REVIEW

Intravenous immunoglobulin in neurological disease: a specialist review

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Treatment of neurological disorders with intravenous immunoglobulin (IVIg) is an increasing feature of our practice for an expanding range of indications. For some there is evidence of benefit from randomised controlled trials, whereas for others evidence is anecdotal. The relative rarity of some of the disorders means that good randomised control trials will be difficult to deliver. Meanwhile, the treatment is costly and pressure to "do something" in often distressing disorders considerable. This review follows a 1 day meeting of the authors in November 2000 and examines current evidence for the use of IVIg in neurological conditions and comments on mechanisms of action, delivery, safety and tolerability, and health economic issues. Evidence of efficacy has been classified into levels for healthcare interventions (tables 1 and 2).

PERIPHERAL NEUROPATHY

Intravenous immunoglobulin was used to treat inflammatory neuropathy after the improvement found in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) treated with plasma.[1] The report of rapid improvement in six of eight patients with Guillain-Barré syndrome (GBS) treated with IVIg was followed by a randomised control trial showing that it was as least as effective as plasma exchange in hastening recovery.[2 3] Two other randomised control trials[4 5] and a systematic review[6] concluded that IVIg was as effective as plasma exchange in hastening recovery from severe GBS when given in the first 2 weeks and the planned dose was much more likely to be administered (level 1a evidence). It is not known whether IVIg is effective in patients who can still walk unaided or more than 2 weeks after disease onset or in Miller Fisher syndrome. IVIg is commonly used in children although the trials were conducted in adults. The regimen used in these trials was 0.4 g/kg daily for 5 days but dose ranging studies have not been published. In particular it is not known whether repeating the treatment benefits patients who remain severely paralysed 2 or more weeks after the first treatment. Nevertheless IVIg has become the standard treatment for GBS in the United Kingdom and most neurology departments in Europe and the United States.

For CIDP IVIg was more effective than placebo in four[7–10] of five published randomised control trials. In the negative trial[11] there were more patients with chronic disease and other adverse prognostic factors in the IVIg than the placebo arm. In other trials IVIg had similar efficacy to plasma exchange[12] and a slightly faster and greater effect than prednisolone.[13] A systematic review is needed but is likely to confirm the clinical experience of experts that two thirds of patients will respond to IVIg at least in the short term (level 1b evidence). At least half of the responders require regular treatment which may need to be given as often as every 4 weeks and very occasionally more often (level IV evidence).

Table 1 Classification of evidence levels for healthcare interventions[157]

Ia	Evidence obtained from meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well designed quasiexperimental study (in which implementation of an intervention is outside the control of the investigators, but an opportunity exists to evaluate its effect)
III	Evidence obtained from well designed non-experimental descriptive studies, such as comparative studies, correlation studies, and case studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

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Abbreviations: IVIg, intravenous immunoglobulin; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; GBS, Guillain-Barré syndrome; MMN, multifocal motor neuropathy; MG, myasthenia gravis; LEMS, Lambert-Eaton myasthenic syndrome; DM, dermatomyositis; PM, polymyositis; IBM, inclusion body myositis; MS, multiple sclerosis; EDSS, expanded disability status score; WS, West syndrome; LGS, Lennox-Gastaut syndrome; RE, Rasmussen encephalitis; LKS, Landau-Kleffner syndrome; PND, paraneoplastic neurological disorders; PEM, paraneoplastic encephalomyelitis (anti-Hu); PCD, progressive cerebellar degeneration (anti-Yo); SSM, subacute sensory neuropathy; ITP, idiopathic thrombocytopenic purpura; PID, primary immune deficiency; CJD, Creuzfeldt-Jakob disease; QALY, quality adjusted life year

Table 2 Summary of evidence

Condition	Evidence level
Guillain-Barré syndrome	1a
Chronic inflammatory demyelinating polyneuropathy	1b
Multifocal motor neuropathy	1b
Other lower motor neuron syndromes	IV
Amyotrophic lateral sclerosis*	III against current use
Neuropathy associated with paraprotein	IV
Myasthenia gravis (acute severe or deteriorating)	1b
Lambert-Eaton syndrome	1b
Inclusion body myositis	1b against current use
Dermatomyositis	1b
Polymyositis	IV
Stiff-man syndrome	III/IV
Multiple sclerosis (relapse rate ?disability)	1b
Kawasaki disease	1a
Sarcoid, Behçet's disease	no evidence
CNS vasculitis	III/IV
CNS lupus, antiphospholipid syndromes	IV
Epilepsy	III/IV
Lennox Gastaut, West syndromes	III/IV
Rasmussen encephalitis	IV
Landau-Kleffner syndrome	IV
Paraneoplastic disorders of the CNS	III/IV
Adrenoleukodystrophy*[158]	III against current use

*Not specifically discussed at one day authors' meeting.

