Treatment of Chronic Inflammatory Demyelinating Polyneuropathy With High-Dose Intermittent Intravenous Methylprednisolone

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Background: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) causes progressive disability due to weakness but responds to immunomodulating medication, including oral prednisone and intravenous (IV) immunoglobulin (IVIg). However, there is no consensus on initial therapy, and both of these treatments have drawbacks with long-term treatment.

Objective: To review the efficacy and safety of high-dose, intermittent IV methylprednisolone (IVMP) as initial and long-term maintenance therapy for patients with CIDP.

Design: A retrospective medical record review between 1992 and 2003 of outcomes in CIDP, comparing patients in 3 cohorts depending on whether their primary treatment was IVMP, IVIg, or oral immunosuppression with prednisone or cyclosporine.

Setting: Washington University Neuromuscular Disease Center (St Louis, Mo), outpatient and inpatient records.

Patients: Patients with clinical and electrophysiologic evidence of CIDP were identified. Of 57 patients, 39 had sufficient data for full analysis.

Main Outcome Measures: Quantitative muscle testing with a handheld dynamometer. Medication profiles and adverse effects were also recorded.

Results: There was no significant difference in the mean improvement in quantitative muscle testing at 6 months or at the last clinic visit (an average of 4.5 years later) among the 3 groups. Fewer patients treated with oral immunosuppression improved at 6 months, but at the last visit, 81% to 88% improved in all 3 groups. Less weight gain and fewer cushingoid features affected patients treated with IVMP (19%) compared with patients treated with oral prednisone (58%).

Conclusions: Treatment of patients with CIDP using high-dose intermittent IVMP results in improved strength equal to that with IVIg and oral prednisone. The frequency of occurrences of weight gain and cushingoid features with IVMP is less than that with oral prednisone. Intravenous methylprednisolone should be considered for initial and long-term therapy in CIDP when patients have disability due to weakness.

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expression and protein synthesis.\(^5,6\) These effects might last for days because of changes in gene expression.\(^5,6\) The glucocorticoid receptor binds to glucocorticoid-responsive elements located in the promoter regions of specific genes and can activate or inhibit gene transcription.\(^5,6\) Although prednisone or other nuclear transcription factors and can activate or inhibit gene transcription.\(^5,6\) Although prednisone is likely involved in multiple effects brought about by the activation of the glucocorticoid receptor.\(^5,6\) The glucocorticoid receptor binds to glucocorticoid-responsive elements located in the promoter regions of specific genes or to other nuclear transcription factors and can activate or inhibit gene transcription.\(^5,6\) Although prednisone has an elimination half-life of 1.5 to 4 hours, some of its effects might last for days because of changes in gene expression and protein synthesis.\(^5,6\)

The mechanism of action of steroids is complex and likely involves multiple effects brought about by the activation of the glucocorticoid receptor.\(^5,6\) The glucocorticoid receptor binds to glucocorticoid-responsive elements located in the promoter regions of specific genes or to other nuclear transcription factors and can activate or inhibit gene transcription.\(^5,6\) Although prednisone has an elimination half-life of 1.5 to 4 hours, some of its effects might last for days because of changes in gene expression and protein synthesis.\(^5,6\)

We began using high-dose intermittent IV methylprednisolone (IVMP) as initial and long-term maintenance therapy for many patients with CIDP in 1992 in an attempt to find an alternative treatment regimen without the problems associated with long-term daily steroids. We now report a retrospective review of all CIDP patients treated in the Washington University Neuromuscular Disease Center (St Louis, Mo) between 1992 and 2003. We compared patients treated with IVMP, IVIg, and long-term oral immunosuppression. We evaluated the efficacy of each treatment by examining changes in quantitative strength measures, medication history, and adverse effects or complications with each type of treatment.

