Rituximab as an effective alternative therapy in refractory idiopathic inflammatory myopathies

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Abstract

Objective

To assess the efficacy and safety of B-lymphocyte depletion therapy (BCDT) utilising rituximab in refractory idiopathic inflammatory myositis.

Methods

We retrospectively evaluated 16 adult patients with active dermatomyositis (DM) or polymyositis (PM) who received 1 gram rituximab intravenous infusions two weeks apart after failing to respond to conventional therapy. The clinical and biochemical response were analysed by the Myositis Intention to Treat index (MITAX) and the serum creatine kinase (CK) levels at baseline and 6 and 12 months after treatment. The primary efficacy outcome was 20% improvement in the MITAX index and 30% reduction in CK.

Results

Eight patients responded to treatment and achieved both the MITAX and CK levels objectives within 6 months of rituximab therapy. Five out of these 8 responders remained clinically stable at 12 months and CK levels were still reduced or normalised. Of note, 4 patients who did not respond were re-assessed and had their diagnoses corrected. All patients showed adequate B cell depletion (BCD) with re-population occurring for a 15.4 months average (range 3–42 months). Those simultaneously treated with cyclophosphamide achieved more long-lasting depletion (average 18.6 months).

Conclusion

The heterogeneous clinical and serological characteristics of patients diagnosed with IIM probably explain why some, but not all patients respond to rituximab. Myositis overlap and anti-synthetase syndromes seem to respond better than other patient subsets.

Key words

polymyositis, dermatomyositis, refractory myositis, B cell depletion therapy, rituximab

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Introduction

Dermatomyositis and polymyositis are idiopathic autoimmune inflammatory myopathies (IIM) characterised by symmetrical and proximal muscle weakness, increased serum muscle enzymes, electromyographic abnormalities and inflammatory cell infiltrates on muscle biopsy (1). IIM mainly affect the skeletal muscle but other organs and systems such as the skin, lungs, heart and gastrointestinal system can also be involved in up to half of the patients. Muscle weakness is directly related to the morbidity and mortality from the disease itself and treatment-related complications (2).

Glucocorticoids (GC) remain the first-line treatment despite the lack of randomised controlled trials. Many patients do not respond adequately to GC alone or are not able to stop them without a flare. In this setting, immunosuppressive agents are added in order to control and stabilise the disease and minimise the GC-related adverse effects. Using this approach, reasonable control of the active disease phase is achieved in most patients and eventually they are managed with very low drug doses. However, there is a significant group of around 20% of patients inadequately controlled. These patients are resistant or refractory to several immunosuppressive drugs (3).

Due to the low incidence and prevalence, the clinical heterogeneity, the increasing identification of antibodies correlated with specific clinical phenotypes and the limited availability of clinical trials, it is extremely difficult to provide optimised and evidence based therapeutic recommendations (4-6). A substantial growing interest in cellular and molecular research has facilitated knowledge of the pathophysiology of myositis, allowing the development of appropriate biological therapies with which to treat it (7, 8). BCDT now has an established role in the treatment of rheumatoid arthritis and, arguably, systemic lupus erythematosus (9, 10). It can be achieved using rituximab (RTX), a monoclonal chimeric antibody against the antigen CD20, which probably acts by suppressing the antigen-presenting or co-stimulatory function of B cells with a downstream inhibitory effect on T cells. The experience so far noted by early reports suggests it may also be useful in IIM (11-17).

The aim of this study is to review our experience of the long-term efficacy and safety of RTX in patients with refractory IIM and to try to resolve which group might benefit the most from this treatment.

