Rituximab therapy in patients with refractory dermatomyositis or polymyositis: differential effects in a real-life population

Leonore Unger, Susanne Kampf, Kirsten Lüthke and Martin Aringer

Abstract

Objectives. While a double-blind trial has not met its endpoint, rituximab (RTX) is still seen as useful in refractory DM and PM. In this study we analysed the charts of all patients receiving RTX for myositis in our institutions for objective outcome parameters.

Methods. In a retrospective way, the charts of all patients with PM or DM who received RTX were analysed for glucocorticoid dose, creatine phosphokinase (CPK) and lung function tests, as well as for serious adverse events.

Results. A total of 19 patients were identified, 1 of whom died from aspiration pneumonia 3 weeks after the first RTX infusion. The charts of 18 patients (13 PM, 5 DM) could be further analysed. In addition to the fatal pneumonia, six more severe infections were seen. One patient developed hypogammaglobulinaemia. Two patients had mild infusion reactions. Under RTX, both CPK and daily prednisolone dose were reduced by week 18. Six of eight patients with alveolitis improved under RTX. Overall, 9 of 13 PM patients responded. Six of the responders and two patients without documented response, all anti-synthetase syndrome patients, were re-treated. In contrast, all five DM patients responded and none required re-treatment.

Conclusion. In a real-life population of patients with severe, refractory PM or DM, objective improvement was seen in the majority of patients with regard to CPK and lung function tests, and glucocorticoids could be reduced. In contrast to the subgroup with DM, where one cycle of RTX appeared sufficient, patients with anti-synthetase syndromes commonly experienced flares necessitating RTX re-treatment. Infections are of concern.

Key words: rituximab, B cell depletion, dermatomyositis, polymyositis, idiopathic inflammatory myositis, interstitial lung disease, relapse, safety.

Introduction

Refractory PM and DM are therapeutically challenging. Permanent damage is a significant concern, and both severe muscle weakness and interstitial lung disease (ILD) can be life threatening. When the combination of glucocorticoids with MTX or immunosuppressives does not control the disease, B cell depletion with rituximab (RTX) has emerged as one therapeutic option [1–12]. This approach is based on the presence of autoantibodies in patients with autoimmune myopathies and the presence of B cells in muscle lesions [13–17].

Recently the results of the large, double-blind, RTX in myositis (RIM) clinical trial were published [18]. This study randomized 200 patients to receive RTX immediately or after 8 weeks. No significant difference between the arms could be detected. However, most patients in both arms reached the primary endpoint of improvement in at least three of six core set measures. The authors concluded that, while formally negative, the results of this study suggest that RTX had an effect [18].
Since this had also been our clinical impression, we analysed the charts of all RTX-treated myositis patients at two institutions in a retrospective way. The results of this analysis are consistent with therapeutic success for both DM and anti-synthetase syndrome patients, but support differences in response between the two entities.

Materials and methods

From the records of both departments, 19 patients with PM or DM treated with RTX from 2005 to 2011 were identified. Eighteen patients (one had died) gave their informed consent to analysis of their clinical data. In the case of the one patient who had died, data were retrieved and anonymized by the treating physician. This approach is in line with German laws and the Declaration of Helsinki and the study was approved by the Ethics Committee of the Medical Faculty and the University Medical Center Dresden.

All clinical and laboratory data were derived from the patients’ charts in a retrospective way. Infusion reactions and severe adverse events were registered if occurring within 1 year after the last RTX infusion. Cases of death were registered during the entire follow-up period. Since standardized measures of muscle strength [e.g. manual muscle testing in eight regions (MMT-8)] had not been consistently performed in clinical routine, creatine phosphokinase (CPK) serum levels as a marker of muscle cell death (formal upper range of normal 2.78 μmol/l/s) and daily prednisolone dose as an estimate of the physician’s impression on disease activity were used as the best available surrogate measures of outcome response. Mean daily prednisolone doses were calculated in 4-week intervals. Before the first RTX infusion, the information on previous steroids was often incomplete, so shorter time spans [16 (s.d. 3 days)] had to be used instead. The efficacy of RTX was assumed after week 12 at the earliest. Response was defined as a reduction of >50% of both the baseline CPK level and the daily prednisolone dose. If the CPK was ≤10 μmol/l/s or the prednisolone dose was ≤20 mg/day at baseline and had not increased later, ≥50% improvement in the other parameter was considered sufficient for a response.

