CLINICAL STUDY

Methylprednisolone pulse therapy for patients with moderately severe Graves’ orbitopathy: a prospecive, randomized, placebo-controlled study

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Abstract

Objective: To assess whether methylprednisolone (MP) pulse therapy is efficacious in the treatment of moderately severe Graves’ orbitopathy (GO).

Design: Prospective, placebo (PL)-controlled, double-blind, randomized study.

Methods: Fifteen previously untreated patients with active, moderately severe GO participated in the study; 6 patients received MP and 9 patients a PL. Moderately severe disease was defined using the NOSPECS classification of clinical signs of GO. Activity was measured with the clinical activity score (CAS). A dose of 500 mg MP or only solvent was administered intravenously, over three consecutive days, in four cycles at 4 weekly intervals (6 g of MP in total). Qualitatively, a successful treatment outcome was defined as an improvement in one major and/or two minor criteria in the worst eye at week 48. The major criteria were: improvement in diplopia grade; improvement in eye movement; a decrease in CAS of three points. The minor criteria were: decrease of eyelid retraction; decrease of proptosis; improvement in grade of soft tissue swelling; a decrease in CAS of two points.

Results: The qualitative treatment outcome was successful at the end of the trial in five out of six (83%) patients receiving MP and in one out of nine (11%) patients given the PL (relative risk Z 7.5; (95% confidence interval 1.1–49.3), \( P = 0.005 \)). The treatment was well tolerated.

Conclusions: In spite of the small number of patients, a significant difference in outcome was observed between MP- and PL-treated patients. We conclude that MP pulse therapy appears to be an effective treatment for active, moderately severe GO.

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Introduction

Graves’ disease is a multisystem, autoimmune disorder, including Graves’ orbitopathy (GO). For summarizing the clinical symptoms of GO, the mnemonic NOSPECS, introduced by Werner, is useful (1). GO has a dynamic (active) phase and static (burnt-out) phase, in which troublesome symptoms may persist (2).

The first step in the treatment of GO is controlling the thyroidal disease, as achieving euthyroidism improves ocular symptoms (3). The next step is to distinguish active GO from burnt-out GO, for which the clinical activity score (CAS), based on the classical signs of inflammation, is commonly used (4, 5). When the disease has become stable, sequels can be dealt with surgically. Within this framework, treatment of active, moderate to severe GO has no clear one-line strategy. So far, various immunosuppressive therapies have been reported, including retrobulbar steroids (6), oral prednisone (6–9), systemic steroids (6–8, 10, 11), radiotherapy (12) and combinations thereof. In spite of its side effects, glucocorticoid therapy, together with retrobulbar irradiation is a widely used method of immunosuppression for GO.

A number of studies comparing intravenously (i.v.) administered glucocorticoids with oral medication showed that i.v. is equally or more effective, with less adverse effects (6–8). Controlled studies have been done by our group, testing oral prednisone versus cyclosporine and radiotherapy (12), indicating that oral prednisone is effective in two out of every three patients with GO. So far, orbital radiotherapy is the only immunomodulatory treatment that has been tested against a placebo (PL; e.g. sham-irradiation). Its efficacy appeared to be limited to improvement of motility (13).

In patients with dysthyroid optic neuropathy (DON), prednisolone pulse therapy (PPT) seems to be efficacious with few side effects. The term pulse therapy refers to discontinuous i.v. infusion of high doses of glucocorticoids.
over a short period of time. PPT shows an impressive improvement of visual acuity. It has been noted that the CAS significantly improves and one-third of DON patients are spared from decompressive surgery (14). Reported side effects of PPT are rare. In small numbers of patients, body weight gain, induction of diabetes mellitus, elevation of blood pressure, pyloric ulcer, increased osteoporosis and increase in insulin dosage were noted (15, 16). Cases of sometimes fatal autoimmune hepatitis following i.v. glucocorticoid pulse therapy have been reported (17–19), but these patients had received excessive cumulative doses of prednisone.

