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Polymyositis, Dermatomyositis, and Statins: A Review

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Abstract

BACKGROUND: Statins are a well-recognized cause of a variety of skeletal myopathic effects, which generally resolve when discontinuing the treatment. Among autoimmune manifestations associated with statins, there are typical polymyositis (PM) and typical dermatomyositis (DM).
OBJECTIVE: To perform a review on published case reports and case series about statin-associated PM and DM.
METHODS: This literature comprehensive search was conducted mainly on PubMed, but also congress abstracts and university websites were considered. Given the paucity of cases, the search was extended to include articles in all languages with English abstract.
RESULTS: Twenty-eight PM and 30 DM cases have been described with prevalence in female (64%) and senile age. The drugs most frequently involved were atorvastatin and simvastatin. The differential diagnosis should be made among the main myositis subtypes: immuno-mediated necrotizing myopathy (IMNM), inclusion body myositis (IBM), and overlap syndrome with myositis (OM), including anti-synthetase syndrome (ASS).
CONCLUSIONS: Even though the onset of polymyositis or dermatomyositis is a rare phenomenon, it is advisable to consider their presence in patients taking statins and with a non-reversible elevation of creatine phosphokinase.

Keywords: Statins; Dermatomyositis; Polymyositis; Autoimmune Myositis
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INTRODUCTION

Statins

Due to the wide diffusion of statins, which have the undoubted merit of increasing the survival rate in patients affected by cardiovascular disease, particular attention should be paid to their side effects. The most common ones are toxic myopathies, affecting 2-20% of patients [1], that generally resolve after drug discontinuation. The risk of statin myopathy and creatine phosphokinase (CPK) increase is dose-dependent.

Polymyositis and Dermatomyositis

Polymyositis (PM) and dermatomyositis (DM) are idiopathic inflammatory myopathies (IIMs) that may be related to statins. All forms of IIMs are considered rare diseases. In USA, DM has prevalence of ~1-6 patients per 100,000 persons, while PM has a prevalence ~10 per 100,000 [2].

In this context, some cases of association of statins with polymyositis [3-16] and with dermatomyositis [10-12,15,17-35] have been described.

A rate of exposure to statins up to 48% was found among patients with PM or DM over 50 years of age [10].

The outdated, but still used, diagnostic criteria for PM and DM, according to Bohan and Peter [36,37], are:

- Increase in muscle enzymes;
- Weakness of proximal muscles;

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Table I. *Criteria for the diagnosis of polymyositis and dermatomyositis. Modified from [36,37]*

	Polymyositis	Dermatomyositis
Definite	4 criteria	3 criteria
Probable	3 criteria	2 criteria
Possible	2 criteria	1 criterion

	DM, JDM	NM	PM	OM, ASS	IBM
Onset and disease course	Acute/subacute onset; short, benign or severe, chronic courses	Acute/subacute onset; chronic, slow progression possible	Acute/subacute onset; variable course	Acute/subacute onset; mostly chronic course	Slowly progressive; always chronic
Weakness, extramuscular symptoms	Amyopathic/proximal tetraparesis ± dysphagia; specific skin- and organ manifestation; malignancy in adults	Proximal tetraparesis; rarely extramuscular manifestation: heart, lung; malignancy	Proximal tetraparesis ± dysphagia. No extramuscular manifestation	Proximal tetraparesis; ASS: ILD, mechanic's hands, arthritis, Raynaud's syndrome. Other OM: scleroderma, SLE	Long finger flexors, knee extensors, dysphagia
CPK level	Normal or around 10 -50 fold elevated	Around 10-50 fold elevated	Around 10-50 fold elevated	Around 10-50 fold elevated	Normal to 15 fold elevated
Autoantibodies	Mi-2, MDA5 (ILD), TIF-1γ (malignancy), NXP2 (malignancy), SAE	SRP, HMGCR (malignancy)	Unspecific	ASS: Jo-1, PL-7, PL-12, HA, EJ, KS, Zo, OJ Other OM: Ku, Ro/SS-A, SS-B, PM/Scl, U-snRNP	cN1A
Muscle pathology	Perimysial inflammation, perifascicular atrophy, MHC class I, complement on capillaries and/or sarcolemma, capillary loss	Scattered necrosis; MHC class I, complement on capillaries and/or sarcolemma	Endomysial $CD8^+$ T cells	Perifascicular necrosis, MHC class I and II, complement on sarcolemma	Endomysial $CD8^+$ T cells, MHC class I, amyloid, vacuoles, tubulofilaments, mitochondrial impairment (COX, paracr, inclusions)
Treatment and its response	Basic: GS, AZA/MTX/MMF; skin and JDM: IVIG; Lung/Escal.: RTX, CYC, IVIG, (CsA); Mostly good response except for malignancy or ILD	Basic: GS, AZA/MTX/MMF; Lung/Escal.: RTX, CYC, IVIG; Overall response good-moderate, but escalation often required	Basic: GS, AZA/MTX/MMF; Escal.: RTX, CYC, IVIG; Mostly good response	Basic: GS, AZA/MTX/MMF; Lung/Escal.: RTX, CYC, IVIG (CsA); Mostly good response except for malignancy or ILD	No basic immunosuppression; Probatory IVIG in selected patients justifiable; Severe dysphagia: local botulinum toxin or myotomy, percutaneous feeding tube. Usually refractory to treatment