Relapse was defined as any duplication of CPK response level or any increase to >10 μmol/l/s, which clinically resulted in intensification of the treatment regime. To generate a clear timeline out of the chart data, data were grouped to 18 (range 12–24) weeks, 30 (range 24–36) weeks and 50 (range 44–56) weeks after the first RTX infusion of each RTX course. For patients with ILD, total lung capacity (TLC) and forced vital capacity (FVC) were followed and an increase of ≥10% of the baseline value was considered significant. Retrospective data were grouped to 7 (range 5–9), 12 (range 9–15) and 21 (range 18–24) months after RTX.

Normality was tested by the D’Agostino and Pearson omnibus normality test. Group results are expressed as mean (s.d.) or as median (range) for normally distributed and not normally distributed parameters. Paired t-test or Wilcoxon signed rank test were used for comparisons to baseline. P-values <0.05 were considered statistically significant.

Results

Patients

Of a total of 19 patients, 1 died within 3 weeks of the first RTX infusion. The other 18 patients [17 females, age 57 years (s.d. 18)] suffered from PM (13/18) or DM (5/18) according to Bohan and Peter [19], with a median disease duration of 5.4 years (range 0.1–15) at the first RTX treatment (Table 1). Myositis-specific antibodies were found in 14 of 18 patients, namely anti-Jo-1 (n = 9), anti-Pl-7 (n = 1), anti-Mi-2 (n = 3) and anti-SRP (n = 1) antibodies. One patient was anti-Ku positive and suffered from a scleroderma overlap syndrome with features of limited cutaneous systemic sclerosis (Raynaud’s syndrome, digital ulcers, sclerodactyly, facial sclerosis), myositis and arthritis. Of the three patients without specific autoantibodies, two had definite DM and one had probable PM according to Bohan and Peter. The two DM patients had typical skin involvement, symmetric proximal muscle weakness, pathological electromyography (EMG) findings and elevated CPK. The PM patient suffered from symmetric proximal muscle weakness and had pathological EMG findings and elevated CPK, but negative biopsy results. A follow-up MRI in remission showed fatty degeneration.

The most common reasons for initiating RTX were refractory myositis (in 12 patients), active ILD (in 11 patients) and/or refractory arthritis (in 7 patients). Inability to swallow, heart involvement, pulmonary hypertension and relapsing fevers supported the decision in single patients. Not all patients with clinically active myositis had CPK values >10 μmol/l/s, but clinical worsening of muscle strength and/or oedema on MRI substantiated active disease in the absence of other severe organ manifestations. In addition to corticosteroids, patients had received a median of 3 (range 1–6) different previous DMARDs or immunosuppressives (Table 1).

RTX therapy

Overall, 12 of 18 patients received 2 × 1000 mg RTX infusions 2 weeks apart for every RTX course. Patient 5 received 4 weekly infusions of 375 mg/m² and an additional 600 mg infusion at week 9. Patients 11 and 12 were switched from 4 × 375 mg/m² to 2 × 1 g after the first cycle. Patient 8 was treated with two 1000 mg infusions 12 weeks apart. Patient 10 received a single 600 mg RTX infusion. Patient 17 was treated with a normal 2 × 1000 mg course first and with a reduced dose of 1 × 1000 mg in further courses. Prednisolone (100 mg) was given routinely as premedication. Antihistamines and paracetamol were given in cases of previous reactions to RTX.

