ASSOCIATION OF BRITISH NEUROLOGISTS

GUIDELINES FOR THE USE OF INTRAVENOUS IMMUNOGLOBULIN IN NEUROLOGICAL DISEASES.

(REVISED JULY 2005)
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SUMMARY

A. The following recommendations are based on randomised controlled trials.

**Guillain-Barré syndrome.**
In adults and children seen within the first two weeks of symptoms with GBS of severity such that they are unable to walk unaided, we recommend IVIg. It is usually easier to give and has similar efficacy to plasma exchange, which in turn is more effective than supportive treatment alone. By extrapolation from the evidence in this group, IVIg may be considered for patients seen more than two weeks from onset, in those seen after that time or those with less severe disease who are still progressing, or patients with similar disorders such as the Miller Fisher syndrome. When improvement after IVIg is followed by an early recurrence (10%), or in those who remain severely affected after a first course, a second course may be considered, but this is not of proven value in either situation. The standard treatment regime of IVIg in GBS is 0.4g/kg daily for five days.

**Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).**
While IVIg is recommended for the treatment of CIDP, for reasons of cost and convenience steroids may be preferred as first-line treatment, and IVIg reserved for treatment failures or where steroid side-effects are troublesome or anticipated. Patients with pure motor CIDP may deteriorate after steroids and for them IVIg is the first choice. The patient should be informed of the advantages and disadvantages of IVIg and steroids and involved in the choice of treatment. See text for dose.

**Multifocal motor neuropathy (MMN).**
IVIg is the only safe treatment which has been shown to work in patients with MMN and is recommended in those who have significant disability. The dose and monitoring are as for CIDP.

**Paraprotein-associated demyelinating neuropathy.**
IVIg is a treatment option in patients with a severe neuropathy associated with an IgM paraprotein or where a paraprotein-associated demyelinating neuropathy resembles CIDP. Doses, monitoring and the need for repeated courses are as for CIDP.

**Myasthenia gravis.**
The use of IVIg is justified to treat acute exacerbations of myasthenia. It is more convenient and possibly safer than plasma exchange. Evidence is lacking to support IVIg use in stable myasthenia or as a long term therapy.

**Lambert-Eaton myasthenic syndrome (LEMS).**
The short term use of IVIg may be appropriate in non-cancer LEMS patients where 3,4-DAP has been unsuccessful, but there is insufficient evidence to justify long term use.

**Dermatomyositis and polymyositis.**
IVIg has a role in dermatomyositis in adults and children which is refractory to other treatments. There is insufficient evidence supporting use as primary or long-term treatment. In severe refractory polymyositis there may also be a place for IVIg but this is not substantiated and in these cases reinvestigation should first consider the possibility of inclusion body myositis.
B. In the following conditions IVIg might be considered as a treatment option under special circumstances as discussed in the text.

Acute disseminated encephalomyelitis
Central nervous system vasculitis
Intractable epilepsy
Multiple sclerosis
Neuromyotonia
Paraneoplastic disorders
Potassium channel antibody-associated, non-neoplastic limbic encephalitis
Stiff person syndrome

C. In these conditions there is no evidence to support the use of IVIg.

Chronic fatigue syndrome
Inclusion body myositis
Peripheral neuropathies other than those described above
1. **Scope of guidelines.**

These guidelines were originally published in March 2002 as the consensus view of an ABN working group (see Appendix 5) on the use of intravenous immunoglobulin (IVIg) in neurological disorders. They drew on the thoroughly referenced specialist review undertaken by Wiles et al. (2002), which contains comprehensive level of evidence data. Other useful reviews were those of Dalakas (1999) and Latov et al. (2001). The guidelines have now been updated by the working group so as to summarise the current evidence for clinical effectiveness and give recommendations for use in each disease category. We performed an up-to-date search of systematic reviews and randomised trials in the Cochrane Library, as well as referring to our own personal collections. We have also drawn on a more recent review (Jolles et al., 2005) and recommend the very detailed consensus document of Kornberg et al. (2004). All described methodological details and numerical data were checked by at least two members of the working group and the guidelines overall are a consensus statement. Mechanisms, products, safety and administration regimes are evaluated, as well as discussion of cost effectiveness and patient concerns. The guidelines are intended to provide advice and support to clinicians and budget holders involved in treating patients with IVIg. They may complement local guidelines.

2. **Introduction.**

IVIg is licensed only for use in Guillain-Barré syndrome (GBS), immunoglobulin deficiency and Kawasaki disease but is widely used in many other neurological conditions. For some, there is a sound evidence base but IVIg has been used speculatively in other neurological diseases with only anecdotal support from the literature. The high cost of IVIg has led to rationing, and there have also been justified concerns regarding its safety and future availability. A single, standard 2.0g/kg course of IVIg costs approximately £3500 and this treatment has become the major drug expenditure item in many neurology units. Most neurologists will have confidence and adequate expertise when using IVIg in, for example, GBS, but for disorders in which IVIg use is considered in the absence of a supportive systematic review or randomised controlled trial(s), non-specialist neurologists may consider it wise to seek advice from a colleague with experience in the condition before starting treatment.