Table II. *Overview of the clinical presentation, auto-antibodies, muscle pathology and treatment in the main subtypes of myositis. Modified from [41].*

Ab = antibody; ASS = anti-synthetase syndrome; AZA = azathioprine; $CD8^+$ T cells = cluster of differentiation 8 of cytotoxic T cells; cN1A = anti-cytosilic 5'-nucleotidase 1A Ab; COX = cytochrome oxidase staining in muscle fibers; CPK = creatine phosphokinase; CsA = cyclosporine A; CYC = cyclophosphamide; DM = dermatomyositis; EJ = anti-glycyl tRNA synthetase Ab; GS = glucocorticoids; HA = anti-tyrosyl tRNA syntethase Ab; HMGCR = anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase autoantibodies; IBM = inclusion body myositis; ILD = interstitial lung disease; IVIG = intravenous immunoglobulin G; JDM = juvenile dermatomyositis; Jo-1 = anti-histidil tRNA synthetase Ab; KS = anti-asparaginyl tRNA synthetase Ab; Ku = antibodies against Ku antigen (p70 and p80 subunits); MDA5 = anti-melanoma differentiation-associated gene 5 Ab; MHC = major histocompatibility complex; Mi-2 = anti-chromodomain helicase DNA binding protein 4 Ab; MMF = mycophenolate mofetil; MTX = methotrexate; NM = necrotizing myopathy; NXP2 = anti-nuclear matrix protein 2 Ab; OJ = anti- isoleucyl tRNA synthetase Ab; OM = overlap myositis; PL-7 = anti-threonyl tRNA synthetase Ab; PL-12 = anti-alanyl tRNA synthetase Ab; PM/Scl = anti-PM-Scl-75 and PM/Scl-100 polypeptides Ab; Ro/SS-A = anti-Sjögren's-syndrome-related antigen A (against the Ro52 and Ro60 autoantigen) Ab; RTX = rituximab; SAE = anti-small ubiquitin-like modifier activating enzyme Ab; SLE = systemic lupus erythematosus; SRP = anti-signal recognition particle autoantibodies; SS-B = anti-Sjögren's-syndrome-related La antigen Ab; TIF-1γ = anti-transcription intermediary factor gamma Ab; U-snRNP = anti-U1 small nuclear ribonucleoprotein particle Ab; Zo = anti-phenylalanyl synthetase Ab

- Electromyographic alterations;
- Bioptic alterations; and
- Characteristic skin rash.

As described in Table I, PM and DM are judged "definite", "probable", or "possible" according to the number of criteria met by the patient.

The classification of inflammatory myopathies has undergone several revisions [38-40] since the earliest descriptions by Bohan and Peter.

Five main subtypes of myositis, i.e. dermatomyositis (DM and juvenile DM), necrotizing myopathy (NM), PM, overlap myositis (OM and anti-synthetase syndrome—ASS), and inclusion body myositis (IBM), have been well described in a recent German review [41] (Table II).

In September 2018, Selva-O'Callaghan and colleagues published on *Lancet Neurology* a new classification of inflammatory myopathies in the adult [42] based on the clinical characteristics of the main clinical and phenotype-specific autoantibody groups, in which they specified also that the diagnosis of PM is a diagnosis of exclusion.

In the same period a further classification was published also based on a targeted clinical-serological approach [43]. In reference to the 708 variables (in particular myositis-specific autoantibodies—MSA) collected in 260 adult patients of the French register on myositis, 4 clusters of patients emerged (IBM, IMNM, DM, ASS), while PM did not more found place.

Besides clinical criteria, magnetic resonance imaging (MRI) [39,44] can be useful to make the right diagnosis. MRI with whole-body technique (WBMRI) is considered particularly useful for identifying the involvement of muscles: parameters such as inflammation, fibrosis, and atrophy can be used to determine the pattern of disease activity even at subclinical level [45-49]. In addition, MRI guides the choice of the site for muscle biopsy.

Figure 1, coming from a personal case report [50], highlights the typical MRI elements, which are suggestive for DM/PM.

IIMs can be treated with glucocorticoids (initial and basic treatment) and with immunosuppressants (methotrexate, azathioprine, mycophenolate mofetil). An additional or alternative therapy may be undertaken with cyclosporin A (or tacrolimus) or intravenous immunoglobulin, with therapy escalation to rituximab or cyclophosphamide.

