Editorial

Intravenous immunoglobulin treatment in neurological diseases

Intravenous immunoglobulin (IVIg) was initially introduced as replacement therapy in antibody deficiency disorders. Later applications include the prophylactic use of IVIg against infections and as an immunomodulating treatment in autoimmune diseases. Overall, the use of intravenous IVIg has increased impressively during the past decade. In 1991, the annual consumption had risen to 428 kg in Canada and 200 kg in the Netherlands, where consumption rose to 250 kg in 1993.

Doubts exist as to whether this increased use is paralleled by a comparable growth of reliable data on the therapeutic effectiveness of IVIg. To assess the level of evidence on the use of IVIg in neurology, we performed a systematic review of publications in English, using MEDLINE, between January 1981 and January 1995. We looked for comparative trials, case series, and case reports.

There are different levels of evidence on which to base treatment recommendations. The highest are quality data from randomised controlled trials, with double blinding and blinded outcome assessment. The lowest is found in anecdotal, single patient case reports. We found papers reporting on the use of IVIg in 23 neurological disorders (table 1).

Guillain-Barré syndrome

One randomised study compared IVIg with plasma exchange, with IVIg being slightly superior. 53% of patients allocated to IVIg improved at least one functional grade on the Guillain-Barré syndrome scale four weeks after onset of treatment against 34% of the patients allocated to plasma exchange. In patients showing signs of deterioration one or two weeks after the initial therapy, a second treatment produced further improvement in most cases.

Of the four open randomised clinical trials that have compared plasma exchange with supportive care, three reports a significant favourable effect. In one of these trials, the rate of one point improvement on the Guillain-Barré syndrome scale four weeks after treatment initiation was 59% in the plasma exchange group versus 39% in the control group. In one study, IVIg in combination with high dose methylprednisolone was compared with historical controls treated with IVIg. The 25 patients with the combination treatment improved earlier than those in the historical control group.

Several ongoing trials are evaluating the effectiveness of IVIg in Guillain-Barré syndrome. These trials are driven by the finding that the success rate in patients allocated to plasma exchange in one trial comparing IVIg with plasma exchange was similar to the success rate in patients allocated to placebo in the trial comparing plasma exchange with supportive care.

Published guidelines are not consistent in their treatment recommendations. The University Hospital Consortium (UHC) Expert Panel6,9 seem to have accepted the results of the Dutch Guillain-Barré syndrome trial as they formulated in a consensus statement that IVIg may be considered as an equivalent alternative to plasma exchange. According to the guidelines of the Australasian Society of Blood Transfusion (ASBT) plasma exchange is still preferred to IVIg.

Review of published articles on IVIg treatment in MEDLINE between January 1981 until January 1995

<table>
<thead>
<tr>
<th>Neurological disorder</th>
<th>Randomised trials</th>
<th>Uncontrolled series*</th>
<th>Total No of patients in series</th>
<th>No of patients responding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillain-Barré syndrome</td>
<td>1: COM</td>
<td>11</td>
<td>75</td>
<td>55 (73)</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polynuropathy</td>
<td>1: PC, 1: CR</td>
<td>7</td>
<td>103</td>
<td>66 (64)</td>
</tr>
<tr>
<td>Multifocal motor neuropathy</td>
<td>1: CR</td>
<td>4</td>
<td>21</td>
<td>17 (81)</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>1: PC</td>
<td>9</td>
<td>119</td>
<td>84 (71)</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>1: PC</td>
<td>5</td>
<td>25</td>
<td>20 (80)</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>1: PC</td>
<td>3</td>
<td>21</td>
<td>13 (62)</td>
</tr>
<tr>
<td>Inclusion body myositis</td>
<td>1: PC</td>
<td>2</td>
<td>15</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Refractory epilepsy of childhood</td>
<td>1: OP</td>
<td>14</td>
<td>180</td>
<td>98 (52)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>1: OP</td>
<td>3</td>
<td>31</td>
<td>?</td>
</tr>
<tr>
<td>-optic neuritis</td>
<td>1: PC</td>
<td>1</td>
<td>5</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Paraproteinaemic polynuropathy</td>
<td>1: PC</td>
<td>1</td>
<td>2</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>1: PC</td>
<td>1</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>HTLV associated myelopathy</td>
<td>1: PC</td>
<td>1</td>
<td>14</td>
<td>10 (71)</td>
</tr>
<tr>
<td>Lumbosacral plexopathy</td>
<td>1: PC</td>
<td>1</td>
<td>2</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Stiff-man syndrome</td>
<td>1: PC</td>
<td>2</td>
<td>6</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Rasmussen’s syndrome</td>
<td>1: PC</td>
<td>1</td>
<td>2</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>1: PC</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lambert-Eaton syndrome</td>
<td>1: PC</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Miller Fisher syndrome</td>
<td>1: PC</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Opiococcous polynuropathy</td>
<td>1: PC</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Isaacs’ syndrome</td>
<td>1: PC</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Paraneoplastic cerebellar syndrome</td>
<td>1: PC</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Echovirus meningocencephalitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Series in which at least two patients were described.
†For these disorders only single case reports have been published.
COM = comparative trial; PC = placebo-controlled trial; CR = cross over trial; OP = open trial.
Chronic inflammatory demyelinating polyneuropathy

