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Concise report

Low-dose rituximab is efficacious in refractory idiopathic inflammatory myopathies

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Abstract

Objectives. Rituximab (RTX) use early in the course of refractory idiopathic inflammatory myopathy (IIM) is not well studied. This study sought to determine the short-term efficacy of RTX in a registry-based cohort of refractory IIM.

Methods. Registry-based observational data about IIM patients receiving RTX between 2018 and 2021 were included. Total improvement score was calculated from the core set measures as per International Myositis Assessment and Clinical Studies group (IMACS) at baseline, 6 months and 12 months of follow-up.

Results. Forty-two patients (F:M, 29:13), with a mean (S.D.) age of 39.5 (11.5) years were studied. Majority of patients received RTX for refractory myositis, after a median (interquartile range) duration of 8 (4,18) months. Twenty-eight received RTX at a dosage of 1 g × two doses, while 14 received 500 mg × two doses with an interval of 15 days. At 6 months and 12 months post-RTX, the improvement was recorded in manual muscle testing (MMT-8) scores, physician global assessment (PGA), patient global assessment (PtGA) and median steroid dosage as compared with the baseline ($P < 0.01$ for all). A mean (S.D.) improvement of 44.5 (16) and 48.7 (19.2) in total improvement score was recorded at 6 and 12 months, respectively. The change in MMT-8, PGA and PtGA scores from baseline between the two dosage regimens of RTX were comparable at 6 and 12 months. Severe lower respiratory tract infections requiring hospitalization occurred in three patients of the cohort.

Conclusion. RTX improved IMACS core set measures and had steroid sparing efficacy at 6 and 12 months in patients with IIM in this registry-based study. Rituximab as an induction regimen of two doses of 500 mg can be as efficacious as 1 g at 6 months and 12 months of follow-up.

Key words: low-dose rituximab, refractory myositis, duration of myositis, MSA positivity

Rheumatology key messages

- Rituximab use leads to improvement in core set measures at 6 and 12 months in IIM patients.
- Rituximab, at an induction dose of 500 mg twice, is as efficacious as 1g twice.
- Serious lower respiratory tract infection is a major safety concern.

Introduction

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of disorders with shared clinical manifestation of muscle weakness and extramuscular manifestations like skin rash and interstitial lung disease. A paucity of controlled clinical trials makes management of IIMs largely experiential. The selection of initial steroid-sparing immunomodulation is largely determined not only by the severity of muscle weakness but also by the presence or absence of associated interstitial lung disease and other related clinical parameters.

Use of rituximab (RTX) in adults and children with IIM is backed by several observational studies and the RIM trial, a placebo-controlled randomized trial. Although the RIM trial failed to meet its primary and secondary endpoints, the majority of enrolled patients (83%) met the preliminary definition of improvement by the end of the study.

The identification of IIM subsets who are likely to respond, when RTX should be administered during the

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disease course, and the optimal regimen and schedule for re-treatment remain to be elucidated. Furthermore, the optimal dose of RTX remains contentious. In the RIM trial, the dose was based on body surface area (adults and children $>1.5\,m^2$ received $750\,mg/m^2$ up to 1 g), while most observational studies have used a fixed dosage of 1 g administered twice [1–5]. Data supporting the use of RTX early in the course of myositis is also inadequate. In this report, we describe our experience of using RTX in adult IIM patients in a real-life setting.

Methods

Study design

This is a multi-centric registry-based retrospective observational study, between 2018 and 2021. The study was approved by Institutional Ethics Committee St John's Medical College, St John's National Academy of Medical Sciences. The study conformed to the rules laid by the Declaration of Helsinki, 2013.

Study population

IIM patients participating in the Myo-IN registry [6] treated with RTX were included. The registry collects data at inception and follow-up prospectively. Data of IIM patients already under follow-up, were collected retrospectively. Written informed consent was obtained from all patients at the time of recruitment into the registry. Autoantibodies, both myositis-specific (MSA) and myositis-associated antibodies, were assayed by EUROIMMUN line-blot assay in respective centres. From this registry, IIM patients prescribed RTX were included in the current study. All patients received two infusions of RTX with a 15-day interval, either a 500 mg/dose or a 1 g/dose, at the treating physician's discretion. Refractory myositis was defined by the intolerance to or an inadequate response to glucocorticoids and at least one other immunosuppressive or immunomodulatory agent. An 'adequate' glucocorticoid regimen was 60 mg prednisone daily in adults and 1.0 mg/kg/day prednisone in paediatric patients—both for at least 1 month. An adequate immunosuppressive regimen was 3 months of the agent at a known effective dose [1].

