RITUXIMAB IN THE TREATMENT OF INFLAMMATORY MYOPATHIES: A REVIEW.

Serena Fasano[1], Patrick Gordon[2], Raouf Hajji[3], Esthela Loyo[4], David A. Isenberg[5]

Affiliations:

[1]Rheumatology Unit, Department of Clinical and Experimental Medicine, Second University of Naples, Naples, Italy

[2] Centre for Rheumatology, Department of Medicine, King's College Hospital, London, UK

[3]Department of Internal Medicine, Sidi Bouzid Hospital, Ibn Aljazzar Medicine, Faculty of Sousse,Tunisia

[4] Jefe de Servicio, Servicio de Reumatología e Inmunología Clinica HRUJMCB,Santiago, Rep. Dominicana

[5]Centre for Rheumatology, Department of Medicine, University College London, London, UK

Correspondence to:

Professor David Isenberg

Centre for Rheumatology

Room 424

4th Floor the Rayne Building

5 University Street

London WC1E 6JF

e-mail: d.isenberg@ucl.ac.uk

ABSTRACT

Background. Several uncontrolled studies encouraged the use of rituximab in patients with myositis. Unfortunately, the first placebo-phase trial in refractory myositis to assess the efficacy of rituximab, the Rituximab in Myositis trial, did not show a significant difference in the two treatment groups, although doubts have been expressed about its study design. In this review we present an up-to-date overview of the experiences of rituximab therapy in myositis.

Methods. A PubMed search was performed to find all the available cases of refractory myositis patients treated with rituximab up to July 2015. The following terms were assessed: "inflammatory myopathies OR antisynthetase syndrome OR polymyositis OR dermatomyositis AND rituximab".

Results. 48 studies were included in this review. We identified 458 patients with myositis treated with rituximab. Dermatomyositis was the most frequent disease (32.9%). The most common index manifestation for rituximab therapy was muscle weakness (89.7%). We found a rate of response to rituximab of 78.3%.

Conclusions. Rituximab can play a role in the management of patients with myositis, most likely in those patients with myositis-specific autoantibodies.

Keywords: inflammatory myopathies; dermatomyositis; polymyositis; antisynthetase syndrome; rituximab

INTRODUCTION

The idiopathic inflammatory myopathies (IIM) are a group of acquired, heterogeneous, systemic diseases of skeletal muscle, including adult polymyositis (PM), adult dermatomyositis (DM), juvenile DM (JDM), juvenile PM (JPM), antisynthetase syndrome (ASS) and inclusion body myositis (IBM). Features common to all of these subtypes include muscle weakness, elevated serum levels of muscle enzymes, myopathic abnormalities on electromyography and inflammatory cell infiltrates on muscle biopsy. However, each subset has distinct clinical, histological and immune-pathological characteristics.

Both DM and PM usually present with symmetrical and proximal muscle involvement, but in DM typical skin lesions can also occur. IBM is predominantly characterized by weakness and atrophy of distal muscles, especially wrist and finger flexors.

As these conditions are rare, current treatment of myositis is based mainly on case reports and a few randomized controlled trials with small numbers of patients enrolled. As a result, the choice of treatment is often empirical. The general clinical consensus among physicians is to use high-dose corticosteroid therapy as the first-line option in patients with myositis. In order to avoid side effects, the prednisolone dose should be reduced based on patient's clinical response (1). However, several patients discontinue steroid treatment early because of a lack of improvement and/or adverse events (2). In clinical practice, an immunosuppressive drug is often added as 'steroid-sparing' agent or in corticosteroid-resistant patients or when disease relapses. Nevertheless, a Cochrane review concluded that there was insufficient evidence from the available studies to confirm the value of immunosuppressive agents in myositis (3).

For refractory DM, intravenous immunoglobulin (IVIG) had short-term clinical efficacy in a double-blind, placebo-controlled trial (4). However, long-term safety and efficacy need to be tested. IVIG can be also effective in some difficult-to-treat patients with PM (5), but offers only partial and short-lived benefit to a small number of cases with IBM, which is refractory to most therapies (6). Cyclophosphamide and tacrolimus might be useful especially in patients with interstitial lung disease (ILD) and severe myopathy (6,7).

In patients with myositis resistant to conventional treatment, Rituximab (RTX) is a potential treatment option. 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. It results in rapid depletion of CD20 positive B lymphocytes from the peripheral blood for up to 6-9 months (8). Although beneficial effects of RTX have been suggested by case reports and case series, the experience in adult and paediatric patients with refractory myositis is limited. The determination of which subset(s) of patients is/are

more likely to be responsive, when RTX should be administered during the disease course, whether to use combination therapies and the optimal regimen and schedule for re-treatment, remain to be elucidated.

In this study we review the most significant published data regarding the use of RTX for patients with PM and DM and try to identify which group of patients might be the most likely to benefit from this treatment.

MATERIALS AND METHODS

We analysed current evidence on the therapeutic use of RTX in refractory patients with IIM by a review of the literature including articles published up to July 2015.This review was based on a bibliographic search in the PubMed database, using the following keywords: inflammatory myopathies OR antisynthetase syndrome OR polymyositis OR dermatomyositis AND rituximab. Furthermore, we also included some relevant studies not present in our PubMed search, but referenced in other articles.

We considered case reports and open label studies according to the authors' definition. We also subdivided case series papers in "large" if they have 4 or more cases and "small" if they have less than 4 subjects.

A total of 48 articles were identified (table 1). In particular, we found 19 case reports, 4 open label studies, 24 case series (8 small, 16 large series) and the Rituximab In Myositis (RIM) trial (9).

