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Favorable rituximab response in patients with refractory idiopathic inflammatory myopathies

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Abstract

Background: Interpretation of rituximab efficacy for refractory idiopathic inflammatory myopathies (IIM) is hampered by the absence of a uniform definition of refractory myositis and clinical response. Therefore, rigorous criteria of refractoriness, together with a homogenous definition of clinical improvement, were used to evaluate rituximab one-year response.

Methods: A retrospective cohort study including 43 IIM (15 antisynthetase syndrome, 16 dermatomyositis, 12 polymyositis) was conducted. All patients had refractory disease (inadequate response to at least two immunosuppressives/immunomodulatories and no less than three months sequentially or concomitantly glucocorticoid tapering) criteria. Clinical/laboratory improvement at one-year was based on modified International Myositis Assessment & Clinical Studies Group (IMACS) core set measures. The patients received two infusions of rituximab (1 g each) at baseline, followed by repeated dose after 6 months. Baseline immunosuppressive therapy was maintained and glucocorticoid dose was tapered according to clinical/laboratory parameters.

Results: Five patients had side effects at the first rituximab application and were excluded. Therefore, 38 out of 43 patients completed the one-year follow up. Almost 75% of the patients attained clinical and laboratory response after one-year. A significant reduction in median glucocorticoid dose (18.8 vs. 6.3 mg/day) was achieved and 42% patients were able to discontinue prednisone. In contrast, young individuals and patients with dysphagia had a tendency to be non-responders to rituximab. No severe infections were observed.

Conclusion: This study provides convincing evidence that rituximab is an effective and safe therapy for refractory IIM.

Keywords: Antibodies, Dermatomyositis, Myositis, Polymyositis, Rituximab

Background

Idiopathic inflammatory myopathies (IIM) constitute a heterogeneous group of chronic systemic autoimmune diseases with a high rate of morbidity and disability [1–3]. Based on their clinical, laboratory, histopathological and progression features, IIM can be classified as polymyositis (PM), dermatomyositis (DM), antisynthetase syndrome (ASS), inclusion body myositis, and others [2, 3].

A number of studies have suggested rituximab efficacy for refractory IIM, with response rates ranging from 61

to 83% [4–11]. This high and wide range of response rate is partly explained by the lack of a standardized definition for refractoriness and/or use of heterogeneous response parameters. In fact, refractory myositis has several definitions including intolerance to or an inadequate response to glucocorticoids and at least one other immunosuppressive agent, but few studies provide a clear description of whether the maximum tolerated therapeutic dose was achieved [5–11].

With regard to rituximab response parameters, most reports are limited to serum level of creatine phosphokinase and muscle strength improvements [6–11]. However, creatine phosphokinase may be not the best parameter, particularly if the evaluation includes different types of myositis,

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such as DM and ASS, in which other target organ involvement is more relevant than muscular involvement [2]. Of note, the disease activity core set measures validated by the International Myositis Assessment & Clinical Studies Group (IMACS) [12, 13] have not been previously used to evaluate refractory IIM response to therapy. These measures defined response as a > 20% improvement on three out of any 6 of the following core set measures: Health Assessment Questionnaire (HAQ); Manual Muscle Testing-8 (MMT-8); Physician Global Activity - Visual Analogue Scale (VAS); Patient Global Activity - VAS; serum muscle enzymes; Myositis Disease Activity Assessment Tool (MDAAT); with no more than two core set measures worsening by > 25%, which cannot include MMT.

Therefore, the aim of the present study was to evaluate the efficacy and predictors of clinical improvement of rituximab in a homogeneous population of refractory IIM cases, using a rigorous definition of refractory disease and modified IMACS core set measures to evaluate long-term response.