A placebo controlled cross over study was performed, in which IVIg was given to a selected group of patients with chronic inflammatory demyelinating polyneuropathy who had all shown a favourable response to IVIg in previous open studies. The disability of all patients improved after IVIg and did not change or deteriorate after placebo. These beneficial effects of IVIg could not be confirmed in a double blind randomised trial in newly diagnosed patients with the disease. Recently, one randomised study (which appeared in MEDLINE after January 1995) compared IVIg with plasma exchange in which no differences were found between the groups in the short term. In a recently completed study from Canada, patients on IVIg had better results than those on placebo. The details of this study have not yet been published.

Alternative therapies are corticosteroids and plasma exchange. For both treatments statistically significant differences in favour of treatment were shown in simple randomised controlled trials. These trials had an outcome measure that was a mixture of impairment and disability scores.

There is still no consensus on the use of IVIg in chronic inflammatory demyelinating polyneuropathy. In 1993, the ASBT recommended IVIg as first line treatment for children who were too small for plasma exchange, but after that publication more information became available. In 1995, the UHC Expert Panel considered IVIg an equivalent alternative to plasma exchange. They did not discuss the role of steroids, which by many are considered as treatment of first choice.

Multifocal motor neuropathy

In a placebo controlled cross over study, in which 12 patients with motor neuron syndromes associated with high titered anti-GM, antibodies were treated, IVIg induced significant increases in muscle strength only in patients with conduction blocks. In uncontrolled series IVIg was usually given at one to two month intervals. Alternative therapies are corticosteroids and cyclophosphamide. Some patients deteriorated after treatment with corticosteroids. Beneficial effects of cyclophosphamide have been described in small uncontrolled series.

In multifocal motor neuropathy IVIg is the only treatment that has been tested in a controlled study but it is unlikely that this treatment is universally accepted as first line treatment. A recent report concluded that patients with multifocal motor neuropathy may temporarily improve after IVIg but that the disease progresses and that patients continue to deteriorate. The UHC Expert Panel did not recommend the use of IVIg in motor neuron syndromes.

Myasthenia gravis

For this disease the use of IVIg has only been studied in anecdotal case series except for one randomised controlled trial which has just been completed. Preliminary analysis does not show any difference from plasma exchange (Ph Gajdos, personal communication). In most studies patients were treated during an acute crisis, in others during a more stable chronic phase of the disease, or the stage of the disease was not described. Comparison of treatment responses in case series was difficult, as many different primary outcome measures were used. Usually, IVIg treatment was given once and was not repeated. Some patients who had failed to respond to plasma exchange responded to IVIg and vice versa. Alternative therapies include immunosuppression and plasma exchange. Plasma exchange has not been tested in randomised trials. In large studies the response rate was estimated at 70%, which is comparable with the estimated response rate reported after IVIg. In both the UHC Expert panel and the ASBT guidelines, plasma exchange is preferred to IVIg.