To assess whether PPT is similarly efficacious and is safe in patients with less severe GO, we designed a prospective, controlled, double-blind, randomized study to compare the effect of methylprednisolone (MP) pulse therapy with the effect of PL treatment in previously untreated patients with moderately severe GO.

Subjects and methods

Patients

The study was approved by the ethics committee of the University Medical Centre Utrecht. Consecutive untreated patients with active, moderately severe GO were included in the trial. The diagnosis was made on typical clinical features of the disease, such as proptosis, eyelid retraction and swelling, impaired motility and enlarged extraocular eye muscles and increased intraorbital fat on orbital computed-tomography scans.

The severity of GO was assessed using an adapted NOSPECS classification (Table 1). Moderately severe GO was defined as marked soft tissue swelling and/or proptosis of 18 mm or more for females and 20 mm or more for male patients (as measured with a modified Zeiss Jena exophthalmometer (Carl Zeiss Meditec AG, Jena, Thuringen, Germany) (18)), and/or diplopia in primary or reading position (NOSPECS classes 2c and/or 3abc and/or 4b). For inclusion, it was sufficient if one eye satisfied these criteria. Patients with mild eye disease or frozen eyes (NOSPECS class 4c), or symptoms of optic nerve compression (NOSPECS class 6: reduced visual functions, oedema of the optic disc; apical crowding of the extraocular muscles on computed tomography; CT scan) were excluded. Disease activity was measured by the CAS; we defined active disease as a CAS of four points or more.

All patients had to be euthyroid for at least 3 months before the date of inclusion with plasma concentrations of thyroid hormones within their reference ranges: free thyroxine (9–27 pmol/l) and free tri-iodothyronine (4.0–7.8 pmol/l) and thyrotropin concentrations within or below the reference range (0.35–5.0 mlE/l). Patients, aged between 20 and 80 years, should not have received treatment (radiotherapy, glucocorticoids, immunosuppressives or surgery) for their orbitopathy, except for local measures. Patients who were medically unfit to receive PPT (cardiac arrhythmias, unexplained gastric pain, history of pulmonary tuberculosis, hepatitis B carrier, hepatitis C positive, HIV, diabetes mellitus, uncontrolled hypertension or hepatic dysfunction), suffering from additional eye disease or treated with glucocorticoids for GO or other diseases (in the past 3 years) were excluded.

Treatment

After the patient had given informed consent, each was assigned to receive either MP or PL, for which they were randomized by an external office (the Centre of Statistics, The Netherlands) by means of a randomization list. All patients were treated on an outpatient basis.

MP 500 mg diluted in 500 ml Ringer solution was administered intravenously during 1 h for three consecutive days, in four cycles at 4 weekly intervals (high-dose pulsed therapy on day 1, 2 and 3 in week 0, 4, 8 and 12). This amounts to a total dose of MP of six grams in 3 months. The PL group received 500 ml of Ringer solution in the same way as the MP group. The ophthalmologist who assessed the treatment results was not informed about the kind of treatment that was given. This was known only to the endocrinologist.

Assessment of efficacy

All patients were examined by the same ophthalmologist at week 0, 4, 8 and 12 before the first infusion on
Assessment of safety

During the infusion the patients were checked for possible side effects: they were asked about pain in the back, fever, weakness, nausea and itching. Nurses checked skin colour and pupil size. The examination before and after the infusions, and at week 24 and 48 included measurement of blood pressure and body weight, and laboratory testing of plasma concentrations of thyroid hormones, glucose and liver enzymes. Changes in liver function were monitored with the enzymes alkaline phosphatase (ALP) and gamma-glutamyl transeptidase (GGT). An increase in serum levels two times the upper limit or higher was considered abnormal.

Statistical analysis

Based on a 30% difference in treatment outcome (65% response in the MP group, compared to 35% in the PL group) following several other studies in which prednisolone was tested, a sample size of 30 patients per treatment group was calculated (power 80%, \( \alpha = 0.05 \)). The results were analysed using the statistical software package SPSS version 12.0.2 (SPSS Inc., Chicago, IL, USA).