Treatment with repository corticotropin injection (RCI) in a recent open label clinical trial [51] was effective, safe and tolerable, and led to a steroid dose reduction in adult patients with myositis refractory to glucocorticoid and traditional immunosuppressive drugs.

In this article, the possible implications of statins in autoimmunity have been thoroughly considered with the support of a literature search.

LITERATURE SEARCH STRATEGY

In this review, the literature search was conducted mainly on PubMed, but also congress abstracts and universities websites

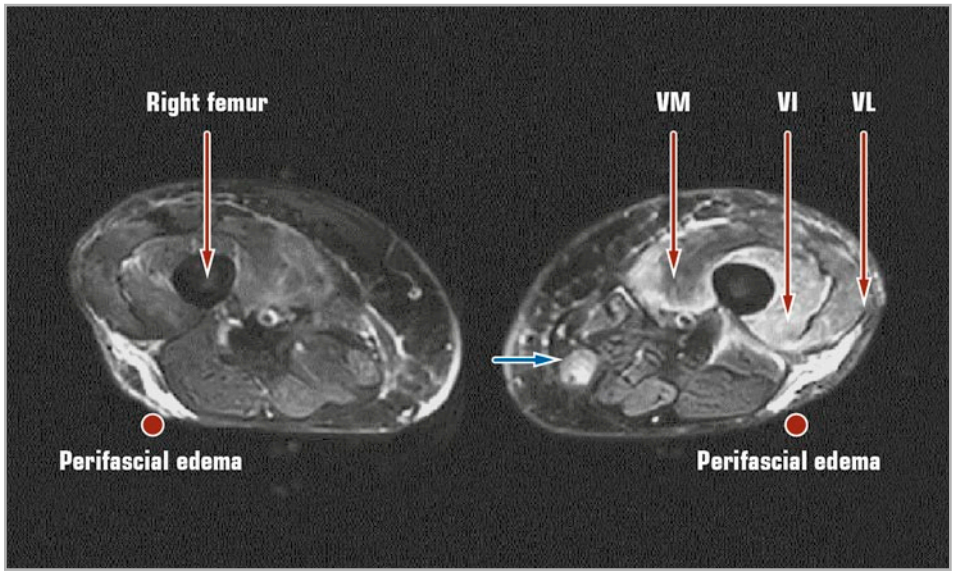

Figure 1. *Example of thighs magnetic resonance imaging (MRI). Axial STIR (short-tau inversion recovery sequences) images: axial fat-suppressed MRI images show increased signal intensity. Intense edema of the muscular bundles of both quadriceps, especially on the left, of the large adductor muscle on the left, of the gracilis (blue arrow), and of the semitendinosus muscles. Subcutaneous edema between muscles and fascia lata on both sides. Modified from [50].*

VI = *vastus intermedius*;
VL = *vastus lateralis*;
VM = *vastus medialis*

were considered. The search terms used were: "myositis", "myopathy", "statins", "muscular manifestations", "dermatomyositis", "polymyositis", "statin-induced autoimmune myopathy", "creatine (phospho) kinase", "myoglobin", and "troponin". The keywords were combined with the Boolean operators "AND" and "OR". Given the paucity of cases, we extended the search to include articles in all languages with English abstract. The selection of the descriptors was carried out in November 2018. No time limit was set in the search.

RESULTS

Tables III and IV describe the main characteristics of case reports, related to the exposure to statins in 28 adult patients with polymyositis [3-10,12-14,16] and in 30 adult patients with dermatomyositis [10,12,17-35].

Author, year [ref], country	Age, sex	Statin, dose (mg)	Exposure duration	Serum CPK (U/l)	ANA - title - pattern	Anti-Jo-1	Anti-HMGCR	EMG	Muscle MRI	Skin biopsy	Muscle biopsy	Diagnosis
Giordano, 1997 [6], Italy	42, M	S 20	4 m	503	n.r.	-	n.p.	Myogenic and neurogenic	n.r.	n.r.	Muscle-fiber necrosis, perivascular and endomysial inflammation	D
Folzenlogen, 2001 [9], USA	76, F	A 20	n.r.	9870	1:1280 speckled	- (anti-Ku positive)	n.p.	Myogenic	n.p.	n.p.	Muscle cells necrosis, endomysial mononuclear infiltrate, atrophy fibers	D
Riesco-Eizaguirre, 2003 [7], Spain	75, M	S 20	6 m	6010	1:160	n.r.	n.p.	n.r.	n.r.	n.r.	Muscle fiber necrosis, perivascular inflammation	Pr
Takagi, 2004 [8], Japan	69, M	P 10	2 w	943	+	+	n.p.	Myopathic	n.r.	n.r	n.r.	Pr*
Fauchais, 2004 [4], France	56, F	S n.r.	2 m	925	1:5120	-	n.p.	Normal	n.r.	n.r.	Endomysial T cell infiltration, type II muscle atrophy	Pr
	54, F	A n.r.	4 m	7400	-	-	n.p.	Normal	n.r.	n.r.	T cell infiltration, type II muscle atrophy	Pr
	78, F	F n.r.	4 m	1417	1:2150	+ (ASS)	n.p.	Normal	n.r.	n.r.	T cell infiltration, type II muscle atrophy	Pr
	68, M	F n.r.	7 m	2517	1:5120	+	n.p.	Normal	Muscle necrosis	n.r.	Non-contributive	Po
Wu Y, 2014 [5], Canada	57, M	n.r. unknown	u.k.	3831	n.r.	n.r.	n.p.	Irritable myopathy	n.p.	n.p.	Mononuclear inflammatory infiltration around intact muscle fiber	D
	56, F	A 10	Few y	946	n.r.	n.r.	n.p.	Irritable myopathy	n.p.	n.p.	Mononuclear inflammatory infiltration around intact muscle fiber	D

