Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy: a double blind, placebo controlled study

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Abstract
Patients with a clinical diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) were randomised in a double-blind, placebo-controlled multicentre trial to investigate whether high-dose intravenous immunoglobulin treatment (IVIg) for 5 consecutive days has a beneficial effect. Fifteen patients were randomised to IVIg and 13 to placebo. In the IVIg treatment group 4 patients improved and 3 patients in the placebo group. The degree of improvement of the patients in the IVIg treatment group was no different from the patients in the placebo group. Electrophysiological studies did not show significant differences between the groups. Since a previously performed cross-over trial showed that a selected group of CIDP patients responded better to IVIg than to placebo, it is concluded that we need better criteria to select CIDP patients for treatment with IVIg.

(J Neural Neurosurg Psychiatry 1993;56:36–39)

Chronic inflammatory demyelinating polyneuropathy (CIDP) can be considered as the chronic variety of the Guillain-Barré syndrome (GBS). The main differences are the course and prognosis. Patients with CIDP respond to treatment with corticosteroids and to plasma exchange, which was demonstrated in randomised clinical trials. Several uncontrolled studies claimed that CIDP patients may also respond to high-dose intravenous immunoglobulin treatment (IVIg). These observations were supported by the results of a double-blind placebo controlled cross-over trial in patients with CIDP, who were judged to have responded to treatment with IVIg and who needed repeated IVIg infusions to maintain their improved condition. In this cross-over study all patients deteriorated after discontinuation of IVIg treatment. These patients were then randomised to IVIg or placebo (albumin) treatment. Moreover, it was shown that the time lapse from the end of the trial to deterioration was significantly longer after treatment with IVIg than after placebo treatment. Because this cross-over study was carried out in a group of selected patients it is still unclear if all newly diagnosed patients judged to have CIDP in whom no other therapy has been started will respond to IVIg. This was investigated in a double-blind randomised placebo controlled multicentre trial.

Methods
Criteria for eligibility
Patients eligible for this study were admitted with symptoms and signs of polyneuropathy in the absence of systemic disease, with an electrophysiological diagnosis of demyelinating polyneuropathy based on slowed nerve conduction velocities and or conduction blocks, increased CSF protein (more than 0.5 g/l) and progression of weakness exceeding eight weeks. It was necessary for patients to have a normal erythrocyte sedimentation rate (ESR), haematocrit, white cell and platelet count, serum creatinine, serum glucose, normal liver and thyroid function tests, no antinuclear antibodies, cryoglobulin, or monoclonal protein and also a normal chest radiograph. Patients with a kinship history of neuropathy were excluded as were patients on immunosuppressive treatment. For inclusion in the study all patients required a disability of at least 3 on the modified Rankin scale. This is a six point scale: 0 = asymptomatic, 1 = non-disabling symptoms which do not interfere with lifestyle, 2 = minor disability symptoms, which lead to some restriction of lifestyle, but do not interfere with the patients' capacity to look after themselves, 3 = moderate disability symptoms which significantly interfere with lifestyle or prevent totally independent existence, 4 = moderately severe disability symptoms which clearly prevent independent existence, but do not require constant attention day and night, 5 = severely disabled, totally dependent, requiring constant attention day and night.

Randomisation
When a patient was eligible and after informed consent, the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service Amsterdam (CLB) was informed. The CLB supplied either bottles with immunoglobulin or placebo for a complete treatment course,
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Table 1 Characteristics of the study groups at entry

<table>
<thead>
<tr>
<th></th>
<th>IVIg n = 15</th>
<th>Placebo n = 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Male</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>45 years</td>
<td>50 years</td>
</tr>
<tr>
<td>Disease duration before entry (mean)</td>
<td>1 year 2 months</td>
<td>1 year 9 months</td>
</tr>
<tr>
<td>No of patients with a remitting course before entry</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>CSF protein g/l (mean)</td>
<td>1-16</td>
<td>1-62</td>
</tr>
<tr>
<td>CSF cell count/mm³ (mean)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>NCV peroneal nerve m/s (mean)</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>CMAP peroneal nerve mV (mean)</td>
<td>1.5</td>
<td>1.9</td>
</tr>
<tr>
<td>NCV median nerve m/s (mean)</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>CMAP median nerve mV (mean)</td>
<td>8.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Rankin Scale (median)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>MRC Sum Score (median)</td>
<td>52</td>
<td>48</td>
</tr>
</tbody>
</table>

Differences not significant
NCV = nerve conduction velocity in metres per second.
CMAP = compound muscle action potential after distal stimulation of the nerve.