Methods

Sixteen cases out of a cohort of 96 patients with IIM (17.7%) followed at University College London Hospital from 1980 to 2010 have been treated with BCDT. All the registered cases of DM and PM had the disease defined according to the Bohan and Peter's classification criteria (18). Some diagnoses were later modified according to the recent recognised categories (19, 20). Five patients were treated as part of an open-label clinical trial and the remaining 11 based on the perceived clinical need. Preliminary data based on 8 of these patients, specifically patients no. 2, 4, 6, 9, 10, 11, 13 and 16**,** have been reported previously (21). This group comprised seven DM cases, including one JDM type, and an initially diagnosed PM/RA. Two of them had their diagnoses modified (patients no. 6 and 9) subsequently as discussed later. All patients had IIM refractory to GC and at least one immunosuppressant properly used in terms of time and doses. They had to be active during the previous weeks before the intention to treat with RTX and this was determined by muscle weakness on clinical examination according to the Medical Research Council's standardised scale and persistent high serum levels of CK.

A careful review of the protocols for the administration of RTX including dosage, infusion frequency, number of cycles and side effects were noted. Particular attention was paid to other concomitant immunosuppressant therapy used during BCDT, especially when cyclophosphamide (CYF) was administered in order to attain a more profound long-lasting immunodepletion. In the main IV CYF was offered to the more severe patients but some patients refused to have it after being informed

about side effects. Steroid intravenous pulses and oral regime during and after the infusion were also recorded.

Clinical outcomes were measured using the MITAX (Myositis Intention to Treat Index) by chart review, a validated tool designed to assess both muscle and systemic disease activity (skin, joints, lung, cardiac, gastrointestinal and constitutional symptoms) (22, 23). According to the degree of inflammatory activity and the principle of the physician's intention to treat, each organ or system is classified in different categories (A, B, C, D, and E). The severity of all A-E grades is considered to be equivalent among the different systems in terms of their therapeutic requirements. The higher the system activity is considered, the more intensive treatment is likely to be required. Thus, Grade A indicates major activity likely to require increasing prednisolone doses or immunosuppressive drugs to control the disease while Grades B, C, D and E point out decreasing degree of activity and subsequently less or no treatment need**.** A complete response was considered when a patient lost all MITAX A and B features while partial response was a loss of some, but not all, MITAX A and B features**.** To facilitate the data analysis, each grade was assigned a numeric value. By adding all of the values in the different categories it is possible to provide a global score to help assess the clinical benefit of BCDT.

The serum CK levels were recorded at the three data collection times. CD19 plasma levels where reviewed periodically via flow cytometry to verify B-cell depletion (CD19 B lymphocytes count <0.001/ml) as well as its duration. The presence or absence of myositis specific antibodies was also recorded besides other laboratory parameters, such as immunoglobulin levels, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Clinical response was classified as an improvement of at least 20% on the MITAX baseline score and a decrease of at least 30% of CK levels in line with the IMACS international consensus for myositis clinical trials (24, 25). Long-term response was accepted when a patient was stable for at least 12 months in accordance with the standards aforementioned. We also paid attention to time to subsequent flare and need for re-treatment. Side effects and infections were recorded and considered serious if led to hospitalisation.

The open-label study as well as the permission to treat in those patients with refractory myositis was approved by the local hospital ethics committee. All patients gave informed consent.

Results

There were 12 women (75%) and 4 men, with a mean age of 51.1 years (range 30–62 yrs). Their characteristics are shown in Table I. Initially, 5 patients were diagnosed with DM, presenting as classic (2 patients), amyopathic, juvenile onset and one case related with pulmonary fibrosis (but negative anti-Jo 1 antibodies). There were 2 cases of PM, 4 patients with anti-synthetase syndrome (anti-Jo-1 positive in all cases) and 5 patients with myositis overlap syndrome (an associated connective tissue disorder): 2 SLE/DM cases, 2 rheumatoid arthritis/PM cases and one with scleroderma/DM. Nine patients (56.25%) had myositis autoantibodies. The mean time from diagnosis to RTX treatment was 9.75 years (range 2–44 yrs).

