Intravenous immunoglobulin – how to use it

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WHAT IS IT?
The immunoglobulin used in intravenous immunoglobulin (IVIg) is prepared from the pooled plasma from about 8000 blood donors. Plasma purification includes steps to remove viruses. Donors at risk for transfusion-related viruses are excluded and IVIg consists almost entirely of IgG with traces of IgM, IgA and soluble plasma factors including cytokines. Its initial use was as replacement therapy in hypogammaglobulinaemia. Its success in treating autoimmune thrombocytopenic purpura led to its use in other immune-mediated diseases.

HOW DOES IT WORK?
We do not really know. There are many proposed mechanisms. Different, possibly multiple, mechanisms may apply in different diseases (Fig. 1).

WHO NEEDS IT?
Guillain–Barré Syndrome (GBS) and Kawasaki disease are the only neurological conditions licensed for IVIg treatment in the United Kingdom. The strength of the evidence for the use of IVIg in other neurological conditions varies. Consensus does not exist. Tables 1, 2 and 3 represent our own interpretation of the evidence based largely on nonsystematic reviews (Wiles et al. 2001; Dalakas 1999). Its use in any of these situations requires informed consent.

WHEN IVIG IS THE TREATMENT OF CHOICE

Guillain–Barré Syndrome
Historically, plasma exchange was first established as superior to no treatment in severe Guillain–Barré Syndrome (GBS) (Raphael et al. 2001). Then IVIg was shown to have equivalent efficacy in early, severe GBS, when the patient cannot walk unaided (Hughes et al. 2001). The traditional regimen is 0.4 g/kg daily for 5 days. It is not known whether IVIg is also effective in children, patients who present after 2 weeks or in patients who can still walk. Common sense dictates that the earlier treatment is started the better the outcome will be. Plasma exchange was more effective in the first week than in weeks 2–4 after onset (The Guillain–Barré Syndrome Study Group 1985).

It is reasonable to repeat the IVIg in the 10% of patients who improve after the first course and then relapse. We do not know whether a second course of IVIg helps patients who have not improved after the first, and attempts to fund a trial to answer the question have failed.

Multifocal motor neuropathy
In multifocal motor neuropathy, IVIg is the treatment of choice but should be reserved for patients with significant disability. Small randomised trials have consistently shown benefit in about 80% of patients (Nobile-Orazio 2001). Unfortunately the duration of this benefit is variable and may be so short that infusions have to be repeated every 4 to 12 weeks. The initial dose is 2.0 g/kg but subsequent doses may be reduced (see infusion regimes below).

Kawasaki disease
In childhood Kawasaki disease, characterized by aseptic meningitis, stroke and encephalopathy, IVIg is the treatment of choice. A regimen of 1.0 g/kg given over 24 h is more effective than spreading 1.6 g/kg over 4 days (Barron et al. 1990).
WHEN IVIG IS A TREATMENT OPTION

Chronic inflammatory demyelinating polyradiculoneuropathy

In chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), IVIg or corticosteroids are equally efficacious as first-line therapy (Hughes et al. 2001). In the impoverished UK National Health Service, we feel compelled to relegate IVIg to second place and try prednisolone first, except in patients with purely motor CIDP. Some patients with purely motor CIDP may worsen with steroids and so IVIg should be used in preference, as in multifocal motor neuropathy. For the majority, IVIg should be reserved for the 30% of patients who do not respond to steroids, and for those whose response to steroids is inadequate or in whom steroids cause unacceptable adverse effects. Intravenous immunoglobulin is less often helpful in paraproteinaemic demyelinating neuropathy.

If the first IVIg course does not result in a full recovery but did afford some improvement, or if the patient subsequently deteriorated, a repeat course is warranted. Regular measures of disability and impairment should be used to monitor response to treatment. As in multifocal motor neuropathy, IVIg may need to be repeated at intervals of 4 to 12 weeks, with doses ranging from 2.0 g/kg to as little as 0.4 g/kg.

Myasthenia gravis

Myasthenia gravis can usually be adequately treated with oral steroids and immunosuppressants. Intravenous immunoglobulin may be considered in preference to plasma exchange in myasthenic crisis, owing to its relative ease of administration. The two treatments were not significantly different in two randomised trials but retrospective studies suggest that plasma exchange may be more efficacious, albeit with a higher risk of complications.

Dermatomyositis

In dermatomyositis a randomised trial supports the use of IVIg, but corticosteroids are the first line treatment.

