Review

Rituximab in the treatment of dermatomyositis and other inflammatory myopathies. A report of 4 cases and review of the literature

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ABSTRACT

Objective. *Rituximab is an anti-CD20 monoclonal antibody targeting B cells, which has been used with success in a wide variety of autoimmune diseases. The experience with this drug in patients with inflammatory myopathies (IM), nonetheless, is still limited. We review the literature and highlight several aspects in relation to therapy with rituximab in IM.*

Methods. *We performed a research in the MEDLINE DATABASE. All cases identified from the literature research and cases diagnosed in our Unit were included in the analysis.*

Results. *We identified 49 patients with IM treated with rituximab in the review of the literature carried out (31 female; 18 male), including our patients. Dermatomyositis (DM) was the most common disorder for which rituximab treatment was administered (69.4%). The other diseases treated included polymyositis (PM) 16.3%, antisynthetase syndrome (AS) 8.2%, one case with anti-SRP-syndrome and other with juvenile dermatomyositis. The median time to diagnosis was 48 (0.75–480) months. Sixty-five per cent (65.3%) of patients presented with skin manifestations, 89.8% with muscle weakness, 7.3% with arthritis, 16.3% with interstitial lung disease, and 7.3% with cardiomyopathy. Seventy-one (71.4%) of the patients received only one course of rituximab, 18.4% two courses, 4.1% three, 2% four and only 4.1% five. We have observed both among our patients and those reported in the literature a high rate of response to rituximab, 75% of our patients and 72.5% of those described in the literature showed a good response. The median time free of symptoms between two courses was 12 (6-19) months. Rituximab was generally well tolerated by all patients, with no serious adverse events. Most of the adverse events reported were mainly infections, particularly respiratory tract infections.*

Conclusions. *It is our belief that rituximab may be an optimal therapeutic choice for inflammatory myopathies. Nevertheless, there is a need for additional studies in order to assess the optimal regimen of treatment in the different subsets, as well as the initial dose, combination of treatments and re-treatment schedule.*

Introduction

Dermatomyositis (DM) is a chronic inflammatory disorder that involves the muscles and the skin, and which is included within the inflammatory myopathies (IM), a group of autoimmune muscular diseases in which inflammation and degeneration of skeletal muscle tissues develop. IM usually respond to steroids, whether associated or not with conventional immunosuppressive agents, such as azathioprine and methotrexate (MTX) or intravenous immunoglobulins (1). However, there are occasionally refractory forms of the disease (2, 3) that are very difficult to treat.

Rituximab (RTX) is an anti-CD20 monoclonal antibody targeting B cells, which has been used with success in a wide variety of autoimmune diseases. The experience with this drug in patients with inflammatory myopathies, nonetheless, is still limited.

In the present study, we report 4 patients with DM treated with RTX. In addition, we review the literature and highlight several aspects in relation to therapy with rituximab in IM.

Table I. General clinical, immunosuppressive therapies before, concomitant and after RTX therapy and response of patients with Inflammatory Myopathies.