Although expensive, treatment can make dramatic differences to dependency but needs carefully monitoring and ongoing review.

Multifocal motor neuropathy (MMN) is related to but distinct from CIDP. Four randomised control trials[14–17] support the view that IVIg is an effective short term treatment in two thirds of patients but no systematic review is yet available (level 1b evidence). Courses of IVIg continue to have some short term effect and may need to be repeated as often as every 4 weeks (level IV evidence).[18] However, increasing disability may necessitate adjunctive treatment with immunosuppressive treatment.[18–20] The use of IVIg in lower motor neuron syndromes without conduction block is experimental (level IV evidence)[21]: certainty about the extent to which conduction block is excluded can be problematic. Two small open studies of patients with amyotrophic lateral sclerosis treated with IVIg gave no indication of benefit.[22 23]

Paraproteins are not infrequently associated with peripheral neuropathies which may resemble CIDP or MMN. There is also a distinct syndrome of slowly progressive sensory and motor neuropathy associated with an IgM κ paraprotein and antibodies to myelin associated glycoprotein. In a crossover design randomised control trial there were short term improvements in motor or sensory impairment in three of 11 patients with IgM paraproteins.[24] In another crossover randomised control trial 24 patients with different paraprotein classes showed a significant reduction in impairment and disability measures 2 and 4 weeks after treatment.[25] Clinical experience and case series suggest that patients with paraproteins associated with CIDP or MMN respond similarly to IVIg as patients without (level IV evidence). For patients with demyelinating neuropathy associated with IgM paraprotein the disease course is usually so indolent that treatment is unnecessary. For those with a rapid course there is limited level 1b evidence[25] of short-term benefit which make it worth trying. For those who respond to the initial course repeated courses may be considered (level IV evidence). A systematic review of treatment for the demyelinating neuropathy associated with IgM paraprotein is in progress but currently there is insufficient evidence on which to base treatment recommendations.

The beneficial effect of IVIg in other autoimmune and inflammatory conditions suggests that it would be worth investigating in vasculitic neuropathy, proximal diabetic neuropathy,[26] idiopathic brachial and lumbar plexopathy, and perhaps Bell's palsy.

MYASTHENIA GRAVIS AND THE LAMBERT-EATON MYASTHENIC SYNDROME

Myasthenia gravis (MG) is an antibody mediated disorder of neuromuscular transmission that leads to loss of functional acetylcholine receptors at the endplate and consequent fatiguable muscle weakness. Intravenous immunoglobulin therapy for MG was first reported in the 1980s.[27 28] Several small early series were reviewed in 1994.[29] Overall, 78% of patients improved, but most received additional immunological therapy, which may account for the exceptionally long duration of improvement (30 days to 2 years). An open retrospective study of IVIg (2.0 g/kg body weight) in 14 patients with generalised MG, many of whom also received additional immunological therapy, reported significant improvement that began within a few days of treatment initiation and peaked at 2 weeks.[30] Whereas severe cases usually responded, those with mild disease did not (level IV evidence). An open prospective study of 5 days IVIg followed by single treatments every 6 weeks in 10 patients with severe generalised MG reported improvement in all[31]: each patient was receiving additional immunological therapies, but it proved possible to reduce these over the year long study (level IV evidence). A retrospective study of IVIg treatment in 10 patients with juvenile MG (age range 2–18) reported improvement in eight[32] and treatment was well tolerated. A consensus meeting on IVIg[33] concluded that IVIg treatment was most useful in acute deteriorating disease, minimising the risk of bulbar or respiratory weakness requiring intensive care support. It was also useful temporarily in patients with severe disease in whom other treatments had not yet become effective. However, a role in chronic disease was not established, and its use as a primary treatment in MG was not recommended (level IV evidence).

