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Intravenous human immunoglobulin and/or methylprednisolone pulse therapies as a possible treat-to-target strategy in immune-mediated necrotizing myopathies

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Abstract

To evaluate the relevance of immunoglobulin (IVIg) and/or methylprednisolone pulse therapies in immune-mediated necrotizing myopathy (IMNM). Secondarily, to analyze the muscle damage measured by late magnetic resonance images (MRI). This retrospective study included 13 patients with defined IMNM (nine patients positive for the anti-signal recognition particle and four patients positive for hydroxyl-methyl-glutaryl coenzyme A reductase) who were followed from 2012 to 2018. International Myositis Assessment and Clinical Studies Group (IMACS) scoring assessed the response to a standardized treat-to-target protocol with disease activity core-set measures and late magnetic resonance imaging (MRI). The patients had a mean age of 53.5 years and were predominantly female and of white ethnicity. Median symptom and mean follow-up durations were 4 and 39 months, respectively. All patients received IVIg and/or methylprednisolone pulse therapies. All IMACS core-set measurements improved significantly after initial treatment. Nine patients achieved complete clinical response and among them 2 had complete remission. Eleven patients had discontinued glucocorticoid use by the end of the study. Only 2 patients had moderate muscle atrophy or fat replacement observed by MRI, with the remainder presenting normal or mild findings. Our patients with IMNM treated with an aggressive immunosuppressant therapy had a marked improvement in all IMACS core-set domains. Moreover, the MRI findings suggest that an early treat-to-target approach could reduce the odds of long-term muscle disability. Methylprednisolone and/or IVIg pulse therapies aiming at a target of complete clinical response are potential treatment strategies for IMNM that should be studied in future prospective studies.

Keywords Glucocorticoids · Intravenous human immunoglobulin · Magnetic resonance · Methylprednisolone · Necrotizing myopathies

Introduction

Systemic autoimmune myopathies (SAM) are a heterogeneous group of chronic muscular disorders highly associated with morbidity and disability [1, 2]. Because of their demographic, clinical, laboratory, histological, and evaluative features, SAM may be classified as immune-mediated necrotizing myopathy (IMNM), dermatomyositis, polymyositis, inclusion body myositis, and others [1, 2].

IMNM is an acute/subacute onset inflammatory disease characterized by significant skeletal muscle weakness with high levels of serum muscle enzymes [3–7]. The disease often shows a relapsing pattern with progressive muscular dysfunction [8–10], which is visualized in magnetic resonance imaging (MRI) as large muscle atrophy areas and/or fat replacement [11, 12]. From a serologic point of view, IMNM can be associated with specific autoantibodies targeted against the hydroxyl-methyl-glutaryl coenzyme A reductase (anti-HMGCR) or the cytoplasmic signal recognition particle (anti-SRP) [13–16].

No consensual treatment for IMNM exists yet, but because of its morbidity and relapsing pattern, it often requires combined glucocorticoids and immunosuppressive drugs. Currently, two studies have shown the possible benefit of human intravenous immunoglobulin (IVIg) [7, 17]. One of these studies evaluated IVIg as monotherapy to treat three patients with anti-HMGCR-associated IMNM [7]. The authors in that study observed muscle strength recovery

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and decreasing levels of serum creatine phosphokinase but did not evaluate life quality or muscle-imaging parameters. Another study consisted of 14 anti-SRP-associated IMNM patients treated with multiple immunosuppressive schemes but mostly with earlier IVIg and/or methylprednisolone pulse therapies [17]. At the end of the study, clinical stability was achieved in 11 out of 14 patients, most of them without glucocorticoids or already tapered to low doses. According to the authors in that study, this good clinical outcome may be the result of IVIg use associated with methylprednisolone pulse therapies at the time of disease diagnosis. However, the authors did not analyze functionality or muscle MRI aspects.

Therefore, the aims of this study were to evaluate the relevance of IVIg and/or methylprednisolone pulse therapies as possible treat-to-target treatments in IMNM patients and to analyze the progression of the muscle damage measured by late MRI.

Materials and methods

At inception, we conducted a single-center retrospective cohort in which we systematically reviewed patients with IMNM associated with anti-SRP or anti-HMGCR-positive autoantibodies between 2012 and 2018.

We admitted patients to our service to investigate subacute symmetrical, predominantly proximal skeletal weakness and significant elevation in the levels of serum creatine phosphokinase without apparent cause (e.g., neoplasms and infections). We submitted the patients to the following complementary tests: electroneuromyography, which reveals the predominance of proximal myopathy without neurogenic pattern; muscle biopsies (vastus lateralis), which disclose the presence of necrotic muscle fibers and absence or scarcity of inflammatory cell infiltrates; and tests for anti-SRP and anti-HMGCR-positive autoantibodies. All patients fulfilled the European League Against Rheumatism / American College of Rheumatology 2017 Classification Criteria [18].

We collected serum samples from patients at disease diagnosis and stored the samples at − 80 °C as part of the internal protocol of our service.

We determined anti-SRP antibodies using a commercial solid-phase immunoblotting kit, a qualitative immunoassay line for detection of 11 human immunoglobulin G (IgG) autoantibodies against specific or associated myositis antigens in serum or plasma. To increase the specificity of the method, we followed the manufacturer's protocol. We defined reaction positivity according to a previously published study [19].