References	Sex/Age (years)	Symptoms	Symptoms duration until RTX therapy (months)	Previous therapies	Concomitant medications	Therapy after RTX	Number of RTX courses/dosage	Longest remission time (months)	Response
Cooper *et al*.	F/10	Skin findings Muscle weakness	27	Pred,MTX, IVIG, MP	MTX, IVIG, CFM, MP		2/375 mg/m^{2}x4 weeks	14	Y
Cooper *et al*.	M/14	Skin findings Muscle weakness	1.25	Pred, MTX, HCQ	Pred, MTX, MP	MTX, Pred	1/375 mg/m^{2}x4 weeks	12	Y
Cooper *et al*.	F/14	Skin findings Muscle weakness	4	Pred, Mtx, IVIG, MP	Pred, MTX, IVIG,MP	MTX, Pred, IVIG,	2/375 mg/m^2 x4 weeks	13	Y
Cooper *et al*.	F/17	Skin findings Muscle weakness	1.5	Pred, MTX	Pred, MTX, MP	IG, CsA, CYC	1/375 mg/m^{2}x4 weeks	0	N
Dinh *et al*.	F/22	Skin findings	96	Pred, MTX, HCQ, CLQ, CsA, AZA, leflunomide	Pred	None	2/375 mg/m^{2}x4 weeks	9	Y
Dinh *et al*.	F/16	Skin findings Muscle weakness	96	Pred, MP,MTX, HCQ,CYA	CsA	None	1/375 mg/m^{2}x4 weeks	20	Y
Dinh *et al*.	F/45	Skin findings	48	Pred, MTX, HCQ, AZA, MMF	Pred		1/	6	Y
Brulhart *et al*.	F/57	Skin findings Muscle weakness Arthritis ILD	2	Pred, MTX	Pred, MTX		2/1gx2 weeks	8	Y
Noss *et al*.	M/47	Skin findings Muscle weakness Transient lung infiltrates	36	Pred, IVIG, MTX, infliximab, etanercept, adalimumab	MTX, Pred	MTX, Pred	2/1gx2 weeks	7	Y
Noss *et al*.	F/54	Muscle weakness Arrhythmias	6	Pred, IVIG, MTX, AZA, etanercept, infliximab	MTX, MP	MTX, Pred	2/1gx2 weeks	10	Y
Noss *et al*.	F/53	Muscle weakness Arrhythmias	4	Pred, IVIG, MTX,AZA, leflunomide, etanercept infliximab	AZA, pred, MP	MMF	1/1gx2 weeks	12	Y
Chiappetta *et al*.	M/56	Skin findings Muscle weakness Arthritis	0.75	CTC, IVIG, MTX, HCQ, AZA, CFM, infliximab	Pred	Pred, AZA, MTX	2/210 mg/m^{2}x3 days and 1 more	20	Y
Lambotte *et al*.	F/47	Skin findings Muscle weakness ILD	48	Pred, MTX, AZA, IVIG	Pred	Pred	1 /375 mg/m^{2}X4 weeks	12	Y
Levine *et al*.	M/64	Skin findings Muscle weakness	3.6	None	None		1/375 mg/m^2 x4weeks	9	Y
Levine *et al*.	F/21	Skin findings Muscle weakness	84	CTC, AZA	IVIG		1/375 mg/m^2 x4weeks	6	Y
Levine *et al*.	F/48	Skin findings Muscle weakness ILD	48	CTC, CFM,AZA	CTC, CYC, AZA		1/375 mg/m^2 x4weeks	9	Y
Levine *et al*.	F/53	Skin findings Muscle weakness ILD	180	CTC, MTX, CYA, etanercept	IVIG, AZA		1/375 mg/m^2 x4weeks	2	Y
Levine *et al*.	F/38	Skin findings Muscle weakness	156	MTX, HCQ, IVIG	CTC		1/375 mg/m^2 x4weeks	2	Y
Levine *et al*.	F/53	Skin findings Muscle weakness ILD	180	MTX, etanercept	CTC, AZA		1/375 mg/m^{2}x4 weeks	6	Y
Gottenberg *et al*.	F/55	Skin findings Muscle weakness	228	IVIG, MTX	Pred	Pred	1/375 mg/m^{2}x4 weeks		Y
Gottenberg *et al*.	F/53	Muscle weakness	72	MTX, AZA, IVIG	Pred	Pred	1/375 mg/m^{2}x4 weeks	5	Y
Chung *et al*.	F/42	Skin findings Muscle weakness	24	CsA, MTX, AZA, tacrolimus, etanercept	Pred, MTX		1/1gx2 weeks		N
Chung *et al*.	M/76	Skin findings Muscle weakness	12	Topical agents	Pred		1/1gx2 weeks		Only muscle strength

