Rituximab treatment in patients with refractory inflammatory myopathies

Elien A. M. Mahler¹, Marlies Blom¹, Nicol C. Voermans², Baziel G. M. van Engelen², Piet L. C. M. van Riel¹ and Madelon C. Vonk¹

Abstract

Objective. To assess the efficacy of rituximab on disease activity and muscle strength in patients with inflammatory myopathies refractory to conventional therapy.

Methods. Thirteen patients were treated with rituximab 1000 mg i.v., twice, with a 2-week interval and followed for a median of 27 months. Primary outcomes were disease activity measured by creatine phosphokinase (CPK), lactate dehydrogenase (LDH) levels and muscle strength measured by hand-held dynamometry and manual muscle testing (MMT). Secondary outcomes were improvement in secondary laboratory measures, global assessment of general health, disease activity and pain, CS dose, functional ability, health-related quality of life and safety. Retreatment with rituximab was conducted if disease activity relapsed.

Results. The median levels of CPK and LDH were significantly reduced by 93.2 and 39.8%, respectively, compared with baseline after 34.6 months. The median muscle strength measured by hand-held dynamometry was significantly improved by 21.5% after 24 months. The median increase in muscle strength measured with MMT was 7.0% after 24 months of follow-up, although this did not reach statistical significance. Secondary outcomes improved as well.

Conclusion. Rituximab is an effective treatment in refractory inflammatory myopathies, showing a decrease in CPK and LDH, an increase in muscle strength and improvement in scores of disease activity, general health, functional ability and health related quality of life with sustained effect during a median of 27.1 months of follow-up.

Key words: Dermatomyositis, Polymyositis, Refractory, Rituximab, Disease activity, Muscle strength, Functional status, Quality of life.

Introduction

Polymyositis (PM) and dermatomyositis (DM) are chronic inflammatory diseases affecting predominately proximal striated muscles, although other organs may also be involved. PM and DM are characterized by elevated serum creatine phosphokinase (CPK) levels, electromyographic abnormalities and inflammatory infiltrates in skeletal muscles. Only DM is associated with immune complex deposition in vessels, and is thought to be humorally mediated with activation of the complement system. In contrast, PM is characterized by cellular infiltrates [1]. B cells may play a role in both underlying pathological processes. In ~30-50% of patients with inflammatory myopathies, disease-specific autoantibodies can be detected, most commonly anti-Jo-1 autoantibodies, which are present in ~20% of patients [2-9].

Most patients show at least a partial response to high-dose CS therapy alone, but often other immunosuppressive agents such as MTX or AZA are needed to control disease or for their steroid-sparing effect. Patients refractory to these therapies have been treated with a variety of drugs [10] such as IVIGs [11], anti-TNF-α, MMF and tacrolimus [1,12-14]. Selection of these immunosuppressive drugs remains empirical and evidence is circumstantial. In a recent framework for drug treatment of DM and PM, an induction of high-dose oral CSs and AZA or MTX is...
suggested [10]. In case of relapse, the best approach is yet to be determined, but so far IVIG in patients without severe pulmonary involvement is suggested. Unfortunately, repeated infusions are needed.

Due to the limited effects of the therapies described above for patients who are refractory to conventional immunosuppressive therapies and the fact that B cells may play a role in both diseases, the effect of rituximab was evaluated in this study. Rituximab is a chimeric mAb directed against CD20 on B cells. Successful trials of rituximab in patients with RA [15] and SLE [16] have been performed. It might act by suppressing the antigen-presenting or costimulatory function of B cells with a downstream inhibitory effect on T cells [14, 17, 18], but the exact role of CD20-positive cells in pathogenesis remains elusive to date. Several open-label studies and case series have shown positive results on muscle strength and CPK levels of rituximab in patients with PM and DM [19–26], but follow-up is short and results are based on individual cases or small groups. In our study, we evaluated the effect of additional courses of rituximab in 13 patients diagnosed with myositis, who were refractory to conventional therapies. As such, it is the largest cohort that has been published to date.