Data collection

Baseline demographics, IIM subsets, extramuscular organ involvement, autoantibody profile, indication, timing and dose of RTX were recorded. The concurrent immunosuppressive therapy and steroid therapy details were retrieved. Glucocorticoid dosage at baseline and follow-up time points was recorded.

Outcome assessments

Changes from the baseline in the clinical and laboratory parameters were recorded as per the International Myositis Assessment and Clinical Studies group (IMACS) core set measures, at 6 months and 1 year post-RTX [7]. Total improvement score was calculated using the IMACS calculator, a web-based application. This calculator allows for calculation if the manual muscle testing in eight groups of muscles (MMT-8), physician global assessment (PGA) and two other core set measures were available at the two time points of interest [8].

Relapse was recorded as worsening of PGA by $\geq$2 cm on a 10 cm visual analogue scale and worsening on MMT-8 by $\geq$20%; extramuscular organ disease activity worsening by $\geq$2 cm on a 10 cm visual analogue scale; or $\geq$30% worsening in any three of six IMACS core set measures [9]. Whenever the objective assessment was unavailable, relapse was determined as per the physician judgement. Relapse was considered as early relapse when it occurred within 1 year post-RTX.

Statistics

The descriptive data are reported as mean (S.D.) or median [interquartile range (IQR)] as appropriate. Repeated measures analysis of variance (ANOVA) was used to compare the change in MMT-8, PGA patient GA (PtGA) and total improvement scores over time from baseline to various time points. Delta change (from baseline to 6 months) in MMT, PGA and PtGA scores set measures were compared between patients receiving low-dose RTX *vs* the rest using Mann–Whitney *U* test. Bivariate logistic regression was performed to assess the factors associated with achieving PGA$\leq$2 and relapse $<$1 year. For all comparisons, *P*-value $<$5% was considered as significant. All analyses were performed using SPSS version 25.0.

Results

The Myo-IN registry has recruited 522 patients since its inception. In this registry, 54 IIM patients received RTX during the course of their illness. However, we have included 42 patients who had at least baseline and 6-month follow-up of MMT-8 score and PGA. The cohort consisted of 29 females and 13 males with a mean (S.D.) age of 39.5 (11.5) years. All were adults except for a single case of JDM. The baseline characteristics are mentioned in supplementary Table S1, available at *Rheumatology* online. A majority (38/42) of patients received RTX for refractory disease, after a median (IQR) duration of 8 (4,18) months. Of these, 47.6% had at least a single previous relapse. None of the patients was given RTX specifically for myositis-associated lung disease, though it was present in a mild form in 10 patients. Twenty-eight received RTX at a dosage of 1 g $\times$ two doses, while 14 received at 500 mg $\times$ two doses.

At 6 and 12 months post-RTX, significant improvement was recorded in MMT-8 scores, PGA, PtGA and median steroid dosage as compared with baseline. These results are represented in Table 1.

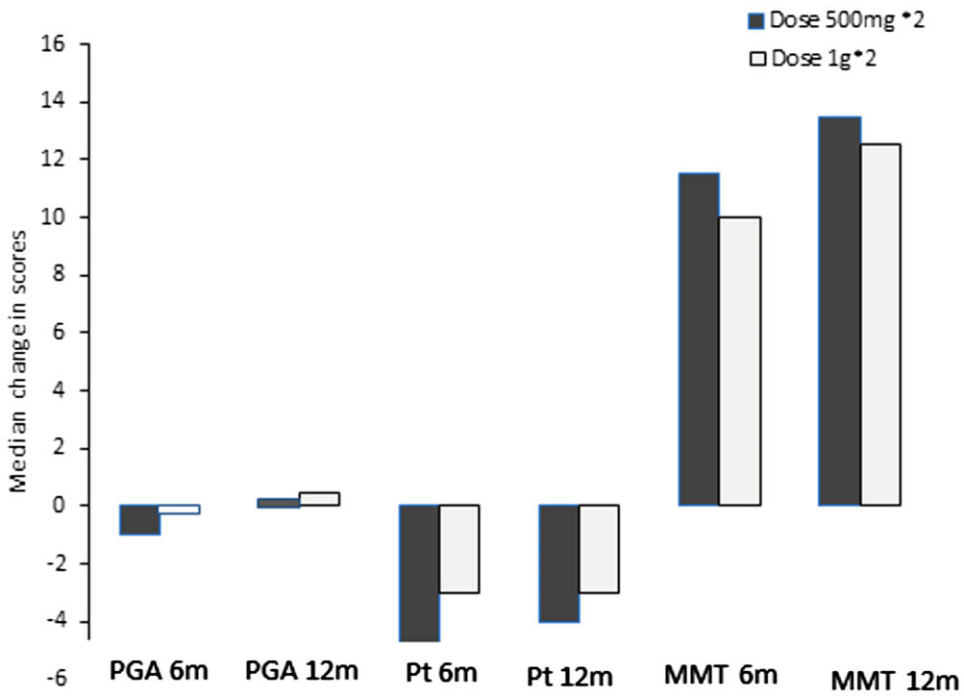
Total improvement score could be calculated in 34 patients at 6 months and 20 patients at 12 months. There was no difference between 500 mg and 1 g dose subsets at 12 months follow-up in these patients ($P = 0.83$). A