Chung *et al.*	M/42	Skin findings Muscle weakness	12	MMF	MMF		1/1gx2 weeks		Only muscle strength
Chung *et al.*	M/54	Skin findings Muscle weakness	72	MTX, HCQ, IVIG, CsA	MTX, MP		1/1gx2 weeks		Only muscle strength
Chung *et al.*	M/65	Skin findings Muscle weakness	24	HCQ;AZA	Pred, HCQ, AZA		1/1gx2 weeks		Only muscle strength
Chung *et al.*	M/38	Skin findings Muscle weakness	288	AZA,HCQ,IVIG	None		1/1gx2 weeks		Only muscle strength
Chung *et al.*	M/42	Skin findings Muscle weakness	60	MTX, AZA, IVIG, MMF, CsA	Pred, MTX		1/1gx2 weeks		N
Chung *et al.*	M/46	Skin findings Muscle weakness	132	MTX, AZA	Pred, AZA		1/1gx2 weeks		N
Touma *et al.*	F/25	Cardiac involvement Muscle weakness Polyartrhalgia	10	Pred, MTX, etanecerpt	MP	Pred	1/1gx2 weeks		Y
Mok *et al.*	F/46	Muscle weakness	93.6	Pred, MP, AZA, CsA, MMF,IVIG	Pred, MMF		1/375 mg/m^{2}X4 weeks		Y
Mok *et al.*	F/51	Muscle weakness	93.6	Pred, AZA, CsA, MTX, MMF, tacrolimus, IVIG	Pred, tacrolimus		1/375 mg/m^{2}X4 weeks		Y
Mok *et al.*	M/69	Muscle weakness	93.6	Pred, AZA, MMF	Pred MMF		1/375 mg/m^{2}X4 weeks		Y
Mok *et al.*	F/47	Muscle weakness	93.6	Pred, MP, AZA, CsA, CYC, IVIG, MMF	Pred, MMF		1/375 mg/m^{2}X4 weeks		Y
Arlet *et al.*	M/20	Muscle weakness	60	Pred, plasma exchange, IVIG, CsA, CYC, sirolimus	Pred	Pred	5/375 mg/m^{2}x4 weeks	24	Y
Arlet *et al.*	F/24	Muscle weakness	44	Pred, plasma exchange, MTX, AZA, CsA	Pred	Pred	5/375 mg/m^{2}x4 weeks	15	Y
Feist *et al.*	M/54	Skin lesions Muscle weakness	6	MP, CYC,	MP, CYC,	Pred, MTX	3/1gx2weeks	53	Y
Sultan *et al.*	F/56	ILD Muscle weakness	168	MTX, Leflunomide, P, CsA, CYC, IVIG, Pred	Pred, etanercept, MP	Pred	2/1gx2 weeks	12	Y
Sultan *et al.*	F/56	Skin lesions	156	Pred, AZA, HCQ, CsA, thalidomide, IVIG	Pred, MTX, MP	MTX, Pred	1/1gx2 weeks		N
Sultan *et al.*	F/50		480	MTX, AZA, IVIG, Pred	MP		1/1gx2 weeks		N
Sultan *et al.*	F/57	Muscle weakness Autoimmune thrombocytopenia	84	MTX, CsA, Pred	MTX, AZA, MP	Pred, MTX	1/1gx2 weeks		N
Sultan *et al.*	M/60	Muscle weakness	48	MTX, CsA IVIG, Pred	Pred, MP	Pred	1/1gx2 weeks		N
Sultan *et al.*	F/63	ILD Muscle weakness	72	AZA, pred	Pred, AZA, MP	Pred, AZA	1/1gx2 weeks	36	Y
Sultan *et al.*	F/31	Muscle weakness	180	Pred, AZA, MTX	Pred, AZA, MP, MTX	Pred, MTX	1/1gx2 weeks		N
Sultan *et al.*	M/58		240	MTX, CsA, IVIG	Pred, MP	Pred	1/1gx2 weeks		N
Lutt *et al.*	M/55	Muscle weakness Skin lesions	100	Pred, MTX, IVIG,MMF	Pred, MMF	Pred	2/375 mg/m^{2}x2 weeks		Y
Lutt *et al.*	F/34	Muscle weakness	108	Pred, AZA, MTX	MTX, AZA, pred	MTX, Pred	1g/2 x weeks 2/750 mg	6	Y
Present report	M/41	Skin lesions Muscle weakness	48	Pred, AZA, IVIG, HCQ, MP	HCQ, AZA, Pred	AZA, Pred	2/375 mg/m^{2}x4 weeks	12	Y
Present report	M/67	Skin lesions Muscle weakness	11	CTC, HCQ, MP, IVIG, mepacrine	Pred, HCQ	Pred, HCQ	2/375 mg/m^2 x4 weeks	18	Y
Present report	F/42	Skin lesions	23	CTC, HCQ; mepacrine, IVIG	Pred, mepacrine, HCQ	Pred HCQ	1/375 mg/m^{2}x4 weeks	0	N
Present report	F/47	Skin lesions Muscle weakness	60	Pred, HCQ, mepacrine, AZA, CsA, MTX, infliximab, etanercept, IVIG, CYC	MTX, HCQ, etanercept	Pred, HCQ	1/1gx2 weeks 1/375 mg/m^{2}x4 weeks	20	Y

Pred: prednisone; MP: metilprednisolone; AZA: azathioprine; CsA: cyclosporine; MTX: methotrexate; MMF: mycophenolate mofetil; IVIG: inmunoglobulins; CYC: cyclophosphamide; HCQ: hydroxichloroquine; CTC: steroids; P: penicillamine.

Methods

We performed a research in the MEDLINE DATABASE (National Library of Medicine, Bethesda, MD) using inflammatory myopathies, dermatomyositis, polymiositis, inclusion body myositis, juvenile dermatomyositis, antisynthetase syndrome and rituximab as key words. All cases identified from the literature research were included in the analysis. These cases, along with the 4 cases diagnosed in our Unit served as the basis of the present report. Patients had a diagnosis of probable or definitive IM according to the criteria of Bohan and Peter (4). Response was considered if it was a 15% improvement in muscle strength, 30% reduction in CPK, 20% in physicians global activity assessment assessed by a 10 cm visual analog scale (VAS), 20% in patient's global activity assessment assessed by 10 cm VAS and 15% improvement in physical function (5). We describe the 4 aforementioned patients below.

