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Safety of statin drugs in patients with dyslipidemia and stable systemic autoimmune myopathies

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Abstract

Recent studies have shown a high prevalence of dyslipidemia in patients with systemic autoimmune myopathies (SAM). However, little is known about the safety of the use of statins in these patients, and this gap in research motivated the accomplishment of the present study. In a retrospective cohort study conducted from 2004 to 2018, 250 patients with SAM were evaluated, and 24 patients had stable forms of SAM (16 dermatomyositis, 1 polymyositis and 7 antisynthetase syndrome) but had dyslipidemia and had received statins. Patients with clinically amyopathic dermatomyositis, immune-mediated necrotizing myopathy, dermatomyositis, or polymyositis induced by statins were excluded. The mean age of the patients was 50.6 years, and they were predominantly women. The median duration of the disease was 5.0 years. Twelve patients received simvastatin (10–60 mg/day), and 11 patients received atorvastatin (20–40 mg/day), and 1 patient received atorvastatin (10 mg/day) which was later replaced by simvastatin (20 mg/day). The median time of exposure to the statin was 22.5 months. The follow-up appointments showed that the patients' lipid profiles had improved and that there had been no recurrences of disease activity or clinical intercurrences. Despite the small sampling, the data showed that the use of statins in patients with SAM was safe. New studies with a larger sample and patients with different degrees of disease activity are necessary to corroborate the results of the present study.

Keywords Dermatomyositis · Dyslipidemia · Metabolic syndrome · Polymyositis · Statins

Introduction

The systemic autoimmune myopathies (SAM) are a group of rare, systemic rheumatic diseases that primarily affect the skeletal striated muscle, leading to high morbidity and functional disability. The SAM can be classified as dermatomyositis, polymyositis, inclusion body myositis, and immune-mediated necrotizing myopathy, among others [1–4].

Recent studies have shown a high prevalence of metabolic syndrome in patients with SAM [5–8]. In fact, the frequency of metabolic syndrome is 41.7%, 45.7%, and 42.9% in patients with dermatomyositis, polymyositis and antisynthetase syndrome, respectively. In addition, from the point of view of dyslipidemia, patients are characterized by high serum levels of total cholesterol, LDL-cholesterol, and triglycerides, as well as low serum levels of HDL-cholesterol [5–8].

In the treatment and prevention of dyslipidemia, statins are the most widely used lipid-lowering agents, because they are inhibitors of the enzyme 3-hydroxy-3-methyl-glutaryl CoA reductase (HMGCR), which is responsible for catalyzing the conversion of HMGCR into mevalonate in the process of cholesterol synthesis [9]. As for musculoskeletal side effects, statins can cause fatigue, non-specific myalgia, increased serum concentrations of muscle enzymes, myositis or rhabdomyolysis [9, 10]. These are reversible frames after the suspension of lipid-lowering agents. However, in some cases, these medications may trigger an irreversible autoimmune condition, such as, immune-mediated necrotizing myopathies, dermatomyositis, and polymyositis [11–17].

However, there are currently no studies on the use of statins in patients diagnosed with SAM and who, as previously mentioned, present a high prevalence of metabolic syndrome. The use of statins in SAM has been avoided in daily clinical practice, since it is believed that these medications

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may eventually reactivate or aggravate the disease activity, although there is no scientific evidence to support this belief.

Therefore, the objective of the present study was to retrospectively evaluate the safety of statin use in patients diagnosed with SAM.

Materials and methods

In this single-center retrospective cohort study, 250 patients with SAM were evaluated at a regular outpatient clinic between 2014 and 2018.

Patients with any of the following criteria were excluded in this study: clinically amyopathic dermatomyositis, immune-mediated necrotizing myopathy (muscle biopsies with the presence of necrosis of muscle fibers and an absence or shortage of inflammatory cell infiltrates. Moreover, all patients had anti-SRP or anti-HMGCR positive autoantibodies), inclusion body myositis, cancer associated with myopathies, or overlap syndrome.

This study was approved by the local ethics committee (CAPPesq/HCFMUSP, No. 0039/10).

Twenty-four consecutive patients with SAM who had used statins were identified:

(a) Sixteen patients had dermatomyositis and 1 had polymyositis, according to the criteria of Bohan and Peter [1]. These patients were also defined according to EULAR/ACR 2017 classification criteria [4]
(b) Seven patients had antisynthetase syndrome, according to the classification criteria of Connors et al. [18]. All patients had anti-Jo-1 positive autoantibody.

All patients were clinically and laboratory stable, and had dyslipidemia (total cholesterol > 200, HDL-cholesterol < 40, LDL-cholesterol > 130 and/or triglycerides > 150 mg/dL) when statins were introduced.