Is IVIg better than plasmapheresis? No significant difference was detected in an randomised control trial[34] comparison of IVIg with plasmapheresis where change in strength between days 1 and 15 was the primary outcome (level Ib evidence); evidently IVIg treatment was easier to implement. However, in a retrospective study[35] of 54 episodes of respiratory crisis plasmapheresis resulted in a significantly better ventilatory outcome than IVIg, although the complication rate was higher (level III evidence).

Lambert-Eaton myasthenic syndrome (LEMS) is a disorder of neurotransmitter release from motor nerve terminals and of cholinergic and adrenergic autonomic function, mediated by anti-calcium channel antibodies. About 60% of patients have an associated small cell lung cancer. Favourable case reports[36–38] were followed by a double blind crossover randomised control trial[39] of IVIg treatment (2 g/kg over 2 days) in nine patients without evidence of lung cancer: significant improvement in strength measures and decline in serum titres of specific (anti-calcium channel) antibodies were found after infusion of IVIg compared with control (albumen) infusion, peaking at 2–4 weeks and declining progressively by 8 weeks (level Ib evidence) Although useful in the short term, none of the patients in the study continued to need IVIg in the long term.

PRIMARY INFLAMMATORY MYOPATHIES

This term refers to two conditions, dermatomyositis (DM) and polymyositis (PM), in which there is probably primary autoimmune pathology with no obvious infective cause, and a third, inclusion body myositis (IBM), which may be a degenerative condition with an inflammatory component. These

three conditions are clinicopathologically distinct and their response to treatment, including IVIg, may differ.[40]

In IBM a prospective study found no benefit from IVIg[41]: in one case improvement in muscle strength occurred[42] and a positive pilot study[43] led to a randomised control trial.[44] Further randomised control trials of IVIg alone[45] and in combination with steroid treatment[46] led to the conclusion that IVIg given monthly for up to 3 to 6 months did not significantly improve overall muscle strength (the primary outcome measure). None of the randomised control trials reported significant adverse effects due to IVIg and longer treatment periods might conceivably result in benefit.

In DM an uncontrolled trial in children[47] showed variable results. In adult DM a single randomised control trial[48] showed benefit in both muscle strength and muscle function assessment as well as marked improvement in the cutaneous features (evidence level 1b). Furthermore laboratory studies give evidence for reversal of the underlying pathophysiology by IVIg that would account for the clinical benefit seen.[49–51]

In PM there are no randomised control trials of IVIg and doubt about diagnosis or absence of stated criteria[52 53] causes difficulties of interpretation. In two cases resistant to conventional treatment dramatic long lasting responses to a single infusion of IVIg occurred[54]: this seems an unlikely response in a primary autoimmune disease so that alternative explanations are needed—for example, these cases may have had underlying common variable immunodeficiency, the response being due to clearing of an infective agent (such as coxsackie or echo virus).

Overall, IVIg is well tolerated in these groups of patients. For IBM, until larger or longer (>6 months) trials suggest otherwise, there is at present insufficient evidence to justify the use of IVIg (level 1b evidence against). For DM, IVIg may be reasonably considered as a first line steroid sparing agent (level 1b evidence). In PM, resistance to steroid treatment should prompt a review of the diagnosis before further treatment including IVIg is considered (level IV evidence).

STIFF MAN SYNDROME

The stiff man syndrome is characterised by persistent stiffness, abnormal posture and spontaneous, action induced and reflex spasms. An autoimmune aetiology seems likely in many cases, given the high incidence of other autoimmune diseases and the presence of high levels of antibodies against glutamic acid decarboxylase. Symptomatic treatment with oral diazepam and baclofen is usually sufficient, but a minority of patients have refractory disease. Therapy with IVIg has emerged as the principal treatment for severe disease, but supporting evidence is limited. Six reports[55–60] describe 10 cases of stiff man syndrome affecting the axial musculature and treated with IVIg. Nine cases improved clinically but only one study included objective tests of response such as a timed walk and patient self assessment.[55] Two single case reports described clinical improvement with IVIg in patients with progressive encephalomyelitis with rigidity[61 62] and one reported improvement with IVIg in a case of "stiff limb syndrome".[63]

In conclusion, only level III/IV evidence supports the use of IVIg in the stiff man syndrome and a randomised control trial is required. In addition, IVIg should be compared with steroids and plasma exchange. Meanwhile IVIg is one possible second line treatment in patients that fail to respond to standard treatment.