The primary aim of this study is to assess the efficacy of rituximab in patients with inflammatory myopathies refractory to conventional immunotherapy. Primary outcome measures are disease activity measured by CPK and lactate dehydrogenase (LDH) levels and muscle strength measured by hand-held dynamometry and manual muscle testing (MMT). Secondary outcomes are secondary laboratory outcomes, scores on validated scales of global assessment of general health, disease activity and pain, CS dose, functional ability, health-related quality of life and safety.

Methods

Patients

Eligible patients were between 18 and 70 years of age, met the Bohan and Peter criteria for DM or PM and showed typical histological abnormalities in muscle biopsy [27, 28]. Being refractory was defined as having failed to respond to at least CSs and one other immunosuppressive drug. Patients previously treated with rituximab or with serious infections at the start of the study were excluded. All patients were screened for latent tuberculosis using a purified protein derivative tuberculin and chest X-ray, and excluded if positive. Infusions for this report were given between August 2005 and December 2008 and follow-up was completed at 1 January 2009. Baseline visit was at the moment of start with the first infusion of rituximab. Patients’ characteristics and previous and current immunosuppressive therapy were noted, a physical examination was performed and laboratory variables were collected. All patients gave written informed consent and the study was approved by the medical ethics committee of Arnhem—Nijmegen.

Treatment and retreatment

Patients were treated with rituximab 1000 mg i.v., twice, with a 2-week interval. Before each infusion methylprednisolone 50 mg i.v. and clemastine 2 mg i.v. were administered. Imunosuppressive therapy and oral CSs at baseline were continued and allowed to taper during follow-up. A next course of rituximab was applied using the same treatment strategy if during follow-up disease activity increased. Usual care consisting of physiofitness twice a week was continued.

Primary outcomes

Primary outcome was disease activity using decrease in muscle enzyme levels of CPK and LDH and increase in muscle strength measured by hand-held dynamometry and MMT. Follow-up of muscle enzymes was evaluated at Weeks 2, 6, 10 and 14 and subsequently every 3 months after each course of rituximab. Muscle strength was measured with hand-held dynamometry and MMT by the Medical Research Council 0–5 point scale (composite score for both techniques consisted of the following muscles: neck extensors, neck flexors and right and left for the following muscle groups: shoulder abductors, elbow extensors, elbow flexors, three point grip (for dynamometry only), hip flexors, knee extensors, knee flexors) and performed at baseline and every 3 months thereafter following each rituximab course. At each study visit, patients were tested by the same independent neurologist.

Secondary outcomes

Secondary outcomes were improvement in other disease activity measures such as ESR and CRP level. Other secondary outcomes were patients’ global assessment of general health (visual analogue scale (VAS) general health), physicians’ global assessment of disease activity (VAS disease activity) and patients’ evaluation of pain (VAS pain), dosage of CSs, functional ability, quality of life, plasma immunoglobulin concentrations and safety. Follow-up of secondary outcomes was evaluated at Weeks 2, 6, 10 and 14 and subsequently every 3 months after each course of rituximab. At each study visit, patients were tested by the same independent examiner and questioned about the occurrence of new adverse events and changes in concomitant medication since the last visit. Global assessments were measured on a 100 mm VAS, where 0 was the most favourable and 100 the worst state. Functional ability was assessed by means of the HAQ [29, 30] and scored using the standard disability index (DI). The HAQ-DI yields a score from 0 till 3 with higher scores indicating more disability. Health-related quality of life was measured by the physical and mental component scales of the Short Form 36 (SF-36) [31, 32]. As defined by the International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines a serious adverse event (SAE) was defined as an untoward medical occurrence that was fatal or immediately life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, resulted in persistent or significant
disability/incapacity or was a congenital anomaly or birth defect (ICH-GCP article 1.50).

The International Myositis Assessment and Clinical Studies Group (IMACS) has proposed a core set of six outcome measures in 2004 to assess three dimensions of myositis: disease activity, disease damage and health-related quality of life (SF-36) to be used in clinical trials [33]. These parameters include physicians’ and patients’ overall assessments of disease activity on a VAS, Health Assessment Questionnaire (HAQ), muscle strength measured with Modified Muscle Test (MMT) and serum levels of at least two of four muscle enzymes (CPK, LDH, aspartate aminotransferase and alanine aminotransferase) and an extra-muscular score. Response is defined as at least 20% improvement in three of any six core set measures [34]. We were able to investigate four of these variables, among which were muscle strength measured by MMT and dynamometry, and calculated a response criteria. Response is defined as two out of four core set measure improvement by ≥20% without worsening of more than one core set measure by >25% (and worsening core cannot be MMT). The proportion of patients who achieved 20% improvement was calculated for primary outcome measures, VAS disease activity and HAQ.