Data about these 24 patients were collected from electronic medical records, with prestandardized and preparameterized information: age at diagnosis of the disease; sex; ethnicity; duration of time between diagnosis and onset of disease symptoms; time of outpatient follow-up; number of disease recurrences; initial and current treatment; serum levels of creatine phosphokinase (reference value: 32–294 U/L), aspartate aminotransferase (< 31 U/L), alanine aminotransferase (< 31 U/L), lactic dehydrogenase (135–214 U/L); muscular strength of the limbs, according to the graduation of muscular strength provided by the Medical Research Council [19].

Serum samples stored at − 20 °C were collected for the analysis of the autoantibodies at the time of the initial investigation of the active disease (laboratory and clinical). Identification of the autoantibodies was performed using a commercial kit (Myositis Profile 3, Euroimmun, Germany) according to the manufacturer's protocol. The evaluation of the results was based on the methods established in a previous study [20]. Anti-HMGCR antibody was assayed by enzyme-linked immunosorbent assay (ELISA), using recombinant HMGCR protein and anti-HMGCR polyclonal antibody (MyBioSource, CA, USA). For the purposes of this study, patients with anti-HMGCR values of greater than three standard deviations from the mean of 8 healthy individuals were considered positive. Antinuclear antibodies were detected by indirect immunofluorescence using HEp-2 cells as the substrate.

The use of glucocorticoids, immunosuppressive and immunomodulatory drugs, and statins, as well their dosages duration of use until the diagnosis of SAM were also evaluated.

Clinical remission was considered to be a continuous 6-month period in which there was no evidence of disease activity and in which the patients did not receive myositis therapy, and the complete clinical response was defined as the continuous 6-month period of no evidence of disease activity while the patients were still receiving myositis therapy. Disease relapses were defined as clinical relapses (i.e., muscle and/or dermatological manifestations) and/or biochemical relapses (i.e., increases of serum muscle enzymes for which there were no other explanation).

Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate the distribution of each of the continuous variables. The results were presented as mean ± standard deviation for continuous variables, and (%) percentages for categorical variables. Median values (interquartile 25th–75th) were calculated for continuous variables that did not present a normal distribution. Wilcoxon's test was used to compare continuous variables, without a normal distribution, pre- and post-exposure to statins. Values of $P < 0.05$ were considered statistically significant. All analyses were done with the statistical software SPSS 15.0 (Chicago, IL, USA).

Results

We evaluated 24 patients: 16 dermatomyositis, 1 polymyositis and 7 antisynthetase syndrome. At the time of introducing statins, mean age of the patients was 50.6 years, and they were predominantly female and white (Table 1).

At disease onset, all patients had muscle weakness (upper and/or lower limbs) with median serum level of creatine phosphokinase of 1406 U/L. All SAS had muscle, joint and pulmonary involvements, and anti-Jo-1 positive antibody. Moreover, 18 (75.0%) patients had ANA positive and 18

Table 1 General data of the 24 patients with systemic autoimmune myopathies in the present study who received statins

No.	Current age (years)	Gender	Ethnicity	Disease	Muscle strength (upper)[a]	Muscle strength (low)[a]	Extra-muscle involvements[a]	Muscle biopsy	Autoantibodies	Disease time (years)	Current disease status	Previous medications	Current medications	Current prednisone (mg/day)	CVD and its risk factors
1	39	M	W	DM	IV	IV	C	N	–	2	Complete clinical response	AZA	0	5	SAH, diabetes
2	38	F	W	ASS	IV	IV	C, A, L	Y	ANA, Jo-1	7	Complete clinical response	AZA	AZA	0	SAH
3	54	F	B	ASS	V	IV	C, A, L	Y	ANA, Jo-1	11	Complete clinical response	MMF	MMF	5	Diabetes, T
4	32	F	B	DM	IV	IV	C	Y	ANA	4	Complete clinical response	AZA	AZA	0	–
5	37	M	W	DM	IV	IV	C	N	ANA	1	Clinical remission	AZA	AZA	5	SAH
6	61	F	W	DM	IV	IV	C	Y	ANA	0	Complete clinical response	AZA, CP	AZA	10	Diabetes
7	34	M	W	ASS	V	IV	C, A, L	Y	ANA, Jo-1	11	Complete clinical response	MTX, LFN	MTX	5	
8	81	M	W	DM	III	III	C, A	Y	–	1	Complete clinical response	AZA	AZA	5	SAH
9	40	M	W	DM	III	III	C, L	Y	ANA, Mi-2	7	Clinical remission	AZA	AZA	0	
10	59	F	B	DM	IV	V	C	Y	ANA	5	Complete clinical response	AZA, MTX	MMF	0	
11	52	F	B	DM	IV	IV	C	Y	–	5	Complete clinical response	MTX, MMF	MMF, MTX	5	
12	52	M	W	ASS	III	III	C, A, L	Y	ANA, Jo-1		Complete clinical response	AZA	AZA	0	–
13	32	M	B	DM	IV	V	C	Y	–		Complete clinical response	MTX	MTX	0	SAH
14	50	F	W	ASS	IV	IV	C, A, L	N	ANA, Jo-1		Complete clinical response	AZA	MMF	5	SAH, diabetes
15	62	F	W	DM	IV	IV	C	N	ANA		Complete clinical response	LFN	LFN	0	Diabetes
16	50	F	W	DM	V	IV	C	Y	ANA		Complete clinical response	–	0	0	–
17	61	F	B	ASS	IV	IV	C, A, L	Y	ANA, Jo-1		Complete clinical response	MMF	MMF	0	T
18	57	F	B	DM	IV	IV	C	Y	ANA		Complete clinical response	MTX	MTX	0	–
19	59	F	W	PM	IV	IV	–	Y	–		Clinical remission	MMF	0	0	–
20	47	F	B	DM	IV	V	C	Y	ANA		Complete clinical response	LFN, MMF	CP	0	–
21	69	F	W	DM	IV	IV	C, L	Y	ANA		Clinical remission	AZA	0	5	SAH

