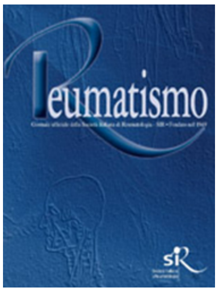

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Real-life effectiveness of rituximab in different subsets of idiopathic inflammatory myopathies

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Summary

Objective. Idiopathic inflammatory myopathies (IIM) are heterogeneous autoimmune diseases including dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myopathy (IMNM), and anti-synthetase syndrome (ASS). Treatment typically involves high-dose corticosteroids (CCS) and conventional synthetic disease-modifying antirheumatic drugs (csDMARD). Rituximab (RTX) has shown effectiveness in refractory cases. Our real-life study aimed to assess the safety and effectiveness of RTX treatment in IIM patients.

Methods. We conducted a retrospective study including patients with IIM refractory to both high-dose CCS and csDMARD. Patients were treated with a full RTX dose (2 g every 6 months). Laboratory and clinical data, along with the total improvement score (TIS), were assessed to evaluate RTX effectiveness and safety. Data were analyzed using GraphPad Prism (v. 9.5.1).

Results. A total of 41 patients received the full RTX dose (15 DM, 15 ASS, 5 PM, and 6 IMNM). This treatment regimen significantly reduced daily CCS usage from 15 mg [interquartile range (IQR) 12.5-25 mg] at baseline to 5 mg (IQR 5-5 mg) after 1 year of treatment ($p<0.001$). Additionally, over 90% of patients achieved at least a minimal TIS at 12 months, which was maintained at 24 months. At 1 year, RTX persistence was 68.3%. Although reductions in serum immunoglobulins (Ig)A and IgM levels were observed, no cases of severe hypogammaglobulinemia (IgG<400 mg/dL) occurred. The most common reason for treatment interruption was adverse skin reaction (6 cases) during RTX infusion, while infections involved most frequently the respiratory tract (5 cases).

Conclusions. RTX demonstrated effectiveness in various subsets of IIMs, often leading to clinical improvement and significantly reducing the CCS dose.

Introduction

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of autoimmune systemic diseases with variable clinical manifestations, treatment responses and prognoses. Muscle weakness, reduced muscle endurance and myalgia are the most classical clinical manifestations, but many organs may be affected, sometimes representing the predominant manifestation of the disease. Extra-muscular manifestations of IIM are relatively common and include different skin manifestations, articular involvement as arthritis or arthralgia, lung involvement, most commonly as interstitial lung disease (ILD), gastrointestinal manifestation, and heart involvement, which may be potentially fatal (1). Among the different gastrointestinal manifestations, esophageal involvement with dysphagia represents a frequently disabling and early symptom of dermatomyositis (DM), reported by 20-50% of patients (2). Due to the rare and heterogeneous nature of IIM and the small number of studies carried out, there is a lack of consensus on the use of the available therapeutic options. Therefore, the choice is often empirical and not based on shared therapeutic algorithms (3-5). According to general clinical consensus, treatment of IIM involves the use of high-dose corticosteroids (CCS) as the first-line drug to induce remission and conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs), including azathioprine, mycophenolate mofetil, calcineurin inhibitors, cyclophosphamide and methotrexate, as steroid-sparing agents to maintain the remission state (6). Unfortunately, many patients are refractory to CCS and immunosuppressive agents; therefore, alternative strategies including immunomodulators such as intravenous immunoglobulins (Ig), and biologic (b) DMARDs, have been employed with variable success (7). The rationale for using bDMARDs in IIM resides in their ability to interfere with the immune-mediated activation of selected inflammatory pathways, avoiding the broader immunosuppressive effect induced by csDMARDs. The growing knowledge about the complex pathophysiology of IIM strongly supports the implementation of bDMARDs, including rituximab (RTX), tocilizumab, tumor necrosis factor α inhibitors, and abatacept, in specific treatment guidelines (8). RTX is a chimeric monoclonal antibody binding the CD20 antigen expressed on the surface of B lymphocytes at most stages of their development, but not on pro-B cells, early pre-B cells, and plasma cells, causing rapid depletion of CD20-positive B lymphocytes from the peripheral blood for up to 6-9 months. Despite the beneficial effects of RTX in IIM being suggested by case reports and case series, the experience in patients with refractory disease is limited, and current evidence supports the off-label use of RTX in patients with refractory IIM (9). The Rituximab in Myositis (RIM) study was the largest randomized, double-blind, placebo-controlled trial comparing early *vs.* late treatment with RTX to achieve clinical improvement and included 195 IIM patient's refractory to CCS and at least one immunosuppressive agent. Although the time to achieve the primary endpoint was not different between the two RTX treatments, many patients (83%) with refractory disease experienced clinical improvement and a steroid-sparing effect. Additionally, the treatment was generally well tolerated, with infections being the most common adverse event (10). In our study, we aimed to evaluate the safety and effectiveness of RTX treatment in patients with various subsets of IIM in a real-world setting.