Methods
Study design
This retrospective single-center cohort study conducted from 2011 to 2016 included 43 consecutive adult patients with refractory IIM: 15 ASS (defined as myositis, arthritis, pulmonary disease, positive antisynthetase antibody, with or without mechanic's hands, fever and/or Raynaud's phenomenon) [14]; 16 DM and 12 PM according to the criteria of Bohan and Peter [15].

Patient data
Patients with clinically amyopathic DM, overlap myositis, neoplasia associated myositis, necrotizing myopathies, acute and/or chronic infections were excluded.

Data were included in an ongoing electronic database protocol. Demographic, clinical, laboratory and therapeutic data were obtained by electronic medical records, containing previously standardized and parameterized data. The following parameters were analyzed: current age, gender, ethnicity, time between diagnosis and symptom onset, disease duration, gastrointestinal (upper dysphagia), pulmonary (moderate dyspnea or computed tomography disclosing evidence of interstitial pneumopathy and/or "ground-glass" pneumopathy), joint (arthralgia and/or arthritis), previous and current drug treatment.

Refractory myositis was defined as an inadequate response to at least two immunosuppressant/immunomodulatory drugs (cyclophosphamide, azathioprine, methotrexate, cyclosporine, leflunomide, mycophenolate mofetil and/or intravenous human immunoglobulin, in their full-dose, for a minimum period of 3 months) given sequentially or concomitantly, hampering glucocorticoid tapering. Upper dysphagia and pulmonary involvement

were considered as disease severity parameters. Severe infection was defined as requiring hospitalization and/or intravenous antibiotic therapy.

Rituximab schedule
Rituximab treatment consisted of two infusions (1 g each, 2 weeks apart) and this same scheme was repeated 6 months after the first dose for patients showing no response or stable disease. The 6-month second dose was contraindicated for patients with recrudescent disease, hypogammaglobulinemia, side effects at first rituximab infusion and recurrent or severe infections. After starting on rituximab only one immunosuppressant was maintained at full-dose, and glucocorticoid tapering was started 2 months after initial rituximab treatment.

Disease activity
At the one-year evaluation, clinical and laboratory improvements were defined as > 20% improvement in at least three of the following modified IMACS core set measures: MMT-8 [12], physician' and patient' VAS [13], HAQ [16] and serum levels of muscle enzymes; with no more than two previous core set measures worsening by > 25%, which cannot include MMT.

Serum levels of creatine phosphokinase (normal range: 24–173 U/L) and aldolase (1.0–7.5 U/L) were evaluated. The following autoantibodies were investigated in this study: antinuclear factor (Hep2) and also anti-Jo-1, anti-OJ, anti-EJ, anti-PL-7, anti-PL-12, anti-Mi-2 and anti-SS-A/ Ro-52. For the myositis-specific and myositis-associated autoantibodies' assessment, a commercially available line blot test kit (Myositis Profile Euroline Blot test kit, Euroimmun, Lübeck, Germany) was used according to the manufacturer's protocol and to the previously published study [17]. Reaction positivity was also defined according to a previously study [17].

Statistical analysis
The Kolmogorov-Smirnov test was used to evaluate the distribution of each parameter. The demographic and clinical features are expressed as mean ± standard deviation (SD) for the continuous variables or frequency (%) for the categorical variables. The median (25th - 75th interquartile range) was calculated for the continuous variables that were not normally distributed. Comparisons between different clinical, laboratory and treatment parameters at baseline and 12 months after rituximab infusion were performed using Student's t-test or the Mann-Whitney U-test for continuous variables, whereas the Chi-squared test or Fisher's exact test was used to evaluate the categorical variables. The 95% confidence interval (95% CI) of percentage was calculated by a binomial distribution. Age at Rituximab application sensitivity and specificity for identifying therapy responder were

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calculated, and a receiver operating characteristic (ROC) curve was constructed. $P < 0.05$ was considered significant. All of the analyses were performed using the SPSS 15.0 statistics software (Chicago, USA).

