

THERAPEUTIC INTERVENTION

Intravenous immunoglobulin – how to use it

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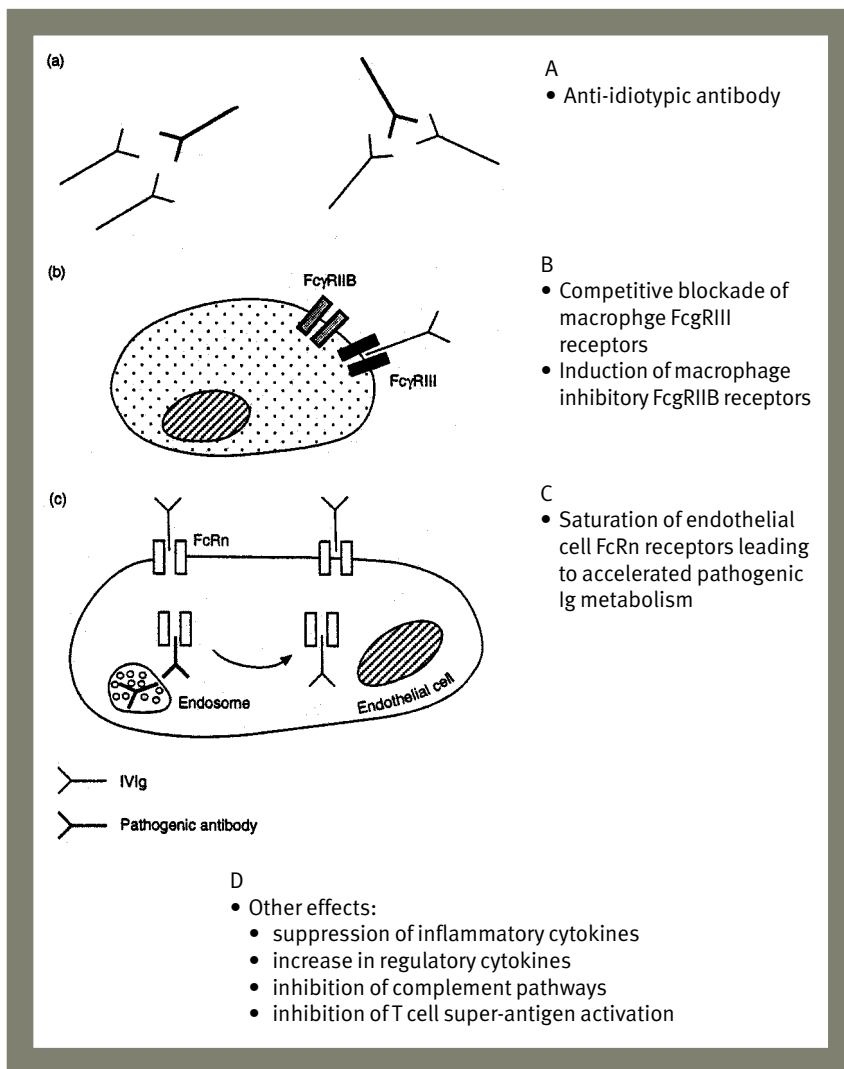
WHAT IS IT?

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).

Figure 1 Possible mechanisms of action of IVIg

**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).

Disease	When to give IVIg	Alternative treatment
Guillain–Barré Syndrome	Within two weeks if severe	Plasma exchange
Multifocal motor neuropathy	If significant disability	None
Kawasaki disease	At diagnosis	Corticosteroids

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

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.