Seven patients received RTX monotherapy, while additional immunomodulatory medication was continued in 11 patients (Table 1). After the first RTX course the patients were followed for 2.5 years (s.d. 1.6; range 0.5–5.4). Within the subset of 12 patients for whom fluorocytometric
## Table 1: Clinical characteristics of 18 patients with DM or PM

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex/age, years/disease duration, years</th>
<th>DM, PM, overlap with scleroderma (O)</th>
<th>Specific antibody</th>
<th>Index manifestations for RTX therapy</th>
<th>Previous treatment</th>
<th>RTX cycles, n</th>
<th>Concomitant therapy with different RTX cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cycle I</td>
</tr>
<tr>
<td>1</td>
<td>F/77/0.1</td>
<td>DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>F/86/0.8</td>
<td>DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>F/19/0.1</td>
<td>DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>F/76/1.3</td>
<td>DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>F/85/0.3</td>
<td>DM</td>
<td></td>
<td>Myositis, inability to swallow</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>F/73/1.9</td>
<td>PM</td>
<td>Ku</td>
<td>Alveolitis, arthritis, heart involvement</td>
<td>MTX, LEF, ADA, ETC</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>F/65/8.3</td>
<td>PM</td>
<td>SRP</td>
<td>Myositis</td>
<td>MTX, AZA, LEF, MMF, HCQ</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>F/64/15</td>
<td>PM</td>
<td></td>
<td>Myositis</td>
<td>MTX, AZA, CYC, IVIG, LEF, MMF</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>F/64/1</td>
<td>PM</td>
<td>Jo-1</td>
<td>Alveolitis, arthritis</td>
<td>CYC</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>F/55/7</td>
<td>PM</td>
<td>Jo-1</td>
<td>Alveolitis, arthritis</td>
<td>MTX, CYC, MMF, ADA, SSZ, IFX</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>F/36/5.3</td>
<td>PM</td>
<td>Jo-1</td>
<td>Myositis, alveolitis, arthritis</td>
<td>MTX, AZA, CYC, LEF, MMF, SSZ</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>F/64/1.1</td>
<td>PM</td>
<td>Jo-1</td>
<td>Myositis, alveolitis, pulmonary hypertension</td>
<td>IVIG</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>F/41/0.5</td>
<td>PM</td>
<td>Jo-1</td>
<td>Myositis, alveolitis, arthritis</td>
<td>ADA</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>F/51/7</td>
<td>PM</td>
<td>Jo-1</td>
<td>Alveolitis</td>
<td>MTX, CYC, IVIG, LEF, CSA, SSZ</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>F/42/3.2</td>
<td>PM</td>
<td>Jo-1</td>
<td>Myositis, alveolitis</td>
<td>MTX, AZA, CYC, IVIG, LEF, CSA</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>M/36/13</td>
<td>PM</td>
<td>Jo-1</td>
<td>Myositis, alveolitis, arthritis</td>
<td>MTX, CYC, IVIG</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>F/43/14.2</td>
<td>PM</td>
<td>Jo-1</td>
<td>Alveolitis</td>
<td>MTX, CYC, CSA, SSZ</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>F/64/3.8</td>
<td>PM</td>
<td>Pt-7</td>
<td>Alveolitis, arthritis, relapsing fevers</td>
<td>MTX, CYC, anakinra</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

ADA: adalimumab; ETC: etanercept; IFX: infliximab. na: not applicable.
analysis had been performed after RTX induction therapy, all were deplete of B cells after RTX.

Safety evaluation before RTX included chest X-rays and hepatitis B and C serology. IgG quantification was not routinely performed before RTX in the beginning, but was added later on.

Safety
One 81-year-old male patient died of aspiration pneumonia 3 weeks after the RTX infusion. He had a history of rapid progressive anti-SRP myositis, became bedridden within 6 months and was unable to swallow. The autopsy also showed myocardial involvement. RTX was introduced as final option after high-dose prednisolone pulse, IVIG and CYC had failed to control the disease. Recurrent urinary infections and pneumonia had already occurred before RTX.