3. **Mechanisms of action.**

The effectiveness of IVIg as an immunomodulator is probably dependent on a range of mechanisms including

- Binding to inhibitory Fc receptors (FcγRIIb) and activating Fc receptors (FcγRI and FcγRIII).
- anti-cytokine effects
- inhibition of complement activation
- enhanced clearance of endogenous pathogenic auto-antibodies via the FcRn receptor
- neutralisation of auto-antibodies
- neutralisation of super antigens
- down regulation of T or B cell function
It is likely that different mechanisms are of primary importance in individual disorders since the various neurological diseases which are treated with IVIg do not have a uniform immune pathogenesis. For a summary see Wiles et al. (2002) and Jolles et al (2005).

4. **IVIg in neurological disorders** (see also summary Appendix 2).

(i). **Guillain-Barré syndrome.**

A meta-analysis of five randomised controlled studies including 536 mostly adult non-ambulant participants seen within the first two weeks, found no significant differences between IVIg or the gold standard of plasma exchange (Hughes et al., 2005). In children limited evidence from three studies including a total of 75 participants suggests that IVIg significantly hastened recovery compared with supportive care. Therefore, in adults and children seen within the first two weeks with GBS of severity such that they are unable to walk unaided, we recommend IVIg. It is usually easier to give and has similar efficacy to plasma exchange, which in turn is more effective than supportive treatment alone (Raphael et al., 2001). By extrapolation from the evidence in this group, IVIg may be considered for patients seen after two weeks from onset, in those seen after that time or those with less severe disease who are still progressing, or patients with similar disorders such as the Miller Fisher syndrome. When improvement after IVIg is followed by an early recurrence (10%), or in those who remain severely affected after a first course, a second course may be considered, but this is not of proven value in either situation. The standard treatment regime of IVIg in GBS is 0.4g/kg daily for five days.

(ii). **Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).**

A Cochrane review of five randomised controlled trials involving 113 patients with CIDP confirmed significantly more short term improvement in disability with IVIg than placebo (van Schaik et al., 2005). Crossover trials showed no significant differences comparing IVIg with plasma exchange (Dyck et al., 1994) or oral prednisolone (Hughes et al., 2001). The cost per quality adjusted life year (QALY) of IVIg compared with oral prednisolone is high (McCrone et al., 2003). While IVIg is recommended for the treatment of CIDP, for reasons of cost and convenience steroids may be preferred as first-line treatment, and IVIg reserved for treatment failures or where steroid side-effects are troublesome or anticipated. Patients with pure motor CIDP may deteriorate after steroids (Donaghy et al., 1994) and for them IVIg is the first choice. The patient should be informed of the advantages and disadvantages of IVIg and steroids and involved in the choice of treatment. The initial course is 0.4 g/kg daily for five days. The effect of IVIg wears off after 2-12 (mean of four) weeks. Repeated courses titrated to individual needs are usually effective, with attention to both the frequency and amount of subsequent interventions. The dose can usually be reduced to 1.0 g/kg or less and can be given in one to two days to reduce the time in hospital. Under treatment might contribute to disease progression. Over treatment may be avoided by skilled monitoring. Placebo responses are known to occur and n-of-1 trials may help to identify the need for continued treatment (Hankey et al., 1994).
(iii). Multifocal motor neuropathy (MMN).

A systematic review of four randomised trials of IVIg including a total of 34 participants (van Schaik et al., 2005) showed a significant short-term improvement in strength and a non-significant improvement in disability compared with placebo. This evidence supports the conclusion from observational studies and expert opinion that IVIg produces short-term benefit. Follow-up studies confirm continued response to repeated courses for several years but some progression may still occur (Nobile-Orazio et al., 2005; Van Den Berg et al., 2002) unless high doses are used (Vucic et al., 2004). **IVIg is the only safe treatment which has been shown to work in patients with MMN and is recommended in those who have significant disability. The dose and monitoring are as for CIDP.**


In IgM paraproteinaemic neuropathy a randomised controlled crossover trial in 11 patients showed short term benefit from IVIg in only three (Dalakas et al., 1996) but another trial in 22 patients showed a significant reduction in average disability compared with placebo (Comi et al., 2002). There is no information about long term effects. IVIg in neuropathy associated with other paraproteins has not been studied in randomised controlled trials. However, the demyelinating neuropathy associated with a “benign” paraprotein may resemble CIDP. There is no reliable information about the effect of IVIg on the neuropathy seen with multiple myeloma or solitary plasmacytoma. **IVIg is a treatment option in patients with a severe neuropathy associated with an IgM paraprotein or where a paraprotein-associated demyelinating neuropathy resembles CIDP. Doses, monitoring and the need for repeated courses are as for CIDP.**

(v). Other peripheral neuropathies.