MULTIPLE SCLEROSIS

There are many theoretical mechanisms by which IVIg may influence multiple sclerosis (MS) including remyelination, anti-idiotype antibody actions, down regulation/ neutralisation of cytokines, modulation of complement pathways, and Fc macrophage receptors. Initial unblinded and often uncontrolled studies reported beneficial effects including a reduction in relapse rate and severity and an improvement in EDSS scores. Two parallel designed randomised control trials[64–66] over 2 years were designed to look at clinical outcomes and one[67] was a crossover study consisting of two 6 month phases (IVIg and placebo or vice versa) with a 3 month washout, measuring monthly MRI activity. Relapse rate was reduced (range 42%-63%) and the relapse free percentage was significantly increased in those on IVIg in all three trials but there was no change in relapse severity. The total number of active lesions (gadolinium enhanced MRI) was reduced by 70% and new enhancing lesions by 55%. The mean change in the Kurtzke expanded disability status score (EDSS) was significantly reduced by IVIg compared with placebo in the larger study.[64] However "confirmed" EDSS progression (measured at intervals of 3 or more months) was not measured and thus sustained or reversible disability was not differentiated. Side effects were troublesome when the IVIg dose used was high but well tolerated at standard doses. In randomised control trials to examine the effect of IVIg on established muscle weakness in MS and on persistent visual deficit after inflammatory demyelinating optic neuritis IVIg had no benefit.[68 69] Thus IVIg seems to be at least as effective (level 1b evidence) at reducing relapses and perhaps disability reduction as other disease modifying agents although there have been no direct comparisons. The results of an international study in secondary progressive MS are awaited.

VASCULITIC AND OTHER "SECONDARY"INFLAMMATORY DISEASES OF THE NERVOUS SYSTEM

Kawasaki disease is an acute febrile illness of childhood, with a pancarditis and coronary arteritis; neurological complications include an aseptic meningitis, stroke, encephalopathy, and facial palsy: a pathogenetic association with anti-endothelial cell antibodies is postulated.[70 71] IVIg is well established as the treatment of choice (level 1a and b evidence).[72–76]

In disorders such as giant cell arteritis and Hashimoto's encephalopathy conventional treatments are broadly effective, providing limited impetus for exploring the value of IVIg. However in diseases such as sarcoidosis and Behçet's disease current treatments are often ineffective and, in the absence of published evidence, a case may be made for exploring IVIg. If serum immunoglobulin concentrations are already high, IVIg related increases in serum viscosity may have more potential for serious adverse effects (vide infra).

In small vessel vasculitis (principally microscopic polyangiitis and Wegener's disease), a recent randomised control trial[77] of single pulse IVIg (17 patients) versus placebo (17 patients), all with resistant systemic ANCA associated disease, showed decreased disease activity in 14 of the actively treated group, compared with six patients in the placebo group, at 2 and 4 weeks but not 12 weeks, and improvement in only some affected organs. However, in neurological vasculitis, there is only case report evidence of benefit.[78 79] In systemic lupus erythematosus, open studies suggested benefit[80–83] and a small randomised control trial (14 patients with renal lupus) suggested that IVIg was at least as effective at maintaining remission as cyclophosphamide[84]: in CNS lupus there is only a single case report.[85] The use of IVIg in anti-phospholipid syndromes has been recommended (level IV evidence).[86] One small pilot multicentre study of secondary prevention of pregnancy loss in women with antiphospholipid syndrome offered no evidence of efficacy.[87] Thus in all these areas IVIg may be worthy of further study but the difficulties of accumulating sufficient numbers of adequately diagnosed cases remain formidable.

EPILEPSY

Gammaglobulin has been used to treat children with severe epilepsy.[88] A favourable response to IVIg was found in 174/373 children (45%) in 29 studies with an average seizure remission rate of 20%.[89] However clear benefit was not confirmed in a double blind placebo controlled study.[90] In general age at which IVIg is given does not seem to influence effectiveness, cryptogenic epilepsies might respond better than symptomatic forms, and IgG deficiency does not increase likelihood of a good response.