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**Table 1** Neurological diseases in which IVIg is the treatment of choice

<table>
<thead>
<tr>
<th>Disease</th>
<th>When to give IVIg</th>
<th>Alternative treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillain–Barré Syndrome</td>
<td>Within two weeks</td>
<td>Plasma exchange</td>
</tr>
<tr>
<td>Multifocal motor neuropathy</td>
<td>If significant disability</td>
<td>None</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>At diagnosis</td>
<td>Corticosteroids</td>
</tr>
</tbody>
</table>

**Table 2** Neurological diseases in which IVIg is a treatment option

<table>
<thead>
<tr>
<th>Disease</th>
<th>First line treatment</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic inflammatory demyelinating polyneuropathy (CIDP)</td>
<td>Corticosteroids</td>
<td>Plasma exchange</td>
</tr>
<tr>
<td>Lambert–Eaton myasthenic syndrome</td>
<td>Corticosteroids</td>
<td>Plasma exchange</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Corticosteroids</td>
<td>—</td>
</tr>
<tr>
<td>Paraproteinaemic demyelinating neuropathy</td>
<td>Not clear</td>
<td>Plasma exchange</td>
</tr>
</tbody>
</table>

**Table 3** Neurological diseases for which there are only case reports describing benefit from IVIg

<table>
<thead>
<tr>
<th>Disease</th>
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<tbody>
<tr>
<td>Stiff man syndrome</td>
</tr>
<tr>
<td>Cerebral vasculitis</td>
</tr>
<tr>
<td>Paraneoplastic neurological disorders</td>
</tr>
<tr>
<td>Lower motor neurone syndromes</td>
</tr>
<tr>
<td>Polymyositis</td>
</tr>
<tr>
<td>CNS lupus</td>
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<tr>
<td>Rasmussen’s encephalitis</td>
</tr>
<tr>
<td>Landau–Kleffner syndrome</td>
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<tr>
<td>West syndrome</td>
</tr>
<tr>
<td>Lennox–Gastaut syndrome</td>
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</tbody>
</table>
Guillain-Barré Syndrome and Kawasaki disease are the only neurological conditions licensed for IVIg treatment in the United Kingdom.

Consent
Explain the benefits and risks. For unlicensed use, give the patient an information sheet and obtain signed consent.

Infusion regimes
There are several preparations. Some are liquid and some powder that requires re-constitution. Some require storing in a refrigerator, others at room temperature. The manufacturer’s instructions should be followed for administration. The infusion should always start at a slow rate to allow for monitoring for adverse effects, especially anaphylaxis (see Table 4). The risks are greatest during the first 30 min. Regular observations are necessary throughout the infusion, so adequate nursing cover must be available.

In GBS, the standard regime is 0.4 g/kg/day for 5 days, although there is no evidence that giving the dose any more quickly or more slowly would be detrimental. For patients needing repeated courses, e.g. in CIDP, and who tolerate IVIg well, doses up to 2.0 g/kg can be given continuously over 24 h or as two separate doses of 1.0 g/kg on consecutive days, thus avoiding the need for an overnight stay. For repeated courses, the total dose may often be reduced to 1.0 g/kg or even 0.4 g/kg without loss of effect.

Frequency
Judging the timing and amount of IVIg for repeated courses in CIDP and multifocal motor neuropathy is difficult. Patients report deterioration of symptoms and fear a significant relapse. Placebo responses occur. Serial measurements of muscle strength and sensory impairment by the same clinician are helpful. It is exceptional for courses to be needed more often than every 4 weeks and many patients manage with courses every 6–12 weeks.

ADVERSE EFFECTS
Most of the adverse effects of IVIg are transient, mild, and respond to slowing the infusion rate (Table 4). Sometimes hydrocortisone and antihistamines may be needed. In children, interference with vaccine efficacy is an additional concern.

Because IVIg is a blood product, transmission of viral infection and Creutzfeldt-Jakob Disease is a theoretical concern. In practice this has never happened with currently marketed preparations.

HOW MUCH DOES IT COST?
In the United Kingdom, IVIg costs £18–22 per
gram, i.e. £2100–£3080 per 2.0 g/kg course for a 70 kg individual. This does not include the cost of hospital admission, nursing and medical staff. There have been few analyses of the cost-effectiveness of IVIg. With the exception of multifocal motor neuropathy, alternative treatments are available for all the conditions in which IVIg is now used. Where the alternative is plasma exchange, the difference in cost is marginal. Where the alternative is corticosteroids, the difference in cost is considerable, but patients may prefer IVIg to risking long-term Cushingoid side-effects.

THE FUTURE FOR IVIG

During the last 20 years, IVIg has become frequently used in neurological practice. Despite this, many questions about its optimal use remain. In GBS, where IVIg treatment is most accepted, studies need to be conducted of the amount and rate of dose, whether or not to treat ‘mild’ cases, and whether or not to give second or third treatment courses in ‘severe’ cases.

In chronic illnesses such as CIDP, where repeated courses of IVIg are needed, establishment of a home treatment programme, like that practiced in the Oxford region, would be desirable. In other diseases, such as multiple sclerosis and the diseases in Table 3, more evidence is needed before IVIg is adopted in practice. For rare diseases such as paraneoplastic disease and cerebral vasculitis, we will need multinational trials.

Investigating the mechanism of action of IVIg would be worthwhile in each disease. If the mechanism were understood, simpler, more specific and perhaps less expensive therapies could be targeted at the crucial component of the immune system, perhaps induction of the inhibitory Fc gamma II receptor (Samuelsson et al. 2001). In the meantime, pharmaceutical companies need to overcome present difficulties with supplying sufficient IVIg for national and international needs. The difficulty in the UK is compounded by the regulation that prevents sourcing IVIg from plasma from countries with variant Creutzfeldt-Jakob Disease.

Finally, investigation of the cost-benefit of IVlg should inform the debate and form the basis of national guidelines on its use.

REFERENCES