Materials and Methods

Population

Patients with IIM refractory to conventional therapy with high-dose CCS and csDMARDs and deemed suitable for RTX therapy based on clinician judgment were included in our retrospective study. The refractoriness to conventional therapy was defined as therapy ineffectiveness, with lack of improvement or worsening of clinical manifestations, according to both clinician assessment and patient subjective evaluation, after at least 3 to 6 months of continuous treatment, or therapy interruption due to any adverse reaction of csDMARDs, or inability to reduce daily CCS dose below 5mg PDN equivalent (PDNeq). Patients affected by DM or polymyositis (PM) were defined according to the 2017 European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology classification criteria. Patients with antisynthetase syndrome (ASS) were defined by the presence of ASS antibodies and at least one clinical manifestation, including arthritis, ILD or myositis, while patients with immune mediated necrotizing myopathy (IMNM) were defined by the presence of anti-SRP or anti-HMGCR antibodies or by histological features of necrotizing myopathy in the absence of autoantibodies (11, 12). All patients included in this study were treated with RTX, administered as two 1g infusions given 2 weeks apart every 6 months. For each patient, refractory disease manifestations requiring RTX prescription were reported, including skin, muscle, joint and lung involvements. The persistence of RTX therapy was defined by the clinical decision, shared with the patient, to continue RTX treatment after 1 year from the first infusion. Patients in remission were defined according to clinician judgment, with physician global assessment and extra-muscular disease activity visual analog scales at 0. Prior to each RTX infusion, patients were appropriately premedicated with methylprednisolone 100 mg intravenously, antihistamines, acetaminophen and proton pump inhibitors, according to the RTX medication administration protocol. Demographic, clinical, and laboratory data of enrolled IIM patients were evaluated at baseline and during follow-up. Lung involvement was defined as ILD confirmed by a lung high-resolution computed tomography scan. Laboratory data included: creatine phosphokinase (CPK), anti-nuclear antibodies, myositis-specific autoantibodies (MSA) and myositis-associated autoantibodies (MAA) (Euroline Autoimmune Inflammatory Myopathies, Euroimmun, Germany or MYO12D-24, D-Tek, Belgium). Ongoing and previous treatments were recorded, including CCS (with their dosages) and immunosuppressive agents. Serum Ig levels were monitored and recorded at baseline, 1 year and 2 years. Significant hypogammaglobulinemia was defined as a serum IgG level below 400 mg/dL (13). Reasons for RTX treatment interruption and adverse drug reactions (ADRs) causing RTX discontinuation up to 1 year after the last administration were recorded during follow-up. According to clinical charts, primary ineffectiveness was defined as the patient stopping RTX within the first year of treatment, while secondary failure was defined as the clinical decision to stop RTX after more than one year of treatment. Treatment effectiveness was evaluated by the total improvement score (TIS), calculated at 1 year and at 2 years since RTX initiation. This score, calculated using the International Myositis Assessment and Clinical Studies Group calculator, classifies clinical improvement as minor, moderate, major or no clinical improvement according to the myositis response criteria. Furthermore, treatment outcome was assessed with appropriate clinical and instrumental exams, monitored at first RTX infusion, 1-year and 2-year follow-up visits. Specifically, in IIM patients with refractory muscle involvement, manual muscle test (MMT) in eight muscular districts bilaterally (MMT-8, score 0-150) and CPK level were monitored, while IIM patients with refractory lung involvement were monitored by forced vital capacity (FVC) and diffusion lung carbon monoxide (DLCO) predicted values (%). All participants signed an informed consent prior to inclusion in the study, which was approved by the local Ethics Committee (INflammatoy MYositis Registry: study no. 6229, approval no. 84762,2020/11/06; comitatoetico@policlinico.ba.it). All examinations were performed according to local guidelines.