IVIg has been used in vasculitic neuropathy and proximal diabetic neuropathy, reported as individual cases (Donofrio 2003; Dalakas 2004a; Dalakas 2004b), but there is insufficient information on which to base recommendations for these and other neuropathies.

(vi). Myasthenia gravis.

A Cochrane Review of IVIg for myasthenia found four randomised controlled trials (147 participants in total), all investigating short-term benefit (Gajdos et al., 2003). The first was a randomised trial in 87 patients with acute exacerbation given IVIg 0.4g/kg daily for five days, or plasma exchange. The second was a randomised cross-over trial, in which 12 people with moderate or severe myasthenia were treated with IVIg or plasma exchange. In the third, 15 patients with mild or moderate myasthenia received IVIg or placebo. The fourth evaluated 33 people with moderate exacerbations of myasthenia who received IVIg or methylprednisolone. None of these trials found statistically significant differences between treatments, but the first found lower complication rates with IVIg. A retrospective review of 54 episodes of myasthenic respiratory crisis showed a better ventilatory outcome with plasma exchange than IVIg but with a higher complication rate (Qureshi et al., 1999). **The use of IVIg is justified to treat acute exacerbations of myasthenia. It is more convenient and possibly safer than plasma exchange. Evidence is lacking to support IVIg use in stable myasthenia or as a long term therapy.**

A Cochrane review (Maddison and Newsom-Davis, 2003) found one randomised crossover trial comparing IVIg 1g/kg daily for two days versus placebo in nine non-cancer LEMS patients. It noted a significant improvement in myometric limb strength and a non-significant improvement of CMAP amplitude with IVIg. The response peaked at two to four weeks and declined by eight weeks. The review also found two trials of 3,4-diaminopyridine versus placebo, which concluded that active treatment improved muscle strength scores and CMAP amplitudes but no direct comparison of IVIg and 3,4-DAP was available. A limited cost benefit estimation strongly favoured 3,4-DAP. There was insufficient data to comment on the use of IVIg in LEMS patients with cancer. The short term use of IVIg may be appropriate in non-cancer LEMS patients where 3,4-DAP has been unsuccessful, but there is insufficient evidence to justify long term use.

(viii). Dermatomyositis and polymyositis.

A Cochrane review (Choy et al., in press) identified one randomised controlled trial using IVIg in adult-onset dermatomyositis (Dalakas et al., 1993) in which fifteen patients received IVIg 2 g/kg or placebo monthly. There was a statistically significant improvement in strength after three months even in those with severe weakness. An uncontrolled study of IVIg in nine patients with juvenile dermatomyositis showed improvement in each case (Sansome and Dubowitz, 1995). There are no controlled studies of IVIg in polymyositis. IVIg has a role in dermatomyositis in adults and children which is refractory to other treatments. There is insufficient evidence supporting use as primary or long-term treatment. In severe refractory polymyositis there may also be a place for IVIg but this is not substantiated and in these cases reinvestigation should first consider the possibility of inclusion body myositis.

(ix). Inclusion body myositis.

Randomised controlled trials (most recently Dalakas et al., 2001) have failed to demonstrate a clinical response to IVIg in IBM and therefore its use is not recommended in this disorder.

(x). Stiff person syndrome.

Anecdotal reports of successful treatment have been supported by a randomised controlled crossover trial in 16 patients with associated anti-GAD65 antibodies, in whom a beneficial response in stiffness scores and clinical features was seen with IVIg 1 g/kg daily for two days on a monthly cycle over three months. The improvement was sustained for six weeks to one year (Dalakas et al., 2001). Where other measures have failed, IVIg may be considered in patients with stiff person syndrome.

(xi). Multiple sclerosis.

A Cochrane review of two randomised trials of IVIg versus placebo in 188 patients with relapsing remitting disease concluded that it may reduce the relapse rate but there were inadequate MRI and disability data to substantiate a disease modifying effect (Gray et al., 2003). Consistent with an effect on relapses, a single randomised trial of IVIg versus placebo in 91 patients within six weeks of a first demyelinating episode suggestive of MS, showed a significantly reduced relative risk (by about 60%) of having a second attack over a year (Achiron et al., 2004). The effect on sustained disability progression has not been
measured in the relapsing remitting trials, but no reduction was seen in a randomised trial of IVIg versus placebo in 318 patients with secondary progressive disease (Hommes et al., 2004). A lack of effect on MRI lesion load and relapses in this latter study is unexplained. There are no published data on the effects of IVIg in primary progressive MS. Despite anecdotal case reports and series, no effect was demonstrated on established weakness or persistent loss of visual acuity in two randomised trials of IVIg versus placebo including 67 and 55 patients respectively (Noseworthy et al., 2000; Noseworthy et al., 2001).

*It is recommended that in multiple sclerosis IVIg should not be used routinely although it may have a role in patients with severe, frequent relapses for whom other disease modifying agents are contraindicated.*

(xii). Acute disseminated encephalomyelitis.