All patients received 2 doses of 1 gram RTX infusions two weeks apart. Interestingly, four patients underwent 2 cycles and another one had 3 set of infusions using the same scheme. Eleven patients received 750 mg of CYF intravenous infusion one day after each RTX pulse. It must be kept in mind that CYF has not been proven to be an effective therapy in myositis on its own apart, possibly, from lung involvement (26). To avoid infusion reactions, 100–250 mg methylprednisolone intravenous pulses were used. GC were maintained at the same pre-treatment doses and then, if possible, tapered. Of note, RTX allowed a reduction in oral GC by 2.5–5 mg/day on average in patients eventually shown to be responders. Previous immunosuppressants were not modified during the period of BCDT apart from 2 no responder patients on a clinical need basis. Prior to treatment, median number of immunosuppressive drugs excluding GC was 3.40 (range1–6), being azathioprine (93.7%) and methotrexate (75%) the most common administered.

All patients but one achieved BCD one month after RTX infusion and lasted for 15.4 months on average (range 3-42 months). The patient who did not deplete had a classic DM with a quick, aggressive deterioration leading to death, felt to be unrelated to RTX, within 5 weeks of treatment. Repopulation of plasma B cells was accompanied by a disease flare in 4 patients (25%) who clinically relapsed 6-8 weeks later. By contrast, another 4 patients improved and remained stable despite repopulation. When further cycles of RTX were required, goal clinical responses were achieved again.

However, there was no clinical response in 7 patients with adequate BCD and further investigations were undertaken. The patient with DM and Jo-1 negative pulmonary fibrosis and that with scleroderma/DM did not show any new findings. Nonetheless, anti-signal recognition particle (anti-SRP) antibodies were demonstrated in both initially PM patients. The classic DM patient with a progressive worsening and another rheumatoid arthritis/PM patient were subsequently re-diagnosed with sporadic muscular dystrophy and inclusion body myositis, respectively, after reassessing their biopsies. Overall, these conditions are known to have a poor response to current treatments. The remaining seventh patient, diagnosed with juvenile DM, had a poor response eventually attributed to chronic muscle damage rather than active myositis after performing muscle MRI.

At study entry, inflammation activity by MITAX mean score was 26.2 (range 12–46), with 24 A and 21 B grades in seven different systems. Apart from the muscle, skin, joints and constitutional were the most frequent affected; no available data in patient no. 16. Six months after RTX, MITAX score improved at least 20% in 8 out of 16 patients: all anti-synthetase syndromes, 3 myositis overlap syndromes (2 SLE-related and the remaining RA) and the amyopathic DM. Finally, 5 out of those 8 patients were still controlled at 12 months, with 17.2 MITAX score

Table I. Demographic data, initial diagnoses and previous medications.

Patient	Diagnosis	Ethnic	Age/sex	Disease Duration (yrs)	Auto-antibodies	Previous Treatment	Treatment at entry
1	PM	C	46/F	2	SRP+	AZA, MTX, MMF, IVIg,	MTX
2*	**DM**	**C**	**62/F**	**6**	**ANA+ Jo-1 +ve**	**AZA**	**AZA**
3	DM	A/C	43/F	2	ANA +ve SRP +ve	AZA, MTX, MMF, IVIg	Pred MTX
4*	**DM**	**C**	**56/F**	**8**	**Jo-1 +ve**	**AZA, MTX, CyP, IVIg**	–
5	PM	A/C	56/M	2	ANA +ve Jo-1 +ve	AZA, CyP, MMF	Pred
6*	**DM**	**AFRIC**	**30/F**	**8**	**ANA +ve**	**AZA, MTX, IVIg, Tacro**	**Pred MTX**
7	DM	ASIA	41/M	2	MSA –ve	AZA, CyP, IVIg	Pred AZA
8	DM/SCL	C	52/F	29	ANA +ve RNP +ve	AZA, MTX, IVIg	Pred
9*	**PM/RA**	**C**	**60/M**	**4**	**ANA +ve RF +ve**	**AZA, MTX, IVIg**	**Pred**
10*	**ADM**	**C**	**46/F**	**15**	**MSA –ve**	**AZA, MTX, CyP, IVIg, MMF**	**Pred AZA**
11	DM/SLE	C	48/F	15	ANA +ve Jo-1 +ve	AZA, MTX, CyP, MMF, CYF, IVIg	Pred MTX
12	DM/SLE	C	58/F	3	ANA +ve	AZA, MTX, CyP, IVIg	Pred
13*	JDM	C	53/F	44	MSA –ve	AZA, MTX, IVIg	Pred AZA
14	PM	C	54/F	3	ANA +ve Jo-1 +ve	AZA, MTX, CyP	Pred AZA
15	PM/RA	C	55/F	12	Jo-1 +ve RF +ve	AZA, MTX, CyP, IVIg	Pred MTX
16*	**DM**	**C**	**58/M**	**20**	**ANA +ve**	**IVIg**	**Pred MTX**