Table continues >

> Table continued

Author, year [ref], country	Age, sex	Statin, dose (mg)	Exposure duration	Serum CPK (U/l)	ANA - title - pattern	Anti-Jo-1	Anti-HMGCR	EMG	Muscle MRI	Skin biopsy	Muscle biopsy	Diagnosis
	77, F	A 40-80	25 y	704	n.r.	n.r.	n.p.	Irritable myopathy	n.p.	n.p.	Mononuclear inflammatory infiltration around intact muscle fiber	D
	58, F	A n.r.	60 m	7000	n.r.	n.r.	n.p.	Irritable myopathy	n.p.	n.p.	Mononuclear inflammatory infiltration around intact muscle fiber	D
	59, F	A 10	54 m	8200	n.r.	n.r.	n.p.	Irritable myopathy	n.p.	n.p.	Mononuclear inflammatory infiltration around intact muscle fiber	D
	75, F	n.r. unknown	u.k.	3741	n.r.	n.r.	n.p.	Irritable myopathy	n.p.	n.p.	Mononuclear inflammatory infiltration around intact muscle fiber	D
	71, F	R n.r.	19 m	974	n.r.	n.r.	n.p.	Irritable myopathy	n.p.	n.p.	Mononuclear inflammatory infiltration around intact muscle fiber	D
	55, M	A n.r.	1 m	1187	n.r.	n.r.	n.p.	Irritable myopathy	n.p.	n.p.	Mononuclear inflammatory infiltration around intact muscle fiber	D
	47, F	R 10	44 m	1656	n.r.	n.r.	n.p.	Irritable myopathy	n.p.	n.p.	Mononuclear inflammatory infiltration around intact muscle fiber	D
Sailler, 2008 [10], France	80, F	P/F n.r.	14 m	355	-	n.r.	n.p.	Normal	n.p.	n.r.	n.p.	Po
	70, F	P n.r.	36 m	1869	-	n.r.	n.p.	Myogenic	n.p.	n.r.	Muscle fiber atrophy and necrosis, HLA-1 overexpression	Pr
	60, F	P/A/S n.r.	42 m	424	1:320	n.r	n.p.	Myogenic	n.p.	n.r.	n.p.	Po
Kanth, 2013 [3], USA	59, M	A^ 20	60 m	10,554	-	-	n.p.	n.p.	Inflammation in the posterior thigh muscles	n.p.	Necrotic and regenerating fibers, perivascular perimysial and endomysial inflammation, MHC-I diffuse positive membranous reactivity	Pr
Borges, 2018 [12], Brazil	71, M	S 20	4 y	5000	n.r.	-	- Anti-SRP: -	Myopathic pattern	Muscle diffuse edema	n.r.	Inflammatory myopathy	D