IVIg has been considered in patients who have failed to respond to high dose steroids, with some support from anecdotal reports in children and adults, for example Sahlas et al. (2000). This advice is based on the potential severity of this disease and the difficulty in performing randomised trials. *A course of treatment using 0.4 g/kg daily for five days may be considered, based on the dose used in the case reports.*

(xiii). Vasculitic disorders of the central nervous system.

In Kawasaki disease, *IVIg is the treatment of choice,* based on good evidence from randomised controlled trials (Newburger et al., 1986; Newburger et al., 1991; Oates-Whitehead et al., 2003). There is evidence from single randomised controlled trials supporting IVIg use in the non-neurological aspects of small vessel vasculitis and in renal lupus, as well as an unsubstantiated recommendation in antiphospholipid syndrome, but *it cannot be advocated for routine use in isolated neurological manifestations of such conditions without reliable data* (Wiles et al., 2002). Other disorders such as Hashimoto’s encephalopathy and giant cell arteritis usually respond to conventional treatments and *the routine use of IVIg is not recommended.*

(xiv). Paraneoplastic disorders.

These include paraneoplastic encephalomyelitis, limbic encephalitis, cerebellar degeneration, peripheral neuropathy and opsoclonus-myoclonus. Dermatomyositis and LEMS are considered above. There are no randomised controlled trials of IVIg. Isolated case reports and small series show conflicting results. Generally the CNS paraneoplastic syndromes appear to respond less well than peripheral disorders (Darnell and Posner, 2003). Since paraneoplastic conditions may stabilise or even improve spontaneously (Byrne et al., 1997), anecdotal reports are impossible to interpret. *The rarity of these syndromes makes randomised studies impractical but IVIg may have a role where conventional treatments have failed.*

(xv). Potassium channel antibody-associated, non-neoplastic limbic encephalitis.

In this recently identified syndrome, Vincent et al (2004) described 10 patients treated with a variety of immunomodulatory interventions including IVIg, as well as with plasma exchange and steroids, with encouraging results. There are no randomised controlled trials of IVIg in this condition. *The severe and progressive nature of this condition justifies a trial of IVIg if other treatments have failed.*
(xvi). Epilepsy.

Uncontrolled observational studies in a total of about 350 patients with intractable epilepsy (mostly children, many of whom had West or Lennox-Gastaut syndromes), suggested a seizure reduction of between a third to a half and some improvements in behaviour (Van Engelen et al., 1994), but the only randomised trial (van Rijckevoorsel-Harmant et al., 1994) in 61 patients did not show a statistically significant difference between IVIg and placebo. Variable responses in a few cases of Landau-Kleffner syndrome (Mikati and Lagae, 1998) and small case series of Rasmussen’s encephalitis (for example Leach et al., 1999) do not give clear evidence in support of IVIg. There is no systematic review of the use of IVIg in epilepsy syndromes. In any of these conditions, IVIg use should preferably be confined to randomised controlled trials. The severe, progressive nature of these intractable epilepsies, and the rarity of some of the syndromes, makes it reasonable to consider the use of IVIg in n-of-1 trials in cases where other treatments have failed.

(xvii). Neuromyotonia.

Since there are anecdotal reports of improvement, no change or worsening with IVIg (Alessi et al., 2000; van den Berg et al., 1999; Ishii et al., 1994) there is no consistent evidence to support its use in this disorder.

(xviii). Chronic fatigue syndrome.

There have been four randomised controlled trials of IVIg versus placebo in a total of 249 people with chronic fatigue syndrome which have been reviewed critically by Bagnall et al. (2002) and Reid et al. (2002). The outcome measures varied, but in general were subjective and liable to observer bias. Adverse effects of treatment were common. IVIg should not be used in the management of chronic fatigue syndrome.

5. Adverse effects.

These are classified in three broad categories. See Pierce and Jain (2003), Wiles et al. (2002), Latov et al. (2001) and Dalakas (1999) for referenced reviews.

(i). Immediate infusion-related.

Mild adverse effects of headache, fever, chills, flushing, and backache are common with high dose infusions, and generally abate on reducing the rate of infusion. Anaphylaxis is very rare and is associated with anti-IgA antibodies in some patients with total IgA deficiency (defined as <0.05 g/l). To minimise the risk in patients in whom treatment is essential it would be prudent to select an IVIg product containing a low concentration of IgA in those with high titre anti-IgA antibodies (see Appendix 3). Anaphylaxis is treated by immediately stopping the infusion, giving adrenaline 0.5 ml of 1:1000 solution (0.5 mg) intramuscularly, and also chlorpheniramine 10-20 mg and hydrocortisone 100-500 mg, both by slow intravenous injection.
(ii). Dose-related.

The infusion of high doses of IVIg (2 g/kg) either as a single dose or divided over two to five days may result in adverse effects which are only rarely seen at lower doses.

