Functional outcome of myositis patients: Can a low-dose glucocorticoid regimen achieve good functional results?

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Abstract
Objective
During the last few years, in an attempt to reduce the side effects of glucocorticoid (GC) therapy, we have been treating polymyositis-dermatomyositis (PM-DM) patients with a lower starting dose of GC than is classically recommended. In order to validate this approach, we performed a functional re-evaluation of these PM-DM patients.

Methods
A comprehensive protocol evaluating muscle strength, muscle function, CK levels, persistence of spontaneous activity on electromyography, disability in daily life activities and degree of dependence was applied in 25 non-cancer-associated biopsy-proven PM-DM patients, 15 of whom had been treated with a high-dose regimen (i.e. > 0.5 mg prednisolone/kg/day) and 10 with a low-dose regimen (i.e. ≤ 0.5 mg prednisolone/kg/day).

Results
Our results indicate that the functional outcome of PM-DM patients given a low-dose starting regimen of GC does not differ from that observed in patients given higher doses. Interestingly, vertebral fractures were less common in patients treated with lower GC doses.

Conclusions
Although our analysis has certain shortcomings, including the small number of patients investigated and their uncontrolled assignment to a low-dose or a high-dose GC regimen, the results of this retrospective study suggest that a low-dose starting regimen of GC can achieve a good functional outcome in PM-DM patients, with a reduction of treatment-related disability. This approach would be welcome as a step forward should it be validated by a longitudinal study.

Key words
Myositis, glucocorticoids, functional evaluation.
Functional outcome in PM-DM patients treated with glucocorticoids / A. Nzeusseu et al.

Introduction

Although the evidence is essentially empirical, glucocorticoids (GC) have dramatically improved survival rates and reduced functional disability in patients suffering from polymyositis-dermatomyositis (PM-DM). It should be stressed, however, that the use of very high starting doses (i.e. 1 - 2 mg prednisolone/kg/day) (1-3) has never been validated. Two retrospective studies have suggested that PM-DM patients given a high dose GC regimen experienced a better biochemical and clinical outcome than patients given lower doses (4, 5), but the response rate in these studies was evaluated by chart review and/or was not studied according to current standards.

During the last few years, in an attempt to reduce the side effects of GC therapy, we have been treating our PM-DM patients with a lower GC starting dose, i.e. 0.5 mg/kg/day, generally in association with other immunosuppressive drugs such as methotrexate or azathioprine. In order to make sure that this steroid-sparing approach did not jeopardize the treatment efficacy, i.e. that the functional outcome of patients given less GC did not differ from that of patients given a standard regimen, we performed a functional evaluation of all biopsy-proven non-cancer-associated, surviving PM-DM patients seen in our University Hospital who agreed to participate.

The results presented here suggest that the functional outcome of PM-DM patients given a low-dose starting regimen of GC does not differ from that observed in patients given higher doses.

Patients and methods

Patients

Between 1983 and 1995, 51 adult patients with biopsy-proven inflammatory myositis fulfilling Peter and Bohan’s criteria for PM-DM (6) were diagnosed at our University Hospital. Ten had cancer-associated myositis and were therefore excluded. Seven of the 41 remaining patients died (3 from infections, one from suicide, one from cerebral aneurysma, one from pulmonary embolism and one from unknown causes) and 9 were lost to follow-up or declined to participate in the study. Taken together, 25 PM-DM patients being followed on a regular basis in our connective tissue disease clinic were examined, after having been informed regarding the objectives of the study. The 16 patients who could not be evaluated did not differ from those who were evaluated regarding disease severity, as assessed by serum CK titers at diagnosis.

Treatment data

Although the study was retrospective and the patients were not treated according to a designed protocol, two reasonably standard therapeutic regimens were followed, based on the decision of the physician and the period of referral. Fifteen PM-DM patients (the high dose group) were treated conventionally with a high starting prednisolone dose ranging between 40 and 100 mg/day (always > 0.5 mg/kg/day and generally 1 mg/kg/day) for 1 to 3 months (usually 3 months), followed by tapering (usually 5 mg/month). Ten other PM-DM patients (the low dose group) were treated with a lower starting prednisolone dose ranging from 7.5 mg/kg/day for 5 consecutive days) and generally 1 mg/kg/day) for 1 to 3 months (usually 3 months), followed by tapering (usually 5 mg/month). In both groups, most patients were maintained on low dose GC therapy (5 to 7.5 mg prednisolone/day). The patients’ characteristics at the time of the PM-DM diagnosis are summarized in Table I.