## METHODS

We reviewed the clinical and laboratory records of all 57 adult patients with a diagnosis of CIDP, established using standard clinical and electrophysiologic criteria,\(^7,8\) who were followed up and evaluated by us at the Washington University Neuromuscular Disease Center between 1992 and 2003. Patients were excluded if they had an alternative cause for their demyelinating neuropathy, including the presence of antineurin-associated glycoprotein antibodies; antismutated antibodies; antiganglioside antibodies; POEMS syndrome (characterized by polineuropathy, organomegaly, endocrinopathy/edema, monoclonal gammopathy, and skin changes); a toxic neuropathy; or clinical or laboratory evidence of a hereditary demyelinating neuropathy. Eighteen patients with CIDP were excluded from further analysis because there was no quantitative muscle testing evaluation prior to initiation of therapy (n=4), they had follow-up for less than 1 year (n=12), or they had a pure sensory syndrome (n=2). Patients with associated conditions were included if their main disability was due to CIDP and not to another cause of neuropathy. Associated conditions were diabetes (n=3) (1 patient with diabetes was also post-renal transplantation), a remote history of Lyme disease (n=1), a mild vitamin B\(_12\) deficiency (n=1), and serum M protein (n=5). The remaining 39 patients were evaluated at least once a year. Medical records were reviewed for the medication history and the presence of adverse effects or complications related to immunomodulating therapy.

## PATIENT CHARACTERISTICS

The 39 patients were divided into 3 groups—IVMP, IVIg, and oral immunosuppression—depending on treatment modalities begun at the Washington University Neuromuscular Disease Center. Table 1 shows the baseline characteristics of the 3 groups. We found no significant differences when comparing male-female ratio, age at evaluation, duration of disease, length of evaluation, incidence of paraproteinemia, or abnormal cerebrospinal fluid protein levels. Patients receiving oral immunosuppression had significantly lower baseline strength than patients receiving IVMP. However, there were no differences in the pattern of neurologic abnormality between the 3 groups. Distal and proximal weakness were common and present in 33 (85%) of the 39 patients. Most often, both legs and arms were weak; isolated weakness in the arms or legs was present in only 4 (10%) of the 39 patients. Mild asymmetric weakness was present in 15 (38%) of the 39 patients. Sensory loss, always in a stocking or stocking-glove pattern, was present in 36 (92%) of the 39 patients, and absent or reduced deep tendon reflexes were present in all patients. Cranial nerve abnormalities, manifested only by facial weakness, were present in only 5 (13%) of the 39 patients. Sixteen patients were treated with long-term intermittent IVMP. The most typical regimen was an initial dose of 1000 mg/d of methylprednisolone on each of 3 to 5 consecutive days, followed by

### Table 1. Baseline Characteristics of Patients With Chronic Inflammatory Demyelinating Polyneuropathy

<table>
<thead>
<tr>
<th>Clinical and Laboratory Characteristics</th>
<th>IVMP (n = 16)</th>
<th>IVIg (n = 7)</th>
<th>Oral Agents (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male-female ratio</td>
<td>8:8</td>
<td>3:4</td>
<td>6:10</td>
</tr>
<tr>
<td>Age at initial visit, mean ± SE, y (range)</td>
<td>56 ± 4 (33-73)</td>
<td>56 ± 8 (31-80)</td>
<td>57 ± 4 (26-84)</td>
</tr>
<tr>
<td>Duration of symptoms, mean ± SE, y (range)</td>
<td>2.8 ± 0.9 (0.2-13)</td>
<td>3.5 ± 2.1 (0.2-15)</td>
<td>1.8 ± 0.5 (0.5-7)</td>
</tr>
<tr>
<td>Length of follow-up, mean ± SE, y (range)</td>
<td>4.6 ± 0.9 (1-12)</td>
<td>3.6 ± 0.7 (1-7)</td>
<td>4.7 ± 0.6 (1-9)</td>
</tr>
<tr>
<td>Baseline strength, mean ± SE, % of normal (range)</td>
<td>64 ± 4 (35-88)</td>
<td>60 ± 7 (23-84)</td>
<td>44 ± 3* (23-63)</td>
</tr>
<tr>
<td>Pattern of weakness, No. of patients/total patients (%)</td>
<td>Distal and proximal 12/16 (75)</td>
<td>7/7 (100)</td>
<td>14/16 (88)</td>
</tr>
<tr>
<td></td>
<td>Arms only 1/16 (6)</td>
<td>1/7 (14)</td>
<td>0/16 (0)</td>
</tr>
<tr>
<td></td>
<td>Legs only 0/16 (0)</td>
<td>1/7 (14)</td>
<td>1/16 (6)</td>
</tr>
<tr>
<td></td>
<td>Asymmetric 6/16 (38)</td>
<td>3/7 (43)</td>
<td>6/16 (38)</td>
</tr>
<tr>
<td></td>
<td>Sensory loss 16/16 (100)</td>
<td>6/7 (86)</td>
<td>14/16 (88)</td>
</tr>
<tr>
<td></td>
<td>Reduced or absent DTRs 16/16 (100)</td>
<td>7/7 (100)</td>
<td>16/16 (100)</td>
</tr>
<tr>
<td></td>
<td>Cranial nerve abnormality 0/16 (0)</td>
<td>2/7 (29)</td>
<td>3/16 (19)</td>
</tr>
<tr>
<td></td>
<td>No. of patients/total patients with elevated CSF protein levels (range, mg/100 mL)</td>
<td>6/8 (36-1377)</td>
<td>3/3 (64-244)</td>
</tr>
<tr>
<td></td>
<td>No. of patients/total patients with M protein</td>
<td>2/16 (both IgG)</td>
<td>1/7 (IgG)</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; DTRs, deep tendon reflexes; IVIg, intravenous immunoglobulin; IVMP, IV methylprednisolone.