Cryptogenic West syndrome (WS) and Lennox-Gastaut syndrome (LGS) are characterised by very frequent seizures, often in series, and by developmental arrest. Quantification of seizures may be difficult and reduction in number does not necessarily translate into measurable overall clinical improvement. Children with cryptogenic Lennox-Gastaut syndrome may have antibodies to brain tissue, an impaired immune response to hemocyanin[91] and HLA associations.[92] In a single blind placebo controlled study in LGS possible benefit from IVIg was reported.[93] High dose IVIg (0.4 g/kg for 5 days, then once every 2 weeks for 3 months) benefitted a homogeneous group of children with cryptogenic WS and LGS in a prospective add on study[94]: reduction in seizure frequency averaged 70% and EEG improvement appeared 4–6 weeks after beginning treatment.

Rasmussen encephalitis (RE) is a rare progressive disorder with onset in childhood causing severe focal epilepsy, hemiparesis, and cognitive deterioration. Antibodies against GluR3 have been detected in the serum of some patients[95 96] and complement fixing anti-GluR3 autoantibodies may have a role in the pathogenesis.[97 98] Plasmapheresis may be beneficial[99] and anecdotal reports in 11 patients suggest short term benefit from IVIg[100 101] but this needs confirmation in a randomised control trial.

Landau-Kleffner syndrome (LKS) is associated with verbal auditory agnosia followed by progressive aphasia, usually when aged 4–7 years, accompanied by focal and multifocal EEG abnormalities, which are thought to cause language dysfunction; severe disability is common. Antiepileptic drugs are usually ineffective but steroids may help and multiple subpial transection is beneficial in selected patients.[102] Autoantibodies directed against endothelial brain cells have been found in some children[103] and anecdotal reports in three patients suggest a possible role for IVIg in LKS (level IV evidence).[104–106]

PARANEOPLASTIC NEUROLOGICAL DISORDERS OF THE CNS

An autoimmune mechanism is probably involved in paraneoplastic neurological disorders (PND) of the CNS. The detection of anti-neuronal antibodies in serum samples from affected patients is regarded as a very specific diagnostic marker of these disorders but there is controversy as to whether these antibodies are pathogenic or an epiphenomenon of cell mediated damage. To date, it has not been possible to induce a good animal model of CNS PND.[107–109] The paucity of case reports[110–112] suggests that, in most patients treated, therapeutic benefit from IVIg has not been impressive. Possible reasons include the finding that PND is associated pathologically with irreversible neuronal loss and intrathecal subacute inflammation minimally susceptible to humoral effects of systemic IVIg.

Twenty two patients with paraneoplastic encephalomyelitis (PEM) (anti-Hu) and four with progressive cerebellar degeneration (PCD) (anti-Yo) had three courses of IVIg over 3 months but only three improved, all ambulatory at the time of treatment: no severely disabled patient improved.[113] Twenty one patients with PND, 17 with anti-Hu (PEM/subacute sensory neuropathy(SSM)), and four with anti-Yo antibodies (PCD) were treated with 1–26 (mean 5.8) cycles of IVIg[114]: a patient with SSN (also receiving concomitant anti-tumour treatment) improved significantly for at least 15 months, 10 remained stable, and 10 deteriorated. Improvement or stabilisation was more frequent in patients with isolated peripheral nervous system involvement (62%) compared with CNS damage (37%) but autoantibody titres did not change significantly. Sixteen patients with progressing neurological disability (nine PEM/SSN (anti-Hu), seven PCD (anti-Yo)) received 1–9 cycles of a combination of IVIg, cyclophosphamide, and methylprednisolone.[115] No ambulatory or bedbound patient improved but three (two SSN and one PCD) experienced "useful stabilisation" for 4, 35, and 16 months.

In conclusion, there are a few convincing case reports of clinical benefit in both central and peripheral PND syndromes especially if treated within 2 weeks of onset (evidence level III).

