Plasma exchange and chlorambucil in polyneuropathy associated with monoclonal IgM gammopathy

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(see annex)

Abstract

The study compared chlorambucil alone with chlorambucil in combination with plasma exchange in patients with polyneuropathy associated with monoclonal IgM. Forty-four patients were prospectively randomly assigned, in a comparative open trial, to receive either 0.1 mg/kg/day chlorambucil orally, for 12 months or chlorambucil associated with 15 courses of plasma exchange, during the first four months of treatment. They were evaluated by a neuropathy disability score and nerve conduction studies. No difference was found between the two treatment groups. The average neuropathy disability score improved by 2-1 points from baseline (21.0 to 18.9) in the chlorambucil group and by 1-8 points (20.4 to 18.6) in the chlorambucil + plasma exchange group (P = 0.70). The mean motor nerve conduction velocity decreased from 20.0 to 18.2 m/s in the chlorambucil group and increased from 20.5 to 22.5 m/s in the chlorambucil + plasma exchange group (P = 0.51). A slight improvement of the sensory component of the neuropathy disability score (from 10.5 to 8.3) was noted in both groups (P = 0.01). At the end of the study and according to self evaluation, 15 patients—eight from the chlorambucil group and seven from the chlorambucil + plasma exchange group—reported clinical improvement, whereas 15—eight from the chlorambucil group and seven from the chlorambucil + plasma exchange group—reported clinical worsening. Neupathy remained stable in the others.

Thus plasma exchange seemed to confer no additional benefit in the treatment of polyneuropathy associated with monoclonal IgM.

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Keywords: polyneuropathy; antimyelin; gammopathy; plasma exchange

Peripheral neuropathy may be associated with a serum monoclonal IgM in the presence or absence of an overt lymphoid proliferative disease such as Waldenström's macroglobulinaemia.1-3 A causal link between the monoclonal IgM and the development of neuropathy is suggested by (a) the specificity of most of these IgMs for the myelin associated glycoprotein (MAG),4-5 nerve glycolipids,6-8 or gangliosides; (b) the detection of IgM and complement deposits by immunofluorescence, on the myelin sheaths of nerve biopsies from patients9-11; (c) the induction, in animal models, of the neuropathological process through the transfer of the anti-MAG IgM12-13 or by the subperineural injection of the IgM in peripheral nerves.14

Because IgM associated neuropathy usually has a progressive course and can be responsible for severe disabling sensory and motor symptoms, effective treatment is important. The rationale for using plasma exchange is that the monoclonal IgM may be directly involved in the demyelination and removal of these pathogenic antibodies may prevent progression of the neuropathy or even lead to improvement. The rationale for using chlorambucil is that even in the absence of a detectable lymphoid proliferation, the monoclonal IgM is associated with an underlying IgM producing B cell clone; chlorambucil is effective in chronic B cell neoplasias such as chronic lymphocytic leukaemia and Waldenström's macroglobulinaemia and could therefore be effective on the anti-MAG secreting B cells. Plasma exchange and chlorambucil have been used with some improvement in uncontrolled studies enrolling few patients.15-17

As evaluation of these therapeutic strategies require long term treatment and as the idea of a placebo arm was considered unethical because of the progressive disability associated with such disease, we designed a comparative open trial of chlorambucil v chlorambucil associated with plasma exchange.

Patients and methods

Patients

Patients had to meet the following criteria: (a) polyneuropathy of at least three months duration, (b) presence of a serum monoclonal IgM; (c) a clinical neuropathy disability score (CNDS) above 6 points; (d) a stable or progressive neuropathy; (e) careful elimination of other causes of peripheral neuropathy, especially diabetes and amyloidosis; (f) no treatment for the past three months. Informed consent was obtained from each patient.

Evaluation of Neuropathy

The CNDS was determined by modification of the score described elsewhere.18-19 Briefly, selected items from the neurological evalua-
tion were scored and summed. The function of 17 muscles (× 2) was scored as 0 if normal and 1 if abnormal; sensation (touch-pressure, joint motion, vibration, pin prick) was scored in the same way; muscle stretch reflexes were scored as 0 if present and 1 if absent; pain and paraesthesia were scored 0 if absent and 1 if present. Scores could range from 0 to 72, summing 0 to 46 points for the motor component (CNDS(M)) and 0 to 26 points for the sensory component (CNDS(S)). In addition, after the neurological examination, the patient was asked to assess the evolution of the symptoms as complete remission, improvement, stability, or worsening.

