Rituximab in the treatment of anti-MDA5 dermatomyositis-associated interstitial lung disease: a case-based literature review

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Abstract

Interstitial lung disease (ILD) occurs with Idiopathic Inflammatory Myopathy (IIM) as a life-threating complication and is considered the most important prognostic determinant in this disease group. The antibody anti-melanoma differentiation–associated gene 5 (anti-MDA5) is associated to rapidly progressive ILD and poor overall survival. Rituximab (RTX) is becoming a drug of choice in management of refractory IIM-ILDs and rapidly progressive ILDs, despite its low level of evidence. We report the case of a 49-year-old man with new-onset clinically amyopathic dermatomyositis (CADM) with severe respiratory symptoms and mixed radiologic pattern of non-specific interstitial and organizing pneumonia, refractory to high dose corticosteroids and intravenous immunoglobulin and oxygen dependent. He was started on RTX 375mg/m2/week of which he completed 4 perfusions, with significant clinical improvement, and has been on maintenance to date with the rheumatology RTX standard protocol with no need for oxygen supplementation.

RTX may represent a rescue therapy for patients with severe anti-MDA5-related CADM-ILD refractory to conventional immunotherapies. We identified reports of a total of 12 patients treated with RTX. Infection was the only reported adverse event (25%). Respiratory improvement (defined by symptoms, imaging or PFTs) was observed in 75% of patients, with 2 (17%) having achieved clinical remission. A total of three deaths occurred (25%), all resulting from ILD progression despite treatment. No therapeutic protocol with RTX seems to be more efficient nor associated with more adverse events than the others. Comparative studies are necessary.

Keywords: Interstitial lung disease; Rituximab; Adult dermatomyositis.

Introduction

Dermatomyositis (DM) is an idiopathic inflammatory myopathy (IIM) with variable phenotypes, courses and responses to therapy. Interstitial lung disease (ILD) occurs with IIM as a life-threating complication and is considered the most important prognostic determinant in this disease group[1]. Clinically Amyopathic DM (CADM) is itself a poor outcome predictor for DM-associated ILD[2]. DM-associated ILD can present with an acute onset or progressive symptoms, or it can be asymptomatic and detected only by abnormalities in pulmonary function tests (PFTs) or high-resolution thoracic CT-scan (HRCT)[3]. The antibody anti-melanoma differentiation–associated gene 5 (anti-MDA5) is associated with a rapidly-progressive ILD in DM, with a prevalence ranging between 22% and 93%[4–9], as well as with poor overall survival, with mortality rates that go up to 70% (3,6,8,9). It has also been demonstrated that anti-MDA5 titers correlates positively to disease activity and severity, and negatively to treatment response, because effective treatment decreases antibody levels[10–12]. Corticosteroids and methotrexate have been used as first-line therapies in DM adult patients, but the addition of other immunomodulators, such as azathioprine or mycophenolate, to corticosteroids, are preferred when ILD is present[12–14]. These are used as steroid-sparing agents, as there is no strong evidence demonstrating benefit of the association over steroid therapy alone[15–19]. Patients with refractory or rapidly progressive ILD may require more aggressive therapies such as cyclophosphamide, tacrolimus and rituximab (RTX[20-21]. The efficacy of RTX may be greater in IIM-ILD than in other connective tissue diseases associated ILDs[22, 23] and, as a consequence, it's becoming a drug of choice in management of refractory or rapidly-progressive IIM-associated ILDs, despite its low level of evidence. There are ongoing randomized trials of rituximab in connective tissue disease-related ILD[24].

Case-report

We report the case of a 49-year-old man, who works as a graphic designer, with long-standing exposition to solvents and ink from graphic printing, and history of smoking (a load of 22,5 units pack/year). He had had three episodes of pericarditis on the previous 2 years, treated with colchicine and non-steroid anti-inflammatories. A year after the third episode of pericarditis he developed odynophagia and oropharyngeal aphthous ulcers, treated with multiple antibiotics but without improvement, and soon presented dysphony, hand skin hyperkeratosis ("mechanic hands"), Gottron's papules and heliotrope rash, followed by