Table continues >

> Table continued

Author, year [ref], country	Age, sex	Statin, dose (mg)	Exposure duration	Serum CPK (U/l)	ANA - title - pattern	Anti-Jo-1	Anti-HMGCR	EMG	Muscle MRI	Skin biopsy	Muscle biopsy	Diagnosis
	66, F	S 20	2 m	3087	n.r	-	- Anti-SRP: -	Myopathic pattern	n.p.	n.r.	Inflammatory myopathy	D
	55, F[§]	S 20	2 days	126,000	n.r.	-	- Anti-SRP: -	Myopathic pattern	Muscle diffuse edema	n.r.	Inflammatory myopathy	D
Protić, 2014 [14], Serbia	67, M	A 20	6 y	7820	1:160	-	n.p. Anti-SRP: n.p.	Myopathic pattern	n.p.	n.p.	n.p.	Pr
Watad, 2015 [13], Israel	71, F	A 20	5 y	>4000	1:160 fine speckled	-	-	Myopathic	n.p.	n.p.	Endomysial perivascular infiltrate, muscle fiber necrosis	D
Gupta, 2001 [16], USA	55, M	C 0.3 mg A 10	2 w	14,611 (aldolase 355[#])	-	+(226.3 U)	n.p.	Markedly increased insertional activity	n.p.	n.p	Degenerating and regenerating muscle fibers with vacuolation, (toxic myopathy) + interstitial lymphocytic infiltrate involving small vessels and accumulation of lymphocytes around intact muscle fibers	D
	69, M	A 10 S n.r.	1 w 2 w	1123 (aldolase 11.7[#])	-	n.r.	n.p.	n.p.	Increasing signal with contrast enhancement	n.p.	Endomysial lymphocytic inflammation embracing degenerating and regenerating muscle fibers, and small vessels and lymphocytes clustered around the intact muscle fibers with attempt to break into the sarcoplasm	D

Table III. *Statin-associated polymyositis (28 case reports). Most Authors used the diagnostic criteria according to Bohan and Peter [36,37].*

* subacute;
^ +gemfibrozil
§ ethnicity: African American
# normal values: 1-7 IU/l
- = negative; + = positive; A = atorvastatin; ANA = Anti-nuclear antibody; anti-HMGCR = 3-hydroxy-3-methylglutaryl-coenzyme A reductase autoantibodies ; anti-Jo-1 = aminoacyl-tRNA histidyl synthetase autoantibodies; ASS = anti-synthetase syndrome; anti-SRP = anti-signal recognition particle autoantibodies; C = cerivastatin; CPK = creatine phosphokinase; D = definite; EMG = electromyography; F = fluvastatin; HLA-1 = human leukocyte antigen-1; m = months; MHC = major histocompatibility complex; MRI = magnetic resonance imaging; n.p. = not performed; n.r. = not reported; P = pravastatin; Po = possible; Pr = probable; R = rosuvastatin; S = simvastatin; u.k. = unknown; y = years; w = weeks

Author, year [ref], country	Age, sex	Statin, dose (mg)	Exposure duration	Serum CPK (U/l)	ANA - title -pattern	Anti-Jo-1	Anti-HMGCR	EMG	Muscle MRI	Skin biopsy	Muscle biopsy	Diagnosis
Schalke, 1992 [27], Germany	66, F	P 10	5 m	>4000	n.r. n.r.	n.r.	n.p.	Myopathic changes	n.p.	Yes	T-cell infiltrates	D
Khattak, 1994 [23], UK	50, M	S n.r.	6 m	1045	1:250 n.r.	n.r.	n.p.	+	n.r.	n.r.	Lymphocytic infiltration, muscle degeneration	D
Hill, 1995 [25], Australia	76, F	S 10	18 m	1246	1:2560 n.r.	-	n.p.	n.r.	n.p.	n.r.	Myositis, atrophy, lymphocytic infiltration	D
Rodriguez-Garcia, 1996 [24], Spain	63, F	L 20	24 m	Increased	n.r. n.r.	n.r.	n.p.	Myopathic changes	n.p.	Inflammatory infiltration	Inflammatory infiltrates, necrosis	D
Noël, 2001 [21], Switzerland	44, M	A 10	12 m	>2000	1:2560 nucleolar	-	n.p.	n.r.	n.r.	Keratinocytes apoptosis	Perifascicular $CD4^+$ T-cells infiltrates, severe necrosis	D
Vasconcelos, 2004 [20], USA	68, M	P 40 S 20	Few months	2354	n.r. n.r.	n.r.	n.p.	Myopathic changes	n.r	Chronic perivasculitis	Necrosis, inflammatory infiltrate, perifascicular fiber atrophy	D
Zuech, 2005 [22], France	69, F	P n.r.	24 m	6246	-	n.p.	n.p.	Normal	n.r.	n.r.	Normal	D
Thual, 2005 [26], France	76, M	F n.r.	2 m	500	-	n.p.	n.p.	n.r.	n.r.	n.r.	Perivascular inflammation, muscle degeneration	D
Sailler, 2008 [10], France	61, F	A n.r.	7 m	288	-	n.r.	n.p.	Myogenic	n.r.	n.r.	Atrophic fibers endomysial hyalinosis $HLA\text{-}1^+$	D
	72, F	A n.r.	48 m	4200	1:2400 n.r.	n.r.	n.p.	Normal	n.r.	n.r.	Perivascular lymphoid infiltrate, fiber necrosis, atrophy, $HLA\text{-}1^+$	D
	74, F	S n.r.	>36 m	n.p.	1:1280 n.r.	n.r.	n.p.	Myogenic	n.r.	n.r.	Fibrosis, perivascular lymphoid infiltrate, $HLA\text{-}1^+$	Pr
	74, F	P n.r.	3 m	4400	n.p. n.p.	n.p.	n.p.	Normal	n.r.	n.r.	Fiber necrosis and atrophy, perivascular lymphoid infiltrate, $HLA\text{-}1^+$ fibrosis	D
	84, F	P n.r.	32 m	712	1:5000 n.r.	n.r.	n.p.	Myogenic	n.r.	n.r.	Lymphocytic infiltrate, fiber necrosis and atrophy, $HLA\text{-}1^+$	D