(a) Haematological.

Mild to moderate reversible neutropenia and lymphopenia are common but do not represent a problem. A modest rise in plasma viscosity is also common and usually well tolerated, but in those with vascular disease or pre-existing elevated viscosity there is a small risk of cerebral or myocardial infarction. Rarely, acute Coombs positive haemolysis has been reported.

(b) Renal.

The carbohydrate stabilisers contained within IVIg may cause osmotic renal tubular damage in patients with renal disease or diabetes. This may occur with any preparation at high dose but especially in those having a high sucrose concentration. Extra caution is therefore advised in patients with pre-existing renal disease. IVIg treatment in patients with cryoglobulinaemia has caused renal failure; patients with IgM paraproteins should be screened for cryoglobulins. A dilutional hyponatraemia may occur.

(c) Aseptic meningitis.

This occurs in <5% of recipients of high dose IVIg and the risk is higher in patients who have a history of migraine. Prophylaxis with betablockade may be considered.

(d). Dermatological.

A range of skin reactions have been reported including urticaria, eczema, erythema multiforme, ill-defined maculopapular rash and leucocytoclastic vasculitis.

(iii). Transmission of infective agents.

HIV and hepatitis B have not been transmitted by IVIg treatment and stringent precautions should avoid this in the future. The hepatitis C virus is known to have been transmitted on ten occasions. The last outbreak in the 1990’s led to the adoption of additional anti-viral safety measures, which it is hoped will be effective. Recent reports of the transmission of variant CJD by blood transfusion (Peden et al., 2004; Llewelyn et al., 2004) has heightened awareness of the theoretical possibility of prion transmission by IVIg. Leucodepletion and the use of plasma from countries free from BSE are measures designed to minimise the risk.


In neurological diseases in which repeated courses of IVIg may be necessary, there should be objective evidence of a significant response followed by a documented deterioration, before second or subsequent courses are considered. The improvement should be measured using a validated scale and the clinician should be satisfied that it is not due to a placebo response. In case of doubt, placebo controlled n-of-1 trials should be considered. Attempts should be made to reduce the dose and frequency of treatment to the lowest
effective amount. Advice from a recognised expert in treatment of the particular disorder may be useful in dose titration and especially in cases of rare or unfamiliar disease. Experience suggests that a single infusion of 0.4-1.0 g/kg every 3-6 weeks may suffice in some disorders, for example in MMN. IVIg treatment is an excellent topic for a department audit, which provides an opportunity to confirm that responsible use and monitoring are in place. For patients receiving a single course, it is sufficient to check pre- and post-treatment the liver and renal function and full blood count, as well as the pre-treatment IgA level. It may be necessary to begin treatment in GBS before the IgA level is available, and if possible a product should therefore be chosen with a low IgA content. The haematology and biochemistry should be rechecked before subsequent infusions. Immunologists who are using IVIg in immunodeficiency states advise that hepatitis C serology should be checked before the first treatment and at intervals thereafter. This advice has not been generally applied in the treatment of neurological diseases, but it may be sensible to store serum for future reference, or alternatively to check hepatitis C antibody initially and the antigen at subsequent courses, for instance at annual intervals. During an IVIg infusion all patients should have close monitoring of the temperature, pulse, blood pressure and respiratory rate. The greatest danger of anaphylaxis is in the first 30 minutes of the infusion. A check list for the use of IVIg is provided in Appendix 4.


There are recognised adverse effects with IVIg use, and absolute safety in terms of viral or prion carriage cannot be guaranteed. Moreover, it is licensed in neurology only for the treatment of GBS and Kawasaki syndromes. Enquiry amongst GBS and CIDP patient groups (R.Price, personal communication) indicated that in few cases had consent been obtained or written information provided before treatment (10%), although most patients circulated expressed a desire to have had more information. A generic information sheet and consent form is attached (Appendix 1) which may be modified for local use. Its use is recommended particularly when IVIg is given in unlicensed indications. Examples of disease-specific information sheets are also attached.


There have been few published analyses of cost-effectiveness in IVIg used for neurological conditions. One study in GBS suggested that the cost of IVIg was 60% more than plasma exchange but this study depended heavily on the basic cost of each (Nagpal et al., 1999); another in CIDP showed that IVIg was much more costly than oral prednisolone (McCrone et al., 2003). These studies excluded other factors that may have favoured IVIg and recognised the need to take a broad, long-term view, including assessment of side effects, when judging cost-effectiveness of IVIg and alternative treatments, and using this as an argument to condone or prohibit a treatment. However, they help to emphasise the importance of making certain that an expensive and potentially scarce product is used wisely.