IMMUNE REGULATORY MECHANISMS OF INTRAVENOUS IMMUNOGLOBULIN THERAPY

The development of purification techniques for human immunoglobulins on a commercial scale began in the early 1940s, leading first to the production of concentrated IgG preparations for intramuscular (IMIG) injection. However, clinicians working with the Swiss Red Cross facility for manufacturing IVIg in Berne in the early 1980s proposed that IVIg might have additional immune regulatory properties because it was likely to contain multiple anti-idiotypes, previously proposed to have an important modulatory role in the immune system. The serendipitous discovery in 1981 that IVIg could increase the platelet count in autoimmune thrombocytopenic purpura led to a plethora of "look and see" attempts to treat a wide variety of autoimmune and chronic inflammatory disorders.[116]

MECHANISMS

Microbial and toxin inhibition

The effects of IgG antibodies on microbes involve both opsonisation and activation of complement with subsequent lysis of capsulated bacteria. Antibodies can neutralise toxins, some of which are known to act as superantigens which can bypass the normal requirement for class II involvement in the stimulation of the T lymphocyte receptor complex.[117] For example, staphylococcal enterotoxin will stimulate T lymphocytes with the subsequent release of inflammatory cytokines, thus compounding the systemic effect in the toxic shock syndrome. Various other bacteria produce toxins which theoretically could stimulate more subtle and prolonged lymphocyte activation and subsequent inflammatory disease, and which could be neutralised by IVIg. However, a direct link between autoimmune/chronic inflammatory diseases and superantigen stimulation has not yet been demonstrated.

Complement "deactivation"

IVIg has a major effect on complement as shown in vitro and by good indirect evidence in vivo.[118] IgG antibodies in IVIg can activate complement and divert the production of lytic complement components into the fluid phase and away from any target cell membrane. This is probably an important mechanism in dermatomyositis where the beneficial effects of IVIg are associated with disappearance of complement in the muscles.[51]

Receptor blockade

Fc Receptor blockade is thought to be a major mechanism of benefit in idiopathic thrombocytopenic purpura (ITP). Fc receptors on phagocytes are "blocked" non-specifically by the pooled IgG, thus preventing the uptake of IgG coated platelets.[119] A similar effect in ITP can be achieved by injecting anti-D (rhesus) antibodies into rhesus positive patients with ITP; in this case IgG coated red cells "block" the splenic phagocytic system.

Fas is a molecule which appears on the surface of activated cells and which, after binding with its ligand, initiates signals for apoptosis. The skin keratinocytes in toxic epidermal necrolysis express high concentrations of Fas, which are thought to mediate the rapid cell destruction and desquamation in this rare condition, which is often triggered by drugs. IVIg contains anti-Fas antibodies which block Fas signalling in vitro, a finding that led to a clinical trial of IVIg which seemed to show a marked beneficial effect.[120] It is surprising that IVIg contains functional anti-Fas autoantibodies, but there are a wide variety of "auto-antibodies" in these preparations, which are assumed to come from a few donors to the immunoglobulin pool.

Anti-idiotypes

Jerne's network theory depends on the production of antibodies to antibodies with the binding sites of the anti-antibodies (anti-idiotypes) being the image of the original antigens. This is thought to provide feedback control of antibody responses. Anti-idiotypes of auto-antibodies can be demonstrated in the serum of some normal people and in IVIg. High resolution electron microscopy of IVIg shows IgG dimers interacting through the antigen binding $F(ab')_2$ ends of the molecule.[121] The numbers of these dimers increases with the numbers of donors to the IgG pool, supporting the view that only rare donors have high titres of particular anti-idiotypes.

In some haemophiliacs a rapid fall in factor 8 antibodies occured after IVIg treatment and similar falls in autoantibody titres, coincident with clinical improvement, occurred in some patients with Lambert-Eaton syndrome although in these patients the IVIg did not contain neutralising anti-idiotypes to the calcium channel autoantibodies.[122] Other reasons for falls in autoantibody concentrations after IVIg treatment include an increase in overall catabolism of IgG by saturation of the FcRB receptors on macrophages: these receptors protect IgG from breakdown, with catabolism increasing as the concentration of IgG rises in the plasma.[123] Another possible mechanism is a general reduction in the numbers of bone marrow B lymphocytes after the infusion of IVIg, apparently through negative signals after binding of IgG to B cell receptors.[124]

Modulating cytokine production

IVIg has been shown to affect the production of cytokines in various systems.[125] An elegant in vitro study has shown that non-specific IgG, reacting with Fc receptors on macrophages, will prevent the release of IL-1 from these cells after lipopolysaccharide stimulation, but does not interfere with the secretion of IL-1 receptor antagonist.[126] This may be an important mechanism whereby IVIg downregulates the vascular inflammation in Kawasaki disease, in which the plasma concentrations of IL-1 have been shown to fall after IVIg treatment.