Analyses

Changes in primary and secondary outcomes for all patients compared with baseline were analysed using mean (±S.D.) in case of normal distribution and medians [with interquartile range (IQR)] if variables turned out to be non-parametric. Difference in mean or median was be non-parametric. Difference in mean or median was calculated at every follow-up moment and analysed for statistical significance by a paired t-test or Wilcoxon signed-rank test, respectively. All analyses were performed using SPSS version 16.0.

Results

Baseline characteristics

Between August 2005 and January 2009, 13 Caucasian patients with a mean (±S.D.) age of 44.4 (12.1) years at the time of diagnosis with DM or PM were included. Of these patients, 54% were females. Median duration of the inflammatory myopathy was 4.0 years (IQR 2.5–6.5 years). Eight (61.5%) patients were diagnosed with DM. Median number of previously used immunosuppressive drugs (CSs excluded) was 3.0 (IQR 2.0–3.5). Besides CSs, 10 (76.9%) patients had used MTX and 8 (61.5%) used AZA before. In seven (53.8%) patients, anti-Jo-1 antibodies were detected. Median follow-up was 27.1 months (IQR 18.5–33.0 months) and none was lost to follow-up. Six (46.2%) patients completed 31.0 months, 8 (61.5%) patients completed 26.6 months and 10 (76.9%) patients completed 19.8 months of follow-up. Table 1 shows individual patient characteristics.

Treatment and retreatment

The median number of rituximab courses was 2.0 (IQR 1.5–3.5). Ten patients who responded well relapsed after a median of 7.4 months (IQR 6.3–11.5 months) and were retreated with a second course of rituximab. The median number of courses in these 10 patients was 3.0 (IQR 2.0–4.0). The other three patients were still in remission at the end of the study after one course of rituximab after a median follow-up of 17.3 months (IQR 15.0–31.4 months). Six patients received the third course after a median of 7.8 months (IQR 6.8–12.2 months) after the second course. Three patients received a fourth course after a median of 8.1 months (IQR 5.8–13.2 months) after the third course. One patient received a fifth and sixth course 5.3 and 5.8 months, respectively, after the previous one.

Primary outcome measures

Figure 1 shows the values of the primary outcomes at different time points. The median CPK level for all patients was significantly reduced compared with baseline at every time point from 6 weeks of follow-up and further. The level reduced by 93.2% after 34.6 months of follow-up. The median LDH level was significantly reduced by 40.1% as compared with baseline after 30 months. For all patients the median muscle strength measured with