Nerve conduction studies were performed on the same lower limb at entry and at the end of the fourth and 12th months. Motor fibres of the peroneal nerve were studied and motor nerve conduction velocities (MNCVs) and distal latencies (DLs) were determined with standard placement of surface electrodes and after control of the limb temperature. Nerve conduction studies were also performed on the sural nerves.

Follow up evaluations on individual subjects were performed by a single examiner.

**ANTIMYELIN ANTIBODY ACTIVITY**

Antimyelin antibody activity was detected by an indirect immunofluorescence assay on human sciatic nerve and confirmed with immunoblotting experiments.

**STUDY DESIGN**

The study was designed to be a prospective, randomised, open clinical trial comparing two treatments. Before the study was designed, little reliable information on the natural history of IgM associated neuropathy was available, and spontaneous improvement had not been reported. Using a unilateral formulation and expecting an improvement of at least 10 points of the initial CNDS in the group treated with chlorambucil and plasma exchange and postulating that the disease would be stable in the group receiving chlorambucil alone, we decided to enroll 44 consecutive patients in the study (α = 0.05, β = 0.05).

**TREATMENT**

The patients were assigned by randomisation to receive chlorambucil alone (0.1 mg/kg/day, orally) for 12 months, or in association with a four month period of plasma exchange.

The planned volume of plasma removed by centrifugation per plasma exchange was 1.5 × total plasma volume. The replacement fluid consisted of a 4% albumin solution (80% of the volume) and macromolecules (20%). Fifteen exchanges were performed during the first four months of treatment: three in the first week, one a week for the next seven weeks, one every 10 days for one month, and one every two weeks for the last month.

**STATISTICAL ANALYSIS**

Student’s t test and χ² test were used for the comparison of the two groups at inclusion. Changes from baseline were compared in the two groups (with and without plasma exchange) by means of the non-parametric Wilcoxon rank sum test. Paired Student’s t test was used to compare results at four and 12 months with baseline data.

**Results**

Inclusion began in December 1986 and ended in August 1990. Forty five patients were enrolled in 15 French centres. Twenty three were assigned to chlorambucil alone and 22 to chlorambucil associated with plasma exchange. One patient from the chlorambucil group had severe chronic hepatopathy, and therefore the data for this patient were not used in the analysis.

The mean (SD) Karnofsky score for the whole population was 73 (12%). Walking was difficult or unstable in twenty eight (64%) patients. Two patients had been previously treated with immunosuppressive agents, one with cyclophosphamide and one with azathioprine. The mean duration (SD) of the peripheral neuropathy was 37 (35) months. Nerve/muscle biopsies were performed in 32 patients before entry. On semi-thin sections the myelinated nerve fibre population was reduced; teased fibre studies showed a mixture of segmental demyelination and remyelination in most cases; muscle atrophy was present in 26 cases (81%). The randomisation procedure resulted in treatment groups that were well balanced with respect to patient characteristics (table 1) and neurological abnormalities (tables 2 and 3).

None of the patients stopped treatment because of toxicity; however, 10 patients experienced temporary suspension of chlorambucil or required tapering of the dosage.
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Table 3: Nerve conduction study at entry according to treatment group

<table>
<thead>
<tr>
<th>Chlorambucil (n = 20)</th>
<th>Chlorambucil and plasma exchange (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peroneal nerve:</strong></td>
<td></td>
</tr>
<tr>
<td>Detectable response</td>
<td>15</td>
</tr>
<tr>
<td>DL (mean (SD))</td>
<td>26.2 (10.9)</td>
</tr>
<tr>
<td>Undetectable response</td>
<td>5</td>
</tr>
<tr>
<td><strong>Sural nerve:</strong></td>
<td></td>
</tr>
<tr>
<td>Detectable response</td>
<td>3</td>
</tr>
<tr>
<td>Undetectable response</td>
<td>17</td>
</tr>
</tbody>
</table>

MNCV = motor nerve conduction velocity (m/s), DL = distal latency (ms).

during the trial because of haematotoxicity. No serious adverse events were reported with plasma exchange. Eight patients stopped the treatment before month 12. In the chlorambucil group, four patients stopped treatment (three because of neurological progression (months 2, 7, and 9) and one because of the absence of improvement (month 4)). Three of them were then treated with plasma exchange but remained in the chlorambucil alone group for an intent to treat analysis. In the chlorambucil + plasma exchange group, one patient died at month 4 with an occlusion of the small bowel and three stopped treatment, two because of worsening of neuropathy at months 4 and 6, and one because of emergency vascular surgery at month 4.