Case reports

Case 1

A 41-year-old male had been diagnosed with DM in February 2002, after progressive proximal weakness graded at 3/5 in proximal arms and legs and typical cutaneous lesions of DM. His laboratory evaluation showed: CRP 0.8 mg/dl (normal value (NV) 0-0.8), ERS 50 mm/h (NV 1-11), AST 308 IU/l (NV 0-32), ALT 219 IU/l (NV 0-35), LDH 1360 IU/l (NV 230-460), CK 3458 IU/l (NV 40-200), ANA, ENA and rheumatoid factor were negative. Electromyography showed spontaneous fibrillations and short-duration polyphased motor potentials, all suggestive of IM. Muscle biopsy findings revealed focal muscle cell necrosis surrounded by lymphocytes and macrophages and perivascular infiltrates. From the diagnosis until February 2006 he received multiple medications (Table I) with only a partial improvement. Thus, we decided to start the patient on intravenous RTX 375 mg/m^2 weekly for 4 consecutive weeks, in association with three intravenous pulses of 6-MP (500 mg). A complete response was achieved with a muscle strength graded at 5/5 in arms and legs, along with normalization of the levels CK (Fig. 1), the patient then being able to reduce his dose of azathioprine and that of prednisone. In February 2007, he had a relapse, which mainly involved the skin. He was on hydroxichloroquine 200 mg/d, prednisone 5 mg/d and azathioprine 100 mg/d by then, and mepacrine (100 mg/d) was thus added. However, no efficacy was noted and the patient received a second course of RTX in May 2007. At that moment IgG was 557 mg/dL (NV 700-1600) and CD19 13 cells/µl. After this second course, his skin lesions significantly improved. His CD19+ B cells levels decreased and CK levels normalised again (Fig. 2); IgG was 602 mg/dl. When we last saw the patient in March 2009, the muscle strength was normal and his CK levels remained within normal ranges.

Case 2

A 67-year-old man with type II diabetes mellitus, hypertension and a history of hemorrhagic cerebrovascular accident, was diagnosed with DM in July 2005, when he presented with skin lesions involving his chest and shoulders, fever, fatigue, myalgias and progressive proximal muscle weakness which was grade 3/5. Laboratory evaluation revealed: ESR 74 mm/h, CRP 10.1 mg/dl and positive rheumatoid factor (68 IU/l, NV <20 IU/l), AST 101 IU/l, ALT 120 IU/l, LDH 556 IU/l, CK 2103 IU/l. ANA and ENA were negative. Electromyography findings were consistent with the diagnosis of IM. Muslce biopsy showed myopathic changes consistent with muscle fiber necrosis and perivascular inflammation with lymphocytes. He was then treated with prednisone, azathioprine and IVIG. However, only the use of cyclophosphamide (CYC) resulted in an appropriate improvement, with normalization of the laboratory parameters and a muscle strength improvement to 4/5. In June 2006, the patient had a new relapse and it was decided to start him on RTX, as in case 1 with 375 mg/m^2 weekly for 4 consecutive weeks. Bolus of steroids were not given simultaneously. Immunoglobulin G was 1390 mg/dl. The patient had a complete clinical response, with resolution of the skin lesions and a normalisation of strength and CK. Immunoglobulin G was 557 mg/dl and CD19 cell count was 14 cells/ul. When prednisone was tapered in May 2007, his exercise tolerance worsened and new skin lesions appeared, with normal CK, but elevated myoglobin. CD19+ cell count was 11 cells/µl and IgG 557 mg/dL. Even though prednisone and azathioprine was increased, the patient did not improve and additional RTX infusions were prescribed in July 2007. We last saw him in February 2009. He was without skin lesions, with complete recovery of the muscle strength (5/5) and normal muscle enzymes.

Case 3

A 42-year-old female with a 10-year history of guttate psoriasis was diagnosed with *in situ* intraductal carcinoma in June 2005, which was treated with mastectomy, chemotherapy and RX. The patient was also prescribed coadjuvant therapy with tamoxifen. From diagnosis, she developed persistent pruritus and rash involving her arms, fingers, neck and upper chest on a "shawl" distribution, and heliotrope discoloration of the eyelids. Inflammatory parameters and muscle enzyme levels were within normal limits. ANA, ENA and rheumatoid factor were negative. Electromyography was also normal. Skin biopsy findings, however, were consistent with DM with perivascular inflammatory infiltrate with mucin deposition. Paraneoplastic amyopathic DM was thus diagnosed, an active coexistent malignant disease being ruled out upon investigation, including PET. She successively received multiple therapies (Table I). Since only intravenous pulses of 6-MP resulted in considerable improvement, we proceeded to administer her 4 doses of RTX in May 2007 (as in case 1). Clinical improvement was only modest and for a limited period of time.