Statistical analysis

Variables were reported as means with standard deviations (SD), medians with interquartile ranges (IQR) or absolute numbers with percentage, as appropriate. The Shapiro-Wilk test was used to check for distribution of data. Continuous variables were compared using paired t-test or Mann-Whitney test, as appropriate. Categorical variables were compared using the Chi-square test. The repeated measures of the analysis of variance (ANOVA) with the Geisser-Greenhouse correction, or the nonparametric Friedman test, were used to assess changes in continuous variables during follow-up, as appropriate. The persistence of RTX therapy was assessed with Kaplan-Meier analysis. Statistical analysis was carried out using GraphPad Prism software (v. 9.5.1), with a p-value of <0.05 considered statistically significant.

Results

Patient characteristics

A total of 41 IIM patients [31 female (75.6%); age 55±15 years old; myositis subset: 15 (36.6%) DM, 15 (36.6%) ASS, 5 (12.2%) PM and 6 (14.6%) IMNM], were treated with RTX (2 g every 6 months, two 1g doses given 2 weeks apart). In our cohort, the median (IQR) disease duration was 6 (4-11) years, while the median (IQR) follow-up duration was 6 (4-9) years (Table 1). All subjects were previously treated with high-dose CCS and at least one csDMARD, according to local guidelines. At the time of RTX indication all patients were on CCS, with a median (IQR) daily administered PDNeq dose of 15 mg (12.5-25 mg), while 30 patients (73.2%) continued csDMARDs therapy in association with RTX, most commonly methotrexate, mycophenolate mofetil or azathioprine. The median (IQR) number of failed csDMARDs before RTX administration was 2 (2-3) in our cohort. The autoantibody profile of IIM patients, including the presence of MSA or MAA, is described in *Supplementary Table 1*. In our cohort, 14 out of 15 DM patients (93.3%) presented skin manifestations such as periungual erythema, heliotrope rash, neck rash, shawl sign, or Gottron's papules, while 2 patients (13.3%) had calcinosis cutis. Cutaneous involvement was less frequently observed in other myositis subsets and was present in 9 out of 15 (60%) ASS patients (3 cases of mechanic's hands and/or hiker's feet, 3 cases skin ulcerations, 3 cases of periungual erythema and 2 cases of erythematous skin rash), one out of 6 (16.7%) IMNM patients with skin rash, and one out of 5 (20%) PM patients with periorbital erythema. Articular involvement was observed in 10 out of 15 (66.7%) ASS patients, 3 out of 5 (60%) PM patients, and 7 out of 15 (46.7%) DM patients, while no IMNM patients presented arthritis. Esophageal involvement was present in 10 out of 41 (24.4%) IIM patients, with dysphagia reported by 5 out of 15 (33.3%) DM patients, 2 out of 15 (13.3%) ASS patients, 2 out of 5 (40%) PM patients and one out of 6 (16.7%) IMNM patients. Other comorbidities were present in 31 out of 41 IIM patients (75.6%) treated with RTX, most commonly systemic hypertension (13 cases, 31.7%), autoimmune thyroiditis (12 cases, 29.3%), and osteoporosis (11 cases, 26.8%). The most frequent reasons for RTX therapy indication were refractory myositis (61.0%), skin (56.1%), lung (53.6%), and joint (48.8%) involvements (*Supplementary Figure 1*).