REVIEW OF PATIENTS TREATED WITH RITUXIMAB

In total, we identified 458 patients with IIM treated with RTX. DM was the most frequent disease reported in 151 cases (32.9%). The response to RTX in refractory PM has been analysed in 144 patients (31.4%), including 19 subjects with anti-signal recognition particle (anti-SRP) antibody positivity. In addition, RTX was administered to 79 patients with ASS (17.2%) and to 72 patients with JDM (15.7%). Only two patients were affected by IBM and undifferentiated inflammatory myositis (UI), respectively. In 10 cases, the IIM subtype is not specified.

The most frequent refractory symptom, for which the RTX was administered, was muscle weakness (411/458; 89.7%). There was some heterogeneity in the RTX regimen used. The majority of the patients that we reviewed (193/458; 42.1%) received the protocol widely used for rheumatoid arthritis (two infusions at a dose of 1000 mg of RTX, giventwo weeks apart). The lymphoma schedule (RTX at a dose of 375 mg/m^2 weekly for four consecutive weeks) was administered in 38 patients. Other schedules (500mg at days 0 and 14 or 100mg/m^2 weekly for six consecutive weeks) were rarely used. Concomitant therapies were corticosteroids, methotrexate, mycophenolate, azathioprine, cyclophosphamide, cyclosporine or IVIG. In the RIM trial (9), RTX dosing was

based on the patient's body surface area (BSA); children with a BSA ≤ 1.5 m^2 received 575 mg/m^2 at each infusion, and adults and children with a BSA>1.5 m^2 received 750 mg/m^2 up to 1 g. Moreover, patients were subdivided in two groups: 96 subjects received two RTX infusions at weeks 0 and 1 (early RTX group), whereas 104 received the drug 8 weeks later (late RTX group).

Overall, 359 (78.3%) out of 458 patients, affected by myositis refractory to conventional therapy, showed an improvement in one or more of the IIM manifestations after RTX treatment (table 1).

RTX was generally well tolerated. The most common side effects were infections (mainly respiratory tract infections), of which approximately 5% were severe, requiring hospitalization. Infusion reactions rarely occurred; they were often mild and easily controlled with steroids.

CONSIDERATION OF RITUXIMAB'S CURRENT ROLE IN THE TREATMENT OF MYOSITIS

Due to the rarity and heterogeneity of IIM, the main concern with their treatment is the lack of adequate controlled trials, with only partially validated outcome measures.

RTX was empirically used off-label in patients who did not show a good response to the conventional therapy. The reasons to try this approach were based on the evidence of circulating auto-antibodies in up to 80% of patients with IIM (10) and on the presence of B cells in the perivascular region of muscles in patients with DM and in the inflammatory muscle fibres in both PM and DM patients (11). Given the likely pathogenetic role of B cells in myositis and favourable data from B-cell depleting therapy from several case series, the largest clinical trial of RTX in myositis (RIM trial) was undertaken (9). In this study, 200 patients with refractory myositis (76 with PM, 76 with DM, and 48 with JDM) were randomized to receive different regimens of RTX (2 infusions at baseline or 8 weeks later). Refractory disease was defined as the failure of steroids and at least one immunosuppressive agent, for a duration of at least 3 months of the agent at a known effective dose. Although the group treated with RTX at onset did not improve significantly earlier than the group treated after a delay of 8 weeks (primary endpoint), the majority of patients (83%) responded to RTX treatment and a significant steroid-sparing effect was reported. Twenty-six serious adverse effects attributed to RTX therapy were observed, most of which were infections. In an accompanying editorial (12), De Visser described several limitations of the RIM study, mainly concerning the trial design. The power calculation was based on the postulated effect of RTX by 8 weeks, but an improvement was observed only after 20 weeks. The selection of a 8-week placebo phase was based on ethical considerations, but it was felt to be too short to detect a significant difference. Moreover, the core set of measures used was only partially validated. The selection of patients was performed according to the

Bohan and Peter criteria (13) and not with the most recent classification criteria (14). For these reasons, the trial was probably not powered to detect an effect of the RTX treatment. Thus, while formally negative, the results of the RIM trial did give some support for the idea that RTX might be an effective treatment strategy in IIM.

In this review, we have observed a rate of therapeutic response to RTX of 78.3% (359/458 patients). To avoid a publication bias of case reports and small series, we subsequently excluded the case series of three or less from the calculation for the response rate. We found that, excluding these studies, 323 out of 420 patients responded to RTX treatment (76.9%). Interestingly, the majority of patients with myositis-specific auto-antibodies (MSA) positivity achieved a good response, often with long term remission (≥12 months). MSA are disease markers closely associated with clinical subsets of IIM and they are found in approximately 30-50% of the patients with myositis (15). The presence of these antibodies seems to predict a better response to B cell depleting therapies. Nalotto et al (16) described a significant improvement in 5 out of 6 patients after RTX treatment. Antibody positivity was found in each responder, supporting the idea of a role for B cells in pathogenesis of myositis. In a post-hoc analysis of the subgroups in the RIM trial, Aggarwal et al investigated predictors of clinical improvement in PM/DM patients treated with RTX (17). The positivity of a myositis autoantibody was the major predictive factor of clinical improvement following B cell depletion therapy (2-3 fold higher chances of improvement as compared to the negative autoantibody group). Among the autoantibody positive subset, patients with anti–Mi-2 or anti-Jo1 demonstrated greater improvement than patients with other MSA (such as anti-SRP, anti–TIF-1γ and anti-MJ) who showed only a non significant trend to faster time to response than antibody negative patients (hazard ratio:1.4).