Disease	First line treatment	Alternative
Chronic inflammatory demyelinating polyneuropathy (CIDP)	Corticosteroids	Plasma exchange
Lambert–Eaton myasthenic syndrome	Corticosteroids	Plasma exchange
Dermatomyositis	Corticosteroids	—
Paraproteinaemic demyelinating neuropathy	Not clear	Plasma exchange

Table 2 Neurological diseases in which IVIg is a treatment option

WHEN THE USE OF IVIG IS EXPERIMENTAL

Multiple sclerosis

Three randomised controlled trials have studied the effect of IVIg in relapsing–remitting multiple sclerosis (Wiles *et al.* 2001). Each showed a reduction in relapse rate, one showed a reduction in the number of MRI gadolinium enhancing lesions, and one showed a reduction in disability progression measured with the Kurtzke Expanded Disability Status Score. The initial results of these studies are similar to the results of treatment with beta interferon. However, the body of evidence is small and the introduction of IVIg for treating multiple sclerosis would be extremely expensive and lead to even greater problems with supply. It seems advisable to await more trial evidence. The effects in secondary progressive multiple sclerosis are not yet known.

Polymyositis

There is only anecdotal evidence to support the use of IVIg in polymyositis. In inclusion body myositis, IVIg has not been shown to be effective in randomised controlled trials and is not worth trying.

In all other conditions, the use of IVIg is experimental (Table 3). It should only be considered when alternative treatments have failed, with appropriate specialist advice, and with informed consent from the patient.

Stiff man syndrome
Cerebral vasculitis
Paraneoplastic neurological disorders
Lower motor neurone syndromes
Polymyositis
CNS lupus
Rasmussen's encephalitis
Landau–Kleffner syndrome
West syndrome
Lennox–Gastaut syndrome

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

WHEN TO BE CAUTIOUS

Renal failure has been reported in 5–10% of patients after IVIg and is more likely if there

Guillain-Barré
Syndrome and
Kawasaki disease
are the only
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is pre-existing renal impairment. All patients should be adequately hydrated before treatment. In cases with pre-existing renal impairment, a switch to a non-sucrose containing brand has been recommended, but a recent review has cast doubt upon the role of sucrose as a cause of renal failure (Levy & Pusey 2000).

Patients with IgA deficiency may possess antibodies to IgA that react with IgA in IVIg and cause anaphylaxis. Serum IgA levels should therefore be assayed before starting IVIg in all patients, especially those with immunodeficiency. In patients with IgA deficiency, it may be possible to use an IVIg preparation with exceptionally low IgA content. Anaphylaxis may occur even in patients without IgA deficiency. In GBS IgA deficiency is unlikely, and it may be reasonable to start treatment before the IgA result becomes available, owing to the need for rapid intervention.

Intravenous immunoglobulin should not be administered to anyone with a past history of a serious allergic reaction to IVIg. Although theoretically it should be avoided in pregnant or breast feeding women, it has been used to treat recurrent miscarriage.

Jehovah's witness patients may object to the use of blood products on religious grounds. Other patients may object to the risk of blood products where alternatives exist.

HOW TO GIVE IT

Routine checks

Before treatment, check the full blood count, renal and liver function and serum immunoglobulin concentrations. Also complete diagnostic serological assays (e.g. anti-ganglioside antibodies). There are rare reports of stroke following IVIg, possibly due to hyperviscosity. In a patient likely to have a raised serum viscosity due to hypercholesterolaemia or hypergammaglobulinaemia, IVIg should be used with particular caution and given slowly (over 5 days, not 1 or 2) (Dalakas 1999). Because of the risks of renal failure, pancytopenia and deranged liver function, monitor the full blood count, renal and liver function after the infusions have been completed. If they become abnormal they should be monitored, treated, and if necessary taken into account when considering future IVIg courses.

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

Frequency	Adverse-effect
Common	Flushing
	Fever
	Myalgia
	Nausea
	Shaking
	Headache
Uncommon	Hypotension
	Urticaria
	Eczema
	Leukopaenia
Rare and serious	Acute renal failure
	Aseptic meningitis
	Cerebral infarction
	Myocardial infarction
	Pancytopenia
Very rare and serious	Anaphylaxis

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

Table 4 Adverse effects of intravenous immunoglobulin

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 IVIg should inform the debate and form the basis of national guidelines on its use.

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