Rituximab efficacy

Treatment with RTX was associated with a significant steroid-sparing effect. The median (IQR) daily dose of PDNeq decreased from 15 mg (12.5-25 mg) at baseline to 5 mg (5-5 mg) after one year of treatment ($p<0.001$ *vs.* baseline), and to 5 mg (0-5 mg) after 2 years ($p<0.001$ *vs.* baseline). Notably, a further significant reduction in the daily PDNeq dose at 2 years compared to the 1-year dose ($p<0.05$) was also observed (Figure 1). Overall, the mean clinical improvement, expressed as a mean (SD) TIS, was 45.4±18.1 at 1 year and 52.3±17.7 at 2 years of follow-up. The percentages of patients who achieved minor, moderate, major, or no response with a TIS score at 1 year and 2 years from the first RTX administration are shown in Figure 2. Of note, 90.6% and 90.9% of patients achieved at least a minor TIS at 1 year and 2 years of follow-up, respectively. Data regarding TIS in each subset of IIM is reported in Figure 3. ANOVA tests showed a significant improvement during follow-up of MMT-8 score ($p<0.0001$), CPK level ($p<0.01$) and FVC predicted level ($p<0.05$), while DLCO change over time was not statistically significant (Table 2). The 1-year RTX treatment persistence was 68.3% in our cohort, with 13 IIM patients (31.7%) discontinuing therapy. Primary inefficacy of RTX treatment was observed in 3 cases (7.3%). Additionally, one patient exhibited secondary inefficacy of RTX therapy, contributing to a total of 4 cases of ineffectiveness (9.8%). Kaplan Meier curves of RTX treatment persistence according to the reason for treatment discontinuation and IIM subset are presented in Figure 4. No significant difference was observed according to the cause of RTX discontinuation (log-rank: 1.14; $p=0.28$). Analyzing RTX persistence according to IIM subsets, we observed a significantly lower drug persistence in the PM group compared to DM (log-rank: 5.84; $p=0.02$) and IMNM (log-rank: 6.27; $p=0.01$) subsets. Among cases of primary inefficacy, two patients were affected by ASS, one with joint involvement and another with both joint and muscle involvement, while one patient had IMNM with muscle involvement. As for secondary inefficacy, one patient with ASS experienced an ILD flare during follow-up. Finally, we assessed the persistence of RTX treatment in monotherapy and combination therapy with csDMARDs. No significant differences were observed between patients treated with RTX monotherapy or csDMARDs combination therapy, both for any cause of discontinuation (log-rank: 4.98; p=0.08) and when specifically assessing discontinuation due to ineffectiveness (log-rank: 1.77; p=0.41) or adverse events (log-rank: 3.23; p=0.21).

Rituximab safety
During the first year of treatment, ADRs were the most common cause of RTX discontinuation (4 skin reactions during RTX infusion, resolved after treatment interruption). Other reasons for RTX discontinuation within the first year included exitus (2 cases: one acute myocardial infarction and one acute respiratory insufficiency secondary to SARS-CoV-2 infection), positive cancer screening (2 cases: one pancreatic neuroendocrine tumor and one multiple myeloma), severe pulmonary infection (one case), and loss to follow-up (one case). During the entire follow-up period on full RTX dose, which had a median (IQR) duration of 22 (9-55) months, 2 additional patients died, totaling 4 deaths. However, the causes of death were known for only one patient, who died due to acute respiratory insufficiency secondary to SARS-CoV-2 infection. One more patient was lost to follow-up, bringing the total to two. Furthermore, there were 2 additional cases of skin reactions (6 in total) and one severe pulmonary infection that led to treatment discontinuation (2 cases in total). The most common reasons for RTX discontinuation are reported in Table 3. All IIM patients undergoing RTX therapy were screened for tuberculosis infection and viral hepatitis according to local guidelines prior to the first RTX infusion. No cases of opportunistic infections, both bacterial and fungal, or viral infections such as CMV, EBV, or HBV reactivations were observed during follow-up. RTX treatment was associated with variations of serum Ig levels during the first two years of follow-up, with a significant decrease in IgA (p<0.001) and IgM (p<0.0001) levels, while the change in IgG levels was not statistically significant (Figure 5). No patients developed severe hypogammaglobulinemia (IgG<400 mg/dL) during the follow-up.