progressive exertional fatigue and dyspnoea and recurrent night fevers. HRCT scan revealed interstitial fibrosis of the superior, medium and inferior lobes with retraction of the parenchyma, ground-glass opacities with areas of consolidation in mixed pattern of non-specific interstitial pneumonia and organizing pneumonia. PFTs reported severe restriction with a Forced Vital Capacity (FVC) of 30% (1.27 L), Forced Expiratory Volume in 1 second (FEV1) of 31% (1.06 L), Total Lung Capacity (TLC) of 42% (27.6 L), Maximal Inspiratory Pressure (MIP) of 58.3% (6.19 Kpa) and Maximal Expiratory Pressure (MEP) of 55.6% (7.62 Kpa). Diffusing Lung Capacity for carbon monoxide (DLCO) could not be determined as acceptability criteria of exam performance were not met. The diffusing capacity divided by the alveolar volume (DLCO/VA) was very low (21.5%). Electromyography showed no signs of myopathy; capillaroscopy documented mild non-specific findings suggestive of diffuse connective tissue disease; echocardiogram estimated a normal pulmonary artery systolic pressure and reported normal systolic function and segmental kinetics, valves and pericardium. Blood gases analysis showed partial respiratory insufficiency, and regular blood tests slight increase of liver enzymes, increased erythrocyte sedimentation rate (30mm), normal muscle enzymes, and a mildly increased C-reactive protein (1.8mg/dL). Viral serologies, as well as blood, urine and bronchoalveolar lavage fluid cultures, were negative. The diagnosis of DM-associated ILD was assumed, and the myositis specific antibodies came strongly positive for anti-MDA5. There were no signs of abdominal or pelvic underlying neoplasm on computed tomography scan. The patient underwent a three-day infusion of intravenous methylprednisolone 1g once daily, followed by prednisolone 1 milligram/kilogram of weight. Because extreme dyspnoea and tiredness persisted, intravenous immunoglobulin 2g/kg was administered during 5 days. After only a mild improvement, the patient started cyclophosphamide 750mg/m2, but soon after the first infusion he developed a lower respiratory tract bacterial infection that required hospital treatment and subsequent monthly infusions were cancelled. Demands for oxygen therapy remained high and with gradual increase, with tiredness for the slightest efforts, again refractory to high-dose corticosteroids. Therapy with RTX 375 milligrams/m^2/week was started, followed by a slow and steady decrease in dyspnoea throughout the cycles. He was discharged after the fourth cycle, with prednisolone 30mg once daily, mycophenolate mofetil 1,5g twice daily as steroid-sparing agent and oxygen therapy need only for exertion. He also maintained respiratory kinesiotherapy that had been initiated in the hospital. The patient has been on maintenance therapy with RTX to date, according to the rheumatology standard protocol (2 perfusions of 1g 2 weeks apart every 6 months) and prednisolone has been progressively tapered to 7,5mg once daily 15 months after initiating RTX. Exercise tolerance has markedly improved, as no exertional oxygen supplementation is currently needed for daily activities or during sleep. PFTs performed 15 months after RTX introduction

demonstrated improvement of lung restriction with FVC of 63% (2.70 L), FEV1 of 66% (2.25 L), TLC of 59% (3.77 L), MIP of 79% (7.25 Kpa), MEP of 71% (9.66 Kpa). DLCO was reduced (53%) but normal when corrected for the alveolar volume (97%).

Discussion

RTX represents a rescue therapy for patients with severe anti-MDA5-related CADM-ILD refractory to conventional immunotherapies, however it has not yet been established as a standard treatment[25]. Treatment with RTX has mostly been grounded in existing evidence from clinical studies in other Connective Tissue Diseases-related ILD[23]. The RIM trial is a randomized clinical trial (RCT) that studied the efficacy of RTX in IIM in adults and children. RTX dosage was based on the patient's body surface area (BSA), with adults receiving 750 mg/m2 up to 1 g. The primary end point was to compare the time to achieve the International Myositis Assessment and Clinical Studies Group preliminary definition of improvement (DOI) between two groups: "RTX early" (RTX given at trial entry) and "RTX late" (RTX given 8 weeks after trial entry). The "RTX early" received RTX at weeks 0 and 1 and placebo infusions were given at weeks 8 and 9, and the "RTX late" arm received placebo infusions at weeks 0 and 1 and RTX at weeks 8 and 9. Although there were no differences regarding the primary endpoint, (differences between groups failed to be demonstrated), 83% of patients that failed two or more immunotherapies in association to glucocorticoids (refractory disease) met the DOI with RTX[26].