In conclusion, there are a confusing plethora of potential mechanisms for the effect of IVIg in patients with autoimmune/inflammatory diseases. These are not mutually exclusive and may operate in concert to produce an overall beneficial effect. The very rapid effects of IVIg seen in ITP, Guillain-Barré syndrome, and Kawasaki disease are likely to be due to effects on macrophages and/or complement deactivation. The amount of anti-idiotype antibody in IVIg is unlikely to be sufficient to "neutralise" an autoantibody in the short term, but may downregulate production as the beneficial effect of IVIg takes several days in most autoimmune diseases.

DELIVERING HIGH DOSE IVIG

Whether immunomodulatory immunoglobulin should be given intravenously (IVIg) or subcutaneously (SCIg) remains unresolved. Whether high dose IVIg should be given as a bolus or as maintenance doses is also unresolved and might depend on the mechanism of action—that is, neutralisation of pathogenic autoantibodies versus down regulation of autoantibody production. Most experience indicates that maintenance therapy is adequate for ongoing improvement in peripheral neuropathies (MMN and CDIP), though whether or not either method would prove "curative" (as shown for ITP in which an increasing interval between infusions has resulted in the ability to discontinue therapy in some patients) remains unclear. Evidence about duration of maintenance therapy needs to be collected by observational studies. The provision of a national database, as in primary immunodeficiencies, would assist this and may contribute to understanding of the mechanisms involved.

In Oxford, UK [127] specific programmes for teaching patients to self infuse at home have been started. This is an established and widespread method of delivery of IVIg for patients with primary immune deficiency (PID) and the Oxford home IVIg programme has been modified for patients with peripheral neuropathies,[128] and allows greater flexibility in relation to dose size and interval. Accreditation of therapy centres and recognition of centres for home therapy programmes ensures the safety and auditability of these programmes.

TOLERABILITY AND SAFETY

Tolerability

Reported adverse reaction rates with IVIg range from 1% to 81%.[129 130] The commonest adverse reactions are headache, backache, nausea, vomiting, diarrhoea, flushing, fever, chills, shaking, shortness of breath, tightness of the chest, hypotension, hypertension, and rashes: these are usually transitory in nature, related to the speed of the infusion and usually occur during the first or second infusion. A large variation in tolerance exists to differing infusion rates and products. Rarely, patients may react even with very slow infusion speeds and may require prophylaxis 30 minutes before IVIg with 50–100 mg hydrocortisone, an antipyretic drug, and/or an antihistamine drug.[131 132] Anaphylactic reactions with IVIg are rare and have not been reported in immunocompetent patients although anaphylactoid reactions have been seen in relation to very fast infusion rates. Anaphylactic reactions due to the formation of IgE antibodies against IgA in immune deficient patients who have no IgA may rarely occur.

Headaches can be severe but CT shows no evidence of intracranial haemorrhage.[133] Patients prone to headache may require slowed infusion rates or administration of low dose β blockers may be effective. A self limiting aseptic meningitis has been reported in up to 11% of neurological patients receiving IVIg[134]: those with a history of migraine seem at higher risk and treatment is symptomatic. The mechanism is unknown but may be due to a vasomotor effect on the meningeal microvasculature from an induced release of histamine, serotonin, or prostagladins. Concentrations of IgG of 1.5 to 7 times the upper limit of normal may be found in CSF.[134] A transient encephalopathy has been reported after IVIg with some evidence that this may be caused by cerebral vasospasm based on transcranial Doppler studies of the middle cerebral arteries.[135–137] Both cerebral infarction and myocardial infarction have been reported in older patients.[138–142]

Arthritic complications have been described.[143] Transient acute renal failure is being seen more often with the high doses used in neurological patients. The products implicated contain sucrose as a stabiliser and result in classic osmotic nephrosis.[144–147] Raised osmolality may be a factor in renal impairment and for thrombogenesis secondary to hyperviscosity: plasma viscosity may rise by as much as 40% though not necessarily into a clinically significant range. Rare dermatological events have been reported[147] including eczema, erythema multiforma, purpuric erythema, and alopecia. Transient leukopenia and neutropenia[148] have been reported.