Inflammatory myopathies

The inflammatory myopathies include dermatomyositis, polymyositis, and inclusion body myositis. In dermatomyositis, IVIg was shown to be effective in a placebo controlled trial in patients who had become resistant to immunosuppressive drugs. IVIg was given in two doses of 1 g/kg on two consecutive days, instead of the usual schedule of 0.4 g/kg for five days. Patients continued to receive prednisone during the trial. The main outcome measure was improvement in muscle strength. In case series IVIg usually was given at monthly intervals to patients in whom steroids were unsuccessful or contraindicated and outcome measures were based on measurement of muscle strength.

Effectiveness of IVIg in polymyositis was studied in three uncontrolled series with various results. In one study beneficial effects of IVIg were described in four patients with inclusion body myositis, a disorder which is considered to be resistant to all therapies. However, in another study in nine patients, none improved after IVIg.

Corticosteroids are usually considered as first line therapy in inflammatory myopathies. If not effective, other immunosuppressive treatment is used, but again there are no controlled studies. In a placebo controlled trial there was no beneficial effect of plasma exchange in patients with dermatomyositis or polymyositis.

Since IVIg was tested in a clinical trial in patients resistant to other therapies, IVIg treatment cannot be recommended as first line therapy as is shown in published guidelines: Dalakas et al recommended IVIg in inflammatory myopathies after failure of steroids and/or azathioprine. The UHC Expert Panel recommend IVIg for both dermatomyositis and polymyositis in patients with severe active illness for whom other interventions have been unsuccessful or intolerable. For inclusion body myositis, evidence from the medical literature does not support the use of IVIg.

Refractory epilepsy of childhood

Treatment with IVIg was studied in a very heterogeneous group of children with refractory epilepsy. All studies were uncontrolled, except one single blind placebo controlled add on trial, in which the children were their own controls. These children had different forms of epilepsy, both focal and generalised. Of all children studied, about 30% had Lennox-Gastaut syndrome and 25% had West syndrome. Anticonvulsive drugs had been unsuccessful in most children, including ACTH in some. Usually, IVIg was given at intervals of two or three weeks and the reduction in the number of seizures was used as the outcome measure, but in many studies an accurate definition of outcome measures was lacking. In a few studies an association was found between deficiencies of IgG subclasses before treatment and a favourable response to IVIg. Recently, a double blind dose/finding clinical trial appeared in MEDLINE after January 1995 showed a positive trend in favour of IVIg, but the difference was not significant in comparison with placebo.

New antiepileptic drugs such as vigabatrin may be considered as alternatives to IVIg. Direct comparison has not been carried out. In adults, clinical trials have shown
effectiveness of vigabatrin\(^1\), in children a beneficial effect was suggested in uncontrolled trials with a response rate of 40–70%.\(^4\)

In the UHC Expert Panel guidelines, there is only a place for IVlg as a last resort, especially in patients who are candidates for surgical resection.

In conclusion, for most of the disorders listed in the table, only case series have been published. Therefore, the data on therapeutic effectiveness to support the use of IVlg are not very strong. The disorders for which there is better evidence than case series to use IVlg treatment, are relatively rare. The large consumption of IVlg, as has been shown, for different indications such as Canada and The Netherlands, can therefore probably not be explained by an increased use of IVlg in neurological patients.

**Department of Neurology**

**Department of Clinical Epidemiology and Biostatistics**

Academisch Medisch Centrum,
University of Amsterdam,
Amsterdam, The Netherlands

**Department of Neurology,**
Leyens Hospital,
The Hague, The Netherlands

**Correspondence to:** Professor M Vermeulen, Department of Neurology, H2-214, Academisch Medisch Centrum, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.


Intravenous immunoglobulin treatment in neurological diseases.

A Otten, M Vermeulen, P M Bossuyt and A Otten

*J Neurol Neurosurg Psychiatry* 1996 60: 359-361
doi: 10.1136/jnnp.60.4.359

Updated information and services can be found at:
[http://jnnp.bmj.com/content/60/4/359.citation](http://jnnp.bmj.com/content/60/4/359.citation)

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
[http://group.bmj.com/group/rights-licensing/permissions](http://group.bmj.com/group/rights-licensing/permissions)

To order reprints go to:
[http://journals.bmj.com/cgi/reprintform](http://journals.bmj.com/cgi/reprintform)

To subscribe to BMJ go to:
[http://group.bmj.com/subscribe/](http://group.bmj.com/subscribe/)