Interestingly, in many reports, levels of Jo-1 antibodies did not correlate with the disease course or relapse, but seem to remain stable (18–22). The probable explanation is that long-lived plasma cells producing auto-antibodies are CD20-negative and are not affected by RTX. Moreover, the effect of RTX may be only partially related to blockade of the antibody production. RTX treatment may have an influence on other cells of the immune system, may ‘normalize’ auto-reactive T cells and re-establish the immune homeostasis (23).

The measurement of autoantibodies is also useful for predicting clinical manifestations and prognosis in patients with myositis. Anti–melanoma differentiation-associated gene 5 (MDA5) and anti–aminoacyl-tRNA synthetase (ARS) antibodies are associated with a high risk of ILD, which is one of the most common causes of mortality in IIM patients (24). However, ILD associated with these two antibodies showed different clinical courses and therapeutic responsiveness. Anti-MDA5-positive patients mostly developed acute, progressive ILD with more severe course and more refractory to treatment (24).

Several reports supported the beneficial effects of CD20 depletion therapy in refractory ILD. In the pilot study of Levine (20), a clinical response was observed in two anti-Jo1 positive patients with pulmonary involvement after RTX therapy. In 2009, a retrospective case series (25) reported a significant improvement on high-resolution CT (HRCT) imaging and/or pulmonary function tests (PFTs) in seven out of 11 ASS patients with ILD, following 6 months of RTX. However, the main concern with these studies is the use of several immunosuppressive agents both prior to and following treatment with RTX. Subsequently, Marie et al (26) published results of seven anti Jo-1 positive patients with refractory ILD treated with RTX in combination only with steroids. After a year, all seven patients had amelioration or resolution of their pulmonary symptoms and significant improvement in PFTs and HRCT findings.

A retrospective study analyzed fifty patients with severe ILD, progressing despite conventional immunosuppression, treated with RTX (27). 33 of whom had ILD associated with connective tissue disease (CTD). B-cell depletion was effective as rescue therapy, stabilizing and/or improving the pulmonary function in 36 of 50 patients (72%). Interestingly, within the CTD-ILD cohort, patients with myositis were most likely to improve in PFTs (FVC and DL_{CO}) following RTX therapy. To avoid potential effects of thoracic muscle weakness on the PFTs, Unger et al (28) analysed the total lung capacity (TLC) improvement. Again, six of eight patients responded and TLC was stable in the other two patients. Interestingly, data from a 52 month follow-up study (29) showed that the most beneficial effects on lung function were observed in patients with disease duration <1 year and acute onset of ILD.

These findings suggest that MSA, which are important prognostic markers, may also predict RTX response in IIM.

Accordingly to aethio-pathological criteria, targeting B cells may also be potentially useful in DM, which is classically considered an humoral mediated disorder (30). Paradoxically, a better response to B cell depleting therapy has been observed in patient with predominant muscle involvement than in those with DM and skin disease. In our review, 52.1% of patients with skin lesions responded to RTX, but we noted a high frequency of relapse (48.6%; 18/37 patients). In a subgroup of subjects enrolled in the RIM trial (31), muscle assessment was more responsive than cutaneous measures to RTX treatment. Moreover, RTX was ineffective in treating skin manifestations in eight patients reported by Chung et al (32). Photosensitive heliotrope rash and violaceous poikiloderma seem to be the DM manifestations more sensitive to RTX (33). In contrast, paraneoplastic skin lesions and calcinosis were often refractory to B cell depleting therapy (34,35).

In addition, the JDM group showed a more rapid improvement in the trial compared to either adult DM or PM group (9). However, this difference was not statistically significant between the treatment arms, possibly related to the too small sample size (17).

These findings confirm the complexity of the disease and suggest that the depletion of B lymphocytes may be an useful therapeutic advance, but is not going to be a cure for IIM.

In conclusion, although it is not yet possible to make definite recommendations, the global analysis of all cases of the literature support the off-label use of RTX in some patients with refractory myositis. The lack of validated criteria to evaluate clinical response and the concomitant use of immunosuppressive drugs limit the ability to determine the specific role of B cell depletion therapy. Further studies of RTX in myositis are needed, particularly in treatment-naïve patients.

Key Message:

- RTX may be an effective strategy in the treatment of patients with refractory IIM.
- Patients with autoantibodies, especially the anti-synthetases (mainly anti-Jo-1) and anti-Mi-2, were more likely to respond to RTX therapy.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

References

1. Dalakas MC. Immunotherapy of myositis: issues, concerns and future prospects. Nat Rev Rheumatol. 2010 Mar;6(3):129–37.

2. van de Vlekkert J, Hoogendijk JE, de Haan RJ, Algra A, van der Tweel I, van der Pol WL, et al. Oral dexamethasone pulse therapy versus daily prednisolone in sub-acute onset myositis, a randomised clinical trial. Neuromuscul Disord NMD. 2010 Jun;20(6):382–9.

3. Gordon PA, Winer JB, Hoogendijk JE, Choy EHS. Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis. Cochrane Database Syst Rev. 2012;8:CD003643.

4. Dalakas MC, Illa I, Dambrosia JM, Soueidan SA, Stein DP, Otero C, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. N Engl J Med. 1993 Dec 30;329(27):1993–2000.

5. Mastaglia FL, Phillips BA, Zilko PJ. Immunoglobulin therapy in inflammatory myopathies. J Neurol Neurosurg Psychiatry. 1998 Jul 1;65(1):107–10.

6. Dalakas MC. Sporadic inclusion body myositis--diagnosis, pathogenesis and therapeutic strategies. Nat Clin Pract Neurol. 2006 Aug;2(8):437–47.