Discussion and Conclusions
In our study, we evaluated the effectiveness of RTX treatment in 41 IIM refractory to conventional therapies. We observed at least a minor improvement according to TIS in more than 90% of IIM patients with cutaneous, pulmonary, articular, or muscular manifestations refractory to multiple csDMARDs and high-dose CCS. The Myositis Response Criteria with TIS were used, as they have recently been shown to perform consistently across multiple studies, further confirming their validity in different IIM subsets (14). Treatment of refractory IIM represents a rheumatological challenge and an unmet clinical need nowadays. In fact, there are no standardized treatment guidelines for IIM, particularly due to the rarity of the disease and the lack of randomized controlled trials. Therefore, the therapeutic approach is mainly guided by expert opinion and case series (15). The first evidence of RTX use in myositis dates back to 2005, when Levine *et al*. demonstrated its efficacy in six patients with DM who were refractory to standard therapy (16). Since then, RTX has been progressively employed for the treatment of IIM, especially in life-threatening situations or when the symptoms do not improve or even get worse despite standard immunosuppressive therapies (17, 18). Despite the results of the RIM trial, most evidence supporting the efficacy of RTX in IIM has come from real-world studies (10, 19-21). Our study highlighted the effectiveness of RTX treatment in a cohort of IIM patients refractory to high-dose CCS and csDMARD therapy, but most notably, its good safety profile. The assessment of TIS during follow-up confirmed a relevant improvement in IIM patients. The effectiveness of RTX treatment for refractory muscle involvement was confirmed by a significant reduction in CPK level and an increase in MMT-8 score over time. Similarly, in IIM patients with refractory lung involvement, a significant improvement in FVC was observed. Other real-life studies of IIM patients confirm the positive effects of RTX treatment on lung function tests, muscle enzymes and muscular weakness, while also permitting a reduction of CCS (22, 23). Notably, infections were

considered the most relevant concern associated with RTX treatment (24, 25). In fact, a significant increase in severe infections was observed in a retrospective study involving 4479 patients following RTX treatment. However, it was also reported that many patients had not been screened or were not properly identified as having hypogammaglobulinemia before RTX administration (26). In our study, we assessed the safety profile of RTX treatment. The most common reason for treatment discontinuation was an adverse skin reaction during RTX infusion, with 6 cases noted during the observational period, but no severe or anaphylactic reactions. A total of 5 pulmonary infections requiring treatment interruption were observed, with 2 of these resulting in the death of the patient. Notably, COVID-19 infections accounted for both deaths. It is important to note that RTX can be a risk factor for a poor prognosis after a COVID-19 infection, highlighting the critical role of vaccinations in RTX-treated patients (27, 28). In our cohort, all patients were informed before starting RTX therapy about the importance of completing the vaccination schedule according to local recommendations, including SARS-CoV-2 vaccination given onsite to all IIM patients before starting RTX treatment, and advice to complete the vaccination schedule with at least the influenza, herpes zoster, and pneumococcal vaccines, ideally administered before the first RTX infusion or at least with the correct timing considering the 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases undergoing RTX treatment (29). The frequency and severity of hypogammaglobulinemia and potential infectious complications following RTX therapy were assessed in a large retrospective cohort of patients with systemic autoimmune diseases including systemic vasculitis and SLE. After RTX treatment, IgM levels showed a significant decrease, but IgG levels remained stable. A high concomitant dose of CCS was identified as the most important risk factor for developing hypogammaglobulinemia (30). In our cohort, IgA and IgM levels decreased during the first 2 years of follow-up, while IgG levels remained stable. No IIM patients developed severe hypogammaglobulinemia. The fact that IgM is more significantly reduced during RTX therapy is not new; in fact, IgM is affected more than the other Ig by RTX (31). This might be attributed to the different impacts of RTX on distinct plasma-cell subsets. Specifically, short-lived plasma cells make a greater contribution to serum IgM than serum IgG, which fact might explain these results. Meanwhile, long-lived plasma cells, which lack CD20 and are therefore spared from RTX's actions, maintain good production of IgG. Finally, the disease itself may contribute to the different effect of RTX on the variation of Ig levels (27). Few studies have assessed RTX-induced hypogammaglobulinemia in IIM. A multicentric Italian study investigating the relevance of serum Ig levels in 30 myositis patients during RTX treatment suggested that hypogammaglobulinemia following RTX administration is uncommon in IIM and is not related to any clinical variables, including CCS dosage and previous treatments (32). The main limitations of our study included the small sample size, which hampered the ability to evaluate the influence of specific IIM biomarkers, such as positivity to MSA/MAA, or clinical biomarkers like disease duration, age, gender or concomitant therapies, as well as the short follow-up duration, which prevented us from estimating the long-term effects of RTX therapy. Notably, according to our data, DM and IMNM patients presented a significantly higher RTX persistence compared to PM patients, maybe secondary to the existence of “myositis chameleons”, including metabolic myopathies, genetic myopathies and neurological diseases, which mimic PM symptoms and represent a diagnostic and therapeutic challenge (33, 34). In conclusion, our results indicate that RTX is an effective and safe choice for refractory IIM patients, allowing for a significant steroid-sparing effect and often inducing disease remission. Nonetheless, particular attention must be given to the risk of infection, especially COVID-19.