Virological safety

Concern centres on the transfusion related viruses such as hepatitis A, B, C, HIV, HTLV I/II, human herpes virus, and parvovirus B-19. Reports of non-A and non-B hepatitis transmission have been published since 1983.[149–154] Other agents recently of concern include include those causing classic and variant Creuzfeldt-Jakob disease (CJD). Manufacturers exclude donors at known risk of CJD (for example, affected relative or recipient of dura mater graft). Although the possibility of nvCJD transmission by IVIg cannot be completely ruled out, it is currently neither proved nor thought likely.

Within Europe and North America, all donor centres must meet either European Community and/or Food and Drug Administration criteria. European commercial manufacturers obtain their plasma from the United States and/or Europe (usually Austria and Germany). No difference in the safety, tolerability, or efficacy of products derived from one or the other types of donor centres has been documented. Donor centres must maintain a high level of quality control in their testing laboratories, absolute matching of donor records with plasma donations (traceability) and provide virological follow up analysis. Donors are given a medical examination, a complicated lifestyle analysis to screen out potential high risk donations, and virological testing. Plasmapheresis donors are often repeat donors (>75%) and may donate more often than whole blood donors: longitudinal records for such donors add a further safety measure. Some manufacturers prefer to use plasmapheresed donors in order to have greater standardisation between lots of IVIg.

Appropriate screening of donors reduces the risks of viral transmission, but manufacturers must still employ methods of viral separation and/or inactivation to reduce the risk of potential viral transmission. No single method of viral separation or primary viral inactivation (for example, solvent detergent or pasteurisation) is known to be totally effective and manufacturers employ a range of additional secondary steps (for example, incubation at pH4, addition of pepsin, caprylic acid, polyethylene glycol, hydrolase treatment, nanofiltration). Some producers set minimum standards of antibody concentrations against certain pathogens to ensure antibody neutralisation.

HEALTH ECONOMIC IMPLICATIONS OF IVIg

The direct costs of intravenous immunoglobulin (IVIg) are high. In the United States costs of $100/g have been reported[155] with substantial increases throughout recent years. In Europe costs are generally lower, particularly in the United Kingdom (around £12–20/g): thus a typical course of treatment (2 g/kg in a 70 kg person) would cost £1680–2800 (excluding inpatient and other costs) and monthly courses are common. Such costs are likely to act as a disincentive to policy makers and hospital managers responsible for allocating scarce resources across and within different specialties. However, to assess whether IVIg does represent value for money it is important to go beyond a simple focus on the direct costs of the intervention itself. To date there have been very few published cost-effectiveness analyses of the use of IVIg for neurological conditions. One that was conducted, based on secondary data and only including health costs, found that for patients with Guillain-Barré syndrome the costs of IVIg were about 60% higher than the costs of plasma exchange with both treatments considered to be equally effective.[156]

The following recommendations provide a framework by which future economic evaluations might take place. Firstly, costs should be measured comprehensively. Patients with neurological conditions are likely to be in receipt of a wide range of different services (inpatient care, social care, etc). and also the family and friends of a patient may provide care giving activities. If the use of such services can be reduced by the use of IVIg then some or all of the intervention costs may be offset.

Secondly, a long term perspective should be taken. IVIg is perceived to have a low side effect profile whereas prolonged use of other products such as corticosteroids can lead to serious health problems in later life, resulting in increased use of health care and other services. On the other hand not all the risks of long term viral transmission are known at present. Resources do not allow trials to capture the long term effects and costs of treatment but it is possible to model what these might be.

Thirdly, costs should be combined with outcomes. Efficient treatments are the ones that achieve the maximum effect from the costs incurred. An intervention that is expensive but highly effective may therefore be preferred to one that is cheap but that has limited benefits. Clinicians, managers, and policy makers, therefore, have to make value judgements as to whether extra resources should be expended to achieve the extra benefit. Costs associated with IVIg should be combined with the primary outcome measure used in a trial to determine its cost effectiveness relative to any comparison intervention. However, it may also be appropriate to estimate the cost per quality adjusted life-year (QALY) so that comparisons can also be made across specialties. This though is subject to the quality of life measure being sensitive enough to detect changes for that relevant patient group.

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Conflicts of interest

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