7. Oddis CV, Sciurba FC, Elmagd KA, Starzl TE. Tacrolimus in refractory polymyositis with interstitial lung disease. Lancet Lond Engl. 1999 May 22;353(9166):1762–3.

8. Leandro MJ, Cambridge G, Ehrenstein MR, Edwards JCW. Reconstitution of peripheral blood B cells after depletion with rituximab in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Feb;54(2):613–20.

9. Oddis CV, Reed AM, Aggarwal R, Rider LG, Ascherman DP, Levesque MC, et al. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: A randomized, placebo-phase trial. Arthritis Rheum. 2013 Feb 1;65(2):314–24.

10. Sultan SM, Ng KP, Edwards JCW, Isenberg DA, Cambridge G. Clinical outcome following B cell depletion therapy in eight patients with refractory idiopathic inflammatory myopathy. Clin Exp Rheumatol. 2008 Oct;26(5):887–93.

11. Shinjo SK, de Souza FHC, de Moraes JCB. Dermatomyositis and polymyositis: from immunopathology to immunotherapy (immunobiologics). Rev Bras Reumatol. 2013 Feb;53(1):101–10.

12. de Visser M. Editorial: The efficacy of rituximab in refractory myositis: The jury is still out. Arthritis Rheum. 2013 Feb 1;65(2):303–6.

13. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975 Feb 13;292(7):344–7.

14. Hoogendijk JE, Amato AA, Lecky BR, Choy EH, Lundberg IE, Rose MR, et al. 119th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10-12 October 2003, Naarden, The Netherlands. Neuromuscul Disord NMD. 2004 May;14(5):337–45.

15. Mahler EAM, Blom M, Voermans NC, van Engelen BGM, van Riel PLCM, Vonk MC. Rituximab treatment in patients with refractory inflammatory myopathies. Rheumatol Oxf Engl. 2011 Dec;50(12):2206–13.

16. Nalotto L, Iaccarino L, Zen M, Gatto M, Borella E, Domenighetti M, et al. Rituximab in refractory idiopathic inflammatory myopathies and antisynthetase syndrome: personal experience and review of the literature. Immunol Res. 2013 Jul;56(2-3):362–70.

17. Aggarwal R, Bandos A, Reed AM, Ascherman DP, Barohn RJ, Feldman BM, et al. Predictors of Clinical Improvement in Rituximab-Treated Refractory Adult and Juvenile Dermatomyositis and Adult Polymyositis. Arthritis Rheumatol Hoboken NJ. 2014 Mar;66(3):740–9.

18. Brulhart L, Waldburger J-M, Gabay C. Rituximab in the treatment of antisynthetase syndrome. Ann Rheum Dis. 2006 Jul;65(7):974–5.

19. Chiappetta N, Steier J, Gruber B. Rituximab in the treatment of refractory dermatomyositis. J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis. 2005 Oct;11(5):264–6.

20. Levine TD. Rituximab in the treatment of dermatomyositis: an open-label pilot study. Arthritis Rheum. 2005 Feb;52(2):601–7.

21. Lambotte O, Kotb R, Maigne G, Blanc F-X, Goujard C, Delfraissy JF. Efficacy of rituximab in refractory polymyositis. J Rheumatol. 2005 Jul;32(7):1369–70.

22. Zappa MC, Trequattrini T, Mattioli F, Rivitti R, Vigliarolo R, Marcoccia A, et al. Rituximab treatment in a case of antisynthetase syndrome with severe interstitial lung disease and acute respiratory failure. Multidiscip Respir Med. 2011;6(3):183–8.

23. Gürcan HM, Keskin DB, Stern JNH, Nitzberg MA, Shekhani H, Ahmed AR. A review of the current use of rituximab in autoimmune diseases. Int Immunopharmacol. 2009 Gennaio;9(1):10–25.

24. Mimori T, Nakashima R, Hosono Y. Interstitial lung disease in myositis: clinical subsets, biomarkers, and treatment. Curr Rheumatol Rep. 2012 Jun;14(3):264–74.

25. Sem M, Molberg O, Lund MB, Gran JT. Rituximab treatment of the anti-synthetase syndrome: a retrospective case series. Rheumatol Oxf Engl. 2009 Aug;48(8):968–71.

26. Marie I, Dominique S, Janvresse A, Levesque H, Menard J-F. Rituximab therapy for refractory interstitial lung disease related to antisynthetase syndrome. Respir Med. 2012 Apr;106(4):581–7.

27. Keir GJ, Maher TM, Ming D, Abdullah R, de Lauretis A, Wickremasinghe M, et al. Rituximab in severe, treatment-refractory interstitial lung disease. Respirol Carlton Vic. 2014 Apr;19(3):353–9.

28. Unger L, Kampf S, Lüthke K, Aringer M. Rituximab therapy in patients with refractory dermatomyositis or polymyositis: differential effects in a real-life population. Rheumatol Oxf Engl. 2014 Sep;53(9):1630–8.

29. Andersson H, Sem M, Lund MB, Aaløkken TM, Günther A, Walle-Hansen R, et al. Long-term experience with rituximab in anti-synthetase syndrome-related interstitial lung disease. Rheumatol Oxf Engl. 2015 Aug;54(8):1420–8.

30. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. Lancet Lond Engl. 2003 Sep 20;362(9388):971–82.

31. Rider LG, Yip AL, Horkayne-Szakaly I, Volochayev R, Shrader JA, Turner ML, et al. Novel assessment tools to evaluate clinical and laboratory responses in a subset of patients enrolled in the Rituximab in Myositis trial. Clin Exp Rheumatol. 2014 Oct;32(5):689–96.

32. Chung L, Genovese MC, Fiorentino DF. A pilot trial of rituximab in the treatment of patients with dermatomyositis. Arch Dermatol. 2007 Jun;143(6):763–7.