DM/SCL: DM overlap scleroderma; PM/AR: PM overlap rheumatoid arthritis; DM/SLE: DM overlap systemic lupus erythematosus; ANA: antinuclear antibodies; RF: rheumatoid factor; RNP: anti-ribonucleoprotein antibodies; Pred: prednisolone AZA: azathioprine; MTX: methotrexate; CyP: cyclosporine; CYF: cyclophosphamide; IVIg: intravenous immunoglobulin; Tacro: tacrolimus. +ve: positive; -ve: negative. **no.***: patient previously reported by Sultan *et al*.

on average; those 3 patients who were unresponsive had a flare between sixth and eighth month of the follow up period but achieved long-lasting clinical response after a second RTX infusion (Table II).

With a baseline average of 4997.3 UI/L, CK levels started to decline within one month after RTX was given in all responder patients. At six months, 10 patients showed at least 30% reduction in serum CK, thus considered responders. No clinical response was correlated to the MITAX score in 2 out of these 10 patients, the scleroderma/DM patient who remained clinically stable and one case of anti-SRP syndrome. CK levels were still controlled at 12 months assessment in 7 patients of the original 10 responders.

Cyclophosphamide intravenous pulses were added to RTX in 11 patients (73.3%) and BCD of 18,6 months average (SD 11,6 months) was noted compared to 9.7 months (SD 4.2 months) in the remaining four patients (26.7%) who did not receive them. These data are not statistically significant (p=0.12) probably due to the scarce number of patients collected. In the "CYF group" 6 out of these 11 patients achieved clinical response and 2 out of 4 patients in the "non CYF group".

These data are in keeping with those 7 cases of partial remission observed at 6 months and with 3 cases who achieved full remission at 12 months based on the loss of MITAX A and B scores (Table III). There were 6 patients who remained in partial response at 12 months, including those 3 patients who needed a second cycle of RTX who in-

Table II. MITAX score and CK levels results.

Patient	MITAX			CK levels (N 24–173 UI/L)			CYF Pulses	BCD (mo)	Clinical benefit/diagnosis
	0 mo	6 mo	12 mo	0 mo	6 mo	12 mo			
1	14	14	14	7375	2449	6000	Yes	5	Non responder / anti-SRP
2*	39	13	5	25000	8388	2560	Yes	>42	Responder / anti-synthetase
3	23	7	19	996	930	4742	Yes	8	Non responder / anti-SRP
4*	28	32	22	4381	3100	2865	Yes	16	Responder (2nd cycle) / anti-synthetase
5	25	25	12	19000	1600	954	Yes	18	Responder (2nd cycle) / anti-synthetase
6*	23	23	23	1366	1268	2197	Yes	8	Non responder / revised diagnosis: limb girdle dystrophy
7	46	32	39	58	45	63	Yes	>19	Non responder / DM Jo-1 –ve
8	23	23	23	331	231	199	Yes	>12	Non responder but stable / Scl/DM
9*	18	25	18	450	600	620	No	>7	Non responder / revised diagnosis: inclusion body myositis
10*	25	22	14	292	107	142	No	>16	Responder / amyopathic DM
11	35	13	16	414	256	207	No	8	Responder / SLE/DM
12	27	8	9	1300	459	165	Yes	>36	Responder / SLE/DM
13*	46	41	31	240	–	205	No	>8	Non responder / JDM
14	15	19	6	13426	12520	3400	Yes	12	Responder (2nd cycle) / anti-synthetase
15	23	4	1	4000	–	968	Yes	16	Responder / PM/RA
16*	26	–	–	1328	–	–	–	Did not deplete	Non responder Died 1 month after BCDT

terestingly achieved full remission 6 months later.