9. Products and administration regimens.

The costs of IVIg preparations are difficult to compare as suppliers negotiate variable prices with individual pharmacies. Although no IVIg preparation has been shown to be superior to another in terms of therapeutic effects, it would be unwise to consider all IVIg preparations as a generic product in view of differences in opsonic activity, Fc receptor
function and complement fixation. For these reasons and the potential difficulty in tracking any outbreak of IVIg-associated viral transmission, it would be prudent for patients requiring long term treatment to be maintained on the same IVIg product. In selecting a product for an individual patient, attention is directed to differences in IgA concentrations and the type of carbohydrate stabiliser since this has a bearing on adverse effects. The range of products available and some details of their constitution are summarised in Appendix 3.

Regimens used to administer high dose IVIg vary between 0.4 g/kg daily for five days to a single infusion of 2 g/kg. These empirical amounts are based on experience in treating thrombocytopenic purpura and Kawasaki disease. There is some evidence to suggest that in Kawasaki disease the single infusion is more effective (Newburger et al., 1991), and it appears to be safe in patients with normal cardiac and renal function. It is uncertain whether this can be extrapolated more generally in neurological disorders.

11. References.


Kornberg A and the Asia Pacific IVIg Advisory Board (2004). Bringing consensus to the use of IVIg in neurology – Expert consensus statements on the use of IVIg in neurology. A.Kornberg (ed); Asia-Pacific IVIg Advisory Board Inc., Aus.


Appendix 1 : Information sheet and consent form.

Information sheet on intravenous immunoglobulin (IVIg) for neurological diseases.

Intravenous immunoglobulin (IVIg) is a blood product made from pooled plasma from many different people.

With the exception of Guillain-Barré syndrome, IVIg is not licensed for use in the treatment of neurological disorders but there is evidence that it is a useful treatment in several other conditions, including chronic inflammatory demyelinating peripheral neuropathies and multifocal motor neuropathy. IVIg is now an accepted treatment for these and some other conditions in most European countries and in the USA.

The way that IVIg works in these conditions is not fully understood but it does block harmful antibodies and influence other immunological factors.

IVIg is given through an intravenous infusion at a rate, dose and time which is individualised for each patient. If the treatment is successful it may need to be repeated several or even many times. At present IVIg is usually only given in hospital.

As with all treatments, side effects can occur with IVIg. These are usually mild and do not require the treatment to be stopped. Transient side effects that usually respond to changes in the rate of administration of the dose include headache and high blood pressure. A rash can sometimes develop. IVIg does thicken the blood slightly so particular caution is practised in patients with previous heart disease, strokes or blood clots. Rarely there may be more serious side effects which include allergic reactions, kidney problems, more severe headache and a form of non-infective meningitis.

As IVIg is a blood product, the blood from which it is made is checked for all known transmissible agents that can be screened (e.g., hepatitis A, B and C, and HIV). Although stringent steps are taken to avoid virus transmission, there remains a remote theoretical risk of such an event. Rare cases of variant Creutzfeldt-Jakob disease have been transmitted by blood transfusion. The theoretical risk that IVIg may transmit vCJD has been greatly minimised by the use of plasma from countries free of the disease. At present there is no test to see if vCJD is present in blood.

Consent form for intravenous immunoglobulin (IVIg) treatment in neurological diseases.

I have discussed the need for IVIg treatment with my doctor. I have read the information sheet on IVIg use in neurological diseases. I understand why this treatment is being given to me and I understand the potential side effects of the treatment.

I consent to treatment with IVIg.

Signed (patient) or next of kin: Date:

Witnessed by doctor: Date:
Information sheet on intravenous immunoglobulin (IVIg) for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

What is IVIg?

Intravenous immunoglobulin is a blood product made from pooled plasma from many different people. IVIg is not licensed for treating CIDP but convincing evidence supports its use. IVIg is an accepted treatment for CIDP in most European countries and in the USA. We do not know exactly how it works but it blocks harmful antibodies and other immune factors. We give IVIg through an intravenous infusion. We work out the dose and rate of infusion individually for each patient. A common regimen is one five-hour infusion daily on five consecutive days. If the treatment works we may need to repeat it several or even many times in hospital.

What are the side effects?

As with most treatments, IVIg may cause side effects. These are usually mild and do not stop treatment. Transient side effects, like headache and high blood pressure, usually respond to changes in the rate of infusion. A rash sometimes develops. More serious side effects are rare. They include allergic reactions, kidney problems, stroke or more severe headache. IVIg thickens the blood slightly so particular care is needed in patients with previous heart disease, strokes or blood clots.

Might IVIg transmit infections?

The blood for making IVIg is checked for all known detectable viruses (for example hepatitis A, B and C, and the AIDS virus HIV). Despite this, and extensive purification of IVIg, virus transmission remains a remote theoretical risk. Variant Creutzfeld Jakob disease is another transmissible disease, but there is no evidence that IVIg transmits it. There is no test for variant Creutzfeld Jakob disease in blood.

What are the alternatives?