We assayed anti-HMGCR antibody through enzyme-linked immunosorbent assay using recombinant HMGCR protein and anti-HMGCR polyclonal antibody (MyBioSource, CA, United States). For the purposes of this study, we considered patients positive when they had anti-HMGCR values of more than three standard deviations of the mean of 8 healthy individuals.

This study was approved by the local ethics committee - Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, SP (CAAE: 68523717.1.0000.0068; Date of approval: Jun 20th, 2017). Informed consent was obtained from all individual participants included in the study.

We obtained the demographic, clinical, and therapeutic data by means of a review of electronic medical records containing previously standardized and parameterized data. We analyzed the following parameters: age at disease diagnosis, sex, time between diagnosis and symptom onset, disease duration, exposure to statins, constitutional symptoms, autoantibodies (as described above), and treatment data (previous and current drugs and dosages). All patients included had also been submitted to (a) muscle strength evaluation through manual muscle testing with 8 muscle groups (MMT-8) [20]; (b) disability evaluation, as measured by the Health Assessment Questionnaire (HAQ) [21, 22]; (c) disease activity evaluations through physicians' and patients' visual analog scales (VAS) [23, 24]; and (d) blood samples for the testing of the serum levels of creatine phosphokinase. All these parameters had been obtained as soon as the patients were diagnosed (e.g., before treatment) and re-collected by the time of the protocol (e.g., after treatment) so that the IMACS improvement score [25] could be established. In this score, improvement is calculated as a formula that compares absolute percent changes in each domain. The percentages are then summed and the result is classified according to a standardized table as no improvement, minor improvement, moderate or major improvement [25].

As a second measure of activity, we also included the MYOACT score [23] before and after treatment. Finally, a mid-third thigh MRI was performed by the time of the protocol for muscle anatomical purposes. This acquisition was performed late in the course of disease, between 2017 and 2018, to assess eventual sequelae. We obtained the former through the fast spin-echo technique in a Philips 1.5 T machine-generating T1-weighted and T2-weighted sequences with fat suppression, with multiple plane acquisitions. Two independent researchers (JMS and SKS) evaluated the middle third of the right thigh in axial view, and they semi-quantitatively classified the degree of muscle edema, fat replacing, or muscle atrophy as 0 for normal, 1 for mild (< 25% of total sectional area), 2 for moderate (25%-50%), or 3 for severe (> 50%). This semi-quantitative measurement was adapted from a previous study [11], adjusted, though, to facilitate quantification. In the former study, authors divided parameters in 4 degrees (0 = normal, no fatty infiltration, edema or atrophy; 1 = mild, up to 1/3

of involvement; 2 = moderate, up to 2/3 of involvement; and 3 = severe, more than 2/3 of muscle involvement). We have changed grading to quarters, (0 = normal, no involvement; 1 = mild, less than 1/4 of involvement; 2 = moderate, less than 1/2 of involvement; 3 = severe, more than 1/2 of involvement), to facilitate counting as we have interpreted images in axial view, thus dividing it in four segments.

Muscle edema was defined as increased signal intensity within muscle tissues on fluid-sensitive sequences (e.g., STIR or fat suppressed T2 weighted images). The fat replacing and muscle atrophy was assessed by T1 weighted images without fat saturation.

As an internal protocol of our Service, the disease induction was based on monthly pulse therapies of methylprednisolone (1 g for 3–5 consecutive days) and/or IVIg (2 g/kg pulse therapy shared on two consecutive days) at disease diagnosis. When possible, patients received both drugs. We repeated these schemas monthly as many times as necessary to obtain a clinical response, defined by a gain in muscle strength plus stabilization or a fall of creatine phosphokinase levels. After induction, we switched the patients to oral immunosuppressive drugs: azathioprine (2–3 mg/kg/day), methotrexate (20–25 mg/week), mycophenolate mofetil (3 g/day), cyclosporine (2.5–3.0 mg/kg/day) or rituximab (1 g, parenteral, at time 0, after 15 days, and repeated after 6 months). When we used it, we repeated the rituximab cycle every 6 months for two consecutive years, in accordance with the internal protocol of the service. Combined with the immunosuppressive drugs, patients also received oral prednisone (1 mg/kg/day) that was quickly tapered (usually in 3 months at most).

All data regarding disease activity described previously were assessed before treatment and by the time of the protocol, approximately at the same moment of late MRI acquisition.

We considered the patient as having a complete clinical response when the patient had 6-month continuous period of no evidence of disease activity while still receiving myositis therapy. We defined clinical remission as the 6-month continuous period of no evidence of disease activity while the patient was not receiving any myositis therapy. A relapse was defined as any clinical and/or laboratory disease activity.

Statistical analysis

We used the Shapiro–Wilk test to evaluate the distribution of continuous variables, which we expressed as mean ± standard deviation (SD) or median (interquartile 25th− 75th). The categorical variables were expressed as percentages. We analyzed differences regarding parametric data through Student's t-test, and we analyzed non-parametric data through the Wilcoxon signed-rank test. All statistical calculations were performed with the software MINITAB version 18 (Pennsylvania, USA).

Results

Thirteen patients with IMNM were assessed. The general patient features are shown in Table 1. Mean age of the patients at the time of diagnosis was 53.5 years old, whereas median time between diagnosis and symptom onset was 4.0 months. Four patients had anti-HMGCR and 9 had anti-SRP-positive autoantibodies. Three patients with anti-HMGCR and 4 out of 9 patients with anti-SRP autoantibodies had been exposed to statins immediately before disease-symptom onset.