*Less than patients receiving IVMP, \(P=.003\).
ELECTROPHYSIOLOGIC STUDIES

A board-certified electrodiagnostician performed nerve conduction studies on all patients. All patients had electrophysiological evidence of demyelination that met at least 1 set of diagnostic criteria for CIDP as proposed by the American Academy of Neurology,7 Albers and Kelly,8 or Barohn et al.9 These criteria have roughly equal sensitivity (48%-64%) and specificity (100%).10 Fulfilling 1 set of criteria was considered evidence of demyelination that met at least 1 set of diagnostic criteria for CIDP. Electrodiagnostic studies on all patients. All patients had electrophysiological evidence of demyelination that met at least 1 set of diagnostic criteria for CIDP as proposed by the American Academy of Neurology,7 Albers and Kelly,8 or Barohn et al.9 These criteria have roughly equal sensitivity (48%-64%) and specificity (100%).10 Fulfilling 1 set of criteria was considered evidence of demyelination that met at least 1 set of diagnostic criteria for CIDP.

<table>
<thead>
<tr>
<th>Treatment Regimens Instituted at Washington University (St Louis, Mo)</th>
<th>IVMP (n = 16)</th>
<th>IVIg (n = 7)</th>
<th>Prednisone (n = 12)</th>
<th>Cyclosporine (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial therapy</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Sole therapy</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other immunomodulating medications added after institution of the primary therapy*</td>
<td>5</td>
<td>5</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Other immunomodulating medications stopped after institution of the primary therapy</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: IVIg, intravenous immunoglobulin; IVMP, intravenous methylprednisolone.

*P<.003 comparing the groups.

1000 mg IV on 1 day each week for the next month. Intravenous methylprednisolone was then tapered in frequency and dose over a period of 2 months to 2 years. All patients continued to receive IVMP no more than once a week. Several patients were maintained with long-term high-dose intermittent IVMP every 2 to 12 weeks for up to 10 years with stable strength. In a few patients, the intermittent high-dose IVMP was changed to intermittent oral corticosteroid administration because of poor IV line access or difficulty getting to an IV infusion center, but there was no change in any measured clinical parameter. Seven patients were treated with long-term IVIg, usually receiving 2 g/kg over 2 days. Treatment was repeated every 1 to 6 months depending on the patient’s response. Sixteen patients were treated with oral immunomodulating therapies, either prednisone (n = 12) or cyclosporine (n = 4). Three patients receiving long-term oral prednisone had an initial dose of IVMP for 5 days followed by oral maintenance therapy.

Medications used by patients before evaluation at Washington University included IVIg (n = 14), oral prednisone (n = 11), plasma exchange (n = 8), azathioprine (n = 6), cyclosporine (n = 4), cyclophosphamide (n = 2), methotrexate (n = 2), and chlorambucil (n = 1). There were no differences among the groups. Further details of the immunomodulating therapy regimens instituted at Washington University appear in Table 2.

STATISTICAL ANALYSIS

Results are expressed as mean ± SE with the level of significance set at P<.05. Comparison between groups for evaluation of baseline characteristics was performed by χ² analysis or 1-way analysis of variance. We evaluated changes in mean quantitative muscle testing with 1-way analysis of variance and compared the number of patients who improved with therapy with a χ² analysis. Medication changes and frequency of adverse effects were compared between groups using χ² analysis or the Fisher exact test.