Case 4

A 47-year-old woman without a remarkable past medical history was referred to our Clinic in 2000 with polyarthritis, fever and proximal muscle weakness graded 3/5. She also referred dysphonia, non-productive cough and dyspnea on moderate exertion. The presence of hyperkeratosis on fingers

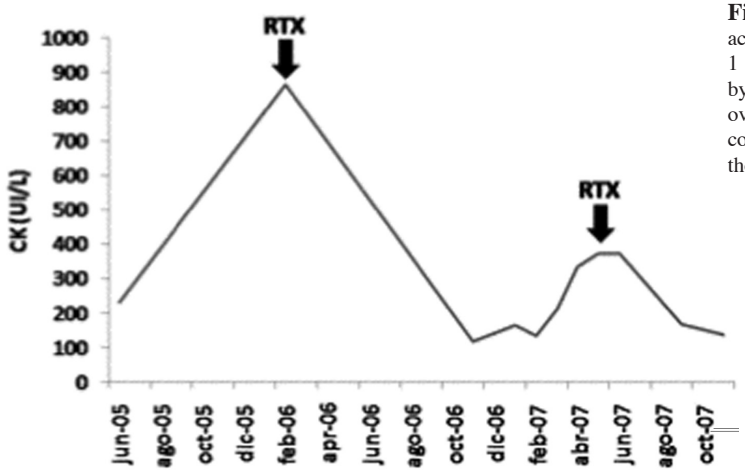

Fig. 1. Disease activity of patient 1 documented by patient's CK over time with correlating RTX therapy.

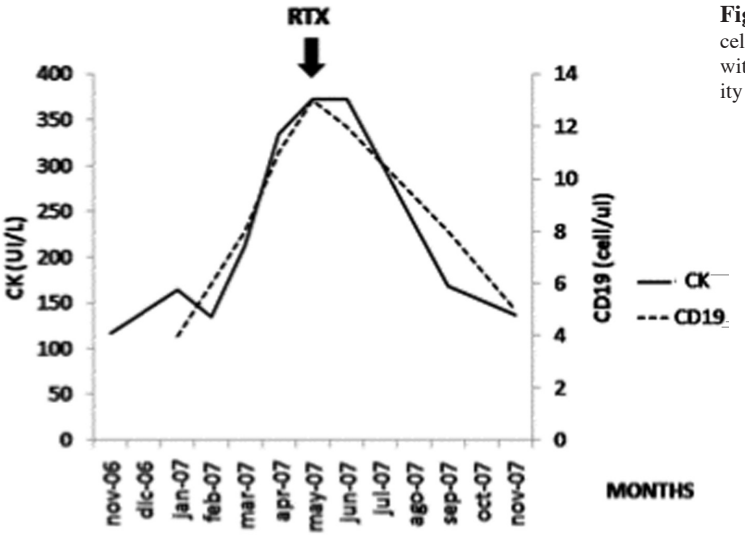

Fig. 2. CD19 +B cells correlating with disease activity in patient 1.

(mechanic's hand lesions), a diffuse erythematous rash over the V-area of the anterior neck and crackles on pulmonary auscultation were evident on physical examination. Her laboratory evaluation showed: lymphocytes 600/mm^3, CRP 7.3 mg/dl and normal CK, AST, ALT and LDH. ANA, ENA and rheumatoid factor were negative. EMG showed marked myopathic changes. Muscle biopsy showed necrosis, myophagocytosis and regenerating fibers. A high resolution CT scan of the chest was performed in June 2005, which showed bilateral ground glass lesions at the lower lobes (Fig. 3). Pulmonary function tests revealed a DLCO/AV of 75.6%. The skin biopsy specimen was consistent with DM, and the lung biopsy specimen confirmed the diagnosis of Usual Interstitial Pneumonia (UIP). She was diagnosed then with dermatomyositis. The patient received multiple therapies (Table I), only yielding a partial response. In August 2005 she received intravenous RTX (2x1g infusions) in combination with 500 mg of metilprednisolone and CYC 750 mg. The arthritis, muscle weakness and skin lesions responded well to the RTX therapy. In January 2006 a new high resolution CT scan of the chest showed that lung abnormalities had disappeared (Fig. 4), and the lung function tests had also improved, with an increase of DLCO/AV to 92%. She had a respiratory tract infection 10 days following the RTX infusions, which resolved with antibiotic treatment. However, in March 2007, she had a relapse, with worsening of articular symptoms, fever and asthenia; CD 19+ was 20 cells/uL and IgG 1075 mg/dL. A second course of RTX (375 mg/m^2 weekly for 4 consecutive weeks), in combination with 250 mg of 6-MP, led to significant improvement. When we last saw the patient in November 2008, she had normal muscle strength (5/5) and was able to lead a normal life; the CD19+ cell count was 96 cells/µl and IgG 754 mg/dL.

Results

We identified 51 patients with IM treated with RTX in the review of the literature carried out (32 female and 19 male), including our patients. The epidemiologic features and characteristics of the patients are shown in Table I. DM was the most common disorder for which RTX treatment was administered (68.6%). The other diseases treated included PM 17.6%, antisynthetase syndrome (AS) 7.8%, two cases with anti-SRP-syndrome and other with juvenile dermatomyositis (Table II). The median time to diagnosis was 54 months (range 0.75–480). Sixty-four percent (64.7%) of patients presented with skin manifestations, 90.2% with muscle weakness, 7.3% with arthritis, 16.3% with interstitial lung disease, and 7.3% with cardiomyopathy. Thirty-six (70.6%) of the patients received only one course of RTX, 19.6% two courses, 3.9% three, 2% four and only 3.9% five. The median number of previous medications was 5 (range 1–37). Most of the patients received additional immunosuppressive therapy along with the course of RTX: 86.3% steroids and 29.4% methotrexate (Table IV).