When considering systemic manifestations, some degree of interstitial lung involvement was recorded in up to eight patients of the series. Spirometry with DLCO and HRCT chest scan were undertaken during the follow up to assess the response but only on an 'as required' basis. Cyclophosphamide was given to 6 out of these 8 patients, that is, no. 2, 4, 5, 7, 14 and 15; by contrast patients no. 11 and no. 16 to the best of our knowledge were not given cyclophosphamide. When evaluating response to treatment, patients no. 2 and no. 11 showed improvement in those pulmonary tests reflected in their MITAX index score improving to grade C (mild activity). Likewise, skin manifestations seem to respond variably to RTX, with a poor response in our patient with amyopathic form. Two patients had non serious cardiac involvement which remained stable. In general, dysphagia due to esophageal involvement did not improve.

Immunoglobulin levels remained in the normal range even in patients with repeated cycles of RTX. Of note, Rituximab was well tolerated by all patients although 2 infusion reactions consisting of rash and generalised arthromyalgias were noted two weeks after treatment. In addition, three patients suffered from frequent lower respiratory tract infections during the follow up period, which quickly resolved with outpatient antibiotic therapy. There were no signs of the fearsome progressive multifocal leukoencephalopathy.

Discussion

This report extends our original study doubling the number of patients and providing more clinical and serological data over a longer follow up period and some support for the idea that BCD may be useful and safe in certain cases of aggressive and refractory myositis (21). Thus, RTX should be considered for those patients most likely to respond and these are evidently those with myositis specific autoantibodies, particularly those with anti-synthetase syndrome (anti-Jo-1 positive) and also in myositis overlap syndromes, subset of patients with encouraging outcomes (27, 28).

The experience with RTX in patients with IIM is still limited. Nonetheless, this drug has already shown promising results since its initial trial in DM reported by Levine (29). Several open-label trials and anecdotal case reports have encouraged such an approach and have borne out its efficacy (30-34). Two recent studies of Mahler and Oddis must be highlighted. Mahler *et al*. reported a worthwhile improvement with sustained effect during a median of 27.1 months of follow-up in a prospective study of 13 patients (36). Despite not reaching primary endpoints, Oddis *et al*. have just communicated that 163 out of 200 patients (83%) enrolled in their double-blind, placebo-controlled trial – the RIM study, the largest clinical trial so far – met the consensus criteria for improvement (37). Furthermore, every national registry recording rituximab treatment, like the Spanish BIOGEAS registry, is reporting encouraging results. Thus, this registry published that up to 17 patients of the series (85%) showed a complete/partial response without significant adverse events (38). In the interim we now provide detailed information on 16 patients closely observed at a single centre and taken together with those previous studies suggest that RTX has the capacity to induce partial, and occasionally full, clinical remission defined by MITAX and CK levels, even in those patients who relapsed and required an additional cycle of the drug. Additionally, RTX allowed the reduction in corticoids doses avoiding potential side effects. Regard-

Table III. Clinical response defined as loss of MITAX A/B categories.