Six more severe infections occurred under RTX treatment in four patients (one infection of unknown primary, one urinary tract infection, one herpes zoster, one respiratory infection and two erysipelas of the lower leg) a mean of 4.2 months (s.d. 3.7) after the RTX infusions. One patient developed chronic kidney damage after recurrent urinary tract infections. This patient had already suffered from recurrent urinary tract infections before the initiation of RTX. All other infections had favourable outcomes after antimicrobial treatment.

One patient developed symptomatic secondary antibody deficiency, first registered more than 1 year after her first RTX course, when the patient was not on immunosuppressive therapy. Substitution with IVIG became necessary 5 months after her second RTX course, when recurrent infections started (two pneumonias, one cholecystitis and several upper respiratory tract infections). Normalization of immunoglobulin levels was not achieved. Recurrent systemic reactions against IVIG preparations despite premedication required changing to subcutaneous immunoglobulin after 2 years. Infections could be managed by antimicrobials. After this experience, IgG was measured before and after RTX in six patients. One patient had 4.7 g/l before and 3.3 g/l after the second RTX infusion, without experiencing infections. In all other patients, IgG levels before RTX were high [12.5 g/l (s.d. 3.5)] and dropped only slightly [to 10.5 g/l (s.d. 2.2)].

Infections occurred in combination with glucocorticoids only, as well as with glucocorticoids with MTX, AZA and MMF. Neither infections nor antibody deficiency appeared to be linked to any specific combination of RTX with other concurrent or previous immunosuppressive therapies (data not shown). In two patients, hypotension and bradycardia occurring during the first RTX course were successfully managed by reducing infusion speed.

CPK levels and corticosteroid dose after the first RTX course
Overall, 14 of 18 patients responded after their first RTX course within 5.6 months (s.d. 2.6) (Fig. 1). Three patients (patients 8, 16 and 17) were non-responders. Numerical assessment of the clinical response of PM patient 18, who was anti-Pl-7 positive, was not possible after the first RTX cycle, since the patient was readmitted only when she experienced a relapse in week 35.

After the initiation of RTX, CPK decreased by >50% in eight of nine patients with CPK levels >10 μmol/l at baseline and by 48% in one patient. The other nine patients had near normal CPK levels at baseline. Most of these patients still had impressive muscle weakness with slightly elevated CPK values, in addition to the impact on other organs (Table 1). In two patients, short-term high-dose glucocorticoids had decreased CPK values to <10 μmol/l without antibody deficiency, first registered more than 1 year after the initiation of RTX.

Infections occurred in combination with glucocorticoids only, as well as with glucocorticoids with MTX, AZA and MMF. Neither infections nor antibody deficiency appeared to be linked to any specific combination of RTX with other concurrent or previous immunosuppressive therapies (data not shown). In two patients, hypotension and bradycardia occurring during the first RTX course were successfully managed by reducing infusion speed.

CPK levels and corticosteroid dose after the first RTX course
Overall, 14 of 18 patients responded after their first RTX course within 5.6 months (s.d. 2.6) (Fig. 1). Three patients (patients 8, 16 and 17) were non-responders. Numerical assessment of the clinical response of PM patient 18, who was anti-Pl-7 positive, was not possible after the first RTX cycle, since the patient was readmitted only when she experienced a relapse in week 35.