The majority of patients had an adequate response (Table III). The median time free of symptoms between two courses was 12 months

RTX was generally well tolerated by all patients, with no serious adverse events. Most of the adverse events reported were mainly infections, particularly respiratory tract infections, as in one of our patients (Table V).

Discussion

Rituximab has shown promising results in the treatment of a variety of autoimmune diseases (6) ever since its initial use in patients with lymphoma.

Table II. Results of published studies on RTX in patients with IM.

References	Patients (n.)	Underlying disease
Cooper *et al*.	4	DM
Dinh *et al*.	3	DM
Brulhart *et al*.	1	AS
Noss *et al*.	2	PM
	1	DM
Chiappetta *et al*.	1	DM
Lambote *et al*.	1	AS
Levine *et al*.	6	DM
Gottenberg *et al*.	2	AS
Chung *et al*.	8	DM
Touma *et al*.	1	DM
Mok *et al*.	4	PM
Feist *et al*.	1	DM
Arlet *et al*.	2	Anti-SRP syndrome
Sultan *et al*.	5	DM
	2	PM
	1	JDM
Lutt *et al*.	1	DM
	1	PM
PR	4	DM

PR: present report; AS: antisynthetase syndrome; DM: dermatomyositis; PM: polymiositis; JDM: juvenile dermatomiositis.

Table III. Characteristics of the patients included.

Characteristic	n.
No. of patients	51
Age in yrs; mediam (range)	47 (8–76)
Female (%)	32 (62.7%)
Time to diagnosis in mo; median (range)	54 (0.75-480)
Clinical findings	
Skin involvement	33 (64.7%)
Muscle weakness	46 (90.2%)
Arthritis	3 (7.3%)
ILD	8 (16.3%)
Heart	3 (7.3%)
Follow-up duration in months; median (range)	8 (1-53)
Number of courses	
1	36 (70.6%)
2	10 (19.6%)
3	2 (3.9%)
4	1 (2%)
5	2 (3.9%)
Dosage of rituximab	
1gx2	23 (45.1%)
375x4	26 (51%)
Others	2 (3.9 %)
Free of symptoms post-therapy; mediam (range)	12 (2–53)
Response	
Y	40 (78.4%)
N	11 (22.4%)

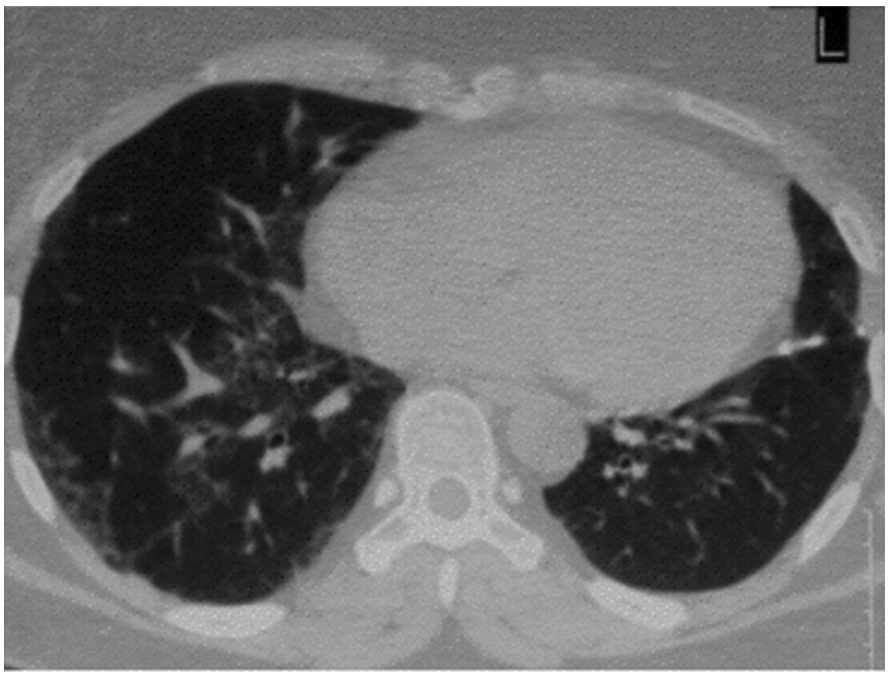

Fig. 3. A high resolution chest CT scan of patient 4 before the treatment with rituximab which shows inflammatory infiltrates.