Table continues >

> Table continued

Author, year [ref], country	Age, sex	Statin, dose (mg)	Exposure duration	Serum CPK (U/l)	ANA - title -pattern	Anti-Jo-1	Anti-HMGCR	EMG	Muscle MRI	Skin biopsy	Muscle biopsy	Diagnosis
	85, F	S n.r.	72 m	239	1:5000 n.r.	n.r.	n.p.	Myogenic	n.r.	n.r.	Perivascular lymphoid infiltrate, fibers necrosis and atrophy, HLA-1+	D
	79, F	A n.r.	60 m	1869	n.p. n.p.	n.p.	n.p.	Myogenic	n.r.	n.r.	Fiber atrophy, perivascular lymphoid infiltrate, HLA-1+	D
Rasch, 2009 [19], Germany	71, F	S 40	72 m	1262	1:2560 n.r.	- Anti Mi-2: +	n.p.	+	n.r.	n.r.	Lymphocytic infiltrate, perivascular CD4+	D
Inhoff, 2009 [28], Germany	70, F	S n.r.	Several y	n.r.	n.r. n.r.	n.r.	n.p.	Normal	n.p.	Interface dermatitis, vacuolar degeneration of nasal keratinocytes, epidermal atrophy	n.p.	ADM
Zaraa, 2011 [17], Tunisia	50, M	S n.r.	12 m	714	1:1600 n.r.	n.r.	n.p.	Normal	n.p.	Interface dermatitis, vacuolar degeneration of basal keratinocytes, epidermal atrophy, interstitial mucin deposits in dermis	n.p.	D
Komai, 2015 [18], Japan	47, F	A 5	2 m	612	+ Cytoplasmic and speckled	n.r.	n.p.	n.r.	n.p.	Inflammatory cells infiltration at the perivascular lesion	Irregularity of muscle fibers with perifascicular T lymphocytes	D
Oztas, 2017 [31], Turkey	49, M	A 10	2 m	2850	-	-	n.r.	Myogenic	n.r.	Interface dermatitis with hydropic degeneration of basal keratinocytes	n.r.	Po
Fania, 2017 [30], Italy	72, F	S 20	3 m	285	1:320	-	n.p.	Myogenic changes	n.p.	Interface dermatitis	n.p.	D
Cannon, 2012 [29], USA	55, M	A 40	10 y	11,900	n.r.	n.r.	n.p.	n.r.	n.r.	Positive, but details n.r.	n.r. (compartment syndrome)	D
Borges, 2018 [12], Brazil	75, F	S 20	2 m	7449	n.r.	-	- anti-SRP: -	Myopathic pattern	n.p.	n.r.	Inflammatory myopathy	D
	78, M	S 20	2 m	2990	n.r.	-	- anti-SRP: -	Myopatic pattern	n.p.	n. r.	n.p.	D
	52, F	S 20	4 m	1280	n.r.	-	- anti-SRP: -	Myopathic pattern	n.p.	n. r.	n.p.	D

Table continues >

> Table continued

Author, year [ref], country	Age, sex	Statin, dose (mg)	Exposure duration	Serum CPK (U/l)	ANA - title -pattern	Anti-Jo-1	Anti-HMGCR	EMG	Muscle MRI	Skin biopsy	Muscle biopsy	Diagnosis
	47, M§	S 20	3 m	20,424	n.r.	-	- anti-SRP: -	Myopathic pattern	n.p.	n.r.	Inflammatory myopathy	D
Chemello 2017 [32], Brazil	69, M	S 20	2 m	617	1:80	-	n.p.	n.p.	Muscle edema, fatty infiltration	Ulcer biopsy: basal layer vasculopathic degeneration of keratinocytes with infiltrate eosinophilic, leukocytoclastic vasculitis	(deltoid): nonspecific findings	D
Tihanyi, 2013 [33], Hungary	59, M	S n.r. A n.r.	3 y 6 y	1723	n.r.	n.r.	n.p.	n.p.	n.p.	n.p.	n.r.	D
Spiro, 2018 [34], USA	55, F	A 80	3 m	207*^	1:1280	-	-	n.p.	Multifocal area of myositis	Interface dermatitis with apoptotic basal keratinocytes, basal layer vacuolar changes	n.p.	D
Hydzik, 2011 [35], Poland	56, F	A 20	6 days	3258^	>1:20,480#	-	n.p	n.p.	n.p.	n.p	n.p.	Pr