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Online supplementary material

Supplementary Table 1. Autoantibody profile of idiopathic inflammatory myopathy patients treated with rituximab.

Supplementary Figure 1. Refractory organ involvement at baseline in idiopathic inflammatory myopathy patients with indication to rituximab treatment.

Table 1. Demographic and clinical characteristics of 41 IIM patients treated with rituximab.

Characteristics	RTX 2g / 6 months
IIM subset:	
- **DM**	15 (36.6)
- **ASS**	15 (36.6)
- **PM**	5 (12.2)
- **IMNM**	6 (14.6)
Female, n. (%)	31 (75.6)
Age (years), mean ± SD	55.4±15.0
Disease duration (years), median (IQR)	6 (4-11)
Follow-up duration (years), median (IQR)	6 (4-9)
ANA positive (≥ 1/160), n (%)	34 (82.9)
MSA/MAA positive, n (%)	38 (92.7)
Muscle involvement, n (%)	25 (61.0)
Skin involvement, n (%)	25 (61.0)
Joint involvement, n (%)	20 (48.8)
Lung involvement, n (%)	22 (53.6)
csDMARD count at first RTX infusion, median and IQR (25-75)	2 (2-3)
Therapy with csDMARD at first RTX infusion, n (%)	30 (73.2)
Therapy with CCS at at first RTX infusion, n (%)	41 (100)

DM, dermatomyositis; ASS, anti-synthetase syndrome; PM, polymyositis; IMNM, immune-mediated necrotizing myopathy; IQR, interquartile range; SD, standard deviation; ANA, anti-nuclear antibody; MSA, myositis-specific antibody; MAA, myositis-associated antibody; RTX, rituximab; csDMARD, conventional synthetic disease-modifying anti-rheumatic drugs; CCS, corticosteroids; AE, adverse events.

Table 2. Laboratory and clinical data in IIM patients during rituximab treatment.