Clinical, biochemical and ophthalmological variables were compared at baseline between the two groups using the Mann–Whitney test. All data were analysed according to the intention to treat principle. When a patient was withdrawn from the study, all outcome measures were assessed, and the patient was analysed with the last value carried forward. The primary outcome was assessed using the relative risk (RR). A RR was calculated with a 95% confidence interval as the percentage of patients with successful treatment outcome to MP divided by the percentage of patients with successful treatment outcome to PL. Statistical significance was calculated with the Pearson \( \chi^2 \) test.

Results

Patients

Recruitment started in February 2003. Two-and-a-half years later we performed an analysis of the patients who had finished the study thus far. Up until then, 355 patients with GO were referred to our department; 309 patients did not meet our inclusion criteria. Of the 46 eligible patients, 30 refused to participate due to various reasons (fear of treatment, a wish to receive other treatment, practical reasons). The remaining 16 patients were randomly assigned to either the MP group (MP, seven patients) or the PL group (PL, nine patients). After randomization, one patient in the MP group had second thoughts about participating and was excluded, leaving six patients in the trial (Fig. 1).
At the time of inclusion, of the 15 trial patients, 9 patients (60%) had motility impairment causing diplopia (of whom 6 scored NOSPECS class 4b), 12 (80%) had proptosis (3 (female) patients had proptosis of more than 23 mm) and all patients (100%) had soft tissue swelling (of whom 4 had NOSPECS class 2c).

Between the two groups, baseline characteristics did not differ significantly (Table 2). Besides the clinical features of eye disease, this included age and smoking habits. The patients in the MP group were all female, the PL group had three male patients. Thyroid function also did not differ between the two groups. All remained euthyroid during the trial.

After the last administration of either MP or PL (week 12), four patients in the PL group were excluded from the trial, due to worsening of eye features (clinical deterioration). Also, one patient in the MP group chose to withdraw at this time point on subjective grounds, even though an improvement in all defined criteria was observed. These patients were included in the analysis, with state of eye at week 12 as the endpoint of study (last value carried forward). One MP patient, by mistake, underwent 131I treatment before week 48 and was also excluded; state of eye at week 24 was included in the analysis.

**Efficacy**

As mentioned, we chose to follow the eye with the worst features at inclusion to determine treatment success (Table 3). Changes in the other eye are also noted in Table 3, but these were not used for the final outcome. Based on improvement in one major and/or two minor criteria, the qualitative treatment outcome was successful at the end of the trial in five out of six (83%) patients receiving MP and in one out of nine (11%) patients given the PL (RR = 7.5; (95% CI 1.1–49.3), \( P = 0.005 \), with the last value of the patients that stopped prematurely carried forward. The one unsuccessful patient in the MP group did improve in CAS, but also had worsening in motility (adduction).

Diplopia improved in 50% (two out of four) of MP patients with diplopia at the time of inclusion and in none of five PL patients (\( P = 0.073 \)). In the MP group, one patient improved from diplopia in primary or reading position to no diplopia and one from extremes of gaze to no diplopia. Conversely, in the PL group one patient showed worsening from no diplopia to diplopia in extremes of gaze. Soft tissue swelling improved in 50% (three out of six) of MP patients and 11% (one out of nine) of PL patients (RR = 4.5; (0.6–33.7), \( P = 0.095 \)). With MP, three out of six patients showed improvement in motility (as measured by the range ofduction); with PL, one out of nine patients with restriction in eye movement did ((one MP and three PL patients showed worsening, \( \geq 8^\circ \) induction); RR = 4.5; (0.6–33.7), \( P = 0.095 \)). The CAS fell in all MP patients; a decrease of three points or more in four out of six MP patients, the remaining two patients both had a two-point decrease of CAS. In the PL group, one out of nine patients had a decrease of three points or
more, two patients had a decrease of two points. (Regarding the RR of a two-point decrease: RR = 3: (1.2–7.6), P = 0.01). No difference was noted in eyelid retraction. Aperture improved in four MP patients compared to five PL patients (RR = 1.2; (0.5–2.7), P = 0.67). Aperture increased in one PL patient. Proptosis improved in two out of five MP patients with proptosis at inclusion and in two out of seven PL patients (RR = 1.5; (0.3–7.9), P = 0.68). Worsening (≥ 2 mm increase) of proptosis was seen in four PL patients, of which one did not show proptosis at inclusion. Changes in SES were as follows (the numbers are given in Table 3). In the MP group: 4 better, 1 equal and 1 worse; In the PL group: 4 better, 1 equal and 4 worse.