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Previously used DMARDs and baseline characteristics</th>
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<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td><strong>n = 13</strong></td>
</tr>
<tr>
<td>Number of previously used DMARDs</td>
<td>3.0 (2.0–3.5)</td>
</tr>
<tr>
<td>MTX, %</td>
<td>76.9</td>
</tr>
<tr>
<td>AZA, %</td>
<td>61.5</td>
</tr>
<tr>
<td>Methy history, %</td>
<td>30.8</td>
</tr>
<tr>
<td>Infliximab, %</td>
<td>23.1</td>
</tr>
<tr>
<td>Etanercept, %</td>
<td>23.1</td>
</tr>
<tr>
<td>Ciclosporin, %</td>
<td>15.4</td>
</tr>
<tr>
<td>Adalimumab, %</td>
<td>7.7</td>
</tr>
<tr>
<td>CYC, %</td>
<td>7.7</td>
</tr>
<tr>
<td>IVIGs, %</td>
<td>7.7</td>
</tr>
<tr>
<td>CPK, U/l</td>
<td>949.0 (235.0–2139.0)</td>
</tr>
<tr>
<td>LDH, U/l</td>
<td>663.0 (502.5–884.5)</td>
</tr>
<tr>
<td>Hand-held dynamometry, Newton</td>
<td>1209.0 (858.0–1855.0)</td>
</tr>
<tr>
<td>MMT (0–70)</td>
<td>57.5 (52.0–63.0)</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>13.0 (5.0–36.0)</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>8.0 (1.0–19.5)</td>
</tr>
<tr>
<td>Patients’ global assessment of general health (0–100 mm VAS), mean (±S.D.)</td>
<td>48.8 (21.4)</td>
</tr>
<tr>
<td>Physicians’ global assessment of disease activity (0–100 mm VAS), mean (±S.D.)</td>
<td>54.5 (7.7)</td>
</tr>
<tr>
<td>Patients’ assessment of pain (0–100 mm VAS), mean (±S.D.)</td>
<td>21.2 (20.8)</td>
</tr>
<tr>
<td>CS dose, mg/day</td>
<td>15.0 (11.3–20.0)</td>
</tr>
<tr>
<td>HAQ (0–3)</td>
<td>1.25 (0.625–1.906)</td>
</tr>
<tr>
<td>SF-36</td>
<td>31.1 (21.4–35.1)</td>
</tr>
<tr>
<td>Physical component score (0–100 scale)</td>
<td>51.5 (49.4–56.7)</td>
</tr>
<tr>
<td>Mental component score (0–100 scale)</td>
<td>63.0 (56.7–73.0)</td>
</tr>
</tbody>
</table>

Values are presented as median (IQR) unless otherwise stated.
hand-held dynamometry significantly improved compared with baseline at 3, 12, 18 and 24 months up to an improvement of 21.5% compared with baseline. Muscle strength measured with MMT increased by 6.1% as compared with baseline after 18 months ($P = 0.06$) and by 7.0% after 24 months ($P = 0.68$) of follow-up, although this did not reach statistical significance. Median CPK was reduced to $<200$ U/l, 4.5 months (IQR 1.9–10.8 months) after starting rituximab.

Three patients already started at a level of CPK $<200$ U/l due to a high dosage of CSs indicated by a disease flare just before the first rituximab infusion started. These three patients showed an (not statistically significant) increase in MMT of 19.2% and in dynamometry of 69.9% after 24 months. Primary outcomes for the patients who started with CPK $>200$ at baseline ($n = 10$) were not different from the whole group. The median CPK level in these patients was significantly reduced by 93.0% after 30 months. The median LDH level was reduced by 48.3% after 30 months ($P = 0.06$) and by 50.0% after 26 months of follow-up ($P = 0.03$). The median muscle strength measured with hand-held dynamometry showed an improvement of 5.2% compared with baseline after 3 months of follow-up ($P = 0.04$). After 6, 12 and 24 months the increase was 29.2, 5.0 and 5.7%, respectively, although this did not reach statistical significance. In these 10 patients, median muscle strength measured with MMT increased by 6.8% as compared with baseline after 18 months and by 4.2% after 24 months follow-up, although this did not reach statistical significance.

In two patients, normalization of CPK values was not achieved; however, both had a significant reduction in CPK values. One of these showed improvement of muscle strength measured by dynamometry and a 50% reduction of CS dose. In all patients, levels of CPK and LDH decreased, and in 11 (85%) patients muscle strength improvement measured by hand-held dynamometry was achieved during follow-up. In these 11 patients, the significant improvement in median dynamometry was 33.2% as compared with baseline after 24 months ($P = 0.028$). However, one patient developed improvement in dynamometry and not in MMT after 24 months. No response in dynamometry was noted in three (23%) patients during the first 2 years, although one of these patients showed improvement of MMT. We found no differences in response between anti-Jo-1-positive and anti-Jo-1-negative patients. Muscle strength measured by dynamometry improved obviously more slowly than CPK levels, which is shown in Fig. 2, where 20% improvement in CPK, LDH level, MMT and hand-held dynamometry are shown. Ten per cent increase in median MMT was 0% after 3 months, 11.1% after 6 months, 33.3% after 12 months, 37.5% after 18 months and 33.3% after 24 months, and this did not reach statistical significance.