Characteristics	Baseline	1 year	2 years	p (ANOVA)
MMT-8 (0-150), median and IQR (25-75)	134 (108-144)	143 (139-149)***	148 (142-150)***;#	**<0.0001**
CPK U/L, median and IQR (25-75)	670 (160-3218)	110 (61-495) ***	129 (56-207)***	**0.0013**
DLCO (%) predicted, median and IQR (25-75)	53 (42-66)	59 (48-76)	63 (43-81)	0.4941
FVC (%) predicted, median and IQR (25-75)	71 (61-91)	83 (74-98)**	85 (74-95)*	**0.0114**

MMT, manual muscle test; CPK, creatine phosphokinase; DLCO, diffusion lung carbon monoxide; FVC, forced vital capacity; IQR, interquartile range; ANOVA, analysis of variance; p (ANOVA) <0.05; p-value *vs.* baseline (*<0.05, **<0.01, ***<0.001); p-value *vs.* 1-year (#<0.05, ##<0.01, ###<0.001).

Table 3. Reasons for rituximab discontinuation*.

Reasons for discontinuation	RTX discontinuation, n. (%)
Adverse event	10 (24.3)
Ineffectiveness	4 (9.8)
Remission	3 (7.3)
Exitus	4 (9.8)
Lost to follow-up	2 (4.9)

*During follow-up, 23 out of 41 patients (56.1%) discontinued RTX treatment for any reason, including persistent remission.

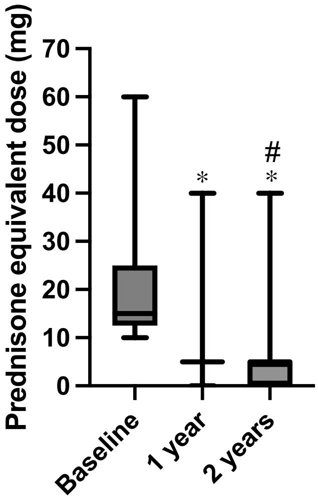

Figure 1. Daily administered prednisone equivalent dose in IIM patients treated with rituximab at baselina, one year, and two years. *p<0.0001 *vs.* baseline; #p<0.05 *vs.* one year.

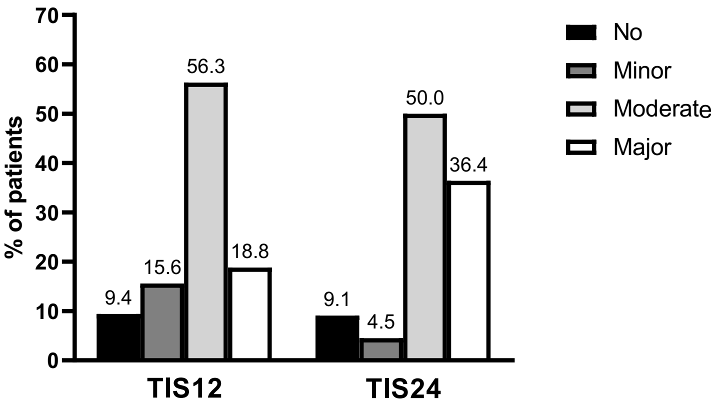

Figure 2. Total improvement score (TIS) in IIM patients treated with rituximab at one year (TIS 12) and at two years (TIS 24). TIS expressed as no improvement (0-19 points), minor (20-39 points), moderate (40-59 points) or major (60-100 points) improvement.

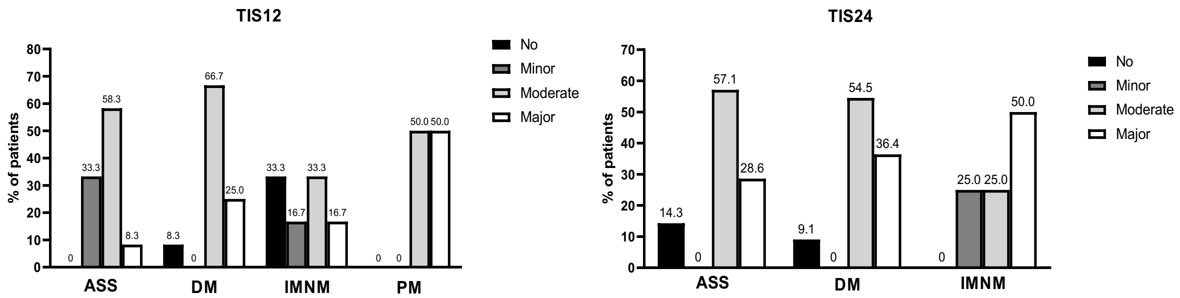

Figure 3. Total improvement score (TIS) of different subsets of IIM patients treated with rituximab at one year (TIS 12) and at two years (TIS 24). TIS expressed as no improvement (0-19 points), minor (20-39 points), moderate (40-59 points) or major (60-100 points) improvement. ASS, anti-synthetase syndrome; DM, dermatomyositis; IMNM, immune-mediated necrotizing myopathy; PM, polymyositis.