### Side effects

No serious side effects were noted. At week 12 (after the last infusion), three patients in the MP group complained about Cushingoid symptoms, which were objectively by the blinded ophthalmologist in one case (facial oedema). In the PL group three patients had symptoms subjectively. Stomach ache occurred in two patients in the MP group and once in the PL group. In both groups, changes in body weight were observed, but only two patients in each group had weight gain exceeding 1%. In the MP group, an increase of 2.4 and 4.1% in body weight at week 12 as compared to baseline was noted.

An increase in liver enzyme levels two times the upper limit or higher occurred in none of the patients. In the MP group, one patient showed a minor increase in ALP, which soon returned to normal. Four out of six patients had a slight elevation of GGT during the trial, which in all cases normalized before the end of the study. All MP patients had an increase of glucose levels above normal at one time during the trial, with a maximum of 10.5 mmol/l. In all cases, blood glucose levels had normalized at the check-up at week 24 and 48. Blood pressure was elevated temporarily during the trial in three MP patients (diastolic value above 95 mmHg). One of these was known to have hypertension, which was controlled with medication. In the PL group, two patients also showed high blood pressure values on occasion (one previously known with hypertension). All patients had normal blood pressures at the end of the trial.

### Follow-up

In the first year following the trial, all patients in the PL group needed additional treatment, two MP patients needed none. Two patients in the PL group received radiotherapy and oral prednisone after the trial. Orbital decompression was done in two out of six MP patients and in eight out of nine PL patients. Extraocular muscle surgery: MP none, PL 3; eyelid retraction repair: MP 2 (plus 1 planned), PL 2; tarsoraphy: MP 1, PL 3; blepharoplasty: MP 2, PL 1.
### Table 3 Treatment outcome.

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### Improvement

**Major criteria**

- **Diplopia**
  - +
  - +

- **Duction**
  - ↓
  - +
  - + / ↓
  - +
  - +
  - +

**Minor criteria**

- **Eyelid retraction**
  - +
  - +
  - +
  - +

- **Proptosis**
  - +
  - +
  - +
  - +
  - +

- **Swelling**
  - +
  - +
  - +
  - +
  - +

**Cas (two points)**

- +
- +
- +
- +
- +

**Success**

- Yes
- Yes
- No
- Yes
- No
- Yes
- Yes
- Yes
- Yes
- Yes
- Yes
- No

**Adjuvant therapy**

- +
- +
- +

- +
- +
- +

- +
- +
- +

**Eyelid surgery**

- +
- +
- +

(continued)
### Table 3  continued.

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<td><strong>Swelling</strong></td>
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<tr>
<td><strong>CAS (two points)</strong></td>
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<tr>
<td><strong>Success</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td><strong>Adjuvant therapy</strong></td>
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<tr>
<td><strong>Decompression</strong></td>
<td>+</td>
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<td>+</td>
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<td><strong>EOM surgery</strong></td>
<td>+</td>
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<td><strong>Eyelid surgery</strong></td>
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</table>

Eye features of all patients at inclusion and their endpoint are listed. 1Worst eye at inclusion (in bold type) is assessed for overall treatment outcome; 2P/R = diplopia in primary or reading position; 3Extr. = diplopia in extremes of gaze; 4Follow-up of 1 year; 5includes: retraction surgery tarsoraphy and blepharoplasty; 6Au = diplopia in all directions; *last value carried forward; + = improvement; ↓ = worsening.
Discussion