**Secondary outcome measures**

ESR decreased from a median baseline level of 13.0 to 6.0 mm/h after 25.4 months. The ESR was significantly reduced by 50.0% after 9 months and by 46.2% after 12 months. CRP was reduced from 8.0 to 1.0 mg/l after 28.2 months. This reduction was statistically significantly different from baseline at 12.0 and 15.0 months of follow-up. Mean VAS general health was reduced by 14.7 mm after 22.6 months, indicating an improvement in general well-being. After 12 months, a statistically significant reduction by 17.6% was seen and after 17.1 months the reduction was 22.8%. Mean VAS disease activity was reduced from 54.5 to 27.0 mm after 15 months. After 3 months, the reduction by 45.8% from baseline was statistically significant and after 12 months the reduction was 34.4%. Mean VAS pain was not reduced. A decrease in oral CS dose was observed from a median of 15.0 to 6.9 mg/day after 25.4 months (Fig. 3). The dose of oral CSs is presented 3 months before the introduction of rituximab as well because three patients received dose intensification of CSs at baseline due to a disease flare. No i.m. or i.v. steroids were given from the time of screening to the end of the study. In one patient, the dose of oral CSs was increased within 3 months of screening from 15 to 35 mg/day, although after 6 months the dose was reduced to 10 mg/day. The dose of oral CSs was decreased from baseline up to the end of the study in
eight patients from a median of 17.5 to 10.0 mg/day and increased in two patients from a median of 20.0 to 25.0 mg/day (both not statistically significant). No additional DMARD was added in any patient after screening up to the end of the study. In two out of five patients, MTX could be stopped after one course of rituximab. The three other patients still used the same dosage.

At all seven follow-up moments during the first year, the median HAQ showed a decrease of 0.69 after 6 months \((P=0.04)\). Afterwards, the reduction remained stable up to 22.6 months. Concerning the SF-36, median score on the physical component scale improved by 10.9 after 22.6 months. After 12 months, a significant median improvement of 3.0 was seen and after 15 months the median improvement was 13.1 compared with baseline. Median score of the mental component scale was improved by 6.3 after 22.6 months. After 6 months, the improvement of 5.5 from baseline was statistically significant. The results of the secondary outcomes with exclusion of the three patients who started with a CPK <200 U/l were reduction of: median ESR by 52.2% after 22 months, median CRP by 90.1% after 22 months, mean VAS general health by 14.7% after 15 months \((P=0.04)\), mean VAS disease activity by 50.4% after 15 months, median HAQ of 0.50 after 12 months and 0.19 after 15 months and median CS dose by 41.3% after 22 months (not statistically significant unless the \(P\)-value is shown). The score on the physical component scale improved by a median of 10.7 points and on the mental component scale by a median of 3.81 points after 15 months (not statistically significant). Response as per IMACS core set measures was 69.2% after 3 months, 46.2% after 6 months and 41.7% after 12 months, all reaching statistical significance.

**Safety assessments**

Rituximab therapy was well tolerated. Three patients were hospitalized during rituximab courses for gastroenteritis, fever and heart failure. All the above-mentioned events were intercurrent and patients recovered completely. These events did not recur during subsequent rituximab therapy. No fall in serum immunoglobulin levels was observed with sustained therapy.

**Discussion**

In this study, we evaluated the efficacy of rituximab treatment in patients with inflammatory myopathies refractory to conventional therapy during a median of 27.1 months of follow-up. Outcome measures used were disease activity, muscle strength, physicians’ and patients’ evaluation of global general health, pain, oral CS dose, functional ability, health-related quality of life and safety. After rituximab therapy, disease activity measured by serum CPK and LDH normalized, and muscle strength measured by hand-held dynamometry increased by 21.5% in the long term. MMT improvement was 7% after 24 months, although this did not reach statistical significance. Obvious are the rapid response of CPK and the slower improvement of muscle strength as expected in refractory disease. The secondary outcome measures improved as well. A few open-label studies and case reports showed positive results on muscle strength and CPK levels in...
patients with DM and PM treated with rituximab. Response as per IMACS core set measures was 69.2% after 3 months, 46.2% after 6 months and 41.7% after 12 months. However, patient numbers and follow-up duration were limited [19-26]. The present study is therefore the largest cohort published to date.

Three patients remained in clinical remission following their initial course of rituximab, while 10 patients relapsed after a median of 7.4 months and received additional courses. Two different groups of responders could be recognized; the first group remained in remission after the initial course and the second group was in need of additional rituximab courses.