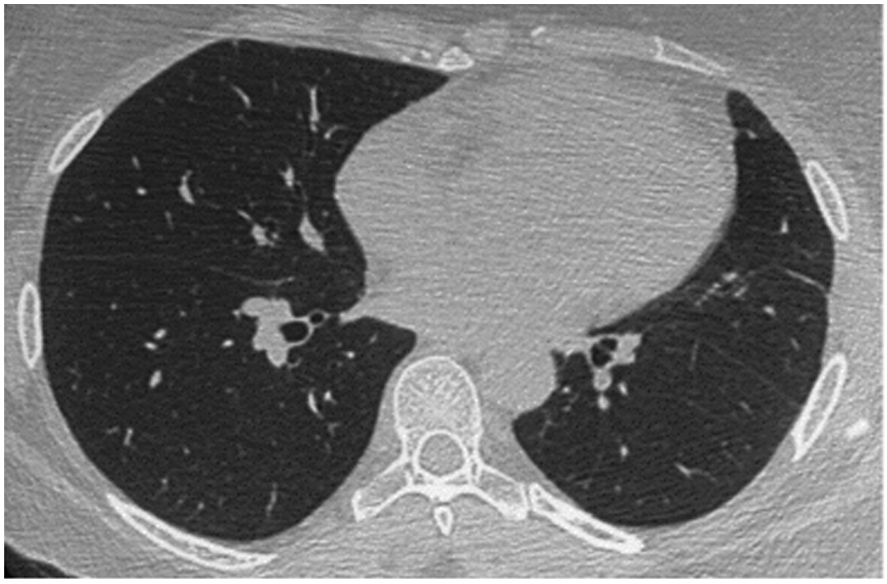

Fig. 4. A high resolution chest CT scan of patient 4 after the therapy with rituximab.

The experience with RTX in IM, however, is limited. There are no clinical trials regarding the efficacy of RTX in these diseases, and its use has often been off-label in patients who have not responded or have developed adverse events with conventional therapy. Thus, it is not known yet when it should be used nor which is the optimal regimen. We have observed both, among our patients and those reported in the literature, a high rate of response to RTX in IM. In fact, 75% of our patients and 72.5% of those described in the literature showed a good response. Although a possible publication bias may be considered as there is a tendency to report more often the positively responding cases.

Almost all patients with PM treated with RTX achieved complete remission. In DM, although most of the patients responded to RTX therapy, five patients (9.8%) had a partial remission

Table IV. Therapy before and concomitant with rituximab.

Therapy	Before n. (%)	With n. (%)
Steroids	37 (72.5)	44 (86.3)
IGIV	28 (54.9)	4 (9.8)
MTX	34 (66.7)	15 (29.4)
HCQ	14 (28.6)	5 (12.2)
CLQ	1 (2.4)	0 (0)
QN	3 (7.3)	1 (2.4)
CsA	17 (34.7)	1 (2.4)
AZA	26 (51)	11 (21.6)
CYC	6 (12)	3 (7.3)
Etanercept	7 (17.1)	2 (4.1)
Adalimumab	1 (2.4)	0 (0)
Infliximab	5 (12.2)	0 (0)
Tacrolimus	2 (4.9)	1 (2.4)
Sirolimus	1 (2.4)	0 (0)
MMF	8 (15.7)	5 (9.8)
Leflunamide	3 (6.1)	0 (0)
Penicillamide	1	
Thalidomide	1	
Plasma exchange	2 (4.9)	0 (0)

IVIG: inmunoglobulins; MTX: methotrexate; HCQ: hidroxicloroquine; CLQ: cloroquine; QN: mepacrine; CsA: cyclosporine; AZA: azathioprine; CYC: cyclophosphamide; MMF: mycophenolate mofetil.

Table V. Adverse events.

	N.
Flare of hepatitis B with delta coinfection	1
Seborreic dermatitis	2
Urinary tract infection	2
Acute sinusitis	3
Superficial skin infections	2
Grade III cellulitis	1
Bronchitis	3
Pneumonia	1
Respiratory infection	1
Otitis media	1
Metastatic cancer	1
Transient flu-like symptoms	2
Mild symptoms of nausea, throat discomfort and diarrhea	1
Headache	3
Transient hypertension	4
Congestion with facial flushing	3
Non-tuberculous mycobacterial infection	2
Increase in liver transaminas levels through week 20 that resolved with the discontinuation of azatioprine therapy	1

(only improving the muscle strength) and there was another 13.7% which did not respond at all. It has also been demonstrated its beneficial effect on cardiac involvement (7). Paradoxically, contrarily to what might have initially been expected, a greater response has been observed in patients with PM than in those with DM. This raises the question of what the exact mechanism of action of RTX in IM is. Although the effects of RTX have classically been considered to occur through B cells, it has also been demonstrated (8) that it may potentially disturb T cells.