As indicated, all but 4 patients received another immunosuppressive (IS) drug in addition to GC. Fifteen of the 21 patients received the IS from the start of therapy, whereas in the 6 remaining patients it was introduced 4, 6, 9, 14, 34 and 72 months after the initiation of GC, respectively. Among the 15 patients given combined therapy (GC + IS) from the start, 9 received azathioprine (100 - 150 mg/day), 4 received methotrexate (15 mg/week orally in 3 patients and 36 mg/week IM in 1 patient), 1 received IV Ig (400 mg/kg/day for 5 consecutive days) and 1 received IV cyclophosphamide (750 mg/month for 6 months). Eight of the 15 patients given IS from the start were in the low-dose GC group, whereas the remaining seven were in the high-dose GC group.

Among the 6 patients in whom additional IS therapy was delayed, 4 were given...
Muscle power was measured by standing proximal muscle power, muscle function and functional independence in daily life activities.

Muscle power was measured by standard manual Proximal Muscle Testing performed by one investigator (FB), who was blind to the treatment data, using the British Medical Research Council’s grading system (7), which assigns values of 0 to 5 to muscle power. To increase the precision, each value (except for “5”) was subdivided into two intermediary scores (e.g. 4- and 4+), resulting in possible scores from 0 to 11 (thus, using this rating system, a score of 4 would be given a value of 9) (8). Eight proximal muscles were tested: the neck flexors, trapezius, deltoid, biceps brachii, iliopsoas, gluteus maximus, gluteus medius, and quadriceps femoris. The maximum score was 88 points. The left and right proximal muscles were tested and the indicated score represents the mean value for the two measurements.

A ‘Timed-Stands’ Test was performed to test the lower limb proximal muscle power as described by Csuka and McCarty (9). Briefly, patients were asked to stand 10 times from a standard chair, as quickly as possible, without using their upper limbs for support. Since the results (expressed in seconds) can vary between normal individuals based on their age and sex, the figures obtained in PM-DM patients were considered as “normal” or “abnormal” if they were lower or higher than the upper normal values for age- and sex-matched controls, respectively.

A Functional Neuro-Muscular Scale was used to assess functional ability of the limb and axial muscles (10). For the limb musculature, the following activities were scored: 0: unable to do; 1: done with great difficulty; 2: done with noticeable difficulty; 3: done without difficulty. For the axial muscles, the following activities were scored: 0: unable to do; 2: done with great difficulty; 4: done with noticeable difficulty; 6: done without difficulty; turning over in bed without help, moving from a lying to a sitting position without help, swallowing liquids, swallowing solids, sitting on the edge of the bed without help, false swallowing (0: always; 2: several episodes per meal; 4: one episode per meal; 6: never), and cough efficiency (0: unable to cough; 2: very much reduced cough efficiency; 4: reduced cough efficiency; 6: normal cough). A Functional Neuro-Muscular Scale score of 75 indicates normal function.

Table I. Comparison between treatment groups.

<table>
<thead>
<tr>
<th>Data at diagnosis</th>
<th>High-dose (≥ 0.5 mg/kg/day) (n = 15)</th>
<th>Low-dose (≤ 0.5 mg/kg/day) (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite PM-DM (a/n%)</td>
<td>13 (87)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Probable PM-DM (a/n%)</td>
<td>2 (13)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Polymyositis (a/n%)</td>
<td>9 (60)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Dermatomyositis (a/n%)</td>
<td>2 (13)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Myositis overlap (a/n%)</td>
<td>4 (27)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Age at diagnosis (years)*</td>
<td>50.6 ± 12.9</td>
<td>44.2 ± 19.7</td>
</tr>
<tr>
<td>ESR at diagnosis (mm/h)*</td>
<td>29 ± 29</td>
<td>36 ± 38</td>
</tr>
<tr>
<td>Serum CK at diagnosis (U/l)*</td>
<td>1.586 ± 2.466</td>
<td>1.783 ± 2.650</td>
</tr>
<tr>
<td>Glucocorticoid starting dose (mg/d)*</td>
<td>59.3 ± 19.8</td>
<td>24.7 ± 8.7</td>
</tr>
<tr>
<td>IS therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never (a/n%)</td>
<td>3 (20)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>From the start (a/n%)</td>
<td>7 (47)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>5 (30)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1 (7)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>IV cyclophosphamide</td>
<td>0 (0)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>IV immunoglobulins</td>
<td>1 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Delayed (a/n%)</td>
<td>5 (30)</td>
<td>1 (10)</td>
</tr>
</tbody>
</table>