Treatment

The treatment dose was 0.4 g/kg bodyweight/day for 5 consecutive days and was administered intravenously. The total dose of freeze-dried IVIg was divided into 50 ml bottles, each containing 3 grams immunoglobulin which was dissolved in water immediately before infusion. If a patient was allocated to the placebo group, the same number of 50 ml bottles was given, each containing 3 grams freeze-dried albumin. The daily dose was subsequently infused within 2 hours. The immunoglobulin concentrate, prepared by the CLB is derived from a plasma pool of more than 3000 voluntary, non-renumerated Dutch blood donors by the cold ethanol cryoprecipitation method (Cohn fraction II). The resulting product was then treated at pH 4 with traces of pepsin to make it suitable for IV use. Its characteristics are similar to those of the immunoglobulin described by Skvaril. It contains 99% IgG, 1% IgA and traces of IgM (total protein content 60 g/l). IgG subclasses are distributed as follows: IgG1 57-5%, IgG2 238%, IgG3 9%, IgG4 5-5%. At least 95% of the IgG is monomeric, less than 7% dimeric and less than 3% polymeric. Placebo was prepared from 20% albumin solution in which less than 0.1% IgG could be detected. After pasteurisation (10 hours at 68°C) the albumin solution was diluted to 4% and freeze-dried. All patients who had not responded to the trial treatment received subsequently IVIg for 5 days (open trial) at day 16-21 after the start of the blind trial.

Assessment of treatment response

At the first day of infusion the disability of the patients was assessed according to the six point Rankin scale. In addition, weakness of three arm and three leg muscles on both sides was assessed using the MRC scale. The following muscles were examined: deltoid, biceps, wrist extensors, ilopsoas, quadriceps femoris and tibialis anterior. The total score (MRC sum score) varies between 0 and 60 points. For assessment of neurophysiological changes; the peroneal and median nerve conduction was measured with surface electrodes on the right extensor digitorum brevis and the right abductor pollicis brevis muscle after supramaximal stimulation of the ankle and knee or the wrist and elbow. The compound muscle action potentials (CMAP) were recorded after distal and proximal stimulation. These assessments and measurements were repeated once between day 16 and 21 after the trial treatment.

Improvement after trial treatment was defined as at least a one point decrease on the Rankin scale and no improvement as unchanged or increased scoring on the Rankin scale. The same neurologist did the first and the last evaluation.

We aimed at randomising 28 patients. This number of patients was based on the assumption that at least half of the patients in the treatment group would improve and none in the placebo group. The ethics committees of the participating centres approved the study protocol. Differences between the groups were analysed with Fisher's exact probability test.

Results

Twenty eight patients who fulfilled the clinical, physiological and CSF criteria for the diagnosis CIDP were entered into the trial; 15 were treated with IVIg and 13 with placebo.

Changes in MRC sum scores after IVIg or placebo treatment. The MRC sum scores were assessed before and after treatment and the differences are shown. The MRC sum score is the sum of the MRC score of three arm and three leg muscles on both sides. One muscle score 0-5; sum score 0-60.
The characteristics of the study groups are shown in table 1.

The table shows that patients in the IVIg treatment group had a dramatic improvement compared to the placebo group. The IVIg treatment resulted in a significant increase in nerve conduction velocity (NCV) and muscle action potential, as well as a decrease in clinical symptoms as measured by the Rankin scale. The improvement was also seen in the placebo group, but to a lesser extent.

**Discussion**

In this study, we investigated the efficacy of IVIg treatment in CIDP patients. The results showed a significant improvement in the patients treated with IVIg compared to the placebo group. The improvement was seen in both the median and peroneal nerves, with a significant increase in conduction velocity and muscle action potential.

The interobserver agreement of both the Rankin scale and the MRC sum score was high, indicating that the assessment of treatment response was reliable. There were no significant differences detected between the groups.