At presentation, constitutional symptoms were present in 10 out of 13 patients, and dysphagia was present in 7 cases.

The median MMT-8 and HAQ values were 68 and 1.80, respectively, indicating moderate–severe disability. The patients' and physicians' VAS medians were 7.0 and 6.0, respectively, whereas the MYOACT median score was 2.6 (Table 3).

All patients were initially treated with either methylprednisolone and/or IVIg pulse therapies, with the aim of inducing disease remission (Table 2). The mean time between symptom onset and prescription of the induction therapy was 4.8 months (Table 4). All patients received IVIg, except from patient #3, since medication was not available at service by the time. Patients with diabetes mellitus (#6, #8 and 10) were spared from intravenous glucocorticoids.

We summarize the comparative data between disease onset and follow-up in Table 3. The time described as "pre" refers to the moment of diagnosis; the moment described as "post" describes data from the visit to our outpatient clinic immediately before the MRI acquisition. The median time of follow-up was 39 months. The patients had a marked decrease in their levels of serum creatine phosphokinase compared to their levels at the beginning of the disease, and most of them completely regained their muscle strength. All three median scores of activity (patients' VAS, physicians' VAS, and MYOACT) reached 0, and the median HAQ was also nearly 0. When calculating the IMACS scores, we noticed that these patients presented major clinical responses. Although only 2 patients were still using oral glucocorticoid, the combination of multiple immunosuppressive drugs was common during the course of treatment, and only 3 patients are currently drug free.

As described in Table 4, the median time between the beginning of the induction phase and the achievement of clinical response was 2.5 months. Patients #5, #11 and #12 were considered non-responders according to our criteria. The median time until total glucocorticoid withdrawal was 17 months and the 3 patients that managed to cease

Table 1 General features of 13 patients with immune-mediated necrotizing myopathy

ID	Gender	Age at diagnosis (years)	Ethnicity	Anti-SRP	Anti-HMGCR	Statin exposure	Symptom duration until diagnosis (months)	Constitutional symptoms	Dysphagia
1	F	66	AD	−	+	+	4	+	+
2	M	68	C	−	+	+	7	+	+
3	F	55	AD	−	+	+	4	−	−
4	F	63	C	−	+	−	8	+	+
5	M	42	AD	+	−	+	4	+	+
6	M	62	C	+	−	+	4	+	−
7	F	56	C	+	−	−	3	+	−
8	M	52	A	+	−	+	6	−	+
9	F	49	C	+	−	−	1	−	+
10	F	77	A	+	−	+	3	+	+
11	F	35	C	+	−	−	6	+	−
12	F	26	AD	+	−	−	1	+	−
13	F	45	C	+	−	−	12	+	−
		53.5 ± 14.2					4.0 (3.0–6.5)		

The data are expressed as median ± standard deviation or median (interquartile 25th − 75th)

A Asiatic, *AD* Afro-descendant, *C* Caucasian, *F* female, *HMGCR* hydroxyl-methyl-glutaryl coenzyme A reductase, *M* male, *SRP* signal recognition particle

Table 2 Treatment description of 13 patients with immune-mediated necrotizing myopathy

ID	Treat-to-target therapy (Number of cycles)			Maintenance therapy			
	MP	IVIg	MP + IVIg	Follow-up	Current	Current GC (mg/day)	Follow-up (months)
1	0	0	2	MTX	MTX	0	27
2	1	0	1	MTX	0	0	49
3	1	0	0	MTX	0	0	49
4	0	0	2	AZA,MMF,MTX	0	0	37
5	2	2	2	AZA,MTX	MTX,RTX	10	17
6	0	3	0	AZA,MTX	AZA,MTX	0	14
7	0	1	0	AZA,MMF,MTX	MMF	0	45
8	0	3	0	AZA,MTX,RTX	AZA	0	65
9	0	0	2	AZA,MTX	AZA	0	33
10	0	2	0	AZA	AZA	0	17
11	2	1	3	AZA,RTX	AZA	0	59
12	1	8	3	AZA,CYP,MTX,RTX	MTX,RTX	10	44
13	0	0	2	AZA,CYP,MMF,MTX	CYP	0	50
						0 (0–0)	39.0 ± 16.4

The data are expressed as mean ± standard deviation or median (interquartile 25th–75th)

AZA azathioprine, *CYP* cyclosporine, *GC* glucocorticoid, *IVIg* intravenous human immunoglobulin, *MMF* mycophenolate mofetil, *MP* methylprednisolone, *MTX* methotrexate, *RTX* rituximab

immunosuppressive drugs accomplished it with a median time of 36 months. During the follow-up, nine patients reached complete clinical response, whereas 2 patients achieved complete remission.

Regarding adverse events, subject #1 had urinary tract infection two months after the induction protocol, with prompt recovery and no need to adjust medications. Patient #7 had pneumonia 3 months after the induction phase, needing hospitalization and immunosuppressive drug withdrawal until clinical recovery. Finally, patient #8 had a mild anaphylaxis during the last IVIg infusion.