33. Dinh HV, McCormack C, Hall S, Prince HM. Rituximab for the treatment of the skin manifestations of dermatomyositis: a report of 3 cases. J Am Acad Dermatol. 2007 Jan;56(1):148–53.

34. Bader-Meunier B, Decaluwe H, Barnerias C, Gherardi R, Quartier P, Faye A, et al. Safety and efficacy of rituximab in severe juvenile dermatomyositis: results from 9 patients from the French Autoimmunity and Rituximab registry. J Rheumatol. 2011 Jul;38(7):1436–40.

35. Rios Fernández R, Callejas Rubio J-L, Sánchez Cano D, Sáez Moreno J-A, Ortego Centeno N. Rituximab in the treatment of dermatomyositis and other inflammatory myopathies. A report of 4 cases and review of the literature. Clin Exp Rheumatol. 2009 Dec;27(6):1009–16.

36. Gottenberg J-E, Guillevin L, Lambotte O, Combe B, Allanore Y, Cantagrel A, et al. Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis. 2005 Jun;64(6):913–20.

37. Noss EH, Hausner-Sypek DL, Weinblatt ME. Rituximab as therapy for refractory polymyositis and dermatomyositis. J Rheumatol. 2006 May;33(5):1021–6.

38. Mok CC, Ho LY, To CH. Rituximab for refractory polymyositis: an open-label prospective study. J Rheumatol. 2007 Sep;34(9):1864–8.

39. Cooper MA, Willingham DL, Brown DE, French AR, Shih FF, White AJ. Rituximab for the treatment of juvenile dermatomyositis: a report of four pediatric patients. Arthritis Rheum. 2007 Sep;56(9):3107–11.

40. Touma Z, Arayssi T, Kibbi L, Masri AF. Successful treatment of cardiac involvement in dermatomyositis with rituximab. Jt Bone Spine Rev Rhum. 2008 May;75(3):334–7.

41. Feist E, Dörner T, Sörensen H, Burmester G-R. Longlasting remissions after treatment with rituximab for autoimmune myositis. J Rheumatol. 2008 Jun;35(6):1230–2.

42. Lutt JR, Pisculli ML, Weinblatt ME, Deodhar A, Winthrop KL. Severe nontuberculous mycobacterial infection in 2 patients receiving rituximab for refractory myositis. J Rheumatol. 2008 Aug;35(8):1683–5.

43. Vandenbroucke E, Grutters JC, Altenburg J, Boersma WG, ter Borg EJ, van den Bosch JMM. Rituximab in life threatening antisynthetase syndrome. Rheumatol Int. 2009 Oct;29(12):1499–502.

44. Whelan BR, Isenberg DA. Poor response of anti-SRP-positive idiopathic immune myositis to B-cell depletion. Rheumatol Oxf Engl. 2009 May;48(5):594–5.

45. Sem M, Molberg O, Lund MB, Gran JT. Rituximab treatment of the anti-synthetase syndrome: a retrospective case series. Rheumatol Oxf Engl. 2009 Aug;48(8):968–71.

46. Frikha F, Rigolet A, Behin A, Fautrel B, Herson S, Benveniste O. Efficacy of rituximab in refractory and relapsing myositis with anti-JO1 antibodies: a report of two cases. Rheumatol Oxf Engl. 2009 Sep;48(9):1166–8.

47. Majmudar S, Hall HA, Zimmermann B. Treatment of adult inflammatory myositis with rituximab: an emerging therapy for refractory patients. J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis. 2009 Oct;15(7):338–40.

48. Valiyil R, Casciola-Rosen L, Hong G, Mammen A, Christopher-Stine L. Rituximab therapy for myopathy associated with anti-signal recognition particle antibodies: a case series. Arthritis Care Res. 2010 Sep;62(9):1328–34.

49. Jois R, Vasudevan N, Srinivasan P, Mehta R. Resistant dermatomyositis complicated by tubercular myositis and successfully treated with rituximab. Neurol India. 2011 Apr;59(2):306–7.

50. Gheita TA, Gheita HA, Kenawy SA. Rituximab restored the muscle power and rescued from a refractory fatal respiratory failure in a patient with elderly-onset polymyositis. Jt Bone Spine Rev Rhum. 2012 Jan;79(1):101–2.

51. Couderc M, Gottenberg J-E, Mariette X, Hachulla E, Sibilia J, Fain O, et al. Efficacy and safety of rituximab in the treatment of refractory inflammatory myopathies in adults: results from the AIR registry. Rheumatol Oxf Engl. 2011 Dec;50(12):2283–9.

52. Parziale N, Kovacs SC, Thomas CB, Srinivasan J. Rituximab and mycophenolate combination therapy in refractory dermatomyositis with multiple autoimmune disorders. J Clin Neuromuscul Dis. 2011 Dec;13(2):63–7.

53. Limaye V, Hissaria P, Liew C-L, Koszyka B. Efficacy of rituximab in refractory antisynthetase syndrome. Intern Med J. 2012 Mar;42(3):e4–7.

54. Luca NJC, Atkinson A, Hawkins C, Feldman BM. Anti-signal recognition particle-positive juvenile polymyositis successfully treated with rituximab. J Rheumatol. 2012 Jul;39(7):1483–5.

55. Sánchez-Fernández SÁ, Carrasco Fernández JA, Rojas Vargas LM. Efficacy of rituximab in dermatomyositis and polymyositis refractory to conventional therapy. Reumatol Clin. 2013 Apr;9(2):117–9.

