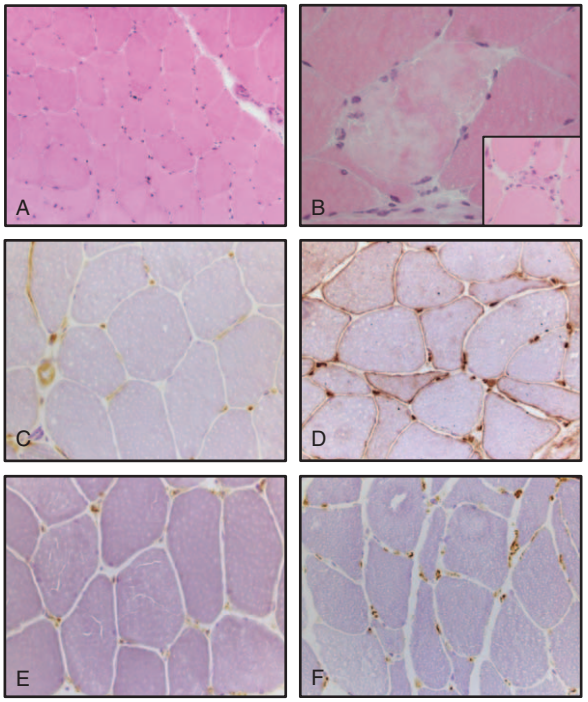

Figure 2. Histopathological and immunohistochemical analysis of sequential skeletal muscle biopsies from patient 3, who presented in stage 1 atorvastatin autoimmune myositis (first biopsy) followed by progression to stage 3 myopathy (second biopsy 15 months later). (A) Normal histologic findings in stage 1 myopathy (biopsy 1, hematoxylin and eosin, H&E; original magnification 30×). (B) Histologic findings of myofiber necrosis and regeneration (inset) in stage 3 myopathy (biopsy 2, H&E, 63×). (C) and (D) Switch from negative (stage 1, biopsy 1) to positive (stage 3, biopsy 2) major histocompatibility complex class I staining by immunohistochemistry (40×). (E) and (F) Increasing granular endomysial capillary membrane attack complex staining by immunohistochemistry on biopsies 1 and 2 from patient 3 (40×).

patients had stage 3 myopathy, whereas the remaining 17% patients had stage 1 myopathy. However, at *presentation*, 50% of patients were in stage 1, 9% were in stage 2, whereas only 40% presented in stage 3. Interestingly, several patients with statin-associated IMNM described by Grable-Esposito et al[19] initially presented with high CK serum and normal strength and were likely in stage 2. In contrast, previous studies have essentially described patients at diagnosis in stage 3 myopathy, with high CK, abnormal EMG and MRI, and a treatment-refractory myopathy despite discontinuation of statin therapy.[21] Thus, clinicians should be aware of the various clinical stages of statin-induced AIM.

Second, *statin-induced AIM should now be included specifically in the differential diagnosis of asymptomatic hyperCKemia*. As shown in this study, CK elevation with preserved strength, defined as stage 1 myopathy, is the initial mode of presentation of statin-induced AIM.

Third, *stage 1 myopathy most commonly progresses to stage 3, despite discontinuation of atorvastatin therapy*. In this cohort, only 2 patients with stage 1 (patients 7 and 10) did not progress to stage 3. Patient 7 was treated in a timely fashion when serum CK was at 6600 U/L and never got weak, whereas patient 10 was observed for 48 months, before treatment with MTX was considered at last follow-up because of a rebound in serum CK. Progression to stage 3 was typically slow, with a mean delay of 38 months. Similarly, 9 out of 25 (36%) patients with statin-induced AIM described by Grable-Esposito et al,[19] all of whom had normal strength at presentation developed proximal muscle weakness in the following months, despite discontinuation of statin therapy. Similar disease progression was noted by Needham et al.[21] Taken altogether, these shifts in staging emphasize the progressive nature of atorAIM despite discontinuation of statin therapy. Moreover, documented progression from stage 2 to stage 3 in patient 1 suggests that in an atorvastatin-treated patient with hyperCKemia but normal strength, an abnormal EMG may predict a high risk of progression to stage 3.