The main alternative to IVIg is steroid treatment. This is given as tablets for several weeks, months or even years. Steroids may cause weight gain, mooning of the face, high blood pressure, sugar diabetes, thinning of the bones (osteoporosis), cataracts and other side effects. Steroids are not suitable for all patients with CIDP. Another possible treatment is plasma exchange, which involves having two tubes inserted, one into each arm, or one large tube into the neck or groin. The tubes are connected to a machine that replaces your blood plasma with artificial plasma. The exchange lasts about 3 hours and is usually done on 5 days over a 10 day period. There is a slight risk of bruising at the site of entry of the tubes, low blood pressure and bleeding. Plasma exchange lowers your resistance to infection and risks introducing bacterial infection. There is a very remote theoretical risk of transmitting virus infection.

Other treatments include immunosuppressive drugs that take much longer to act than IVIg. They have other side effects, especially bone marrow suppression, causing increased liability to infections. Sometimes we combine these treatments with IVIg to get the maximum benefit.
Information sheet on intravenous immunoglobulin (IVIg) for Guillain-Barré syndrome (GBS)

What is IVIg?

Intravenous immunoglobulin is a blood product made from pooled plasma from many different people. It hastens recovery from GBS. It is licensed for use in severe GBS in Great Britain. We do not know exactly how it works but it does block harmful antibodies and other immune factors. We give IVIg through an infusion into a vein. You usually get one infusion daily for five consecutive days. The amount given depends on your weight. The infusion lasts about six hours depending on the amount you need.

What are the side effects?

IVIg may cause side effects. These are usually mild and do not stop treatment. Most, like headache and high blood pressure, usually respond to slowing the infusion. A rash sometimes develops. More serious side effects are rare. They include allergic reactions, kidney problems, stroke or more severe headache. IVIg thickens the blood slightly so particular care is needed in patients with previous heart disease, strokes or blood clots.

Might IVIg transmit infections?

The blood for making IVIg is checked for all known detectable viruses (for example hepatitis A, B and C, and the AIDS virus HIV). Despite this, and extensive purification of IVIg, virus transmission remains a remote theoretical risk. Variant Creutzfeld Jakob disease is another transmissible disease, but there is no evidence that IVIg transmits it. There is no test for variant Creutzfeld Jakob disease in blood.

What are the alternatives?

The only alternative to IVIg is plasma exchange. This involves having two tubes inserted, one into each arm, or one large tube into the neck or groin. The tubes are connected to a machine that replaces your blood plasma with artificial plasma. The exchange lasts about 3 hours and is usually done on 5 days over a 10 day period. There is a risk of bruising where the tubes go into the skin and slight risk of low blood pressure and bleeding. Plasma exchange lowers your resistance to infection and risks introducing bacterial infection. There is a very remote theoretical risk of transmitting virus infection. Plasma exchange is much less comfortable and convenient than IVIg and slightly more likely to cause side-effects.
Information sheet on intravenous immunoglobulin (IVIg) for multifocal motor neuropathy (MMN)

What is IVIg?

Intravenous immunoglobulin is a blood product made from pooled plasma from many different people. IVIg is not licensed for treating MMN but convincing evidence supports its use. IVIg is an accepted treatment for MMN in most European countries and in the USA. We do not know exactly how it works but it blocks harmful antibodies and other immune factors. We give IVIg through an intravenous infusion. We work out the dose and rate of infusion individually for each patient. A common regimen is one five-hour infusion daily on five consecutive days. If the treatment works we may need to repeat it several or even many times in hospital.

What are the side effects?

As with most treatments, IVIg may cause side effects. These are usually mild and do not stop treatment. Transient side effects, like headache and high blood pressure, usually respond to changes in the rate of infusion. A rash sometimes develops. More serious side effects are rare. They include allergic reactions, kidney problems, stroke or more severe headache. IVIg thickens the blood slightly so particular care is needed in patients with previous heart disease, strokes or blood clots.

Might IVIg transmit infections?

The blood for making IVIg is checked for all known detectable viruses (for example hepatitis A, B and C, and the AIDS virus HIV). Despite this, and extensive purification of IVIg, virus transmission remains a remote theoretical risk. Variant Creutzfeld Jakob disease is another transmissible disease, but there is no evidence that IVIg transmits it. There is no test for variant Creutzfeld Jakob disease in blood.

What are the alternatives?

