

# **ASSOCIATION OF BRITISH NEUROLOGISTS GUIDELINES FOR THE USE OF INTRAVENOUS IMMUNOGLOBULIN IN NEUROLOGICAL DISEASES (MARCH 2002)**

## **1. Scope of guidelines.**

These guidelines are the consensus views of an ABN working group (see Appendix 5) on the use of intravenous immunoglobulin (IVIg) in neurological disorders. They have drawn on the thoroughly referenced specialist review undertaken by Wiles et al. (2002), which contains comprehensive level of evidence data. Other useful reviews are given by Dalakas (1999) and Latov et al. (2001). The guidelines summarise the evidence for clinical effectiveness and give recommendations for use in each disease category. They evaluate mechanisms, products, safety and administration regimes, as well as discussing 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. The standard course of IVIg costs approximately £2500 and 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

- blockade of Fc receptors
- 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).

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

##### (i). Guillain-Barré syndrome.

No adequate trials have compared IVIg with placebo. However, a systematic review of four randomised controlled studies including 495 adults with severe disease seen within the first two weeks, found no significant differences between IVIg or the gold standard of plasma exchange (Hughes et al., 2001). *Therefore, in adults seen within the first two weeks with GBS of severity such that they are unable to walk unaided, we recommend IVIg since 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 children, in adult patients seen after two weeks of onset, in those with less severe disease who are still progressing, or patients with similar disorders such as Miller Fisher syndrome. When improvement after IVIg is followed by a relapse (10%), or in those who remain severely affected after the first treatment, a second course may be considered, although this is not of proven value in either situation. The standard treatment regimen of IVIg in GBS is 0.4 g/kg daily for five days.*

##### (ii). Chronic inflammatory demyelinating neuropathy (CIDP).

Five randomised controlled trials involving 113 patients with CIDP confirmed significantly more improvement in disability with IVIg than placebo (Van Schaik et al., 2001). 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. *While IVIg is recommended for the treatment of CIDP, 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 initial course is 0.4 g/kg daily for five days but 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. Undertreatment might contribute to disease progression. Overtreatment is 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).

The short term efficacy of IVIg has been shown in four randomised controlled trials including a total of 46 patients (Nobile-Orazio, 2001). Follow-up studies confirm continued response for several years but some progression may still occur (Nobile-Orazio, 2001). *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.*

There is no evidence that IVIg is of benefit in motor neuron disease (amyotrophic lateral sclerosis).

**(iv). Paraprotein-associated demyelinating neuropathy.**

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 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 therefore 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, but *there is insufficient information on which to base recommendations for these and other neuropathies.*

**(vi). Myasthenia gravis.**

A randomised trial in 87 patients with acute exacerbation given IVIg 0.4 g/kg daily for five days or plasma exchange, showed similar responses but lower complication rates with IVIg (Gajdos et al., 1997). However, 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). *IVIg is an option for treating an acute exacerbation of myasthenia gravis, but some experts prefer plasma exchange. There is no evidence to support its use as a routine or long-term treatment.*

**(vii). Lambert-Eaton myasthenic syndrome (LEMS).**

A clear improvement clinically and in strength measurements was seen in a randomised crossover trial of nine non-cancer LEMS patients who were given IVIg 1 g/kg daily for two days. The response peaked at two to four weeks and declined by eight weeks (Bain et al., 1996). There have been no acceptable trials to confirm anecdotal responses reported in cases associated with malignancy. *The short term use of IVIg is therefore appropriate in LEMS not associated with cancer. These patients do not appear to need long-term treatment.*

**(viii). Dermatomyositis and polymyositis.**

Fifteen patients with dermatomyositis were treated in a randomised, controlled trial using IVIg 2 g/kg monthly. There was a statistically significant improvement in strength, with clinical benefit seen even in those with severe weakness (Dalakas et al., 1993). 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. *Therefore 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 man 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 man syndrome.*

**(xi). Multiple sclerosis.**

There is evidence that IVIg has a biological effect in relapsing-remitting multiple sclerosis, as shown by reduced MRI activity, and some suggestion from small randomised trials of a reduction in relapse rate, but evidence on disease progression is insufficiently robust (Achiron et al., 1998; Fazekas et al., 1997; Strasser-Fuchs et al., 2000; Sorenson et al., 1998). There is no effect on established disability, secondary progressive disease or in isolated syndromes (Noseworthy et al., 2000; Noseworthy et al., 2001). *It is therefore recommended that in multiple sclerosis IVIg should not be used outside well designed trials.*