Fourth, *isolated and persistent CK elevation following statin discontinuation should raise early suspicion for statin-induced AIM*. Importantly, complete CK normalization was never seen in the present study after atorvastatin discontinuation. Isolated and progressive CK elevation is an uncommon mode of presentation of AIM and it was not seen as a presenting feature in a cohort of 100 French Canadians with AIM.[2] The slowly progressive presentation of statin-induced AIM is consequently at high risk for mimicking nonautoimmune myopathies and eventually delaying treatment. A diagnosis of statin-induced AIM should therefore be evoked in any patient who was previously exposed to statin therapy and in whom isolated but persistent CK elevation is documented.

Fifth, *the deceptive nature of atorAIM is indicated by the initial decrease in serum CK levels* that suggested improvement in several patients with stage 1 myopathy after atorvastatin discontinuation and by the shifting CK dynamics shown in Tables 2 and 3 that may suggest a relatively stable condition, thus delaying the introduction of definitive treatment. Furthermore, regardless of staging at presentation, not only did CK levels never normalize following statin discontinuation in all patients reported herein, but in all cases CK levels eventually rose to significantly higher levels than at baseline as atorAIM progressed to stage 3. Thus, even mild but persistent CK elevation following statin discontinuation may later progress clinically and justify introduction of treatment.

Sixth, *atorAIM is uniformly corticosteroid resistant but responsive to IVIG as induction and maintenance therapy. Combination therapy is frequently needed to maintain remission*. However, this study was observational and cannot answer definitively the question of the recommended treatments for atorAIM. No trials thus far have defined the optimal treatments for this condition. As shown in Table 4, in all patients treated with oral corticosteroids alone as induction therapy, this approach was unable to normalize CK levels and induce remission of the myopathy. Thus, the precise role of corticosteroids and the necessity, if any, to include them in the treatment of atorAIM are yet to be defined. However, atorAIM was clearly responsive to IVIG for induction and maintenance therapy. Therefore, the authors suggest MTX therapy (without or with corticosteroids) or combination MTX and IVIG therapy as the initial approach for treating atorAIM. If remission is not attained with this initial approach, or if remission is not sustained on tapering of either corticosteroids or IVIG, early addition of AZA or MMF may be contemplated. With this aggressive therapeutic approach, most patients (n=8) were successfully tapered off corticosteroids and normal or near-normal strength could be restored at last follow-up. The need for combination therapy is supported by a recent trial of IVIG monotherapy in 3 patients with statin-induced AIM. While associated with improved strength, IVIG monotherapy failed to normalize serum CK in 2 patients.[22]

Seventh, *MAC deposition on non-necrotic fibers and endomysial capillaries, while non pathognomonic, is an important pathological clue to atorAIM*. MAC deposition was observed in all 13 muscle biopsies in 3 patterns: isolated sarcolemmal deposition on non-necrotic fibers, isolated granular deposition on endomysial capillaries and a mixed pattern. Such MAC deposition represents a new feature of atorAIM. MAC deposition on capillaries, although initially thought of as a specific feature of dermatomyositis, has also been documented in anti-SRP (with capillary loss)[23] and in anti-HMGCR-associated myopathies,[24] suggesting that the latter myopathies are microangiopathies. The present report confirms the study by Chung et al,[24] where MAC deposition was noted in 85.7% of cases either on endomysial capillaries or on non-necrotic muscle fibers or a combination of both.

Eight, *the pathophysiological sequence in atorAIM may be characterized first by MAC deposition in the capillaries followed later by necrosis*. This is suggested by sequential muscle biopsies in patient 3 (Fig. 2 and Table 6), which revealed MAC deposition in the capillaries as the only pathological abnormality in stage 1, whereas a subsequent biopsy 15 months later in stage 3 demonstrated necrosis, regeneration, and MHC-I staining on non-necrotic muscle fibers, in addition to MAC deposition. However, since this conclusion is based only on 2 biopsies in a single patient, it cannot be generalized, and sequential biopsies from additional patients will be of interest. Necrosis and regeneration without significant inflammation were also noted in muscle biopsies of most of atorAIM patients (Table 6). The efficacy of IVIG therapy to induce and maintain remission in atorAIM adds weight to the pathophysiological importance of MAC deposition. An effort should be made to routinely document pathology in the capillaries, as well as MAC deposition on capillaries and non-necrotic muscle fibers, to fully appreciate the spectrum of NAM.