This is the first PL-controlled study of the efficacy of prednisone in patients with GO. Our results support the expectation that MP pulse therapy is effective in patients with active, moderately severe GO. The outcome of this study depends on predefined criteria of treatment success. We used the (slightly modified) assessment method based on major and minor criteria, introduced by Bartalena et al. (22). This is the same method we applied in a previous study on the effect of radiotherapy versus sham-irradiation on GO, with the addition of changes in the CAS. We found that five out of six patients in the MP group improved based on these criteria, compared to one out of nine patients who received a PL (a RR of 7.5). In spite of the small number of patients, this is a significant difference in treatment outcome. Moreover, not only did just one patient in the PL group meet the success criteria, seven showed worsening of one or more features of their eye disease, for which reason four patients were prematurely withdrawn from the trial. Diplopia improved in two out of four patients with double vision in the MP group and in none of the patients given the PL. There were also remarkable differences in changes in soft tissue swelling (50% improved with MP versus 11% with PL), motility (50% improved in eye movement with MP versus 11% with PL), disease activity (a significant two-point decrease of the CAS in all patients receiving MP versus 33% of PL patients) and proptosis (40% improved with MP versus 29% with PL). In this study, we have based treatment success on changes in the worst eye at inclusion. Obviously, eyes do not always respond similarly. If we would have defined success based on the overall outcome of both eyes, numbers would have been slightly different, but the conclusion would have remained unchanged. For example, using an ‘overall both eyes outcome’ would mean patient MP6 became a failure due to worsening of proptosis in the other eye, while the single successful patient in the PL group (PL4) would be regarded a failure due to a decrease in motility in his left eye (Table 3).

The above-mentioned results are the outcome of a preterm analysis on 15 patients, whereas the original study had been designed for a much larger sample size. However, as the differences between the two arms of the study in terms of results were thus striking and already highly significant, we considered it unethical to continue the study. Moreover, comparison of the baseline characteristics of our small groups with some prior studies (12, 13, 25) did not disclose serious differences, indicating that although our sample size was small, it was nevertheless representative.

The beneficial effect of i.v. MP is in line with results presented by others in recent years. In a randomized single-blind study, Marcocci et al. noted that i.v. glucocorticoids are more effective than oral glucocorticoids with a lower rate of side effects, in 82 patients with moderate to severe GO (11). Both treatment modalities were combined with orbital radiotherapy. Kahaly et al. also concluded that in 70 patients with active and severe GO, compared to oral corticoids, i.v. administration had a better outcome and was safe (8).

In this study, no serious adverse effects were noted. We carefully assessed patients for risk factors of liver toxicity prior to inclusion. A slight increase in liver enzymes was noted in a number of MP patients, but this was temporary. There were no cases of hepatitis as was reported by others (11, 17). The four reported cases of fatal liver failure were all associated with high-dose glucocorticoid treatments (18, 19). The cumulative dose of MP in this study amounted to six grams. This agrees with the recommendation by Krassas & Boboridis, that doses should be kept low (24). Even though no serious adverse effects were seen, the small number of patients receiving MP is insufficient to make a clear statement on the safety issue. Nevertheless, in the above-mentioned larger studies of Marcocci & Kahaly, the administration of i.v. MP was shown to be safe, with less side effects in comparison with oral glucocorticoids.

Additional treatment was required less frequently in the MP group. Two-thirds of the patients in the MP group were spared from orbital decompression. Except for one, all PL patients underwent this operation in the year following the trial.

In line with others, our study confirms efficacy of i.v. glucocorticoids. Moreover, ours is the only PL-controlled study to date and did not include severe patients, for whom PPT has previously been shown to be beneficial (14). MP pulse therapy thus appears to be an effective treatment for active, moderately severe GO. In our patients the treatment was well tolerated and appeared to be safe. The dose of i.v. glucocorticoid used varies among studies. As of yet, there is no standard PPT dosage scheme. As mentioned, the cumulative amount must be high enough to distinguish effect and low enough to prevent adversities. One of the next steps in GO research, therefore, should be a study to find evidence for an optimal dose.

Acknowledgements

R J van Geest and J V Sasim contributed equally to this work and therefore should be considered equivalent authors.

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