QUANTITATIVE MUSCLE TESTING

The mean increase in strength after the first 6 months of treatment was 18% ± 4% (mean ± SE) for patients receiving IVMP, 26% ± 5% for patients receiving IVIg, and 12% ± 6% for patients receiving oral immunosuppression (Figure). There were no statistically significant differences between the 3 groups. After the first 6 months, 10 (77%) of 13 patients treated with IVMP and 5 (100%) of 5 patients treated with IVIg but only 3 (38%) of 8 patients treated with oral immunosuppression had im-
proven strength (P = .04 comparing the 3 groups). Four patients worsened during the first 6 months, including 1 receiving IVMP and 3 taking oral prednisone. All showed improvement at the time of the last clinic visit.

The mean increase in strength at the last clinic visit was 27% ± 5% for patients treated with IVMP, 33% ± 6% for patients treated with IVIg, and 40% ± 5% for patients treated with oral immunosuppression. There were no statistically significant differences among the 3 groups. At the last clinic visit, 13 (81%) of 16 patients treated with IVMP, 6 (86%) of 7 patients treated with IVIg, and 14 (88%) of 16 patients treated with oral immunosuppression had improved strength, with no statistically significant differences between the groups. In only 1 patient was the strength worse at the time of the last clinic visit. This patient’s condition, treated with IVMP, had also been unresponsive to oral prednisone and IVIg.

ADVERSE EFFECTS

Table 3 lists the adverse effects for all patients taking any given immunosuppressive medication regardless of their primary treatment modality. The most common adverse effect from IVMP (38%) was a 24- to 48-hour syndrome typically described as including insomnia, restlessness, heartburn, flushing, sweating, and facial erythema. This syndrome was never considered significant enough to discontinue treatment. This syndrome did not occur with oral prednisone. A different syndrome, similar to previous reports and consisting of headache, nausea, and chills lasting 24 to 48 hours, occurred in 22% of patients after treatment with IVIg.14

The most common adverse effects from oral prednisone concerned weight gain and cushingoid appearance (58%). They were less common in patients treated with IVMP (19%) (P = .03). Glucose intolerance occurred in 6% of patients receiving IVMP and in 17% of patients receiving oral prednisone. Rare adverse effects, occurring in only 1 or 2 patients receiving IVMP or oral prednisone, included cataracts, insomnia, pneumonia, ruptured diverticula, zoster, mood changes, and cramps. Only 1 patient required hospitalization, for pneumonia, pulmonary embolus, and renal insufficiency. Treatment with IVMP was continued after the patient recovered from the illness. Lymphoma developed in 1 patient receiving IVMP and in 1 patient receiving oral prednisone.

Nausea and emesis were more common in patients receiving methotrexate (38%) and azathioprine (28%) than in patients treated with IVMP (0%) (P = .03 comparing IVMP and oral prednisone). Other adverse effects not listed in Table 3 were rare in patients receiving methotrexate, azathioprine, or cyclosporine, occurring in only 1 patient each; they included hirsutism, tremor, and diarrhea.

CONCOMITANT MEDICATIONS

We found no differences when comparing treatment groups except those related to the addition of immunomodulating medications after treatment with IVMP or oral prednisone (Table 2). In 31% of patients treated with IVMP, an additional therapy was added as a steroid-sparing agent, compared with 100% of patients treated with oral prednisone (P = .003).

Patients with CIDP improve after treatment with a variety of immunomodulating therapies. The best documentation of benefits, from placebo-controlled randomized studies, is for IVIg, plasma exchange, and oral prednisone. Overall reported response rates of patients with CIDP after using single, multiple, or sequential therapies range from 40% to 95%.

Table 3. Major Adverse Effects of Immunosuppressive Medication

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>IVMP (n = 16)</th>
<th>Prednisone (n = 24)</th>
<th>IVIg (n = 27)</th>
<th>Methotrexate (n = 8)</th>
<th>Cyclosporine (n = 13)</th>
<th>Azathioprine (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug administration syndrome</td>
<td>6†</td>
<td>0</td>
<td>6‡</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cushingoid/weight gain</td>
<td>3</td>
<td>14§</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Glucose intolerance/diabetes</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Increased LFT results</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Anemia/cytopenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/emesis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>5¶</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastritis/peptic ulcer</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin changes</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: IVIg, intravenous immunoglobulin; IVMP, IV methylprednisolone; LFT, liver function test.