After the initiation of RTX, CPK decreased by >50% in eight of nine patients with CPK levels >10 μmol/l at baseline and by 48% in one patient. The other nine patients had near normal CPK levels at baseline. Most of these patients still had impressive muscle weakness with slightly elevated CPK values, in addition to the impact on other organs (Table 1). In two patients, short-term high-dose glucocorticoids had decreased CPK values to <10 μmol/l. CPK stayed below 10 μmol/l in all these patients, decreasing by at least 10% in seven, while slightly increasing in the other two patients. On a group level, CPK decreased from a median 10.03 μmol/l (range 0.55–63.65) at baseline to 3.27 μmol/l (0.96–19.81), 1.77 μmol/l (0.92–8.87) and 2.83 μmol/l (0.96–21.96) after 18, 30 and 50 weeks, respectively (Fig. 2, first column). For those 12 of 18 patients for whom CPK values for week 18 were available, the decrease was significant at a P < 0.005 level. In an additional 5 of 18 patients, CPK values were available for week 30 only. The overall CPK reduction from baseline to week 30 failed to reach significance (P = 0.0522), but values remained stable from week 18 on. Patient 6 only had a CPK control at week 50, which showed a decrease to 2.83 μmol/l from a baseline value of 3.59 μmol/l. All available CPK values taken together, a significant drop in CPK (P < 0.05) could be observed until up to 1 year after RTX treatment.

In all 10 patients with an initial prednisolone dose of ≥20 mg/day, prednisolone could be reduced by >50% after one RTX course. For the eight patients with a lower corticosteroid dose at baseline, further reduction was possible in four patients, while the dose was kept stable in two patients. Two patients with a prednisolone dose of <20 mg required more prednisolone after RTX. Median daily prednisolone dose decreased from 23 mg/day (range 8–523) to 8 mg/day (5–40), 8 mg/day (3–75) and 6 mg/day (0–216) at 18, 30 and 50 weeks, respectively (Fig. 2, first column). Corticosteroid reduction from baseline was significant (P < 0.005) 18 weeks after RTX and remained significant (P < 0.005, data available for n = 17) at week 30 and week 50 (P < 0.0005, data available for n = 14).

Anti-Jo-1 antibodies were quantitatively assessed before and after the first RTX course in five patients only. Group changes were not significant [from 139.8 (s.d. 77.8) to 95.6 (s.d. 80.3) U/ml], but one patient showed a decrease in anti-Jo-1 antibody levels from 148.0 to 8.4 U/ml without a concomitant decrease in total IgG.

Need for re-treatment in PM vs DM
In the PM subgroup, 9 of 13 patients responded according to the preset criteria (Fig. 2, second column). The responders were positive for anti-Jo-1 (n = 7), anti-SRP (n = 1) or anti-Ku (n = 1). The three non-responders were
CPK levels (in μmol/l/s; triangles, left y-axis) and prednisolone doses (in mg/day; loops, right y-axis) are shown. The dotted line indicates the cut-off level of elevated CPK (2.78 μmol/l/s). The x-axis is the timeline in months with yearly or 2-yearly marks, adapted at the follow-up period. Arrows represent the RTX cycles. RTX: rituximab; CPK: creatine phosphokinase.
positive for anti-Jo-1 (patients 16 and 17) or had no detectable antibody (patient 8). Six of the nine initial responders relapsed 18.2 months (S.D. 9.6) after their first RTX course. These six patients, and two patients without obvious initial response, received additional RTX courses. All re-treated patients were positive for anti-synthetase antibodies (anti-Jo-1 antibody, \( n = 7 \); anti-Pl-7 antibody, \( n = 1 \)) (Fig. 1). Eight patients received a second, seven a third and two a fourth course of RTX, administered after a median 11 months (range 6–37). Only 2 of these 17 additional courses were given as monotherapy, while 15 of 17 were accompanied by additional DMARDs (Table 1).

Eight of the 17 additional courses led to therapeutic responses, while 3 courses failed to achieve therapeutic success. In 6 of 17 courses, response could not be assessed because of missing data (Fig. 2, third column). After re-treatment, corticosteroid doses were significantly decreased \( (P < 0.05) \), while CPK was not improved significantly.

Of the 5 of 13 PM patients without further RTX courses, 1 continued concomitant treatment with MTX and started additional LEF after 86 weeks. Two started with AZA and CSA after 28 and 41 weeks, respectively. One patient could stop all immunosuppressives and discontinued steroids after 43 weeks.