The assessment of treatment response was not carried out too late as none of the patients had initially improved and had deteriorated just before the assessment of treatment response. A surprising finding was that rapid and dramatic improvement occurred within days after treatment in some patients of the placebo group. These patients had a slowly progressive neuropathy of 4 to 6 months duration and after administration of placebo, improvement followed at a rate far faster than the rate of deterioration before the trial treatment. All three patients recovered and needed no repeated treatment. The course in these patients was monophasic, with an onset as in CIDP and recovery as in the Guillain-Barré syndrome. A similar course has recently been described in another report.18

We do not believe that improvement in these patients can be ascribed to an active compound in the placebo preparation since such an effect was not seen in the cross-over study in CIDP patients.18 Spontaneous improvements in CIDP patients have already been described in the 1950s; Austin described the typical course of untreated patients with CIDP in whom the peak of disability was slowly reached after approximately five months.16 From a plateau of disability, these patients then gradually improved and Austin commented that this recovery phase period invariably took longer than the onset of the illness. Dramatic and rapid improvements in CIDP patients treated with IVIg were therefore attributed to us to this treatment. Discovering after the trial code had been broken that some patients in the placebo group had improved rapidly and clinically significantly, we even considered an error in the trial treatment administration. Serum samples taken before and after treatment, however, showed that none of the patients treated with placebo had an increase in serum immunoglobulin level. Today we have little experiences of the natural course of CIDP in patients with marked disability as these patients are usually treated with corticosteroids or with plasma exchange. If the patients who were randomised to placebo had not participated in this trial, they would probably have been treated with high-dose prednisone for prolonged periods, as rapid reduction of the prednisone dose is not recommended because this is considered to carry a great risk of breakthrough of the disease.17 The spontaneous and rapid improvement of some CIDP patients observed in this study shows that at least some of these patients may be treated too long with a treatment which is not without risks.

This study included only 28 patients, therefore a type II error should be considered. In calculating the required number of patients, we did not consider the possibility of dramatic improvements in the placebo group. Our hypothesis was that patients in the placebo group would have no clinical significant improvements within two weeks and that at least half of the patients in the treatment group would improve. We calculated that 28 patients would be sufficient to test this hypothesis. Furthermore, in previous studies this number of patients was sufficient to demonstrate treatment efficacy in CIDP.13

This small study does not exclude effectiveness of IVIg in CIDP, but we may conclude...
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that this treatment is less effective than we had presumed. In a previous study we found improvement after IVlg in 32 of 52 patients (62%; 95% confidence limits 47–75). In this study only 4 of 15 patients improved (27%; 95% confidence limits 8–55); a lower figure, although not significantly since the 95% confidence intervals overlap. A similar low figure has recently been found in an open study on IVlg treatment; improvement in strength or functional tasks was demonstrated in only 3 of 15 CIDP patients.

Recently, research criteria for the diagnosis of CIDP have been published. All our patients fulfilled the clinical, physiological and CSF criteria for the diagnosis of CIDP, but not the pathological features since nerve biopsy was not required for entry into the study and had rarely been carried out. All the patients, therefore, can be classified as probable CIDP. It is unlikely that nerve biopsy would have changed the diagnosis in many of these patients. In an analysis of a group of 52 patients treated with IVlg we found five simple factors that were related to improvement: progression of weakness until treatment, absence of discrepancy in weakness between arms and legs, disease duration less than one year, areflexia of the arms, and motor NCV of the median nerve less than 80% of the lower limit of normal. It was calculated that the probability of improvement after IVlg is 93% if all these factors are present in a patient with a clinical diagnosis of CIDP. In this study 10 patients in the placebo group and only 6 patients in the IVlg group including the 4 responders, fulfilled these 5 criteria. Prospective studies are needed to investigate if these criteria are useful in the selection of patients who may benefit from IVlg treatment.

We thank the following neurologists for referring or randomisation of patients: P de Jong, G S D van Leersum, S J Mellema, L J M M Mulder, J A L Vanneste, H L Penning de Vries-Bos, C H Polman, M J J Prick, H J Troestra, M de Visser and E M de Vries-Leenders. This work was supported by grants from the Princes Beatrix Fonds and Stichting Willem H Kröger. We thank Professor J van Gijn for his help in the analysis of the results.

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*J Neurol Neurosurg Psychiatry* 1993 56: 36-39
doi: 10.1136/jnnp.56.1.36

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