Table IV. *Statin-associated dermatomyositis (30 case reports). Most Authors used the diagnostic criteria according to Bohan and Peter [36,37]*

§ ethnicity: African American
* aldolase high: peak = 13.8 IU/l
^ anti-Mi-2 positive
# Polish normal values: <1:160
- = negative; + = positive; A = atorvastatin; ADM = amyopathic dermatomyositis; ANA = anti-nuclear antibody; anti-HMGCR = anti -3-hydroxy-3-methylglutaryl-coenzyme A reductase autoantibodies; anti-Jo-1 = anti-aminoacyl-tRNA histidyl synthetase autoantibodies; anti-Mi-2 = anti-chromodomain helicase DNA binding proetin 4 Ab; anti-SRP = anti-signal recognition particle autoantibodies; CPK = creatine phosphokinase; D = definite; EMG = electromyography; F = fluvastatin; HLA-1 = human leukocyte antigen-1; L = lovastatin; m = months; MRI = magnetic resonance imaging; n.p. = not performed; n.r. = not reported; P = pravastatin; Po = possible; Pr = probable; R = rosuvastatin; S = simvastatin; u.k. = unknown; y = years

On the basis of the results shown in Tables III and IV, these diseases were more frequent in women (66%) and in senile age (the median age at the time of diagnosis was 68 years). The drugs most frequently associated with the disease were atorvastatin and simvastatin in PM and DM, respectively.

The exposure period was very variable: in the PM there was a minimum of two days, in a case concerning an African American patients with CPK peak very high [12], while the maximum exposure time was of 25 years in an elderly woman. In DM, the exposure duration was shorter (median = 6 months; range = 6 days-10 years).

The CPK peak was higher in PM (median = 2802 U/l; range = 355-126,000) than in DM (median = 1574 U/l; range = 207-20,424), but the difference was not statistically significant.

In one case of dermatomyositis (55 years, F, atorvastatin 80 mg) [34], a normal value of CPK was found associated with increased aldolase. In three further cases, the CPK was lower than 300 U/l.

The determination of ANAs refers only to 33 patients: they were positive in 76% of patients, i.e. 23 cases (14/18 DM and 9/15 PM).

Anti-HMGCR antibodies were dosed in a total of 9 patients: those described in the

Brazilian series published in 2018 [12] and the recent case published in October 2018 [34]. All were negative. These antibodies, discovered in 2010 [52,53], are currently being measured in a few specialized centers. Even the anti-signal recognition particle autoantibodies (anti-SRPs), mentioned in the same series, were negative.

In PM, anti-Jo antibodies were negative in 10 out of 14 assays performed. Among the 4 positive patients, one had antisynthetase syndrome. In DM, 12 patients were tested, but none was positive.

We found also a case of polymyositis during therapy with atorvastatin diagnosed after an episode of rhabdomyolysis (CPK = 14.611 U/l with myoglobinuria) from cerivastatin, with subsequent detection of positive anti-Jo-1 [16].

DISCUSSION

According to the literature [11,54-57], statins are involved also in other autoimmune diseases, such as interstitial lung disease, myasthenia gravis, systemic lupus erythematosus, cutaneous lupus, vasculitis, autoimmune hepatitis, lichen planus pemphigoides, and pemphigus erythematosus.

Even more cases appeared in recent years in literature concerning necrotizing myopathies associated with statins and with the coexistence of autoimmune phenomena [11,55].

From 1992 to November 2018 at least 58 defined cases of DM (n. 30) and PM (n. 28), with histological confirmation, associated with exposure to statins were described.

It should be noticed that in the analysis of the South Australian Myositis database including 221 patients with histologically confirmed idiopathic inflammatory myositis, 68 patients (30.8% of cases) were found exposed to statins, at the time of diagnosis: 27/89 PM, 4/23 DM, 12/24 necrotizing myopathy, 20/66 inclusion body myositis, and 5/19 nonspecific chronic inflammatory myositis patients. Exposure to statins was found in 30.3% of PM and in 17.4% of DM, thereby highlighting an almost 2-fold increased likelihood compared with controls. However, details on the type of statin, dosage, or duration of statin exposure was not available in this study [58].

Another serious muscle complication associated with statin use has recently been described: autoimmune necrotizing myopathy (IMNM: immune-mediated necrotizing myopathy). It is associated with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies (anti-HMGCR) [59].

According to some Authors, most patients affected by necrotizing myopathy with a history of statins, before the discovery of anti-HMGCR were classified as polymyositis. Statin-triggered IMNM and polymyositis would therefore not be two distinct entities, but part of the same pathophysiological spectrum also because they respond well to immunosuppressive treatment [5,60].