Studies that preceded the RIM trial were conflicting regarding the benefit of RTX in DM, possibly due to methodological problems[5, 27]. None of these studies evaluated DM-related ILD outcomes. The best evidence available to date regarding the use of RTX in DM-related ILD arrives from case series that reported good results[22, 28, 29]. Moreover, RTX was shown to decrease the levels of SSA-related antibodies, particularly of anti-Jo1, whose titres strongly correlate with disease activity[30, 31].

Case-series and single case-reports of anti-MDA5-related CADM-ILD patients have been published reporting favourable outcomes of RTX in refractory disease. We identified in the literature 6 case-reports and 2 small case series, with a total of 12 patients studied (Table I)[12, 25, 32–37]. All patients had ILD. Treatment with RTX was due to refractory mucocutaneous lesions in one patient[32] and in all other patients was motivated by refractory lung disease alone[12, 25, 33–37]. Infection was the only reported adverse event (25%)[37]. A total of three deaths occurred (25%),

all resulting from ILD progression despite treatment, but respiratory improvement, whether determined by symptoms, imaging or PFTs, was observed in all remaining patients (75%), with 2 (17%) having achieved clinical remission (Table II).

We here emphasize that, although there are no definite recommendations on this disease, RTX is a therapeutic option in severe and refractory anti-MDA5-related CADM-ILD that has shown positive results in clinical practice. According to the published reports, no therapeutic protocol appears to be more efficient nor associated with more adverse events than the others.

	Year	References	Type of study	Number of patients	Age	Sex	Clinical manifestations	HRCT findings
1	2012	Clottu et al	Case report	1	68	FeMale	ILD, skin lesions, oral ulcers, vasculopathy, B symptoms, arthralgia, sicca syndrome	Interstitial infiltrate, lower and middle filed bilateral ground-glass opacities, subpleural reticulations, bronchiectasis
2	2015	Koichi et al	Case report	1	71	FeMale	ILD, skin lesions	Lower field bilateral ground glass opacities
3	2015	Watanabe et al	Case report	1	58	FeMale	ILD, skin lesions, deltoid weakness	Lower field unilateral ground-glass opacities
4	2016	Tokunaga et al	Small series	2	71	FeMale	ILD, skin lesions, B symptoms	Ground-glass opacities
					69	FeMale	ILD, skin lesions, 'mechanic hands'	Interstitial lung disease, ground-glass opacities and septal thickening
5	2015	Gil et al	Case report	1	55	FeMale	ILD, skin lesions, vasculopathy	Diffuse interstitial changes, ground-glass opacities
6	2017	Hisanaga et al	Case report	1	57	FeMale	ILD, skin lesions, fever	Lower field bilateral linear opacities and focal areas of consolidation, middle field unilateral ground-glass opacities
7	2017	Ogawa et al	Case report	1	48	Male	ILD, skin lesions, 'mechanic hands', mild proximal lower limb weakness	Lower and middle field ground-glass opacities
8	2018	So et al	Small series	4	49	FeMale	ILD, skin lesions, fever, alopecia, vasculopathy	Septal thickening, lower lung fields´ consolidations, pleural and pericardial fluid
					50	Male	ILD, skin lesions, B symptoms, vasculopathy	Consolidations, septal thickening, reticulation with traction bronquiectasis
					38	Male	ILD, skin lesions, fever, alopecia, vasculopathy	Ground-glass opacities, reticulation and septal thickening
					48	Male	ILD, skin lesions, weight loss, vasculopathy, arthralgia	Ground-glass opacities, reticulation and septal thickening, traction bronquiectasis

Table I. Twelve anti-MDA5-related CADM-ILD patients treated with RTX in refractory disease have been published (6 case-reports and 2 small case series).