Table 1 Outcomes at 6 months and 12 months

	Baseline	6 months	12 months	*P*-value
MMT-8[a], mean (S.D.)	61.9 (11.2)	72.1 (8.6)	76.5 (3.8)	<0.001
PGA[a], mean (S.D.)	5.3 (1.5)	2.7 (1.5)	1.7 (1.2)	<0.001
PtGA[a], mean (S.D.)	5.7 (1.8)	2.2 (1.6)	1.9 (1.6)	<0.001
Improvement in muscle enzymes >20%, *n* (%)		27 (87)	19 (95)	<0.001
Dose of steroids, mg/day, median (IQR)	15 (5, 30)	5 (0, 7.5)	5 (0, 5)	<0.001
Total improvement score, mean (S.D.)		44.5 (16)	48.7 (19.2)	<0.001
		n = 34	*n* = 20	
At least minimal improvement in total improvement score, *n*/*N* (%)		32/34 (94.1)	18/20 (90)	

Data are reported as mean (S.D.); median (25th, 75th percentile); *P*-value using repeated measured ANOVA. [a]Six months is significantly different from baseline; 12 months is significantly different from 6 months and baseline. IQR: Interquartile range; PGA: physician global assessment; PtGA: patient global assessment; MMT-8: manual muscle testing-8.

Fig. 1 Outcomes* at 6 months compared with baseline in patients receiving low-dose rituximab *vs* the rest



*Not significant between dosage levels for PGA, PtGA and MMT-8. Median values are represented using change in score from baseline to 6 months and 12 months. PGA: physician global assessment; PtGA: patient global assessment; MMT-8: manual muscle testing-8.

mean (S.D.) improvement of 44.5 (16) and 48.7 (19.2) was recorded at 6 and 12 months post-RTX respectively. At least minimal response was recorded in 94.1% and 90%, respectively, at 6 and 12 months post-RTX. These results are represented in Table 1. There were two patients who had no response at 6 months post-RTX; one was a case of DM with anti-Mi-2 positivity and refractory skin lesions and the other was a case of overlap myositis with anti-RNP and anti-Ro52 positivity.

There were no differences noted in baseline characteristics of patients receiving 500 mg *vs* 1 g RTX (supplementary Table S2, available at *Rheumatology* online). Patients who received 500 mg (two doses) *vs* those who received 1000 mg (two doses) of RTX fared similarly with respect to median change in MMT-8, PGA and PtGA at 6 and 12 months (Fig. 1).

Absence of dysphagia was associated with achieving a PGA ≤2 in univariate analysis. Female gender, MSA

positivity and shorter duration of immunosuppression prior to RTX tended to be associated with PGA ≤2 at 6 months. However, none of the factors remained significant in multivariate regression analysis (supplementary Table S3, available at *Rheumatology* online).

Among 42 patients included, 7 (16.6%) patients had early relapse. None of the baseline factors studied was associated with early relapse post RTX (supplementary Table S3, available at *Rheumatology* online).