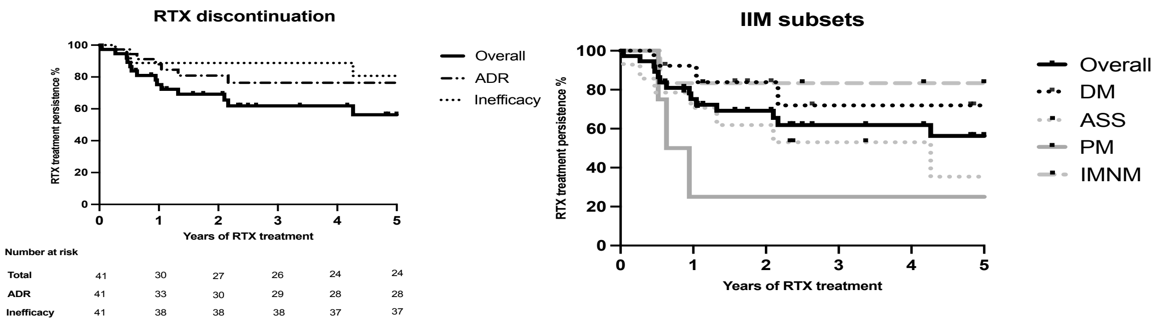

Figure 4. Kaplan-Meier curves of rituximab (RTX) treatment persistency with the reason for treatment discontinuation in different idiopathic inflammatory myopathy (IIM) subsets.

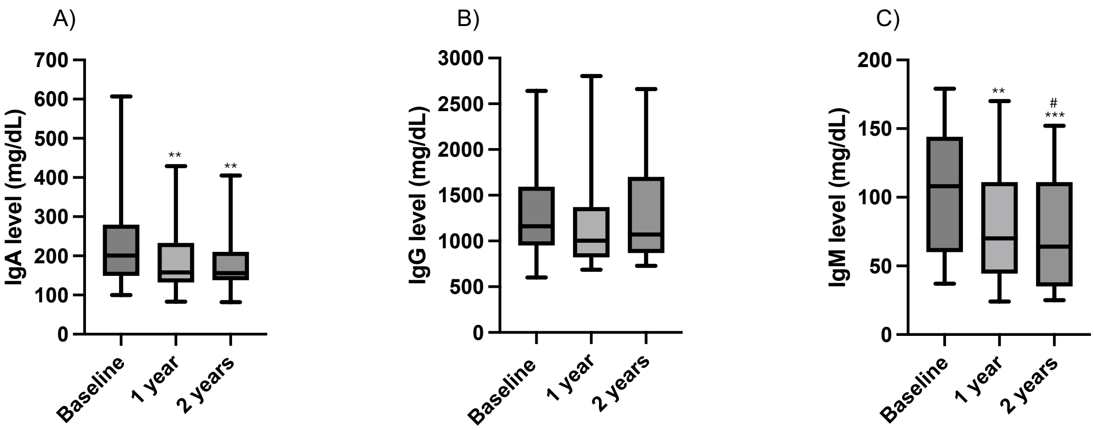

Figure 5. Peripheral blood level of immunoglobulin (Ig)A (A), IgG (B) and IgM (C) in idiopathic inflammatory myopathy patients treated with rituximab at baseline, 1 year and 2 years. p-value *vs.* baseline (*<0.05, **<0.01, *<0.001); p-value *vs.* 1-year (#<0.05, ##<0.01, ###<0.001).**