**(xii). Acute disseminated encephalomyelitis.**

It is reasonable to consider IVIg in patients who have failed to respond to high dose steroids, as supported by 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 and 1991). 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 the 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

mostly showed no benefit. Since these conditions may stabilise or even improve spontaneously (Byrne et al., 1997), anecdotal reports are impossible to interpret. *We do not recommend IVIg in these conditions.*

#### **(xv). 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 Rijckevorsel-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. *Therefore in any of these conditions, IVIg use should preferably be confined to randomised controlled trials. The severe, progressive nature of these intractable epilepsies makes it reasonable to consider the use of IVIg in n-of-1 trials in cases where other treatments have failed.*

#### **(xvi). Neuromyotonia.**

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

### **5. Adverse effects.**

These are classified in three broad categories. See Wiles et al. (2002), Latov et al. (2001) or 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.

There is a theoretical risk of the transmission of prions by blood products which led the Department of Health to stop the use of British plasma for IVIg production until more data are available.

**6. Monitoring treatment.**

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.

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.

## **7. Informed consent and patient information.**

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) indicates that in very few cases is consent obtained or written information provided before treatment (10%), although most patients recently circulated expressed a desire to have had more information. An information sheet and consent form is attached (Appendix 1) which may be modified for local use. Its use is recommended particularly when IVIg is used in unlicensed indications.

## **8. Cost effectiveness.**

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 (Nagpal et al., 1999), and another in chronic inflammatory demyelinating polyradiculoneuropathy showed that IVIg was much more costly than oral prednisolone (McCrone et al., personal communication). 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. No IVIg preparation is superior to another in terms of therapeutic effects. 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.

## **10. Proposed review of recommendations – Spring 2004.**

## 11. References.

- Achiron A, Gubbay U, Gilad R et al. (1998) Intravenous immunoglobulin treatment in multiple sclerosis: Effect on relapses. *Neurology* 50, 398-402.
- Alessi G, de Rueck J, de Bleecker J, Vancayzeele S (2000) Successful immunoglobulin treatment in a patient with neuromyotonia. *Clinics in Neurology and Neurosurgery* 102, 173-75.
- Bain PG, Motomura M, Newsom-Davis J et al. (1996) Effects of intravenous immunoglobulin on muscle weakness and calcium channel autoantibodies in the Lambert-Eaton syndrome. *Neurology* 47, 678-683.
- Byrne T, Mason WP, Posner JB, Dalmau J (1997) Spontaneous neurological improvement in anti-Hu associated encephalomyelitis. *Journal of Neurology, Neurosurgery and Psychiatry* 62, 276-278 .
- Comi G, Roveri L, Swan A et al. (2002) A randomised controlled trial of IVIg in IgM paraproteinaemic demyelinating neuropathy. *Journal of Neurology*, in press.
- Dalakas MC, Illa I, Dambrosia JM et al. (1993) A controlled trial of high-dose intravenous immunoglobulin infusions as treatment for dermatomyositis. *New England Journal of Medicine* 329, 1993-2000.
- Dalakas MC (1999) Intravenous immunoglobulin in the treatment of autoimmune neuromuscular diseases: present status and practical therapeutic guidelines. *Muscle and Nerve* 22, 1479-1497.
- Dalakas MC, Quarles RH, Farrer RG et al. (1996) A controlled study of intravenous immunoglobulin in demyelinating neuropathy with IgM gammopathy. *Annals of Neurology* 40, 792-795.
- Dalakas MC, Fujii M, Li M et al. (2001) High dose intravenous immune globulin for stiff-person syndrome. *New England Journal of Medicine* 345, 1870-1876.
- Dalakas MC, Koffman B, Fujii M et al. (2001) A controlled trial of intravenous immunoglobulin combined with prednisolone in the treatment of IBM. *Neurology* 56, 323-327.
- Donaghy M, Mills KR, Boniface SJ, Simmons J et al. (1994) Pure motor demyelinating neuropathy: Deterioration after steroid treatment and improvement with intravenous immunoglobulin. *Journal of Neurology, Neurosurgery and Psychiatry* 57, 778-783.
- Dyck PJ, Litchy WJ, Kratz KM, Suarez GA et al. (1994) A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. *Annals of Neurology* 36, 838-845.
- Fazekas F, Deisenhammer F, Strasser-Fuchs et al. (1997) Randomised placebo-controlled trial of monthly immunoglobulin therapy in relapsing-remitting multiple sclerosis. *Lancet* 349,589-93.