Secondary outcome measures—ESR, CRP, VAS general health, VAS disease activity, CS dose, HAQ and physical and mental component scales of SF-36—improved as well. Mok et al. [26] showed a trend of reduction in patients’ and physicians’ global impression of disease activity, improvement in HAQ and physical and mental component scores on SF-36 in four patients with refractory PM treated with rituximab. Infusions were given at weekly intervals during 4 weeks [36]. In our study, improvement of HAQ-DI was found at all follow-up moments up to 12 months. The HAQ has been used for many years to assess patients with inflammatory myopathies. However, the HAQ was designed for arthritis patients and has not been validated for adult myositis. The generic SF-36 questionnaire has proved to be a valid and sensitive tool for assessment of perceived health in patients with inflammatory myopathies. It is also known that later in the disease course, perception of health is better. Therefore, it is more difficult to measure differences during long-standing follow-up. In secondary outcome measures, a trend towards improvement was found, not reaching statistical significance. This could be explained by the limited group size. Our patients received 34 rituximab courses in total and hospitalization occurred three times for gastroenteritis, fever and heart failure. These events did not recur during subsequent rituximab therapy.

Results of muscle strength measured by MMT did not consistently show statistically different effects compared with baseline but only trends. This could be caused by the fact that all patients included in our study had refractory, long-standing disease. In those patients, muscle strength may not improve significantly because of fixed deficits due to muscle atrophy [35]. Muscle strength measurement does not discriminate between active myositis and atrophy due to long-standing disease. Furthermore, immunomodulatory agents will probably not improve strength or function in long-standing myositis that is characterized by major atrophy and muscle fat replacement. MMT is known to be less sensitive to changes than dynamometry. Furthermore, in contrast to dynamometry measurements, MMT scores are not linearly distributed [36].

The results of our study suggest a stronger role for B cells in the pathogenesis of PM and DM than may have been previously recognized. CYC has been known to mainly suppress B cells as well although the precise pharmacological mechanisms remain unclear. It has been shown to be an effective treatment of interstitial lung disease in PM/DM [37, 38]. Further research is needed to examine the role of rituximab in treating interstitial lung disease in PM/DM. Although subsets of patients with PM and DM both have myositis-specific antibodies, the pathogenic role of these antibodies is not clear [11, 39-43]. We found no differences in responses between anti-Jo-1-positive and anti-Jo-1-negative patients. Nevertheless, the efficacy of rituximab in DM and PM supports the concept that both diseases have a B-cell-mediated humoral pathogenesis. Previous reports have shown inconsistent results concerning disease flare and reappearance of B cells [19, 20, 22]. Accordingly, the decision to provide additional courses of rituximab must include clinical assessment of disease activity apart from B-cell counts as is suggested in RA [15].

Our study has several flaws. We should realize that not all patients had high CPK levels at baseline because they flared a few weeks before the start of rituximab therapy and started high dosages of CSs. CPK levels from those three patients were therefore already normalized at baseline. However, we found a good response at the group level. Analyses of the remaining 10 patients showed the same results. The role of regression to the mean is less important because not all baseline values were measured at the time of flare. Also during the study, patients flared at diverse moments just before a new course of rituximab was given, so the outcome is reduced. It is also known that muscle enzymes alone have limited diagnostic value in inflammatory myopathies, because their levels do not necessarily reflect disease activity or muscle function. For this reason a combination of outcome measures was used. Although our study includes the largest group of refractory myositis patients to date, the sample size could have reduced the power of this study to find significant treatment effects. Therefore, our findings have to be confirmed in a larger cohort of patients in a controlled study.

In short, this study shows that rituximab can be an effective and safe treatment in refractory DM and PM, showing a decrease in disease activity, an increase in muscle strength, patients’ global assessment of general health, physicians’ global assessment of disease activity, functional ability and health-related quality of life with sustained effect during a median of 27.1 months of follow-up. Further research is needed to verify these results.

Rheumatology key messages

- Rituximab treatment can be effective in patients with refractory inflammatory myopathies.
- We showed improvement in dynamometry and MMT in the long term.

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