56. Clottu A, Laffitte E, Prins C, Chizzolini C. Response of mucocutaneous lesions to rituximab in a case of melanoma differentiation antigen 5-related dermatomyositis. Dermatol Basel Switz. 2012;225(4):376–80.

57. Salimbene I, Leli I, Valente S. Respiratory failure in a patient with dermatomyositis. Multidiscip Respir Med. 2013;8(1):27.

58. Cuttner J, Spiera H, Gorevic P. Rituximab in refractory and relapsed dermatomyositis and polymyositis: comment on the article by Oddis et al. Arthritis Rheum. 2013 Sep;65(9):2497–8.

59. Muñoz-Beamud F, Isenberg DA. Rituximab as an effective alternative therapy in refractory idiopathic inflammatory myopathies. Clin Exp Rheumatol. 2013 Dec;31(6):896–903.

60. Néel A, Colman N, Germaud P, Gaborit B, Hamidou M, Pineau CA. Salvage B-cell depletion therapy in rapidly progressive dermatomyositis-associated interstitial lung disease. Jt Bone Spine Rev Rhum. 2014 Mar;81(2):192–3.

61. Basnayake C, Cash K, Blumbergs P, Limaye V. Use of rituximab in histologically confirmed idiopathic inflammatory myositis: a case series. Clin Rheumatol. 2015 Feb;34(2):371–7.

62. Mecchella JN, Rigby WFC, Zbehlik AJ. Pancytopenia and cough in a man with amyopathic dermatomyositis. Arthritis Care Res. 2014 Oct;66(10):1587–90.

63. Belhassen-Garcia M, Rábano-Gutiérrez A, Velasco-Tirado V, Romero-Alegria A, Pérez-Garcia M-L, Martin-Oterino JA. Atypical progressive multifocal leukoencephalopathy in a patient with antisynthetase syndrome. Intern Med Tokyo Jpn. 2015;54(5):519–24.

64. Grajales CM, Velásquez Mendez MP. Rituximab en población pediátrica: experiencia en el tratamiento de enfermedades reumatológicas, en un hospital infantil de Medellín, Colombia. Rev Colomb Reumatol. 2012 Dicembre;19(4):201–7.

Table 1. Summary of the general characteristics and response of patients with IIM to RTX therapy.

References	Type of study	N. pts	Disease	Symptoms	RTX dosage	Outcome	Response and comments
Levine (20)	Open Label	6	DM	Skin lesions and myositis in 6 pts; ILD in 2pts	375mg/m^2 weekly for 4 wks	Improvement in muscle strength, CK levels, skin lesions. PFTs in 2 pts	*Response in all pts.4pts experienced a return of symptoms after 2-9 months*
Lambotte (21)	Case report	1	ASS	Myositis, ILD	375 mg/m^2 weekly for 4wks	Improvement in MDS, CK and PFTs.	*Long-term Remission (12 months)*
Chiappetta (19)	Case report	1	DM	Myositis, Skin lesions	100 mg/m^2 weekly for 6wks	Improvement in Muscle strength, CK levels, skin lesions.	*Long-term remission (20months). Retreatment with RTX every 3months*
Gottenberg (36)	Small series	2	ASS	Myositis	375 mg/m^2 weekly for 4 wks	Improvement in Muscle strength, CK levels.	*Response*
Noss(37)	Small series	3	2 PM 1 DM	Myositis in all pts. Arrhythmias in 2 pt.	1 g I.V. at days 0 and 14	Improvement in Muscle strength, CK levels.	*Short term Response in 2pts (Relapse by 6–9 months), Long term remission in 1 pt with PM*
Brulhart (18)	case report	1	ASS	Myositis, arthritis, alveolitis, rash	1 g I.V. at days 0 and 14	Improvement in muscle strength, CK, CRP, and ESR levels, lung findings on CT scan.	*Short term Response. Relapse by8 months. Urinary tract infection and acute sinusitis after RTX.*
Dinh(33)	Small series	3	2JDM 1DM	Skin lesions	375 mg/m^2 weekly for 4wks	Improvement in skin lesions.	*Response. Relapse by 9 months in 1pt. Transient flu symptoms in 2 pts*
Chung (32)	open-label	8	DM	Skin lesions and Myositis	1 g I.V. at days 0 and 14	At least 50% reduction in CK levels, muscle deficit (MMT) or skin disease (DM Skin Severity Index)at wk 24.	*3 pts met criteria for improvement in muscle strength. No significant improvement in skin disease. CK levels not reflect muscle strength.*

Mok(38)	Open Label	4	PM	Myositis	375 mg/m^2 weekly for 4 wks	Significant improvement in the mean proximal muscle power scores and reduction in CK levels.	*Response. There is also a trend of improvement in disability scores and in both the mental and physical components of SF-36*
Cooper(39)	large series	4	JDM	Myositis, skin Lesions	375 mg/m^2 weekly for 4 wks	improvement in skin lesions, CK, aldolase levels.	*Response in 3 pts. 1 pt had a persistent disease.*
Touma(40)	Case report	1	DM	Myositis, skin lesions, cardiac involvement	1 g I.V. at days 0 and 14	improvement in muscle strength, CK, ESR, CRP, CK-MB, TT, Holter ECG.	*Long-term remission*
Feist(41)	Case report	1	DM	Skin lesions, miositi	1 g I.V. at days 0 and 14	Improvement in Skin lesions, muscle strength, CK.	*Long-term remission*
Lutt(42)	Small series	2	1DM 1PM	Skin lesions, miositi	1 pt: 375 mg/m^2 weekly For 2 weeks; 1pt: 1 g I.V. at days0 and 14	Improvement in Skin lesions, muscle strength, CK.	*Response but complications of mycobacterial infections*
Sultan (10)	Open Label	8	2 PM 5DM 1JDM	Myositis in 8pts; ILD in 2pts; skin lesions in 1 pt; autoimmune thrombocytopenia in 1 pt	1 g I.V. at days 0 and 14	Primary outcomes: ≥15% improvement in muscle strength by myometry and 30% reduction in CPK at 6months.	*2 pts with DM had a response.6pt were non-responder but:1pt subsequently diagnosed with IBMs. 1pt subsequently diagnosed with nodular sclerosing lymphoma;1pt subsequently diagnosed with sporadic dystrophy. 1pt died 1month after RTX.*
Vandenbroucke(43)	Case report	1	ASS	ILD	1 g I.V. at days 0 and 14	Decrease of ground glass.	*Response*
Whelan(44)	Small series	2	PM anti-SRP+	Myositis	1 g I.V. at days 0 and 14	Improvement in Muscle strength, CK levels.	*Poor clinical response. herpes zoster infection in 1pt*