The major endpoint of the study had been defined as the CNDS after 12 months of treatment. On average, the CNDS decreased (improved) by 2.1 points in the chlorambucil group and by 1.8 points in the chlorambucil + plasma exchange group. The difference between the two groups was not statistically significant (P = 0.70). The slight improvement in both groups was related to an improvement of the sensory component of the CNDS: 2.4 points in the chlorambucil group and 1.5 points in the chlorambucil + plasma exchange group. In the whole population of patients this improvement of the CNDS score from 10.5 to 8.3 was statistically significant (P < 0.01).

Electrophysiological data were available in 39 patients. Nerve conduction studies showed that with chlorambucil alone, the mean value of MNCV (peroneal nerve) worsened by 1.8 m/s and that of DL improved by 3.3 ms. In the chlorambucil + plasma exchange group the mean value of MNCV improved by 2 m/s and the mean value of DL by 3 ms. The differences between the two groups were not significant. Sensory nerve conduction velocities in the sural nerve were undetectable in 32 of the 39 patients at entry, and in 21 of the 32 patients evaluated at month 12.

Twenty nine patients remained stable or worsened, and 15 improved after treatment. We looked for baseline covariates that could be predictive for the response, and failed to find any predictive value for age, sex, bone marrow lymphoid infiltration, serum IgM concentration, antimyelin activity, or initial CNDS: There was a trend for shorter duration of the neuropathy in the responders (26.3 (23) months) than in the non-responders (42.6 (40) months), but it did not reach significance (P = 0.15). The response was not associated with a significant decrease in the serum IgM concentration in the 29 patients in whom it could be evaluated.

Long term follow up (47 to 83 months) was available for 14 of the 15 patients who had responded to treatment. At the end of the study two of them stopped taking chlorambucil; one patient had achieved a complete response and remained symptom free after 80 months while the serum monoclonal IgM was still detectable (2 to 3 g/l); the other relapsed at month 24 but improved again when chlorambucil was reintroduced. Of the 12 patients who were maintained on chlorambucil, six remained stable on treatment, four stopped treatment because of haematotoxicity.

Table 4: Evolution from baseline in neuropathic indices during the 12 month treatment period, according to treatment group

<table>
<thead>
<tr>
<th></th>
<th>Chlorambucil</th>
<th>Chlorambucil and plasma exchange</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CNDS:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At entry</td>
<td>21.0 (9.0)</td>
<td>20.4 (6.5)</td>
<td>0.74</td>
</tr>
<tr>
<td>Month 4</td>
<td>20.6 (7.8)</td>
<td>21.1 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td>18.9 (8.2)</td>
<td>18.6 (7.6)</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>CNDS(M):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At entry</td>
<td>9.6 (5.7)</td>
<td>11.2 (4.8)</td>
<td>0.21</td>
</tr>
<tr>
<td>Month 4</td>
<td>10.0 (4.3)</td>
<td>11.6 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td>10.0 (4.3)</td>
<td>10.9 (4.7)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>CNDS(S):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At entry</td>
<td>11.3 (5.0)</td>
<td>9.2 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Month 4</td>
<td>10.3 (4.8)</td>
<td>9.5 (5.4)</td>
<td>0.57</td>
</tr>
<tr>
<td>Month 12</td>
<td>9.6 (5.4)</td>
<td>7.7 (4.3)</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>MNCV:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At entry</td>
<td>20.0 (14.8)</td>
<td>20.5 (15.3)</td>
<td>0.79</td>
</tr>
<tr>
<td>Month 4</td>
<td>20.6 (13.0)</td>
<td>22.0 (18.0)</td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td>18.2 (10.1)</td>
<td>22.5 (14.7)</td>
<td>0.51</td>
</tr>
<tr>
<td>Patients with detectable response at baseline:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At entry</td>
<td>26.2 (10.9)</td>
<td>26.7 (11.3)</td>
<td>0.72</td>
</tr>
<tr>
<td>Month 4</td>
<td>25.7 (12.0)</td>
<td>27.9 (15.4)</td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td>24.3 (12.4)</td>
<td>27.4 (13.8)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Values are means (SD). CDNS = clinical neuropathy (M) = motor component; (S) = sensory component; MNCV = motor nerve conduction velocity.