Table 3 Clinical and laboratory outcomes of 13 patients with immune-mediated necrotizing myopathy

ID	CPK		MMT-8		Patients' VAS scores		Physicians' VAS scores		HAQ		MYOACT		Complete clinical response	Complete remission
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
1	3000	228	50	80	8	1	8	0	2.0	0.0	2.6	0	+	−
2	4300	149	55	80	8	0	8	0	2.0	0.0	2.4	0	+	+
3	126,000	165	74	80	7	2	6	0	1.5	0.7	2.6	0	+	−
4	8342	39	60	80	6	0	5	0	1.7	0.0	2.6	0	+	+
5	18,350	4993	75	78	7	2.2	7	3	1.3	0.8	2.8	0	−	−
6	16,594	3970	70	80	5	1	4	2	1.8	0.1	2.2	0	−	−
7	7000	180	78	80	4	0	4	0	1.2	0.1	2.1	0	+	−
8	7000	108	71	80	9	0	7	0	1.5	0.0	2.7	0	+	−
9	3707	51	58	80	9	0	8	1	2.5	0.2	2.7	0	+	−
10	11,350	1337	68	80	7	3	5	0	1.2	0.5	2.1	0	+	−
11	26,000	2412	54	78	9	0	9	0	2.2	0.0	2.8	0	−	−
12	14,676	2954	68	51	8	6	6	5	1.8	1.2	2.4	1.8	−	−
13	13,654	468	69	80	7	0	6	0	1.9	0.0	2.4	0	+	−
	11,350 (7000–16,594)	228 (149–2412)	68 (56–72)	80 (79–80)	7.0 (6.5–8.5)	0.0 (0.0–2.0)	6.0 (5.0–8.0)	0.0 (0.0–1.5)	1.8 (1.4–2.0)	0.1 (0.1–0.6)	2.6 (2.3–2.7)	0.0 (0.0–0.0)		
	$P=0.001$		$P=0.009$		$P=0.023$		$P=0.001$		$P=0.001$		$P=0.001$			

The data are expressed as a median (interquartile 25th–75th)

CPK creatine phosphokinase, *MMT* manual muscle testing, *VAS* visual analogue scale, *HAQ* Health Assessment Questionnaire, *MYOACT* Myositis Disease Activity Assessment Visual Analogue Scales

Table 4 Correlation between clinical response and late magnetic resonance imaging assessment

ID	Treatment response				Late muscle assessment			
	Time between symptoms onset and induction therapy (months)	Time between induction therapy and clinical response (months)	Disease duration until glucocorticoid withdrawal (months)	Disease duration until immunosuppressive drug withdrawal (months)	Disease length until magnetic resonance imaging (months)	Muscle atrophy	Fat replacement	Muscle edema
1	4	3	5	n/a[b]	–	–	–	–
2	7	2	7	36	44	0	0	0
3	4	1	7	40	41	1	1	0
4	8	2	6	19	40	0	1	0
5	4	n/a[a]	n/a[b]	n/a[b]	14	0	0	1
6	4	5	0[c]	n/a[b]	16	0	1	1
7	3	3	18	n/a[b]	48	0	0	0
8	6	3	50	n/a[b]	66	0	1	0
9	1	2	17	n/a[b]	23	0	1	0
10	3	3	0[c]	n/a[b]	11	0	0	0
11	6	n/a[a]	52	n/a[b]	56	0	2	1
12	1	n/a[a]	n/a[b]	n/a[b]	33	0	1	1
13	12	2	28	n/a[b]	63	0	2	0
	4.8 ± 3.0	2.5 (2.0–3.0)	17 (7–28)	36.0 (27.5–38.0)	37.9 ± 18.8			

The data are expressed as mean ± standard deviation or median (interquartile 25th–75th)

The degrees of muscle atrophy, fat replacement or muscle edema in the middle third of the thigh muscle sectional area were classified semi-quantitatively as 0 for normal, 1 for mild (< 25% of the total area), 2 for moderate (25% − 50%), or 3 for severe (> 50%)

[a]Not available: no clinical response achieved

[b]Not available: drug is still being used

[c]Spared from glucocorticoids

MRI was performed late in the course of disease, with a median disease length of 37.9 months. Since patients were enrolled at different times, the duration of disease ranged from 14 to 66 months. As for the MRI analysis during the follow-up, eight patients developed fat replacement; however, it was considered mild in 6 cases and moderate in 2 (Fig. 1). Three patients (#5, #11 and #12) maintained elevated levels of serum creatine phosphokinase and sustained muscle weakness. Moreover, these patients had muscle edema signals in the MRI assessment. Finally, one patient developed mild muscle atrophy, but no important fat replacement or atrophy was found.

Patient #1 died of subtle cardiac arrest of undetermined origin after the clinical evaluation but before the MRI acquisition. This patient was classified as being in complete clinical response with no signs of disease activity for a long time. Therefore, we do not believe the fatal event was related to IMNM.