Sem(45)	Large Series	11	ASS	ILD in 11 pts. Myositis in 5pts.	1 g I.V. at days 0 and 14	Improvement in PFTs, HRCT, MMT, CK levels.	*Short-term beneficial effects.1 pt died of a Pneumocystis jirovecii infection*
Frikha(46)	Small series	2	ASS	Myositis in 2pts, ILD in 1pt	1 g I.V. at days 0 and 14	Improvement in Muscle strength, CK, HRCT.	*Response*
Majmudar (47)	Small series	3	1DM 1DM SRP+ 1PM	Myositis	1 g I.V. at days 0 and 14	Improvement in Muscle strength, CK levels.	*Response. Relapse by 12 months in 2 pts (retreated)*
Rios Fernández (35)	Large series	4	3 DM 1ADM	Myositis, Skin lesions. ILD in 1pt	375 mg/m2 weekly for 4 wks	Improvement in Muscle strength, CK levels, skin lesions, and PFTs.	*Poor response in Paraneoplastic ADM.*
Valiyil(48)	Large series	8	PM anti-SRP+	Myositis	1 g I.V. at days 0 and 14	Improvement in Muscle strength, CK levels	*Short-term beneficial effects in 6 pts.1pt died for pneumonia and a congestive heart failure exacerbation. 1pt lost to follow-up*
Zappa(22)	Case report	1	ASS	Myositis , ILD	Not specified	Improvement in Muscle strength, HRTC, PFTs and 6-minute walking test.	*Response*
Jois(49)	Case report	1	DM	Myositis	1 g I.V. at days 0 and 14	Improvement in Muscle strength, CK.	*Long-term remission*

Mahler (15)	Open label	13	5 DM 8 PM	Myositis	1 g I.V. at days 0 and 14	Primary outcome: Improvement in Muscle strength (hand-held dynamometry and MMT), in CK and LDH levels. Secondary outcomes: ESR and CRP level, VAS general Health, VAS disease activity and VAS pain, dosage of CS, functional ability, HAQ-DI,SF-36, plasma Ig concentrations and safety	*CPK and LDH normalized, and muscle strength measured by hand-held dynamometry increased by 21.5%. MMT improvement did not reach statistical significance. Secondary outcome measures improved as well. 3 pts remained in clinical remission, while 10 pts relapsed after a median of 7.4 months. No differences between anti-Jo-1- and anti-Jo-1+pts*
Bader-Meunier (34)	Open label	9	JDM	Myositis in 7 pts, calcinosis in 1 pt, abdominal pain associated with abdominal lipomatosis in 1 pt	375 mg/m^2 weekly for 4 wks in 7 pts; 500 mg/m^2 at days 0 and 14 in 3 pts	Significant improvement in Muscle strength, CK, calcinosis.	*Response in 3pts treated for muscle involvement. Calcinosis and abdominal pain did not improve. Plasma exchange associated in 3 pts. 5 pts received IGIV after RTX.*
Gheita(50)	Case Report	1	PM	Myositis	500 mg I.V. at days 0 and 14	Significant improvement in Muscle strength, CK.	*Response*
Couderc (51)	Large series	30	6 DM 12PM 12 ASS	Myositis in all pts	25pts: 1 g I.V. at days 0 and14 5pts: 375 mg/m^2 weekly for 4 wks	Significant improvement in3 criteria(>25%): CK, daily CS dose, physicians'opinion.	*Response in 16pts (duration 15.5 months).5 pts had a history ofcancer.9pts had a systemic disease associated with the IIM. MMT done only in 5pts.*
Marie (26)	Large series	7	ASS	ILD	1 g I.V. at days 0 and 14	Significant improvement of pulmonary symptoms, PFTs (FVC and DLCO) and HRCT findings.	*Clinical Response in all pts. Improvement in HRCT in 5pts.(The 2 remaining pts had no progression of ILD at 1-year follow-up)*