	PFT	Medication pre-Rituximab	RTX dosage	Response	Follow-up	Adverse effects	Level of evidence
1	n. m.	PSL, IVIg, CY, MMF, CsA	2 x 1000mg 15 days apart	Improvement of mucocutaneous lesions	Unknown	n. m.	3
2	n. m.	MethylPSL, PSL, Tac, CY, IVIG, PMX	375mg/m2 weekly for 4 weeks	Improvement of HRCT findings, decreased serum levels of ferritin	2 months	n. m.	3
3	n. m.	PSL, Tac, CY	375mg/m2 weekly for 4 weeks	Clinical remission and no further progression of HRCT findings	6 months	n. m.	3
4	n. m.	MethylPSL, PSL, Tac, CY, CsA	375mg/m2 weekly for 4 weeks	Death	51 days	n. m.	3
	n. m.	MethylPSL, PSL, CsA, CY	1 x 375mg/m2		18 days		
5	Restrictive pattern, reduced DLCO	MethylPSL, CY	n. m.	Death	3 months	n. m.	3
6	n. m.	PSL, CsA, CY, MMF	375mg/m2 weekly for 4 weeks	Clinical remission, improvement of HRCT findings, decreased of serum levels of ferritin	Unknown	n. m.	3
7	n. m.	MethylPSL, PSL, CsA, CY	375mg/m2 weekly for 4 weeks	Improvement of skin lesions, respiratory symptoms and HRCT findings, decreased of serum levels of ferritin and anti-MDA-5 titers; PSL and CsA after RTX	Unknown	n. m.	3
8	FVC 39% predicted	PSL, CsA, CY, IVIg	2 x 1000mg 15 days apart or 500mg at 0, 7, 14 and 28 days	Improvement of symptoms and PFT	6 months to 2 years	Vasculitic ulcer wound infection	3
	FVC 76% predicted	MMF, CY, Tac		Improvement of symptoms and PFT		Chest infection	
	FVC 94% predicted	MMF, Tac, IVIg		Improvement of symptoms and PFT, decreased serum levels of ferritin		Chest infection	
	DLCOcor 54% predicted	CsA		Improvement of symptoms and PFT		Nil	

Table I *(cont.)*. Twelve anti-MDA5-related CADM-ILD patients treated with RTX in refractory disease have been published (6 case-reports and 2 small case series).

	PFT	Medication pre-Rituximab	RTX dosage	Response	Follow-up	Adverse effects	Level of evidence
1	n. m.	PSL, IVIg, CY, MMF, CsA	2 x 1000mg 15 days apart	Improvement of mucocutaneous lesions	Unknown	n. m.	3
2	n. m.	MethylPSL, PSL, Tac, CY, IVIg, PMX	375mg/m2 weekly for 4 weeks	Improvement of HRCT findings, decreased serum levels of ferritin	2 months	n. m.	3
3	n. m.	PSL, Tac, CY	375mg/m2 weekly for 4 weeks	Clinical remission and no further progression of HRCT findings	6 months	n. m.	3
4	n. m.	MethylPSL, PSL, Tac, CY, CsA	375mg/m2 weekly for 4 weeks	Death	51 days	n. m.	3
	n. m.	MethylPSL, PSL, CsA, CY	1 x 375mg/m2		18 days		
5	Restrictive pattern, reduced DLCO	MethylPSL, CY	n. m.	Death	3 months	n. m.	3
6	n. m.	PSL, CsA, CY, MMF	375mg/m2 weekly for 4 weeks	Clinical remission, improvement of HRCT findings, decreased of serum levels of ferritin	Unknown	n. m.	3
7	n. m.	MethylPSL, PSL, CsA, CY	375mg/m2 weekly for 4 weeks	Improvement of skin lesions, respiratory symptoms and HRCT findings, decreased of serum levels of ferritin and anti-MDA-5 titers; PSL and CsA after RTX	Unknown	n. m.	3
8	FVC 39% predicted	PSL, CsA, CY, IVIg	2 x 1000mg 15 days apart or 500mg at 0, 7, 14 and 28 days	Improvement of symptoms and PFT (FVC 39 > 67%)	6 months to 2 years	Vasculitic ulcer wound infection	3
	FVC 76% predicted	MMF, CY, Tac		Improvement of symptoms and PFT (FVC 76 > 105%)		Chest infection	
	FVC 94% predicted	MMF, Tac, IVIg		Improvement of symptoms and PFT (FVC 94 > 121%), decreased serum levels of ferritin		Chest infection	
	DLCOcor 54% predicted	CsA		Improvement of symptoms and PFT (DLCOcor 54 > 72%)		Nil	

Table II. Treatment strategy and outcomes of the twelve anti-MDA5-related CADM-ILD patients treated with RTX in refractory disease that have been published to date. CY – cyclophosphamide; CsA – cyclosporine; HRCT – high resolution CT scan; IVIg – intravenous immunoglobulin; MethylPSL – methylprednisolone; MMF – mycophenolate mofetil; n.m. – not mentioned; PMX – polymyxin; PSL – prednisolone; Tac – tacrolimus.

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