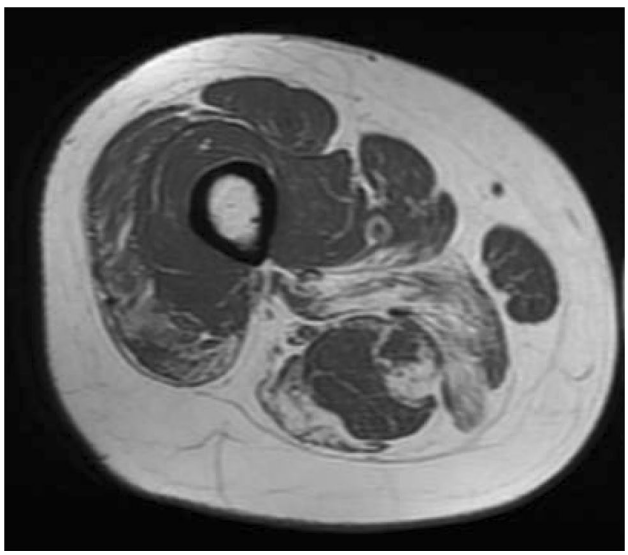

Fig. 1 Example of T1-weighted fast spin-echo sequence showing fat replacement (white areas inside the muscle) notably in the posterior and medial compartments. This is our patient with the greatest degree of fat replacement

Discussion

The highlights of the findings of the present study are the following: (a) The early and aggressive approach with serial pulses of methylprednisolone and/or IVIg until induction of

remission was capable of promoting major clinical response according to the IMACS improvement score; (b) this strategy might reduce the risk of residual weakness and disability during the course of the disease; and (c) these clinical findings could be translated into muscle imaging, with less muscle atrophy and fat replacement in the long term.

Previous studies have documented prognostic features [8–10, 17] and MRI findings in IMNM [11, 12], but to our knowledge, this is the first study to describe clinical and radiological outcomes following a standardized treatment approach. Furthermore, our sample presented results that are significantly different from what has been reported so far regarding disease control and late imaging findings, suggesting the role of an early induction of remission strategy.

This sample comprised only patients with serological markers of IMNM, ensuring diagnosis accuracy. Patients with both autoantibodies could be enrolled, and we did not observe a difference regarding treatment response. At diagnosis, our sample presented the same findings as described in the literature (marked muscle weakness, elevated muscle enzymes, and a high degree of dysfunction) but responded differently from how we expected.

For example, a study [9] reported that 80% of the sample had clinical muscle atrophy during disease follow-up, but only one of our patients presented muscle atrophy (reported by MRI) after a 41-month period. Likewise, another previous study [10] showed a 16% rate of complete strength recovery after immunosuppression, but 10 out of 13 patients of our sample could demonstrate normal strength after treatment.

In the long term, the IMACS core-set measures of the sample indicated a major clinical response, with positive gains in all domains and maximal improvement in the MMT, HAQ, and VAS parameters. Moreover, the median levels of serum creatine phosphokinase also returned to normal.

Nevertheless, we could sense the fierceness of the disease in the maintenance drugs since, even after a median time of 39.0 months of follow-up, only three patients could remain drug free and 2 remained on glucocorticoids. These findings corroborate with the literature's elevated relapse rates [9].

Two previous studies reported the MRI findings of patients with IMNM [11, 12]. One of them analyzed thigh MRI of 101 patients with IMNM, with a mean length of disease of 4.3 years, depicting a mean fat-replacement extent of 38% [11]. Another study performed thigh MRI in 12 patients before treatment, with a mean disease length of 22.8 months, and concluded that 100% presented some degree of fat replacement, with a degree of 33% considered severe [12]. The two previous studies mentioned have not focused on therapy. Therefore, as study limitations, these studies had not given detailed information regarding treatment schemes. In contrast, our study is the first one to attempt a correlation between treatment modality and radiologic progression in IMNM. Of note, MRI was performed after a standardized therapy with a mean time of disease of 37.9 months and the images depicted relatively spared muscles. In this context, only 2 patients presented atrophy or fat replacement of more than 25% of the sectional area (Fig. 1). Therefore, the present study suggests that an early treat-to-target approach could reduce the odds of long-term muscle disability. To clarify these perceptions, we have provided a brief description of each case in Appendix 1.

The pathogenesis of IMNM is still obscure. The most immediate and striking feature to elucidate the disease's mechanism is the scarcity of lymphocytic inflammatory infiltrate and the presence of macrophages. Pestronk [26] and Preuße *et al*. [27] have described the expression of C5b9 not only perivascular, but also inside the muscle cells. Preuße *et al*. [27] also have found that CXCL13, a B lymphocyte-related chemokine, is also overexpressed in muscle fibers. The combination of these data suggests that IMNM is an antibody-dependent entity, with complement-mediated cell toxicity related to its pathogenesis. These features are fairly singular when compared to the other SAM.

In addition, at least three mechanisms possibly related to the IMNM's pathogenesis could be modulated by IVIg: (a) reduction of the cleavage of complement fractions [28]; (b) blockage of the Fc fraction of the autoantibodies attached to the vascular wall, thus preventing contact with effector cells [29]; and (*c*) inhibition of activated T helper cells [30, 31]. These mechanisms could at least partially explain the effect of IVIg on IMNM.

The current study has some limitations. The sample is small and from a single center, which compromises the external validity. Second, we did not have a control group, which would be necessary for calculating the absolute-effect measures for a risk of outcome. Moreover, we cannot establish a cause-and-effect relationship between the treat-to-target intervention and the outcomes in the current study design; therefore, prospective studies with standardized interventions are necessary to verify the most effective treatments for patients with IMNM. Finally, the genetic background was not assessed. Therefore, we could not make correlations between HLA associations and the severity of disease or even treatment outcome. These correlations may also be subject to future analyzes.

In summary, early treatment with monthly pulses of methylprednisolone and/or IVIg with the aim of clinical response is a potential treatment strategy for IMNM. Larger, controlled studies might be able to corroborate our findings.