Results

Five of the initial 43 patients were later excluded due to moderate allergic reactions to the first rituximab infusion ($N = 4$) or lost to follow-up ($N = 1$). There were no cases of patients with recrudescent disease, hypogamma-globulinemia or severe infections. Therefore, 38 patients remained in the study for 1 year: 15 (39.5%) patients with DM, 10 (26.3%) with PM, and 13 (34.2%) with ASS (Table 1).

Among the 38 patients assessed, mean current age was 42.6 ± 10.9 years, 84.2% were female gender and 68.4% had white ethnicity. Median disease time was 3.0 years, whereas median time between disease diagnosis and symptom onset was 4.5 months.

The antinuclear factor was present in 81.6% of patients with the following autoantibodies specificities: anti-Ro-52

Table 1 Demographic features, types of idiopathic inflammatory myopathies, autoantibody distribution and therapy of 38 patients immediately before rituximab application (Baseline)

Parameters	$N = 38$
Current age (years)	42.6 ± 10.9
Female gender	32 (84.2)
White ethnicity	26 (68.4)
Disease duration (years)	3.0 (2.0–6.5)
Duration time: diagnosis - symptom onset (months)	4.5 (3.9–9.0)
Idiopathic inflammatory myopathies	
Dermatomyositis	15 (39.5)
Polymyositis	10 (26.3)
Antisynthetase syndrome	13 (34.2)
Autoantibodies	
Antinuclear factor	31 (81.6)
Anti-Ro-52	16 (42.1)
Anti-Jo-1	13 (34.2)
Anti-Mi-2	4 (10.5)
Anti-OJ	0
Anti-EJ	0
Anti-PL-7	0
Anti-PL-12	0
Prednisone dose (mg/day)	18.8 (10.0–36.3)
Methylprednisolone + intravenous human immunoglobulin pulse therapy	23 (60.5)

Results expressed as mean ± standard deviation, median (25th - 75th interquartile range) or frequency (%)

(42.1%), anti Jo-1 (34.2%), anti-Mi-2 (10.5%), and no cases of anti-OJ, anti-EJ, anti-PL-7 or anti-PL-12 autoantibodies.

All 38 patients were in concomitant use of at least two immunosuppressive / immunomodulatory drugs, in their full-dose, for a minimum period of 3 months, hampering glucocorticoid tapering. Due to disease severity, 34 (89.5%) patients had also received methylprednisolone pulse therapy 1 g/day, for three consecutive days, and/or intravenous human immunoglobulin (1 g/kg/day, for 2 days, for two consecutive days). Moreover, immediately before the first dose of rituximab, 23 (60.5%) of 38 patients received again this same scheme (methylprednisolone and intravenous human immunoglobulin pulse therapies). At the time of rituximab application, median dose of prednisone was 18.8 mg/day.

Comparison of therapies at study entry vs. 12 months after rituximab application revealed a reduction in median glucocorticoid dose (18.8 vs. 6.3 mg/day; $P < 0.001$) (Table 2) and complete discontinuation of prednisone in 16 (42.1%) of the 38 patients.

Twenty-nine (72.5%) of the 38 patients achieved overall progress according to the modified core set of IMACS after 12 months of rituximab treatment.

With regard to adverse events in the 38 patients at one-year follow-up, none had severe infection, two (5.3%) patients had mild allergic reactions and one (2.6%) patient was diagnosed with non-Hodgkin's lymphoma (Table 2).

Further analysis of responders vs. non-responders at baseline identified younger age ($P = 0.008$) and higher frequency of dysphagia ($P = 0.038$) in non-responders (Table 3). The area under the ROC curve was 0.669 and age at 32 had 72% sensitivity and 67% specificity.

Female gender, ethnicity, disease duration and time between diagnosis and symptom onset were comparable between responder and non-responder groups. There was also no differences in myositis type (DM, PM or ASS), joint and pulmonary clinical symptoms, initial serum level of muscle enzymes, autoantibodies, or pre-treatment with methylprednisolone and intravenous human immunoglobulin pulse therapies ($P > 0.05$).