	MITAX A/B SCORES			
Patient	At baseline	At 6 months	At 12 months	Remission (6/12 months)
1	Muscle A	Muscle A	Muscle A	Non responder
2*	Constitutional B Joint B Muscle A Lung A	Constitutional C Joint C Muscle B Lung C	Constitutional C Joint C Muscle C Lung C	Partial / Full
3	Constitutional B Muscle A Esophageal B	Constitutional C Muscle B Esophageal C	Constitutional C Muscle B Esophageal B	Partial / Partial
4*	Joint A Muscle A	Joint A Muscle A	Joint C/ Joint C Muscle B/ Muscle C	No response / Partial
5	Joint A Muscle A	Joint A Muscle A	Joint B / Joint C Muscle B / Muscle C	No response / Partial
6*	Joint B Muscle A Skin B	Joint B Muscle A Skin B	Joint B Muscle A Skin B	Non responder
7	Constitutional A Joint B Muscle A Lung A Skin B	Constitutional B Joint B Muscle B Lung A Skin B	Constitutional A Joint B Muscle A Lung A Skin B	Non responder
8	Constitutional B Muscle A Skin B	Constitutional B Muscle A Skin B	Constitutional B Muscle A Skin B	Non responder
9*	Constitutional B Muscle A	Constitutional A Muscle A	Constitutional B Muscle A	Non responder
10*	Joint B Muscle A Skin A	Joint B Muscle B Skin A	Joint C Muscle C Skin A	Partial / Partial
11	Joint B Muscle A Lung B Skin A	Joint C Muscle B Lung C Skin B	Joint C Muscle C Lung C Skin B	Partial / Partial
12	Constitutional B Joint B Muscle A Skin B	Constitutional C Joint B Muscle C Skin C	Constitutional C Joint C Muscle C Skin C	Partial / Full
13*	Constitutional B Joint A Muscle A Esophageal B Skin A	Constitutional B Joint A Muscle A Esophageal C Skin A	Constitutional B Joint A Muscle A Esophageal C Skin B	Non responder
14	Muscle A	Muscle A Lung B	Muscle B /Muscle C Lung C / Lung C	Partial / Partial
15	Constitutional B Joint B Muscle A	Constitutional C Joint C Muscle C	Constitutional C Joint C Muscle C	Partial / Full
16*	Muscle A Lung A	– –	– –	Non responder

ing its safety, serious adverse events did not appear, nor did hypogammaglobulinaemia despite repeated therapy.

It is worthy of note how cyclophosphamide use extends the period of immunodepletion, much longer than the 9 months average described by Oddis, and thereby potentially allows a greater period free of symptoms. Therefore, cyclophosphamide could play an interesting role as an adjuvant treatment in this condition. Furthermore, we found that immunodepletion in myositis may be longer than in RA and SLE patients suggesting that other pathophysiologic

mechanisms might be involved in the B cells repopulation in these conditions (39).

Although response to RTX appeared to be dependent upon adequate immunodepletion, relapses did not invariably correlate with the return of B cells and need for retreatment did not correlate with levels of CD19+cells in some cases. Likewise, the way CK levels change after treatment should not lead any therapeutic intervention in the absence of clinical deterioration. No data were available on changes in myositis autoantibodies titres. Human Anti-chimeric Antibodies (HACA) essays were not available though we wondered whether they could have any role in non responder patients. However, data from patients with rheumatoid arthritis reviews suggest this is unlikely (39).

There have been postulated several predictors of outcome such as the specific type of myositis, disease severity, delay in diagnosis, selected extra-muscular disease features, autoantibody profile, certain cytokine and chemokine levels changes (IL-2, TNF-α) as well as pharmacokinetic and pharmacodynamic properties which could explain the response heterogeneity (40). However, when an adequate B cell depletion is not followed by a clinical or biochemical improvement, other possibilities need to be considered including other myopathies or underlying neoplasm. Whether the symptoms the physician observes represent activity or damage must be carefully considered (41, 42). Imaging and serological tests need to be repeated or reviewed and we strongly recommend re-appraising or even repeating muscle biopsy especially in cases of PM to evaluate the possibilities of muscle dystrophy or inclusion body myositis. Recent studies of MRI images indicate that they may be an effective alternative technique and obviously quite less "aggressive" than biopsy. It is of the utmost importance to distinguish between chronic muscle damage and inflammatory activity before embarking on therapeutic interventions.

We are aware about of the limitations of our study. It is in essence a retrospective review. Some of the evaluations were incomplete. In addition, this series encompass a modest number of patients and a heterogeneous group of myopathies which make it difficult to draw definite conclusions. We found no bias from additional or increased doses of concomitant immunosuppressive therapy during the study period. The optimal dosing regime, duration of therapy, when re-treatment should be considered, whether to use combination therapies and safety profile of RTX therapy in the treatment of autoimmune myositis remains to be elucidated and open to debate. Further randomised clinical trials with RTX are underway to shed light on these questions and probably today's most important challenge is to know how to use it more effectively.

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