Gajdos P, Chevret S, Clair B et al. (1997) Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. *Annals of Neurology* 41, 789-796.

Hankey GJ, Todd AA, Yap PL, Warlow CP (1994) An “n of 1” trial of intravenous immunoglobulin treatment for chronic inflammatory demyelinating polyneuropathy. *Journal of Neurology, Neurosurgery and Psychiatry* 57, 1137.

Hughes RAC, Raphael J-C, Swan AV and van Doorn PA (2001) Intravenous immunoglobulin for Guillain-Barre syndrome (Cochrane Review). *Cochrane Library* 3. Oxford: Update Software.

Hughes RAC, Bensa S, Willison HJ et al. (2001) Randomised controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Annals of Neurology* 50,195-201.

Ishii A, Hayashi A, Ohkoshi N et al. (1994) Clinical evaluation of plasma exchange and high dose intravenous immunoglobulin in a patient with Isaac’s syndrome. *Journal of Neurology, Neurosurgery and Psychiatry* 57, 840.

Latov N, Chaudhry V, Koski CL et al. (2001) Use of intravenous gamma globulins in neuroimmunologic diseases. *Journal of Allergy and Clinical Immunology* 108, 126-132.

Leach JP, Chadwick DW, Miles JB, Hart IK (1999) Improvement in adult-onset Rasmussen’s encephalitis with long-term immunomodulatory therapy. *Neurology* 52, 738-742.

Mikati M, Lagae L (1998) IVIg in Landau- Kleffner syndrome. *Pediatric Neurology* 19, 399-400.

Nagpal S, Benstead T, Shumak K et al. (1999) Treatment of Guillain-Barre syndrome: a cost-effectiveness analysis. *Journal of Clinical Apheresis* 14, 107-113.

Newburger JW, Takahashi M, Burns JC et al. (1986) The treatment of Kawasaki disease with intravenous immunoglobulin. *New England Journal of Medicine* 315, 341-7.

Newburger JW, Takahashi M, Beiser AS et al. (1991) A single infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *New England Journal of Medicine* 324, 1633-9.

Nobile-Orazio E (2001) Multifocal motor neuropathy. *Journal of Neuroimmunology* 115,4-18.

Noseworthy JH, O’Brien PC, Weinshenker BG et al. (2000) Immunoglobulin does not reverse established weakness in multiple sclerosis. *Neurology* 55, 1135-43.

Noseworthy JH, O’Brien PC, Petterson TM et al. (2001) A randomised trial of intravenous immunoglobulin in inflammatory demyelinating optic neuritis. *Neurology* 56, 1514-22.

Qureshi AI, Choudhry MA, Akbar MS et al. (1999) Plasma exchange versus intravenous immunoglobulin treatment in myasthenic crisis. *Neurology* 52, 629-632.

Raphael J-C, Chevret S, Hughes RAC, Annane D (2001) Plasma exchange for

Guillain-Barré syndrome (Cochrane Review). Cochrane Library 2. Oxford: Update Software.

Sahlas DJ, Miller SP, Guerin M et al. (2000) Treatment of acute disseminated encephalomyelitis with intravenous immunoglobulin. *Neurology* 54, 1370-72.

Sansome A and Dubowitz V (1995) Intravenous immunoglobulin in juvenile dermatomyositis – four year review of nine cases. *Archives of Diseases of Childhood* 72, 25-28.

Sorenson PS, Wanschel B, Jensen CV et al. (1998) Intravenous immunoglobulin G reduces MRI activity in relapsing-remitting multiple sclerosis. *Neurology* 50, 1273-81.

Strasser-Fuchs S, Fazekas F, Deisenhammer F et al. (2000) The Austrian Immunoglobulin in MS (AIMS) study: final analysis. *Multiple Sclerosis* 6 (Supplement 2), S9-13.

Van den Berg JSP, van Engelen BGM, Boerman RH, de Baets MH (1999) Acquired neuromyotonia: superiority of plasma exchange over high-dose intravenous human immunoglobulin. *Journal of Neurology* 246, 623-625.

Van Engelen BGM, Renier WO, Weemaes CMR et al. (1994) Immunoglobulin treatment in epilepsy: a review of the literature. *Epilepsy Research* 19, 181-90.

Van Rijckevorsel-Harmant K, Delire M, Schmitz-Moorman W, Wieser HG (1994) Treatment of refractory epilepsy with intravenous immunoglobulins. Results of the first double-blind/ dose-finding clinical study. *International Journal of Clinical and Laboratory Research* 24, 162-66.