Discussion

In the present one-year study, long-term rituximab efficacy in refractory patients with IIM was demonstrated.

Rigorous criteria of refractoriness and also the modified IMACS disease activity response parameters were adopted in this research. Notably, due to disease severity, more than half of the patients also needed to receive methylprednisolone associated with intravenous human immunoglobulin pulse therapy to induce disease remission. In contrast, a less strict criterion of refractoriness was observed in previous studies and data on severe symptoms such as dysphagia were not reported hampering comparison with the present

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Table 2 Evaluation at baseline, 6 and 12 months of 38 patients with idiopathic inflammatory myopathies after rituximab therapy

	Baseline	6 months	12 months	Δ% (12 months vs. Baseline)
Prednisone dose (mg/day)	18.8 (10.0–36.3)	8.8 (2.5–15.0)	6.3 (0.0–16.3)	–
MMT-8 (0–80)	68.5 (56.8–72.5)	72.0 (67.0–78.0)	74.0 (70.0–78.0)	+ 11.3
HAQ (0.00–3.00)	1.00 (0.50–1.51)	0.63 (0.25–1.00)	0.50 (0.03–1.16)	−53.0
Patient's VAS (0–10 cm)	5.0 (3.0–7.0)	3.0 (1.0–5.0)	2.0 (0.0–4.0)	− 57.0
Physician's VAS (0–10 cm)	5.0 (3.8–7.0)	3.0 (1.0–4.3)	2.0 (1.0–4.0)	−60.0
Creatine phosphokinase (U/L)	429 (123–971)	224 (83–527)	254 (83–551)	−8.6
Aldolase (U/L)	5.5 (4.0–10.6)	3.9 (3.2–6.9)	3.6 (3.2–7.0)	−29.0
Severe infections	–	0	0	–
Adverse events	–	0	2 (5.3)	–
Neoplasia	–	0	1 (2.6)	–

Results expressed as percentage (%), or median (25th - 75th). *VAS* Visual Analogue Scale, *MMT* Manual Muscle Testing, *HAQ* Healthy Assessment Questionnaire, **Δ**% percentage variation

Table 3 Frequency of rituximab response according to myositis type, clinical involvement, autoantibody profile and treatment

	Responders (*N* = 29)	Non-responders (*N* = 9)	*P*
Age at disease diagnosis (years)	39.6 ± 12.2	28.3 ± 9.0	0.008
Age at Rituximab application (years)	44.7 ± 11.0	35.8 ± 8.1	0.017
Female gender	24 (82.7)	8 (88.9)	1.000
White ethnicity	19 (65.5)	7 (77.8)	0.689
Disease duration (years)	3.0 (1.5–5.5)	3.0 (2.0–10.0)	0.919
Duration: diagnosis - symptoms (months)	5.0 (3.0–8.0)	4.0 (2.5–12.0)	0.589
Myositis			
Dermatomyositis	14 (48.3)	1 (11.2)	0.061
Polymyositis	6 (20.7)	4 (44.4)	0.205
Antisynthetase syndrome	9 (31.0)	4 (44.4)	0.389
Clinical and laboratory features			
Dysphagia	18 (62.1)	9 (100.0)	0.038
Articular	11 (37.9)	5 (55.6)	0.450
Pulmonary	11 (37.9)	3 (33.3)	1.000
Creatine phosphokinase (U/L)	5798 (2796–13,630)	9000 (4484–12,472)	0.457
Aldolase (U/L)	36.1(18.7–42.3)	28.2 (20.6–40.6)	0.664
Autoantibodies			
Anti-Ro-52	11 (37.9)	5 (55.6)	0.450
Anti-Jo-1	9 (31.0)	4 (44.4)	0.689
Anti-Mi-2	4 (13.8)	0	–
Anti-OJ	0	0	–
Anti-EJ	0	0	–
Anti-PL-7	0	0	–
Anti-PL-12	0	0	–
Antinuclear factor	23 (73.9)	8 (88.9)	1.000
Pre-RTX infusion protocol			
Methylprednisolone + intravenous human immunoglobulin pulse therapy	16 (55.2)	7 (77.8)	0.273