In DM, the heliotrope changes and violaceus poikiloderma seemed to be the cutaneous manifestations that best responded to RTX therapy, but also, prominent recalcitrant skin manifestations that had not responded to other therapies, achieved a response with RTX with minimal side effects (9, 10). However, in the series reported by Chung, skin disease was stable over time (11). Only one patient of our series, who had a paraneoplastic DM with exclusively skin involvement, did not respond to RTX. Paraneoplastic DM is sometimes recalcitrant to conventional therapy (12), and until now, there is no experience in the utilization of RTX in paraneoplastic DM, except our case number three.

Interstitial lung disease (ILD) affects negatively the prognosis of polymyositis/dermatomyositis and was present in 16.3% in this series. Some patients respond favourably to corticosteroid treatment, while others do not, and other immunosuppressive therapy is required (13). The patients with ILD here in reported had received therapy with MTX, azathioprine, leflunomide, penicillamide, CsA, CYC and IVIG, all of them being ineffective. The response to RTX, however, was excellent. Levine *et al*. described improvement of FVC with RTX, which could be consistent with improvement in muscle strength, although the CT scan findings as well as the ratio of diffusing capacity for carbon monoxide/alveolar volume (DLCO/AV) are not described (10). Only in one case reported by Sultan (14), the case reported by Brulhart (15) and in the one described by us there is an improvement in the diffusion capacity and the pulmonary infiltrates. Nevertheless, therapy with RTX has recently been associated with the development of pneumonitis and interstitial lung disease (16, 17). These observations emphasise the need for additional studies to clarify the efficacy of RTX on the ILD.

There are only four cases with AS treated with RTX in the literature, one with a partial remission (6) and three with a complete response (6, 15, 18). In these cases, autoantibody levels remained high after RTX therapy and showed no correlation with disease activity or relapse (15, 18)

Regarding the administration schedule of RTX, both protocols, that of rheumatoid arthritis (2 doses of 1000mg with a 2-week interval) and that of lymphoma (weekly doses of 375 mg/m^2 for 4 weeks) have been used in IM. However, the former schedule yielded a worse response in the cases reviewed (9 cases without remission and 5 with partial remission) than the latter (2 cases without remission).

It is not clear if the addition of steroids and/or immunosuppressive therapy with each infusion could be the responsible of the alleged response to RTX, even though each patient had failed to respond to those therapies in the past. The absence of clinical trials makes it difficult to know which way is best.

As for the time to response to RTX, the onset of action seems to be relatively rapid and its short-term safety profile is favourable. Remission persists for 24-48 weeks (2, 10, 19) or longer (20) and patients being usually able to reduce the dose of their concomitant medications after RTX treatment. However, in most cases a single course of RTX does not protect indefinitely from relapse (2, 10, 15) and patients often need a second course. An optimal treatment schedule for administering repeated courses is based on periodic monitoring of B cells levels. In some cases, a depletion of circulating B cells precedes the clinical response, and the disease flare coincides with a rise in B cells levels (2, 10, 15). Conversely, other patients have recurrence of symptoms even though CD19+ cells levels remain suppressed (2, 21). Furthermore, others continued to being free of disease activity, despite the evidence of re-emergence of CD19+ cells (21). Probably, the optimal therapeutic decision for re-treatment should be made on the basis of recurrence of the clinical symptoms. Nevertheless,

there is a need for additional studies in order to assess the optimal regimen of treatment in the different subsets, as well as the initial dose, combination of treatments and re-treatment schedule.

RTX is generally well tolerated, with few adverse events. In most patients, RTX induces a rapid depletion of normal CD20-expressing B cells in the peripheral blood, and so clinicians should be aware of possible infections. The series reported by Chung (11) experienced the larger number of infections, although none of them were serious. Arlet *et al*. reported a flare of hepatitis B with delta co-infection after a second single additional RTX infusion (22). Lutt *et al*. reported two cases of nontuberculous mycobacterial infection (23) but they were also receiving other immunosuppressants. Case 4 also had a respiratory tract infection that was attributed to the use of cyclophosphamide. Other adverse effects described are seborrheic dermatitis, transient flu-like symptoms, nausea, throat discomfort and diarrhea (9). Moreover, in the series of Chung *et al*. there is one patient who died from metastatic cancer after RTX infusion (11).

In conclusion, it is our belief that RTX may be an optimal therapeutic choice for IM (polymyositis/dermatomyositis) in patients without response to conventional therapy. In order to evaluate its actual efficacy in these diseases, future controlled trials should be carried out. Because in the review of the literature we have performed the experience reported regards only refractory cases, it is uncertain the exact moment when therapy with RTX should be started, or whether its efficacy is enhanced by concomitant immunosuppressive medications. The good responses achieved in ILD are promising data, although they should be used with caution. In the same way, even though no serious adverse events have been reported for the time being, clinicians should be aware of this possibility, at least, until further evidence is available.

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