In contrast to the situation in PM, all five DM patients responded to their first RTX course (Fig. 2, fourth column). The five DM patients all stayed stable without further RTX treatment for an observation period of 27 months (S.D. 22) (Fig. 1). Two patients continued concomitant treatment with AZA or MTX. Two patients started MTX 20 and 30 weeks after the first RTX infusion. One patient stopped DMARDs, and discontinued prednisolone 49 weeks after RTX.

Since two different approaches, i.e. the RA approach of 2 g and the lymphoma regimen of \( 375 \, mg/m^2 \), were used, we analysed for potential differences, but found none between the two regimens (data not shown).

**ILD**

TLC follow-up values were available for 8 of 11 patients with fibrosing alveolitis (Fig. 2). All patients with ILD had PM and were positive for anti-Jo-1 antibody \( (n = 9) \), anti-Pl-7 antibody \( (n = 1) \) or anti-Ku antibody \( (n = 1) \). The three
patients without documented TLC were anti-Jo-1 positive. TLC increased by >10% in six of eight patients and stayed stable in the other two patients. Long-term observation in two patients until close to 2 years after RTX infusion showed further improvement by >10% in one and stability of TLC in the other. TLC increased from 71% (S.D. 15) of the expected reference value to 83% (S.D. 15), 86% (S.D. 10) and 102% (S.D. 16) after 7, 12 and 21 months (Fig. 2, third row; month 21 not shown). Improvement at month 7, documented in seven of eight patients, was significant (P < 0.05 in a paired t-test). Likewise, FVC increased after the first RTX course, from 74% (S.D. 19%) of the expected reference value to 83% (S.D. 21%), 91% (S.D. 21%) and 108% (S.D. 15%) after 7, 12 and 21 months. The diffusing capacity of carbon monoxide (DLCO), measured in six patients only, showed a nonsignificant increase from 50% (S.D. 15%) to 55% (S.D. 16%) of expected. The eight re-treated patients all suffered from ILD. For five of these patients, TLC was documented for a total of seven re-treatment cycles (four second and three third RTX cycles). Following RTX re-treatment, a >10% TLC improvement was found after two cycles (by 7 and 12 months), a stable situation after four cycles and worsening 7 months after one RTX cycle. The initial TLC of 77% (S.D. 12%) stayed approximately stable at 73% (S.D. 11%) in six of seven cycles at 7 months. Improvement was seen in three of seven cycles after 1 year to 91% (S.D. 8%) and long-lasting stability in two re-treatment courses nearly 2 years after, with 89% and 94% (Fig. 2, third row; follow-up after >1 year not shown).

Discussion

We here present a retrospective analysis of RTX effects on 19 patients suffering from refractory PM or DM. In this complete sample of two institutions, we used the combination of a >50% improvement in both CPK and glucocorticoid dose as a rather robust objective outcome parameter. The lack of consistent evaluation of muscle strength is a clear limitation of our study, since the CK level often is not a good marker of disease activity and may not correlate with muscle weakness [20]. Under these circumstances, 14 of 19 patients responded to RTX, which is in the range of responses of both the Rituximab in Myositis (RIM) study [18] and the German Registry of Autoimmune Diseases (GRAD) [4].

More clearly than in previous publications, we saw a difference between DM and PM patients, although both had been refractory to various immunosuppressives before undergoing RTX therapy. In fact, among the smaller group of DM patients, all responded and none required RTX re-treatment. Patients with anti-synthetase syndrome still responded in the vast majority of cases. However, 8 of 10 PM patients with anti-synthetase antibodies received a second cycle of RTX and 7 of 10 received a third cycle, with 2 of 10 requiring a fourth cycle.