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Compliance with ethical standards

Conflict of interest Jean Marcos de Souza, Leonardo Santos Hoff and Samuel Katsuyuki Shinjo declare that they have 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.

Informed consent Informed consent was obtained from all individual participants included in the study.

Appendix 1

Brief report of the analyzed subjects

Patient 1

Afro-descendant female with 66 years old complaining of muscle weakness, weight loss and fatigue starting days after statin use. The serum creatine phosphokinase (CPK) levels were around 3000 U/L and the manual muscle test with eight muscle groups (MMT-8) was 50. She was promptly treated with 3 days of methylprednisolone (MP), 1 g each day, intravenous immunoglobulin (IVIg), 2 g/kg, divided in 2 days and oral prednisone, 0.5 mg/kg/day. After 1 month, she returned feeling subjective improvement, but the MMT-8 was nearly unchanged and she maintained CPK levels at 1093 U/L. New MP and IVIg pulse therapy was prescribed, prednisone was tapered to 0.25 mg/kg/day and methotrexate 15 mg/week was begun. A few days later, the patient evolved with pneumonia and urinary tract infection, warranting hospital admission, but treated without major complications. One month later, she returned to the outpatient clinic with normal muscle strength and CPK levels within normal ranges. No disease relapsing was ever noticed and prednisone was completely withdrawn 5 months after the beginning of the treatment. Unfortunately, this patient died before acquisition of the MRI. The cause of death was sudden cardiac arrest, unrelated to the immune-mediated necrotizing myopathy.

Patient 2

Caucasian man with 66 years old complaining of subtle muscle weakness. He was using statins for 2 years. The initial CPK was 4300 U/L and the MMT-8 was 55. He was promptly treated with 3 days of MP, 1 g each day, IVIg, 2 g/kg, divided in 2 days and oral prednisone, 0.25 mg/kg/day. Two months after the initial treatment he returned with normal muscle strength and a CPK level of 181 U/L. He was then started on methotrexate, that was adjusted until 25 mg/week and started the tapering of the prednisone that was concluded 7 months later. No flares were reported and he could withdraw the immunosuppressive drug within 36 months. The MRI was obtained 44 months after disease onset depicting no relevant alterations.

Patient 3

Female afro-descendant of 55 years old that presented myalgia right after the introduction of simvastatin. Five months later, despite having ceased statin use she started feeling a mild muscle weakness and exams showed an elevated serum CPK (around 100.000 U/L). The MMT-8 assessment summed 74 points. MP was prescribed for 3 days, 1 g per day, followed by oral prednisone, 0.5 mg/kg/day. IVIg was unavailable at the time of induction. One month later, the patient was reassessed presenting normal muscle strength and a CPK of 224 U/L. Prednisone tapering started and methotrexate was prescribed. The dose of the immunosuppressive drug was adjusted until 25 mg/week and prednisone was totally removed 7 months after the induction. Within 40 months, methotrexate was stopped. No disease relapsing occurred. MRI was obtained 41 months after disease onset with only mild fat replacing and muscle atrophy.

Patient 4

A 63 years old female was using fibrates for a few months. The drug was stopped when she complained of muscle pain. Eight months later, the pain persisted and she evolved with muscle weakness (MMT-8 of 60) and a CPK of 8342 U/L. She was treated with 3 days of MP, 1 g each day, IVIg, 2 g/kg, divided in two days and oral prednisone, 1 mg/kg/day. One month after, she was still felling weak, the MMT-8 summed 69 and CPK levels were around 1500 U/L. The induction protocol was, thus, repeated and prednisone was tapered to 0.5 mg/kg/day. After another month, the patient returned with improving muscle strength (MMT-8 of 78) and CPK levels of 603 U/L. Azathioprine was started and prednisone tapering progressed. During the course of treatment, the patient had to exchange azathioprine to mycophenolate mofetil due to elevated liver enzymes. Prednisone was completely withdrawn within 6 months. One year after the exchange to mycophenolate, the patient complained of blurred vision that she attributed to the drug. She was then switched to methotrexate that she used until a total time of 19 months of immunosuppression. The MRI was obtained with 40 months of disease length, many months after drug withdrawal, showing only mild fat replacement.

Patient 5

A healthy 42 years old male of Afro-descendant family started experiencing subtle muscle weakness some weeks after statin introduction. Four months later he arrived to the service with nearly normal muscle strength (MMT-8 of 75) and CPK levels of 18,350 U/L. He was promptly treated with 3 days of MP, 1 g each day, IVIg, 2 g/kg, divided in 2 days, oral prednisone, 1 mg/kg/day, and methotrexate, 15 mg/week. One month later, he maintained the same MMT-8 and CPK of 3159 U/L. The protocol was repeated, methotrexate was adjusted to maximal dosage (25 mg/week) and prednisone was tapered to 0.25 mg/kg/day. Another month passed and he returned with similar findings; another round of induction was prescribed and azathioprine (1.5 mg/kg/day) was associated. He was assessed again with a modest gain in MMT-8 (78) and CPK levels of 1265 U/L. By this moment, prednisone was tapered to 10 mg/day and the patient was assigned to receive rituximab due to resistant disease. While the patient waited to rituximab, he received in different occasions 6 IVIg or MP pulse therapies. This patient never reached normal levels of CPK or substantial recovery in muscle strength. The MRI was obtained 14 months after symptoms onset and revealed mild muscle edema, suggesting disease activity, but no atrophy or fat replacement.