There is no proven alternative treatment to IVIg for MMN. Steroids are not suitable for patients with MMN and may make it worse. Treatment with immunosuppressive drugs has been tried and thought effective in some patients. However it takes much longer to act than IVIg and has not been proved to be effective. Immunosuppressive drugs have side effects, especially bone marrow suppression, causing increased liability to infections and to cancer.
Appendix 2: Projected use of IVIg in neurological conditions based on ABN recommendations.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Frequency</th>
<th>IVIg courses</th>
<th>Proportion of cases treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBS</td>
<td>Incidence approx. 2/100000/annum</td>
<td>Single or occasionally second course</td>
<td>Most cases</td>
</tr>
<tr>
<td>CIDP</td>
<td>Prevalence about 5/100000</td>
<td>Repeated courses @ 2-12 weeks</td>
<td>&lt;50% cases</td>
</tr>
<tr>
<td>Paraprotein associated neuropathy</td>
<td>Prevalence about 1/100000</td>
<td>Repeated courses @ 4-12 weeks</td>
<td>&lt;10% cases</td>
</tr>
<tr>
<td>MMN</td>
<td>Prevalence about 1/100000</td>
<td>Repeated courses @ 2-12 weeks</td>
<td>At least 50% cases</td>
</tr>
<tr>
<td>Myasthenia</td>
<td>Prevalence 14/100000</td>
<td>Single course to induce remission</td>
<td>Rarely necessary</td>
</tr>
<tr>
<td>Non-cancer LEMS</td>
<td>N/K – rare</td>
<td>Single or repeated courses</td>
<td>&lt; 50% cases</td>
</tr>
<tr>
<td>Refractory dermatomyositis (?polymyositis)</td>
<td>N/K</td>
<td>Repeated courses @ 4-12 weeks</td>
<td>&lt;10% of total cases</td>
</tr>
<tr>
<td>Stiff person syndrome</td>
<td>N/K – rare</td>
<td>Possibly monthly cycles</td>
<td>Approx. 50% cases</td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>N/K – rare</td>
<td>Single course</td>
<td>&lt;25% cases</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>N/K – very rare</td>
<td>Repeated cycles</td>
<td>Most cases</td>
</tr>
<tr>
<td>Specified refractory epileptic syndromes</td>
<td>N/K – rare</td>
<td>Repeated cycles</td>
<td>Infrequent use in selected cases in a small number of special centres</td>
</tr>
</tbody>
</table>
## Appendix 3: IVIG preparations in the UK

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Manufacturing procedure</th>
<th>Additional anti-viral step</th>
<th>IgA content mg/L</th>
<th>Carbohydrate stabiliser</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flebogamma *</td>
<td>Liquid</td>
<td>PEG Precipitation DEA sephadex</td>
<td>Yes</td>
<td>4.3</td>
<td>D-Sorbitol</td>
</tr>
<tr>
<td>Gammagard-SD *</td>
<td>Powder</td>
<td>DEA sephadex</td>
<td>Yes</td>
<td>0.4 - 1.9</td>
<td>Glucose Glycine</td>
</tr>
<tr>
<td>Octagam</td>
<td>Liquid</td>
<td>pH4</td>
<td>Yes</td>
<td>&lt;100</td>
<td>Maltose</td>
</tr>
<tr>
<td>Scottish National BTS</td>
<td>Powder</td>
<td>pH4</td>
<td>No</td>
<td>920</td>
<td>Sucrose</td>
</tr>
<tr>
<td>Sandoglobulin*</td>
<td>Liquid 12%</td>
<td>pH4</td>
<td>Nanofiltration</td>
<td>&lt;10</td>
<td>None</td>
</tr>
<tr>
<td>Vigam-S *</td>
<td>Liquid</td>
<td>Ion-exchange chromatography</td>
<td>Yes</td>
<td>5</td>
<td>Sucrose</td>
</tr>
</tbody>
</table>

* Preparations with low IgA content.

Note that while the manufacturing process for all IVIg products has proven in-built anti-viral procedures, some manufacturers have introduced an additional step.
Appendix 4: Check list for the use of high dose IVIg

1. Prior to first infusion:
   Check renal and liver function, full blood count, serum immunoglobulins and electrophoresis. Check plasma viscosity if, for example, high levels of IgG or IgM are likely, and consider storing or testing serum for hepatitis C antibodies.

<table>
<thead>
<tr>
<th>Normal renal and liver function, and serum protein electrophoresis</th>
<th>Impaired renal function</th>
<th>Total IgA deficiency (&lt;0.05g/L)</th>
<th>Partial IgA deficiency</th>
<th>IgM / IgG paraprotein</th>
<th>Patients at risk of hyperviscosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proceed with any IVIg product</td>
<td>Avoid sucrose containing IVIg and exercise caution; suggest using 0.4g/kg/daily for 5 days and slower rate of infusion (for example, halving rate). Check creatinine daily before repeat dose is given</td>
<td>Use IVIg product containing low IgA content (see Appendix 3) Check anti-IgA antibodies</td>
<td>Proceed with any IVIg product</td>
<td>Consider possibility of mixed cryoglobulinaemia. Seek immunological advice before proceeding with IVIg</td>
<td>Exercise caution; use slower rate of infusion (suggest halving rate) and lower daily dose (0.4g/kg). Before and after infusion check viscosity.</td>
</tr>
</tbody>
</table>

2. Adhere to manufacturer’s recommendations regarding reconstitution and rate of infusion

3. Record batch number of product
Appendix 5: Members of the ABN Working Party.

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Declarations of interests of Members of the Panel are provided on a Register of Interests which is available on the ABN website at www.theabn.org