Results expressed as mean ± standard deviation, median (25th - 75th) or percentage (%)
RTX Rituximab

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analysis [4–11]. In fact, among patients evaluated in the present study, more than two-thirds had dysphagia, a known serious problem in patients with IIM that can be associated with nutritional deficiency, aspiration pneumonia and poor prognosis [18].

The rituximab protocol was a more aggressive approach than others previously reported [4–11], and included pre-infusion of methylprednisolone and intravenous human immunoglobulin for the majority of the patients. In addition, the rituximab fixed dose retreatment protocol was chosen as opposed to on-demand retreatment [4–11], taking into account refractoriness.

The long-term IMACS modified response rate obtained with the present protocol was comparable to that reported for the RIM trial [5], a remarkable result taking into consideration the disease severity and refractoriness of the patients selected. Our data reveals that this outcome occurred for all patients at 6 months and the improvement persisted at 1 year. In this regard, a highly successful prednisone taper was obtained, with a significant early mean dose reduction at 6 months and a substantial number of patients (42%) able to completely discontinue prednisone at 12 months. Reinforcing these results, a parallel improvement in MMT-8, HAQ, physician and patient' VAS, as well as in muscle enzymes occurred at 12 months.

Autoantibodies, especially anti-Jo-1 and anti-Mi-2, proved predictors of clinical improvement in a cohort of rituximab-treated myositis' patients, whereas at lack of definable autoantibodies was a predictor of no improvement [5]. Although this association was not found in the present study, the majority of patients with anti-Jo-1 and all with anti-Mi-2 autoantibodies, responded to a rituximab.

During the follow-up, rituximab was well-tolerated with few adverse reactions. The most common side effects in literature are infections (mainly respiratory tract infections), of which 5% were severe, requiring hospitalization. Infusion reactions rarely occurred and these were often mild and easily controlled with glucocorticoid. Notably, there were no cases of severe infections requiring hospitalization in the present study. The intravenous human immunoglobulin pre-rituximab may be contributed for these data. However, sustained clinical and laboratory improvement may be due to rituximab, since there was no difference between responders and non-responders regarding previous use of intravenous human immunoglobulin.

As a limitation of the present study, a small sample was included, given the rarity of the IIM and the strict inclusion and exclusion criteria applied. Moreover, a sequential analysis of the dysphagia (i.e.: manometry) and pulmonary function were not performed. Finally, it should be emphasized that the concomitant use of methylprednisolone associated with intravenous human immunoglobulin for the majority of the patients might have affected the outcomes.

Conclusions

The present study provides convincing evidence that rituximab treatment is an effective and safe therapy for refractory IIM with a sustained 1 year response and significant tapering/discontinuation of glucocorticoid therapy. Moreover, young individuals and patients with dysphagia have a tendency to be more refractory to rituximab.

Abbreviations
ASS: Antisynthetase syndrome; CI: Confidence interval; DM: Dermatomyositis; HAQ: Health Assessment Questionnaire; IIM: Idiopathic inflammatory myopathies; IMACS: International Myositis Assessment & Clinical Studies Group; MDAAT: Myositis Disease Activity Assessment Tool; MMT: Manual muscle testing; PM: Polymyositis; ROC: Receiver operating characteristic; SD: Standard deviation; VAS: Visual analogue scale

Authors' contributions
All authors contributed to write and review the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was approved by the local Ethics Committee (HCFMUSP, CAPPesq Number #0324/11).

Consent for publication
Not applicable.

Competing interests
All authors declare that they have no competing interests.

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