Table 1 (continued)

No.	Current age (years)	Gender	Ethnicity	Disease	Muscle strength (upper)[a]	Muscle strength (low)[a]	Extra-muscle involvements[a]	Muscle biopsy	Autoantibodies	Disease time (years)	Current disease status	Previous medications	Current medications	Current prednisone (mg/day)	CVD and its risk factors
22	29	F	W	DM	III	III	C	Y	–		Clinical remission	AZA	0	5	–
23	46	F	B	ASS	V	IV	C, A, L	N	ANA, Jo-1		Complete clinical response	MMF	MMF	5	SAH
24	73	F	W	DM	III	IV	C	N	ANA		Clinical remission	–	0	0	SAH
	50.6 ± 13.8														

Data presented in average ± standard deviation

Muscle strength according to Medical Research Council

A articular involvement, *ASS* antisynthetase syndrome, *AZA* azathioprine, *B* black, *C* cutaneous involvement, *CP* cyclosporine, *DM* dermatomyositis, *F* female, *IVIg* intravenous immunoglobulin, *L* lung involvement, *LFN* leflunomide, *M* male, *MMF* mycophenolate mofetil, *MP* methylprednisolone, *MTX* methotrexate, *N* no, *PM* polymyositis, *SAH* systemic arterial hypertension, *T* tobacco, *Y* yes, *W* white

[a]At disease onset

(75.0%) had muscle biopsies—inflammatory myopathy features (Table 1).

The median duration of the disease was 5.0 years. By the time of diagnosis of the disease, the patients had received various types of immunosuppressive or immunomodulatory drugs as well as glucocorticoids.

At the time of introducing statins, 11 out of the 24 patients were using prednisone, at doses ranging from 5.0 to 10.0 mg/day. Out of the 24 patients, 17 were using an immunosuppressive or immunomodulatory drugs, one was using two drugs simultaneously, and six patients were not using any immunosuppressive or immunomodulatory drugs (Table 1). Nine patients had systemic arterial hypertension and 5 had diabetes mellitus. Two patients were smokers.

As for statin use, 12 patients received simvastatin (10–60 mg/day), 11 received atorvastatin (20–40 mg/day), and 1 patient received atorvastatin (10 mg/day), which was then replaced by simvastatin (20 mg/day). The statins were introduced to primary prevention. The median time of exposure to statins was 22.5 (3.0–67.5) months (Table 2).

The follow-up appointments showed that lipid profiles had improved (total cholesterol and LDL-cholesterol) and

Table 2 General characteristics of the statins used by the 24 patients with systemic autoimmune myopathies included in the present study

Patient	Statins	Daily dose (mg)	Exposure time (months)
1	Simvastatin	10, 20	87
2	Atorvastatin	20	2
3	Atorvastatin	20, 40	27
4	Atorvastatin	20	3
5	Atorvastatin	20	39
6	Atorvastatin/simvastatin	10, 20	42
7	Atorvastatin	20	4
8	Sinvastatin	10	26
9	Simvastatin	20	12
10	Atorvastatin	20	3
11	Simvastatin	20	3
12	Atorvastatin	20	3
13	Atorvastatin	20	2
14	Simvastatin	10, 20	118
15	Simvastatin	20, 40	72
16	Simvastatin	20	142
17	Atorvastatin	20	1
18	Atorvastatin	20	3
19	Simvastatin	40	25
20	Simvastatin	20	20
21	Simvastatin	20, 30, 40	123
22	Simvastatin	10, 20, 40, 60	96
23	Atorvastatin	20	3
24	Simvastatin	20	54

that there had been no recurrences of the disease or clinical intercurrences (Table 3). All patients had muscle strength of V degree (upper and lower limbs), pre- and post-exposition to statins. In addition, after the introduction of statins, of the 11 patients who were taking prednisone, only 3 patients continued to use prednisone (5.0 mg/day). In addition, after the end of treatment with the lipid-lowering drugs, five could stop taking immunosuppressive drugs because the disease had gone into remission.