* n = total number of patients regardless of primary treatment group.
† Typical syndrome: insomnia, heartburn, flushing/sweating/erythema, restlessness.
‡ Typical syndrome: headache, nausea, chills.
§ P = .03 comparing IVMP and oral prednisone.
¶ P < .05 between IVMP and methotrexate/azathioprine.
* Nausea and emesis usually associated with flu-like allergic reaction.
domized studies comparing IVlg with plasma exchange and IVlg with oral prednisone, there was no significant difference in benefits.

Our data show that IVMP appears to be as effective as IVlg and oral prednisone in the initial and long-term management of patients with CIDP. In patients treated with IVlg, strength, as measured by quantitative muscle testing, improved on average by 18% within the first 6 months and by 27% at the time of last follow-up, on average after 4.6 years. There were no statistically significant differences in mean improvement in strength within 6 months, or at the last follow-up, when compared with patients treated with IVlg (26% at 6 months, 31% at 3.6 years) or oral immunosuppression (12% at 6 months, 40% at 4.7 years). We also found no statistically significant difference in the frequency of improvement when comparing our 3 groups at the time of last follow-up, with more than 80% of patients improved in each group. However, within the first 6 months, more patients treated with IVMP (77%) and IVlg (100%) improved than with oral immunosuppression (38%) ($P=0.04$). Previous studies also suggest that relatively prolonged treatment of CIDP with oral corticosteroids might be needed before patients improve. Although the presence of less severe baseline weakness in patients treated with IVMP compared with oral immunosuppression might partly explain the benefit in this group, we think it unlikely. Even though patients receiving IVMP started out with greater baseline strength, all 3 groups improved to a similar degree, suggesting similar beneficial effects from all 3 medications. Furthermore, there was no significant difference in baseline strength between patients receiving IVMP compared with IVlg, and improvement was similar in these 2 groups, suggesting that each of these 2 medications had comparable beneficial effects.

Two prior reports discuss the shorter-term use of IV corticosteroids to treat CIDP. Molenaar et al described 10 patients treated with 6 cycles of 40 mg of dexamethasone for 4 consecutive days over 19 weeks. Three patients discontinued treatment, 1 because of adverse effects and 2 because of deterioration. The patients who completed the treatment course all had objective improvement. In another study, reported only as an abstract, 5 patients were treated with IVMP 1000 mg/d for 5 days and then with 1000 mg every 1 to 8 weeks, depending on the clinical response. All patients had improved motor and sensory function. No adverse effects were noted except for flushing and euphoria with the infusion.

Drawbacks of our study include its open-label, retrospective nature and nonstandardized treatment regimes and evaluations. To simplify comparisons, we included patients treated with oral prednisone and oral cyclosporine in the same group. A randomized prospective trial could definitively address whether IVMP is as efficacious as IVlg or oral prednisone. However, even with these drawbacks, our data are consistent with the earlier findings that IVMP treatment is followed by improvement in strength and can be used as initial therapy in patients with CIDP, even those with severe weakness.

Our data are the first to suggest that IVMP can be used long-term for many years to maintain improved strength. One of the main drawbacks of long-term oral corticosteroid administration is the high likelihood of adverse effects. In our study, 58% of patients treated with oral corticosteroids had weight gain or cushingoid appearance. In contrast, only 19% of patients treated with IVMP had similar adverse effects. Another outcome indicated that the addition of a steroid-sparing agent was uncommon (31%) and less frequent than in patients receiving oral prednisone (100%)—suggesting a low incidence of prominent adverse effects in patients receiving IVMP. Although not statistically significant, the development of hyperglycemia or diabetes was more than 2.5 times as common in patients treated with oral prednisone compared with IVMP. Other adverse effects were rare and not significantly more common with IVMP than with oral prednisone.

The most common adverse effect in patients treated with IVMP was a 24- to 48-hour syndrome characterized by insomnia, restlessness, heartburn, flushing, sweating, and facial erythema, occurring in 38% of patients. This syndrome was transient and not severe enough to warrant discontinuation of the medication. This syndrome was as common as the transient syndrome of headache, nausea, and chills that occurred in patients treated with IVlg.

In summary, our study shows that IVMP is as effective in improving and maintaining strength as IVlg or oral immunomodulating treatments. It is much less expensive than IVlg, oral prednisone, or plasma exchange and is easily administered over a period of a few hours in an outpatient infusion center or at home. Intermittent high-dose IVMP also has fewer adverse effects than daily administration of prednisone, whose adverse effects often limit its use. Intermittent IV methylprednisolone should be considered as an initial therapy and for long-term use in patients with weakness or disability due to CIDP.

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