Patient 6

A Caucasian male of 62 years was just started on statins presented to our outpatient clinic with 4 months of muscle weakness and pain. His CPK levels were around 16,000 U/L and his MMT-8 summed 70. This patient was diabetic and considered of elevated cardiovascular risk by his cardiologist, so he was assigned to receive only IVIg, 2 g/kg, as induction. One month later, the patient returned with CPK levels of 4000 U/L and maintained muscle weakness. Another round of induction was prescribed, and the patient was started on azathioprine, 2.0 mg/kg/day. After 2 months, CPK levels were 2800 U/L and the pain subsided, but the patient still maintained weakness (MMT-8 of 76). Our service decided to associate methotrexate 10 mg/week to his treatment and to perform another round of induction with IVIg. After one month, the patient was reassessed with normal muscle strength, but CPK levels were still elevated (2500 U/L). Since he was asymptomatic, it was assumed that the patient reached clinical response and pulse therapies were ceased, in spite of the elevated CPK. The MRI was obtained 16 months after the disease onset and showed mild fat replacement and mild edema.

Patient 7

A female patient of 56 years old and Caucasian ethnicity presented with 3 months of mild muscle weakness (MMT-8 of 78) and elevated levels of CPK (around 7000 U/L). Before referral to our service, she was treated with prednisone 1 mg/kg/day for 1 month. Since the patient was diabetic, she was spared from intravenous glucocorticoid, receiving only IVIg, 2 g/kg, methotrexate, 15 mg/week, and maintaining the prednisone. Two months after induction, the patient was admitted with a respiratory distress syndrome attributed to pneumonia. After an initial course of antibiotics and withdrawal of methotrexate, as a possible source of lung injury, she recovered and the drug was switched to mycophenolate. After 1 month, the patient returned to the outpatient clinic with preserved muscle strength and normal CPK levels. By this moment, tapering of prednisone was started and completed 18 months later. No flares were reported. MRI was performed 48 months after disease onset with normal findings.

Patient 8

An Asiatic male patient of 52 years old experienced muscle weakness (MMT-8 of 71) and CPK elevation (until 7000 U/L) after introduction of rosuvastatin by his cardiologist. He was treated with IVIg (2 g/kg) and prednisone 20 mg/day. No intravenous glucocorticoid was used due to diabetes mellitus and presumed elevated cardiovascular risk. After 1 month, CPK levels were still high and it was decided to repeat the IVIg, to maintain the oral glucocorticoid and to add azathioprine (2.0 mg/kg/day). After another month, CPK levels returned to normal (80 U/L), but the patient still complained of muscle weakness and pain. By this moment, it was decided to associate methotrexate (10 mg/week) to the treatment and to start prednisone withdrawal. The patient returned the next month with normal MMT-8 and CPK and further reduction of prednisone was attempted, from 10 mg to 5 mg per day. Two months later, the patient returned with stable muscle activity, but presented dyspnea and pulmonary infiltrate, attributed presumably to the myopathy. During the next 5 months, although no muscle inflammation was perceived, the patient was first started on mycophenolate and afterward assigned to 4 intravenous pulses of cyclophosphamide to treat the respiratory symptoms, without success. In the end of this protocol of cyclophosphamide induction, muscle activity relapsed, with new onset of muscle enzymes elevation (up to 1758 U/L). Another round of IVIg was prescribed and prednisone was maintained at 5 mg/day. During the infusion of this cycle of IVIg, the patient presented a mild anaphylactic reaction, controlled with hydrocortisone, anti-histaminic drugs and adjustment of the infusion time. By this point, the patient was candidate to rituximab, especially due to lung disease. After starting rituximab, the lung

parameters improved and the patient was asymptomatic. Prednisone was fully removed 50 months after the beginning of the treatment. The MRI, obtained 66 months after disease onset, showed only mild fat replacement.

Patient 9

A 49 years old Caucasian female presented with 1 month of fever and weakness. The initial assessment showed a CPK of 3707 U/L and a MMT-8 of 60. She was treated with 3 days of MP, 1 g each day, IVIg, 2 g/kg, divided in 2 days and oral prednisone, 0.5 mg/kg/day. After 1 month, the patient was still feeling weak, with a MMT-8 with minor improvement and a CPK of 1186 U/L. It was decided to repeat the induction and to start prednisone tapering. The patient returned 1 month later with muscle strength preserved and a CPK of 52 U/L. Thus, she was assigned to methotrexate, 15 mg/week, and prednisone reduction was progressed. After adjustment of methotrexate to maximal dosage (25 mg/week), the patient presented mild hepatic toxicity and the drug was switched to azathioprine (2.0 mg/kg/day). No more muscle activity was ever reported and the patient was free from prednisone after 17 months of treatment. MRI was acquired 23 months after disease onset and depicted only mild fat replacement.