These results are in line with published work. A subanalysis of the RIM study found that anti-synthetase antibodies and anti-Mi-2 antibodies predicted reaching the clinical endpoint [21]. Within this 44-week study, 9 of the 200 patients were re-treated for flares [18]. Mahler et al. [2] saw a somewhat earlier relapse and re-treated 10 of their 13 myositis patients, 6 of them also for a third time. Similar to our analysis, Couderc et al. [1] found a significantly higher chance of response for DM patients in the Arthritis Internet Registry (AIR), with five of six responding and only one requiring re-treatment.

Pulmonary involvement is the most common reason for mortality in idiopathic inflammatory myopathy patients. There are several reports of good efficacy of RTX in ILD. Sem et al. [6] published results of 11 patients with anti-synthetase syndrome. They found amelioration of ground glass attenuation in 5 of 11 patients on high-resolution CT, while >10% improvement in FVC and >15% improvement in DLCO was seen in 6 and 3 of 11 patients, respectively [6]. Marie et al. [22] recently showed significant improvements in clinical findings of ILD, as well as CT and pulmonary function tests in seven patients positive for anti-synthetase antibodies with ILD. Eight of our 11 ILD patients had follow-up pulmonary function tests. To avoid potential influences of muscle weakness on the pulmonary function tests, we decided to primarily evaluate TLC. Again, a >10% improvement in TLC was documented for six of eight patients, suggesting beneficial effects on ILD in anti-synthetase syndrome. FVC results were in line with such improvement.

One SRP antibody–positive patient died 3 weeks after the initiation of RTX from septic aspiration pneumonia. He was affected by rapid progressive muscle weakness, inability to swallow and myocarditis. His death was caused by rapid disease progression. In our opinion, the RTX treatment had no bearing on his death.

In contrast, RTX may well have played a role when another patient developed secondary antibody deficiency syndrome with recurrent infections after her second RTX course [23], and consecutively received substitution with human immunoglobulin. Four patients acquired a total of six severe infections. While all of these infections were manageable, these observations stress the severity of the underlying disease and call for a circumspect approach when using RTX in these patients.

The obvious weaknesses of our approach all stem from the fact that the data were extracted from routine clinical work. Thus we cannot provide an adequate control group other than the previous course of the patients, and many of the core set parameters [20] were not available for the majority of patients. In particular, standardized muscle testing was either not continuously done or not adequately documented. In fact, MMT-8, as recommended [24], has only recently become routine in our institutions. However, both CPK values and the longer-term daily dose for prednisolone are fairly objective measures of disease activity, as is TLC for ILD. Moreover, we have included all of the patients treated with RTX for myositis, and accordingly present a complete picture on a difficult-to-treat subset of patients. Under these circumstances, a number of 19 appears relevant, and some of the therapeutic success was rather impressive.
For 18 of the 19 patients, the diagnosis was unequivocal. In one patient without specific autoantibodies, however, probable polymyositis was not confirmed by a first muscle biopsy, and a repeat biopsy, as usually recommended [25, 26], was not performed. Since this patient remained a non-responder, a potential diagnostic error could only have strengthened the other outcome findings. Given that she had received RTX for probably myositis, this patient was not removed from the sample.

Taken together, our retrospective analysis supports the idea that RTX is a therapeutic option for patients with refractory DM or PM. Moreover, RTX appears to provide for a therapeutic option for ILD in patients with anti-synthetase syndromes. While DM may usually be controlled with one cycle of RTX, our data suggest that most patients with anti-synthetase syndromes will need additional cycles. The safety profile appeared acceptable overall, but the number of serious infections is a concern.

**Rheumatology key messages**

- Improvement in refractory disease and after relapses suggests rituximab (RTX) efficacy in DM and PM.
- In contrast to DM, relapses and need for re-treatment were rather common in PM.
- Maximum RTX effects on myositis were typically found about 30 weeks after the first infusion.

**Disclosure statement:** L.U. and M.A. have served on advisory boards and speakers’ bureaus for Roche, the manufacturer of RTX. S.K. received an honorarium for presenting the data reported here at a Roche symposium. K.L. has declared no conflicts of interest.

**References**