Ninth, *MHC-I staining is not a sensitive marker for atorAIM*. Overall, MHC-I staining was absent in 43% of tested biopsies. Similarly, MHC-I staining on non-necrotic fibers was seen in only 50% of patients in the study by Christopher-Stine et al.[9] Although the sample size in the present study is small, not only was MHC-I staining not present in several patients with stage 3 myopathy, it might very well be absent in many patients with stage 1 myopathy. Thus, treating stage 1 myopathy could be considered in individual patients without MHC-I staining at muscle biopsy if the clinical, serological, and, possibly, pathological manifestations (i.e., capillary MAC deposition at muscle biopsy, with or without necrosis and regeneration) suggest a statin-induced AIM.

Tenth, *anti-HMGCR aAb testing demonstrated excellent (100%) sensitivity for the clinicopathological phenotype of atorAIM as defined herein*. Anti-HMGCR aAbs were present in all 12 patients suspected of having atorAIM. All patients had a negative or weakly positive ANA, without cytoplasmic staining. No additional aAbs were detected. Previous studies by Mammen et al[25,26] found anti-HMGCR aAbs to be highly specific for NAM, with only 0% to 4% of false positives.

Last, *whether atorvastatin-exposed patients are more at risk for the development of NAM, and whether the natural history of NAM is worst with atorvastatin than with other statins are important questions*. The former question is raised given that all patients in the present study were treated only with atorvastatin. Statins prescribed in the Province of Quebec are not restricted to atorvastatin and include simvastatin, pravastatin, and rosuvastatin. However, atorvastatin is locally the most commonly prescribed statin. Therefore, the association between NAM and atorvastatin reported herein may simply reflect prescription frequency. No dose–response effect was noted, as half of the patients were on a low dose (20 mg) of atorvastatin. That being said, statin-associated NAM is not restricted to atorvastatin. For example, in the report by Needham et al,[21] 4 of 8 patients with NAM had been treated with simvastatin, 3 with atorvastatin, and 1 with a combination of these drugs. In the report by Grable-Esposito et al,[19] although 21 of 25 patients had received atorvastatin, 4 were exposed to simvastatin or pravastatin. Importantly, Basharat et al recently used multiple regression analysis to identify independent variables that may be associated with the risk for the development of anti-HMGCR-positive NAM in statin-exposed patients. After adjusting for age and sex, type 2 diabetes mellitus and atorvastatin use (vs rosuvastatin and simvastatin) were significantly associated with anti-HMGCR NAM.[27] In support of the data of Basharat et al, 75% of patients with atorAIM in the present study had type 2 diabetes mellitus. Thus, atorvastatin-exposed patients with type 2 diabetes mellitus appear more at-risk for atorAIM.

This study had some limitations, including a small sample size and a retrospective design. In addition, patient recruitment was restricted to 2 academic hospitals (although such patients are typically seen in such institutions) from the same city. As indicated, these limitations may limit the generalizability of the results. Restriction of patients to the pure PM phenotype may have underestimated the full clinical spectrum of atorAIM. Additional multicenter studies with a larger number of patients and serial muscle biopsies will be of interest to confirm that atorAIM is becoming the leading cause of pure PM phenotype and to define the optimal treatment for this condition.

In conclusion, in the present study, atorAIM emerged as the dominant entity in patients with a pure PM phenotype and treatment-responsive myopathy. Isolated CK elevation, that is, stage 1 myopathy, was the initial mode of presentation of atorAIM. Thus, the new onset of isolated CK elevation on atorvastatin and persistent CK elevation on statin discontinuation should raise early suspicion for atorAIM. Three patterns of MAC deposition were seen and, while nonpathognomonic, were pathological clues to atorAIM. AtorAIM was uniformly corticosteroid resistant but responsive to IVIG as induction and maintenance therapy.

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