Van Schaik IS, Winer JB, de Haan R, Vermeulen M (2002) Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy (Protocol for a Cochrane Review). Cochrane Library 2. Oxford: Update Software.

Wiles CM, Brown P, Chapel H, Guerrini R et al. (2002) Intravenous immunoglobulin in neurological disease: a specialist review. *Journal of Neurology, Neurosurgery and Psychiatry* – in press.

## **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 Guillian-Barré syndrome, IVIg is not licensed for use in the treatment of neurological disorders but there is convincing evidence that it is a useful treatment in many different 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 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 in its use 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 or more severe headache.

As IVIg is a blood product, the blood from which it is made is checked for all known transmissible agents that can be screened (eg. 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. Variant Creutzfeld Jakob disease (vCJD) is a transmissible disease but there is no evidence that it can be transmitted by blood or IVIg. 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:

## Appendix 2: Projected use of IVIg in neurological conditions based on ABN recommendations.

<u>Disease</u>	<u>Frequency</u>	<u>IVIg courses</u>	<u>Proportion of cases treated</u>
GBS	Incidence approx. 2/100000/annum	Single or occasionally second course	Most cases
CIDP	Prevalence at least 2/100000	Repeated courses @ 4-12 weeks	<50% cases
Paraprotein associated neuropathy	N/K	Repeated courses @ 4-12 weeks	<10% cases
MMN	N/K	Repeated courses @ 4-12 weeks	At least 50% cases
Myasthenia	Prevalence 14/100000	Single course to induce remission	Rarely necessary
Non-cancer LEMS	N/K - rare	Single or repeated courses	< 50% cases
Refractory dermatomyositis (?polymyositis)	N/K	Repeated courses @ 4-12 weeks	<10% of total cases
Stiff man syndrome	N/K – rare	Possibly monthly cycles	Approx. 50% cases
Acute disseminated encephalomyelitis	N/K - rare	Single course	<25% cases
Kawasaki disease	N/K – very rare	Repeated cycles	Most cases
Specified refractory epileptic syndromes	N/K - rare	Repeated cycles	Infrequent use in selected cases in a small number of special centres

### Appendix 3: IVIG preparations in the UK

Product	Formulation	Manufacturing procedure	Additional anti-viral step	IgA content mg/L	Carbohydrate stabiliser
Flebogamma *	Liquid	PEG Precipitation DEA sephadex	Yes	4.3	D-Sorbitol
Gammagard-SD *	Powder	DEA sephadex	Yes	0.4 - 1.9	Glucose Glycine
Octagam	Liquid	pH4	Yes	<100	Maltose
Scottish National BTS	Powder	pH4	No	920	Sucrose
Sandoglobulin	Powder	pH4	Nanofiltration awaited	720	Sucrose
Vigam-S *	Liquid	Ion-exchange chromatography	Yes	5	Sucrose

\* 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.

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### 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.					
<b>Normal renal and liver function, and serum protein electrophoresis</b>	<b>Impaired renal function</b>	<b>Total IgA deficiency (&lt;0.05g/L)</b>	<b>Partial IgA deficiency</b>	<b>IgM / IgG paraprotein</b>	<b>Patients at risk of hyperviscosity &gt;3cp (i.e. serum IgG &gt;50g/L or with serum IgM &gt;30g/L) or with background arterial disease</b>
Proceed with any IVIg product	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	Use IVIg product containing low IgA content (see Appendix 3) Check anti-IgA antibodies	Proceed with any IVIg product	Consider possibility of mixed cryoglobulinaemia. Seek immunological advice before proceeding with IVIg	Exercise caution; use slower rate of infusion (suggest halving rate) and lower daily dose (0.4g/kg). Before and after infusion check viscosity.
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.**

Dr. Phillip Barnes, (Consultant Neurologist, London)

Professor Richard Hughes, (Professor of Neurology, London)

Dr. Bryan Lecky, (Consultant Neurologist, Liverpool)

Dr. Paul McCrone, (Health Economist, London)

Dr. Siraj Misbah, (Consultant Immunologist, Oxford)

Dr. Peter Newman, Chairman, (Consultant Neurologist, Middlesbrough)

Mr. Roland Price, (Chairman of GBS Support Group, Sleaford, Lincs.)

Dr. Cathie Sudlow, (Wellcome Clinical Scientist, Edinburgh)

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](http://www.theabn.org)