*Means ± SD; no statistical difference between groups, except (by definition) for the GC starting dose.
Electromyography

Needle electromyography (EMG) examination of the deltoid, biceps brachii and quadriceps femoris was carried out in 23 patients by the same investigator (PK), who was blind to the treatment data, after blood sampling for the CK determination and after performing the functional tests. Only 5 of the 23 patients examined had an entirely normal EMG, defined as the absence of spontaneous activity and the absence of short-duration, low-amplitude polyphasic units on voluntary activation. Given the obvious difficulties in interpreting the electromyographic pattern in the patients treated with GC, only the presence or absence of spontaneous activity was taken into account, as the latter is considered to be less influenced by GC.

Statistical analyses

Linear regression analyses were used to correlate the results of the functional tests with each other and with the prognostic factors. Unpaired t-testing, Mann-Whitney U testing, or chi-square testing was used, as appropriate, to compare the demographic, functional and treatment data obtained in the patients treated with low-dose or high-dose GC therapy.

Results

Functional, biochemical and electromyographic evaluation of PM-DM patients

Functional evaluation was performed in a group of 25 patients being treated with GC for non-cancer-associated PM-DM; they had been followed up on a regular basis in our connective tissue disease clinic for a mean (± SD) period of 49 ± 36 months (range 7 - 157).

The data presented in Figure 1 indicate that about half of these patients had reduced proximal muscle power, as assessed by Proximal Muscle Testing; reduced muscle function, evaluated by the Functional Neuro-Muscular Scale score; and reduced functional independence in daily life activities, as measured by the Functional Independence Measure Scale score. Only 28% of the patients had elevated serum CK levels at the time of the evaluation. The result of the ‘Timed-Stands’ Test (i.e. the time needed to stand up 10 times from a chair of standard height) was abnormal in 14 of the 21 patients in whom it was performed (data not shown). Needle electromyography was obtained in 23 patients and spontaneous activity was observed in 8 of them. Interestingly, while the three functional indices (Proximal Muscle Testing score, Functional Neuro-Muscular Scale score and Functional Independence Measure Scale score) correlated positively and very significantly with each other (Table II), serum CK values and the presence of spontaneous activity on electromyographic examination did not correlate with any of the functional indices (data not shown).

Comparative functional evaluation of the two patient groups

In the last few years, we have treated patients suffering from PM-DM with lower doses of GC, in an attempt to reduce the incidence of side effects. To check whether this this steroid-sparing approach was jeopardizing treatment efficacy, we compared the functional outcome of patients treated with a starting prednisolone dose > 0.5 mg/kg/day (high-dose group; n = 15), with the functional outcome of those treated with a maximum starting prednisolone dose of 0.5 mg/kg/day (low-dose group; n = 10). Although the patients were not randomly assigned to one of these two regimens, the two groups were comparable at diagnosis regarding myositis subtype, age, ESR and serum CK values (Table I), thereby making it unlikely that the patients in the second group were given lower starting GC doses because they were suffering from less severe disease. By definition, the mean starting GC dose was very different between the two groups. As anticipated from the starting GC regimen, patients given > 0.5 mg/kg/day of prednisolone had received a much higher mean (± SD) cumulative oral prednisolone dose by the time of the

![Figure 1. Functional outcome in individual PM-DM patients. Scores on Proximal Muscle Testing (range: 0 - 88), on the Functional Neuro-Muscular Scale (range: 0 - 126) and on the Functional Independence Measure Scale (range: 0 - 75) are indicated. Closed circles (●) represent the individual scores measured in patients started on high-dose GC therapy, while open circles (○) correspond to individual values measured in patients started on low-dose GC therapy. Data were obtained at follow-up.](image)

<table>
<thead>
<tr>
<th>Data at follow-up</th>
<th>Functional Neuro-Muscular Scale score</th>
<th>Functional Independence Measure Scale score</th>
<th>Serum CK levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal Muscle Testing score</td>
<td>r = +0.89*</td>
<td>r = +0.90*</td>
<td>r = -0.09</td>
</tr>
<tr>
<td>Functional Neuro-Muscular Scale score</td>
<td>NA</td>
<td>r = +0.91*</td>
<td>r = -0.22</td>
</tr>
<tr>
<td>Functional Independence Measure Scale score</td>
<td>r = +0.91*</td>
<td>NA</td>
<td>r = -0.23</td>
</tr>
</tbody>
</table>

*p < 0.0001.
Table III. Comparison of functional outcome between treatment groups.