Patient 10

A female patient of Asiatic ascendance with 77 years was using statin for a few months when started presenting fatigue, weakness and weight loss. Physical examination showed a MMT-8 of 68 and laboratory evaluation showed a CPK of 11,350. Due to previous diabetes mellitus and advanced age, she was assigned to receive only IVIg, 2 g/kg. After 2 months, the patient presented weight gain, but maintained elevated levels of CPK (3800 U/L) and unaltered muscle strength. Thus, it was decided to repeat the induction protocol and to associate azathioprine, 2.0 mg/kg/day. After 1 month, the patient returned asymptomatic and with lower CPK levels (around 1900 U/L). Although the patient maintained persistently elevated muscle enzymes, strength was always preserved and the induction protocol was not repeated thus far. The MRI was obtained with 11 months of disease length and no alterations were observed.

Patient 11

A Caucasian female of 35 years old that was otherwise healthy presented with 6 months of muscle weakness and CPK levels up to 26,000 U/L. She was initially treated outside our service, with methylprednisolone pulses (3 g divided in 3 days) and prednisone 1 mg/kg/day. Maintaining muscle weakness, she received 1 cycle of rituximab 9 months after disease onset. The patient arrived to our outpatient clinic within 14 months after the disease beginning with a MMT-8 of 54 and CPK levels around 3000 U/L. She was treated with 3 days of MP, 1 g each day, IVIg, 2 g/kg, divided in 2 days, azathioprine (2 mg/kg) and prednisone was tapered to 0.25 mg/kg/day. For the next 4 months, the patient would receive 2 pulses of MP and IVIg combined, 1 pulse of isolated MP and 1 pulse of isolated IVIg, until finally regain muscle strength and return muscle enzymes values closer to normality (around 1000 U/L). Maintenance therapy was achieved with azathioprine (2.0 mg/kg/day) and rituximab every 6 months. Prednisone cessation was concluded 52 months after initiation and MRI was acquired after 56 months of disease length. The former showed the greatest degree of fat replacement of the sample, considered moderate.

Patient 12

An afro-descendant young female of 26 years that was otherwise healthy presented with rapid onset muscle weakness that lasted 1 month. Her MMT-8 summed 68 and her CPK levels were 14,000 U/L. She was promptly treated with 3 days of MP, 1 g each day, IVIg, 2 g/kg, divided in two days, prednisone, 1.0 mg/kg/day, and azathioprine, 2.0 mg/kg/day. Since the patient had a poor educational and socioeconomic condition and frequently missed visits, skipped doses and manipulated medications on her own, it was decided to maintain methotrexate as maintenance, since the weekly administration could eventually improve adherence. Four months later, after many dosing adjustments and reorientation, the patient sustained muscle weakness and CPK levels were around 2000 U/L with methotrexate 20 mg/week and 1.0 mg/kg/day of prednisone. It was decided to repeat the IVIg infusion, at the same dose. One month later, almost no result was achieved and another round of combined MP and IVIg was prescribed. After another month, the patient returned with improved muscle strength (MMT-8 of 74) and CPK levels near normality (approximately 800 U/L). Prednisone tapering was finally started, and methotrexate was adjusted to full-dose. Two months later, the patient returned with subjective sensation of weakness, but without CPK elevations or alterations on physical examination. It was decided to associate cyclosporine, 2 mg/kg/day. In the next visit, the patient reported that skipped many doses of the immunosuppressive drugs and the weakness had returned. Indeed, her MMT-8 dropped to below 60 points and CPK levels once again raised to beyond 3000 U/L. Another round of MP and IVIg was prescribed and the patient was assigned to rituximab in association with methotrexate. In the next months, before approval and adequate prophylaxis for the biologic, the patient deteriorated muscle activity, needing monthly pulses of IVIg to sustain muscle strength. Even

after 2 cycles of rituximab, the patient sustained elevated levels of CPK and muscle strength stabilized, but no gains were achieved. Prednisone was never completely tapered and the MRI, obtained within 33 months of the disease onset, showed active edema and fat replacement, surprisingly quantified as mild. It is important to highlight, though, that lack of adherence to the treatment schemes was remarkably high in this case, contributing to the poor prognosis.

Patient 13

The patient #13 is a previously healthy Caucasian woman of 45 years old that presented with progressive fatigue over a year that, in the last 5 months, evolved to proximal muscle weakness and dysphagia. She arrived to our outpatient clinic with a MMT-8 of 69 and CPK levels of 13,600 U/L. She was promptly treated with 3 days of MP, 1 g each day, IVIg, 2 g/kg, divided in two days and prednisone, 1 mg/kg/day. After 1 month, she returned with some improvement in dysphagia, but maintaining muscle weakness and a serum CPK of 1161 U/L. Another round of MP and IVIg was prescribed and prednisone tapering commenced. Another month passed and she returned with an important improvement in muscle strength (MMT-8 of 78) and normal CPK levels (272 U/L). At this point, methotrexate was started at 15 mg/week and prednisone was once again tapered to 0.25 mg/kg/day. Four months later, the patient returned with a mild increase in CPK levels (up to 500 U/L), but asymptomatic. It was decided to associate azathioprine (2.0 mg/kg/day) to the previous schema. Further prednisone tapering was also attempted. The treatment was successful, and the oral glucocorticoid was fully removed 28 months after the beginning of the treatment, without new flares. By the 36th month of treatment, the patient presented a mild elevation of liver enzymes and lymphopenia; thus, the maintenance schema was switched to mycophenolate, that the patient did not tolerate due to side effects, and finally to cyclosporine (3 mg/kg/day), the final drug before MRI acquisition. The former was obtained within 63 months of the disease onset and showed moderate fat replacement, without atrophy or edema.

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