Most common adverse events were infections [8 (19%)] consisting of 4 (9.5%) episodes of severe lower respiratory tract infections (LRTI) in three patients requiring admission, infected hand ulcer in one and unidermatomal herpes zoster in three patients. LRTIs were bacterial pneumonias, which responded to antibiotics. Of the entire cohort (54), two patients (both have received 500 mg dose of RTX) died within 6 months of receiving RTX, one due to severe LRTI, and the other death was at home preceded by vomiting and seizure (cause not identified).

Discussion

In this multicentric cohort of 42 patients who received RTX for refractory IIM (majority of cases), response to RTX was observed in >90% at 6 and 12 months post-infusion. Significant improvement in 3/6 core set measures and steroid sparing effect was observed at 6 and 12 months post-infusion. Patients who received 500 mg (two doses) fared as well those who received 1000 mg (two doses) of RTX at 6 and 12 months post-infusion.

The efficacy of RTX at 6 and 12 months in terms of significant improvement in the three core set measures studied is comparable to other observational cohort studies as well RIM trial [1–3]. Steroid sparing effect as seen in our cohort, has also been well described previously [1–3].

An important aspect of our study is the use of lower doses of RTX than what is used in the RIM trial and observational studies. Use of low-dose RTX in IIM has not been published in IIM literature to the best of our knowledge. We have shown that change in 3/6 core set measures is similar in both dosing subsets at 6- and 12-month intervals. However, we need to note the tendency of early relapse in those receiving low-dose RTX; this aspect needs to be studied in future studies before arriving at any conclusion. Low-dose RTX has been well studied in the treatment of RA, and found to be non-inferior to high dose [10]. Results contrary to this have also been noted in some trials on RA such as the MIRROR trial [11]. Various dosing regimens were associated with similar levels of B cell depletion in observational studies of lupus patients [12]. Hence, low-dose RTX in the treatment of refractory IIM needs further exploration through prospective studies.

The median (IQR) duration of immunosuppressant use prior to RTX [8 (4, 18) months] is shorter in our cohort compared with the RIM trial cohort (60 months) as well as other observational studies (36 months). Among our cohort, shorter duration prior to RTX tended to be associated with better chance of achieving a PGA ≤2 at 6 months. Another study, by Barsotti *et al*., has also shown that shorter duration of disease prior to RTX is associated with better chances of major response [3]. The multivariate analysis of the RIM trial showed that lower physician global damage (damage likely with longer disease duration) predicted better response to RTX [13]. Given the good efficacy, RTX needs to be considered early in the course of refractory myositis rather than later.

Of the baseline factors studied, presence of dysphagia anytime during the course of IIM was associated with a reduced chance of achieving PGA ≤2 at 6 months in our cohort. A similar observation was also made in a retrospective series by de Souza *et al*. [2]. Since this aspect was not noted in other series and randomized controlled trials, its significance needs to be reviewed in future studies.

Patients with MSA positivity primarily Jo-1 and Mi-2 have been shown to have 2- to 3-fold higher chances of improvement as compared with no autoantibodies subgroup in the RIM trial [13]. Another cohort study by Barsotti *et al*. has also shown a higher number of patients with major response in autoantibody positive subset of myositis [3]. A similar result was observed in our cohort, MSA positivity tended to be associated with PGA ≤2 at 6 months. However, MSA data were not available in eight patients, hence this result needs to be interpreted cautiously. Also, we need to be cognizant of a registry-based study by Leclair *et al*. where no significant difference in total improvement score between antisynthetase antibody-negative and -positive subsets receiving RTX was noted [5].

Risk of infection, particularly LRTI, is of concern with the use of RTX. We lack a control population, hence causal association of infection and RTX cannot be made from our study. Likewise, infections were the most frequent serious adverse events (34.8% of patients) in the study by Leclair *et al*. and the RIM trial [1, 5].

Strengths and limitations

Ours is a real-world registry data and outcomes were measured with validated outcome measures.

We have included all the subtypes of IIMs, therefore the population studied is heterogeneous. The retrospective design limits the availability of data on MSA, core set measures in all patients at the 12-month time point in our cohort. We have not analysed the baseline B cell population or evaluated for reconstitution. Adverse events may be under-represented as compared with clinical trials.

Conclusion

RTX leads to improvement in IMACS core set measures and has a steroid-sparing effect at 6 and 12 months in IIM patients. RTX, at an induction dose of 500 mg twice,

is as efficacious as 1 g twice. Serious LRTI is a major safety concern.

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Data availability statement

The data analysed in this manuscript is available with the authors and shall be provided on request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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