<table>
<thead>
<tr>
<th>Data at follow-up</th>
<th>High-dose (&gt; 0.5 mg/kg/day) (n = 15)</th>
<th>Low-dose (≤ 0.5 mg/kg/day) (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal Muscle Testing (mean ± SD)</td>
<td>83.6 ± 5.6</td>
<td>86.7 ± 2.2</td>
</tr>
<tr>
<td>Functional Neuro-Muscular Scale (mean ± SD)</td>
<td>66.6 ± 14</td>
<td>73.2 ± 3.3</td>
</tr>
<tr>
<td>Functional Independence Measure Scale (mean ± SD)</td>
<td>116 ± 17.3</td>
<td>124.7 ± 2.3*</td>
</tr>
<tr>
<td>Serum CK (UI/l)</td>
<td>294 ± 274</td>
<td>149 ± 156</td>
</tr>
<tr>
<td>Abnormal &quot;Timed-Stands&quot; Test (no./no. tested)</td>
<td>10/13</td>
<td>4/9</td>
</tr>
<tr>
<td>Spontaneous activity on EMG (no./no. tested)</td>
<td>4/14</td>
<td>4/9</td>
</tr>
<tr>
<td>Relapses (no.)</td>
<td>7</td>
<td>0*</td>
</tr>
<tr>
<td>Follow-up in months (mean ± SD)</td>
<td>57 ± 40</td>
<td>38 ± 26</td>
</tr>
</tbody>
</table>

*p < 0.05 versus high-dose group.

functional evaluation (16.9 ± 9.4 versus 9.2 ± 3.7; p = 0.02). As indicated in Figure 1 and Table III, the Proximal Muscle Testing score, the Functional Neuro-Muscular Scale score, the Functional Independence Measure Scale score, the results of the 'Timed-Stands' Test, the serum CK levels and the presence of spontaneous activity on electromyography were all comparable in the two groups. Incidentally, a trend towards better results, in particular for the Functional Independence Measure Scale score, was observed in the group treated with lower starting doses of GC. Moreover, the incidence of relapses was statistically different, with a 50% relapse rate in patients given a high-dose GC starting regimen and no relapses in the low-dose group.

GC-related side effects in patients given high- or low-dose GC therapy

We investigated whether patients treated with a lower GC regimen suffered less frequently from GC-related side effects compared to patients treated with a high-dose regimen. As anticipated, clinical signs of overt hypercorticism were more frequently noted in patients treated with high starting doses of GC (60% of the patients) than in those treated with lower doses (30% of the patients), although the difference was not statistically significant probably due to the low numbers of patients investigated. Interestingly, a radiologically-confirmed vertebral fracture was reported in one of the 10 patients given a low-dose regimen (1/170 vertebrae), while 15 vertebral crushes were noted in 3 out of the 15 other patients treated with higher doses of GC (15/255 vertebrae; p = 0.01).

Factors predictive of functional outcome

Finally we investigated whether the functional outcome of our 25 PM-DM patients was influenced by different variables or events observed at diagnosis or during follow-up that could be considered as predictive factors. Based on the results of their functional tests, the patients were divided into 2 groups, those who had no or marginal functional disability (i.e. a Proximal Muscle Testing score < 87 and a Functional Neuro-Muscular Scale score ≥ 74 and a Functional Independence Measure Scale score ≥ 124), referred to as the 'good outcome' group (n = 12), and those with clinically significant disability (i.e. a Proximal Muscle Testing score ≥ 87 or a Functional Neuro-Muscular Scale score < 74 or a Functional Independence Measure Scale score < 124), referred to as the 'poor outcome' group (n = 13).

The only variable that was significantly associated with a better functional outcome was a younger age at diagnosis (39 ± 14 versus 56 ± 13 years in the 'good outcome' and 'poor outcome' groups, respectively; p < 0.01). Other variables investigated, such as the delay in diagnosis, myositis subtype, initial serum CK levels, initial ESR, initial GC dose, and visceral involvement, did not differ between the two groups (data not shown).