Pathognomonic clinical manifestations for dermatomyositis and polymyositis have been reported in three adult patients with autoimmune necrotizing myopathy positive for anti-HMGCR [61-63].

In the IMNM, magnetic resonance detects a characteristic pattern of muscular abnormalities involving mainly hip rotators and glutei: IMNM have significantly more widespread muscle edema, atrophy, and fatty replacement compared with those with polymyositis and dermatomyositis, unlike the fascial edema is more common and widespread in dermatomyositis [44].

In 2013, a Canadian Working Group Consensus defined the main predisposing conditions that promote intolerance or side effects of statins [64]:

- Hypothyroidism;
- Hypovitaminosis D;
- Low body mass index;
- Low CoQ10 enzyme level;
- Excessive use of alcohol;
- Excessive use of cranberry or grapefruit juice;
- Illicit drugs (amphetamine, cocaine, heroin);
- Drug-statin interaction;
- Renal failure;
- Liver failure;
- Diabetes mellitus;
- Biliary obstruction;
- History of pre-existing asymptomatic increase in CPK.

However, a more recent meta-analysis conducted by Nguyen in 2018 found that the significant risk factors for myopathy and/or rhabdomyolysis associated with statins were [65]:

- Age > 65 years;
- Female gender;
- Diabetes mellitus;
- Renal insufficiency;

- Cardiovascular disease;
- Drug-drug interactions (clarithromycin, erythromycin, cyclosporin, mibefradil, verapamil, diltiazem, nefazodone, itraconazole, fibrates, gemfibrozil, amiodarone, and protease inhibitors);
- Statin dose;
- Genetic factors (SLCO1B1 gene mutation).

It is useful to dose CPK before starting statin therapy to discover a subclinical myopathy and to exclude, even if very rare, the presence of macro-creatinekinase [66].

Subsequent CPK checks should be done in the third, sixth, and twelfth months because most statin myopathies occur within the first six months of therapy.

Concerning the case with high aldolase [50], it should be pointed out that aldolase dosage is useful because its isolated increase reflects preferential immune-mediated damage affecting early regenerating cells [67].

Regarding the therapy of hypercholesterolemia to be implemented after clinical recovery in patients with IIMs, to my knowledge specific indications do not exist in the literature. Drugs with no side effects on the muscle should be used. In primary prevention, the range of therapy extends from nutraceuticals to ezetimibe. As for nutraceuticals, monacolin K should not be prescribed because it is chemically identical to lovastatin.

Berberine does not modify CPK [68], while for ezetimibe the incidence of myopathy/rhabdomyolysis was identical (0.2%) to that found in placebo patients. PCSK9 inhibitors may be used in myopathic patients at high cardiovascular risk. These fully human monoclonal antibodies (e.g. evolucumab, alirocumab), which act against the proprotein convertase subtilisin/kexyn type 9, could be an alternative to statin therapy in severe cases of drug toxicity, such as rhabdomyolysis [1]. Clinical studies comparing statins versus statins + anti-PCSK9 found no differences in muscle and CPK side effects between the two groups [69,70]. For patients with idiopathic inflammatory myositis and with coexistent dyslipidemia, anti-cholesterol therapy should be implemented, obviously, with defined drugs without toxic effects on the muscle.

CONCLUSIONS

The present literature review identified 28 cases of polymyositis and 30 cases of dermatomyositis related to exposure to statins.

To my knowledge, this is currently the widest research about these two rare statin-triggered pathologies.

Key points

- *Besides the more common side effects on muscle, statins can give rise to autoimmune phenomena*
- *Inflammatory myopathies are a very heterogeneous group of illnesses that can present with a very different clinical phenotype*
- *The main subtypes of myositis should be considered in the differential diagnosis: PM, DM, IMNM, OM/ASS, and IBM*
- *The international literature reports 28 cases of polymyositis and 30 cases of dermatomyositis related to exposure to statins*
- *It is useful to dose the CPK (and aldolase) before starting statin therapy*
- *In case of skin rash or muscular symptoms, antinuclear antibody screening is recommended in patients treated with statins*
- *Patients who have failed to normalize high CPK (> 10 times the upper range of normal) after statin withdrawal and after cortisone therapy should be tested (in addition to ANA and ENA) for myositis-associated and myositis-specific antibodies (MAAs and MSAs), in particular anti-SRP and anti-HMGCR antibodies and, if these are positive, undergo muscle biopsy to confirm the diagnosis of inflammatory or autoimmune myopathy*
- *Drug therapy is challenging and requires, in addition to corticosteroids, immunosuppressive medications, and intravenous immunoglobulin.*
- *New anti-PCSK9 monoclonal antibodies may be used in high-risk cardiovascular myopathic patients*
- *The choice of anti-cholesterol therapy in myopathic patients after clinical recovery is yet not defined*

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