Table 5: Evolution from baseline in neuropathic indices during the 12 month treatment period

<table>
<thead>
<tr>
<th></th>
<th>At entry</th>
<th>Month 12</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CNDS:</strong></td>
<td>21.0 (7.8)</td>
<td>18.8 (7.8)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>CNDS(M):</strong></td>
<td>10.5 (5.3)</td>
<td>10.5 (4.4)</td>
<td>0.97</td>
</tr>
<tr>
<td><strong>CNDS(S):</strong></td>
<td>10.5 (4.5)</td>
<td>8.3 (4.9)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>MNCV:</strong></td>
<td>20.2 (14.8)</td>
<td>19.9 (12.0)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

For explanations see table 4.
chlorambucil after 19 to 36 months and remained stable, and two worsened on treatment.

Discussion
Peripheral neuropathy associated with monoclonal IgM gammopathy is usually considered as a sporadic entity. The clinical features are somewhat different from those with IgG or IgA gammopathies, with more sensory loss and ataxia. A causal link between the monoclonal IgM and the development of neuropathy is suggested by the antibody activity of the IgM to nerve polypeptides or glycolipids, the detection of IgM deposits on the myelin sheaths of patients' nerve biopsies, and the induction of the neuropathological process through the transfer of the anti-MAG IgM in animal models. These data provide a firm basis to evaluate plasma exchange as well as chlorambucil in such patients with the aim of obtaining a significant reduction of IgM production or circulation.

Previous reports that plasma exchange might be efficient in polyneuropathy associated with IgM monoclonal gammopathy of undetermined significance needed to be confirmed, as most trials were uncontrolled and performed in selected patients, without prospective evaluation of the neurological symptoms.

In the present study, the association of plasma exchange with chlorambucil offered no additional benefit as measured by the neuropathy disability score (P = 0.70), its motor component (P = 0.12), its sensory component (P = 0.70), or the motor nerve conduction velocity (P = 0.51). Interestingly, after four months of treatment, when the patients of one group had completed their plasma exchange—that is, at the time at which we were most likely to detect a difference between the two groups—we failed to show any usefulness of plasma exchange (table 4).

For both groups together, treatment was associated with a slight improvement of the CNDS, from 21.0 to 18.8 (P = 0.05) as a sole result of improvement its sensory component, from 10.5 to 8.3 (P = 0.01). There was no significant modification of the nerve conduction velocity neither of the distal latency. Of note, after 12 months of treatment, there was no obvious modification of the serum IgM concentration in patients reporting improvement.

These results are consistent with those of Dyck et al in their double blind trial in which plasma exchange might be effective in improving the neuropathy disability score in patients with neuropathy associated with monoclonal IgG or IgA gammopathies but not in the patients with monoclonal IgM. The conditions in our study were, however, different: (a) the study was open, without a placebo arm, (b) the plasma exchange programme was longer (15 courses over four months v six courses over three weeks), (c) the effectiveness of treatment was evaluated at month 4, however, we still did not detect any differences between the groups.

Our data suggest that in polyneuropathy associated with monoclonal IgM gammopathy, plasma exchange does not offer benefit over chlorambucil alone. Previous data pointing to an improvement of the neuropathy with chlorambucil in such a scenario, and that this drug could be effective in a limited subset of patients not detected in the present study. Chlorambucil may improve the symptoms in some patients and therefore can be considered as a possible treatment in severely disabled patients. Because of the possible risk of secondary leukaemia during long term chlorambucil treatment, future prospective randomised trials should evaluate the effects of other types of immune modulation such as intravenous high dose polyvalent immunoglobulin

Annex: the IgM associated polyneuropathy study group

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