Discussion

We performed a functional evaluation in a group of 25 biopsy-proven PM-DM patients in order to specifically address two questions. First, we wondered whether certain variables could predict functional outcome. In this respect our study was essentially negative, with the exception that it confirmed that younger patients have a better outcome, as was already found in other series of PM-DM patients (4, 12, 13). Secondly and more importantly, we compared the outcome of patients given either a high- or a low-dose GC regimen. The preliminary data presented here suggest that patients given lower doses of GC achieved a similar functional outcome compared to those given a standard high-dose regimen, with less GC-related side effects, in particular vertebral fractures.

When faced with a classical case of PM-DM, most clinicians prescribe a high-dose GC regimen (≥ 1 mg equivalent prednisolone/kg/day), in accordance with the guidelines proposed by experienced groups in the United States (1, 2). It should be stressed, however, that although there is no doubt that GC remains the cornerstone treatment of PM-DM, the minimal dose requirements (initial dose and tapering regimen) have never been investigated. Given the well-known side effects of GC and the significant contribution of GC-related morbidity to functional disability in PM-DM patients (14), the optimal GC regimen remains a critical issue in the care of PM-DM patients. Ideally, the dose should be kept as low as possible without jeopardizing survival and long-term functional results.

Henriksson and Sandstedt observed that the subgroup of adult PM-DM patients who responded best to treatment, as assessed by a standardized disability scale, had received a slightly higher starting GC dose than patients who did not. Interestingly, they also mention that 13% of their patients experienced significant clinical improvement with as low a dose as 0.3 mg prednisolone/kg/day (4). Odds and Medsger studied the relationships between biochemical outcome (serum CK levels), clinical outcome (muscle strength) and the method of administration of prednisone in 42 GC-treated episodes of serum CK elevations in 30 PM-DM patients. A good outcome was associated with a high initial GC dose, the
continuation of a high-dose regimen until the CK returned to normal, and a slow tapering rate (5). These conclusions were drawn from an analysis of CK levels and from clinical data extracted from chart reviews; they were not obtained through a protocol specifically designed to evaluate the patients functionally.

The favourable functional results obtained in many of our patients, including those who received a low-dose GC regimen, might be explained in several ways. First, although we still see very severe cases of PM-DM presenting with major functional disability, more patients seek medical advice very early in their disease course, thereby allowing the diagnosis of milder cases. In this respect, it is possible that our PM-DM population does not compare with other groups of patients in whom the diagnosis was delayed, perhaps for socioeconomic reasons.

Another explanation for the favourable functional outcome in many of our patients might be related to the fact that most of them received another immunosuppressive drug, in addition to GC, from the start of therapy. Although our study does not address this issue, i.e. that a combination of GC and another immunosuppressive drug may be beneficial in PM-DM patients through a steroid-sparing effect, some data from the literature lend credence to this hypothesis. Bunch et al. compared the outcome of 8 patients given GC and placebo with that of 8 patients given combined therapy with GC and azathioprine. Interestingly, they report that in a non-blinded re-evaluation after 3 years of follow-up the group treated with both active drugs had less disability and required less GC to control their disease (15). A more recent prospective placebo-controlled study on the use of intravenous (IV) immunoglobulins (Ig) demonstrated the superiority of combined therapy with GC plus i.v. Ig versus GC plus placebo (16). Further prospective studies are obviously required to study the benefits of combined therapy with GC and drugs such as methotrexate, which have yielded promising results in open trials and in a retrospective analysis (17).

Our analysis clearly has important shortcomings, in particular the relatively small number of patients studied, the absence of longitudinal data, the uncontrolled assignment of our patients to a higher or lower-dose GC regimen, and the use of various immunosuppressive drugs in addition to GC. Moreover, although the difference was not statistically significant, the duration of follow-up of the patients given a low-dose GC regimen was shorter. Finally, we cannot exclude the possibility that steroid myopathy interfered in the functional results of our patients. On the other hand, contrary to most retrospective studies dealing with prognostic factors and/or treatment efficacy - whose conclusions are based on chart reviews (12, 18, 19) - we designed and applied a comprehensive protocol to assess functional outcome in our PM-DM patients, including the evaluation of muscle strength, muscle function, CK levels, persistence of spontaneous activity on electromyography, disability in daily life activities, and degree of dependence.

Taken together, we believe that our results show that a lower GC regimen can be used successfully to treat PM-DM, at least that subset of patients presenting with milder disease, probably in combination with other immunosuppressive drugs acting as steroid-sparing agents. Should this approach be validated in a prospective study performed on a large series of PM-DM patients followed longitudinally, this would be a step forward to reduce treatment-related functional disability.

Acknowledgements

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References