Discussion

Despite the small sample size, the use of lipid-lowering drugs was safe in patients who already had diagnoses and stable forms SAM or dyslipidemia. There were no cases of relapse of the disease or of adverse hypolipidemic-related events.

As advantages of the present study, strict exclusion criteria were used, such as patients with immune-mediated necrotizing myopathy, as well as histories of polymyositis or dermatomyositis induced by lipid-lowering agents. Patients diagnosed with inclusion body myopathy, muscular dystrophy, metabolic myopathy, cancer associated with myositis, and overlapping syndrome were excluded, as well as patients with active diseases, to avoid any confounding factors that could interfere with the final results.

Metabolic syndrome is characterized by the presence of increased abdominal circumference, systemic arterial hypertension, dyslipidemia and insulin resistance. This set of factors triggers cardiovascular risks, thereby increasing overall mortality by about 1.5 times [21, 22]. Recent studies have shown a high prevalence of metabolic syndrome, as well as dyslipidemia, in patients with SAM [5–8]. In studies on patients with dyslipidemia, they were shown to have high levels of LDL-cholesterol, total cholesterol, and triglycerides and to have low levels of HDL-cholesterol; however, the higher lipid profiles do seem to be related to the activity of the disease and glucocorticoid treatment [5–8].

Despite this evidence of pertaining to dyslipidemia in patients with SAM and although there is no scientific evidence, the use of statins in patients with SAM has been avoided in clinical practice. It is believed that this class of medication can reactivate or worsen SAM activity. According to Charles-Schoeman et al. study [23], statins are frequently used by experts in the treatment of SAM and that some patients worsen with these drugs and may improve on dechallenge [23].

As musculoskeletal side effects, lipid-lowering agents can cause fatigue, non-specific myalgia, increases in serum levels of muscle enzymes, and even rhabdomyolysis [9, 10]. These events are self-limiting and usually cease after the use of lipid-lowering agents is halted. However, although uncommon, lipid-lowering agents can trigger irreversible clinical conditions, such as immune-mediated necrotizing myopathy, dermatomyositis, and polymyositis [11–17]. Moreover, in the large population-based study, statin exposure was associated also with histologically confirmed SAM [16]. In these cases, in addition to stopping the use of lipid-lowering agents, the introduction of glucocorticoids and/or immunosuppressive drugs necessary for inducting a remission of SAM [11–17]. However, to date, no studies have evaluated the use of lipid-lowering drugs in patients with diagnoses of SAM.

In the present study, the use of lipid-lowering agents in patients diagnosed with stable SAM was shown to be safe, and the agents did not reactivate the disease or lead to clinical intercurrences. In addition, lipid profiles improved after the introduction of the lipid-lowering agents.

As a main limitation, the present study design consisted in the retrospective cohort analysis. However, the data were obtained through electronic records with prestandardized

Table 3 Muscle strength and laboratory profile of patients with systemic autoimmune myopathies with dyslipidemia submitted to different types of statins

	Pre	Post	*P* value
Muscle strength[a]			
Upper limbs (degree V)	24 (100.0)	24 (100.0)	1.000
Lower limbs (degree V)	24 (100.0)	24 (100.0)	1.000
Creatinophosphokinase (U/L)	106 (62–159)	115 (79–180)	0.140
Alanine aminotransferase (U/L)	22 (18–30)	25 (15–34)	0.626
Aspartate aminotransferase (U/L)	22 (17–40)	25 (18–37)	0.570
Lactic dehydrogenase (U/L)	280 (217–339)	235 (185–253)	0.084
Total cholesterol (mg/dL)	241 (207–268)	182 (150–228)	0.003
LDL-cholesterol (mg/dL)	165 (130–186)	106 (107–137)	0.001
HDL-cholesterol (mg/dL)	54 (48–64)	53 (42–67)	0.520
Triglycerides (mg/dL)	173 (125–215)	139 (86–183)	0.162

Data presented in median (interquartile, 25th–75th) or percentage (%)

[a]Muscle strength according to Medical Research Council

and preparameterized data, which allowed relevant and reliable information to be obtained for the present study.

In summary, despite the small number of cases, it was verified that the use of lipid-lowering drugs was safe in patients who had stable forms of SAM or dyslipidemia. However, studies that incorporate large number cases and include patients with different levels of disease activity should be conducted to corroborate the findings of the present study.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The present study was approved by the local ethics committee.

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