Parziale (52)	Case report	1	DM with AR	Myositis	375 mg/ m^2 weekly for 4 wks	Improvement in strength and CK.	*Long term remission*
Limaye(53)	Case report	1	ASS	Myositis	500 mg/ m^2 weekly for 4 wks	Improvement in muscle strength and CK.	*Response. 2 relapse successfully retreated. Subsequent diagnosis of cervical intra-epithelial neoplasia*
Luca (54)	Case report	1	JDM anti-SRP+	Myositis	500 mg I.V. at days 0 and 14	Significant improvement in Muscle strength, CMAS and in CK levels	*Response*
Sánchez-Fernández (55)	Small series	2	1PM 1DM	Myositis	1 g I.V. at days 0 and 14	Improvement in muscle strength and CK levels.	*Long-term remission*
Oddis(9)	Trial	195	'RTX early' 37 PM 36 DM 23 JDM 'RTX late' 39 PM 40 DM 25 JDM	Myositis	575mg mg/m2 up to 1g/infusion based on BSA. 'early' arm: RTX atwks 0 and 1. 'late' arm: RTX at wks8 and 9.	Primary endpoint: time to achieve the IMACS DOI. Secondary endpoints: time to achieve ≥20% improvement in muscle strength, and the proportion of pts achieving DOI at wk 8.	*It failed to achieve its primary and secondary endpoints*
Clottu(56)	Case report	1	DM anti-MDA5+	Skin lesions	1 g I.V. at days 0 and 14	Improvement in skin lesions.	*Response*
Salimbene (57)	Case report	1	DM	Myositis	Not specified	Improvement in muscle strength and CK levels.	*Response. 2 yrs after RTX, the pt developed a pulmonary infection*
Nalotto(16)	Large series	6	3PM 3 ASS	Myositis in 6pts. Arthritis in 2 pt. ILD in 1 pt.	1 g I.V. at days 0 and 14	Improvement in muscle strength (MMT8) and CK levels. Disease activity score (in 2 pts). Improvement in PFTs (in 1 pt).	*Long term remission in 5 pts.1 pt no responder.*

Cuttner (58)	Large series	10	6DM 1 ADM 3PM	Myositis in 9pts. Skin lesions in 7 pts.	375 mg/ m^2 weekly for 4 wks	Improvement in skin lesions, muscle strength and CK levels.	*Partial response was achieved in all 10 pts, with a complete response reached in8pts.*
Muñoz-Beamud (59)	Large series	16	2 PM 2PM/RA 1 ADM 1JDM 1DM/SCL 2DM/SLE 4ASS 3DM	Myositis	1 g I.V. at days 0 and 14	Improvement of at least 20% on theMITAX baseline score and a decreaseof at least 30% of CK levels.	*MITAX Response in 8pts: 4ASS, 2DM/ SLE and 1PM/RA andthe ADM. Long term remission in 5/8 pts. 10 pts showed at least 30% reduction in serum CK.No clinical response was correlated to the MITAX score in 2 out of these 10*
Néel(60)	Case report	1	DM	ILD	1 g I.V. at days 0 and 14	Improvement in dyspnea, PFTs and HRTC lesions.	*Response*
Basnayake (61)	Large series	7	1UI 2DM 4PM	Myositis in 6pts. ILD in 5 pts	1g at days0and 14 in1 pt. 500m/m^2 weekly for4 wks in4pts. 750mg/m^2 weekly for 4wks in 2 pts.	Significant improvement in Muscle strength and CK levels. Improvement in PFTs.	*Response continued for at least5 months.*
Unger (28)	Large series	18	13 PM, 5 DM	myositis (in 12 pts), ILD (in 11 pts), Arthritis (in 7 pts).	12pts: 1 g I.V. at days 0 and 14. 6pts: 375 mg/m^2 weekly for 4 wks	reduction of >50% of both the baseline CK level and the daily CS dose or an increase of >10% of FVC and TLC baseline value.	*9 of 13 PM pts responded. all 5 DM pts responded.*
Mecchella(62)	Case report	1	ADM	ILD	1 g I.V. at days 0 and 14	Improvement in dyspnea and stabilized lung function	*Response but the pt developed Babesia microti infection*
Andersson (29)	Large series	24	ASS	ILD	1 g I.V. at days 0 and 14	Improvement in PFTs and in HRCT images.	*Long term remission. 21% of the patients died. Most of the deaths being related to infections.*

Rider (31)	Trial	18	8 PM, 5 DM, 5 JDM	Myositis in all pts, skin lesions in 10 pts.	6Pts (early group): RTX at wks 0 and 1; 12 pts(late group) : RTX at wks 8 and 9	The primary DOI was met if, at 2 consecutive visits, there was ≥20% improvement in 3 of 6 core set activity measures.	*8 (44%) pts met the DOI by wk 16, and 15 met the DOI by week 44. 50% of pts met a DOI 50% response and 22% met a DOI 70% response. The muscle assessments were more sensitive to change than skin assessments.*
Belhassen-Garcia (63)	Case report	1	PM	Myositis	375 mg/ m^2 weekly for 4 wks	Improvement in Muscle strength, CK levels.	*Response but 10 months later, the pt showed progressive multifocal leukoencephalopathy*
Carolina Muñoz Grajales (64)	Case report	1	JDM	Myositis	Not specified	Improvement in Muscle strength, CK levels.	*No responder*
Keir (27)	Large case series	10	IIM	ILD	1 g I.V. at days 0 and 14	Improvement in PFTs	*5 responders. Within the CTD-ILD group, patients with IIM were most likely to show an improvement in PFTs following RTX*

Abbreviations: IIM: idiopathic inflammatory myopathies; PM: polymyositis; DM: dermatomyositis; JDM: juvenile DM; ADM: amyopathic DM; ASS: antisynthetase syndrome; IBM: inclusion body myositis; ILD: interstitial lung disease; CTD: connective tissue disease; SLE: systemic lupus erythematosus; SCL: systemic sclerosis; RA: rheumatoid arthritis; RTX: rituximab; pt: patient; wk: week; PFTs: pulmonary function tests; CS: corticosteroids; DOI: definition of improvement; MMT: Manual Muscle Testing; VAS: visual analogue scale; MDS: Muscle disability scale; CMAS: Childhood Myositis Assessment Scale; MITAX: myositis intention to treat activity index; SRP: signal recognition particle; MDA5: Anti–melanoma differentiation-associated gene 5.