Current clinical uses of intravenous immunoglobulin

T El-Shanawany MRCP, Specialist Registrar in Immunology, *University Hospital of Wales, Cardiff*

WAC Sewell PhD FRCP MRCPath, Visiting Professor of Immunology, *University of Lincoln, Lincoln*

SA Misbah FRCP FRCPath, Consultant Immunologist, *Churchill Hospital, Oxford*

Stephen Jolles PhD MRCP MRCPath, Consultant Immunologist and Allergist, *University Hospital of Wales, Cardiff*

Clin Med 2006;6:356–9

Intravenous immunoglobulin (IVIG) is a batched blood product prepared from 1,000–15,000 plasmapheresis and blood donations. It contains over 95% IgG with trace amounts of IgA and IgM and is used in two main ways:

- as replacement therapy to supplement low serum IgG levels at a dose of 200–400 mg/kg body weight, usually at three-weekly intervals
- at higher doses, 1–2 g/kg given monthly, IVIG exerts an immunomodulatory effect in a wide range of autoimmune and inflammatory conditions.

Key Points

Intravenous immunoglobulin (IVIG) therapy can be used to supplement low IgG levels (replacement therapy) or to modulate the immune system (high-dose therapy)

IVIG operates by a range of mechanisms depending on the condition being treated

IVIG products are different from one another and not interchangeable

There is good evidence of efficacy for IVIG in many conditions, including antibody deficiency syndromes, autoimmune neuropathies, Kawasaki disease, idiopathic thrombocytopenic purpura and some vasculitides

Careful patient selection is essential, given the world shortage of IVIG, the cost and time needed to administer it

KEY WORDS: blistering diseases, chronic inflammatory demyelinating polyneuropathy, hypogammaglobulinaemia, immunomodulation, intravenous immunoglobulin

Mechanism of action

It is often said that the mechanism of action of IVIG is unknown, but many mechanisms have been identified, the predominant one depending on the condition treated. They may be considered in four main groups (summarised in Fig 1)[1] as those due to:

- the antigen-binding part of the Ig molecule
- binding to the Fc receptor
- effects on complement
- effects of other molecules present in IVIG preparations.

IVIG replacement therapy

Intravenous therapy replaced intramuscular therapy in the 1970s and 1980s because the latter injections are painful, associated with significant side effects and poor at attaining adequate levels of serum IgG. Replacement therapy is used for patients with primary antibody deficiencies such as common variable immunodeficiency, X-linked agammaglobulinaemia and similar conditions. It also has a role in secondary antibody deficiency states such as chronic lymphatic leukaemia or multiple myeloma, particularly in patients who cannot mount adequate antibody responses, as assessed by failure to respond to Pneumovax II immunisation. Replacement therapy used to be considered in premature or low birthweight infants who are frequently mildly hypogammaglobulinaemic. However, large meta-analyses have failed to demonstrate a useful effect either as prophylactic[2] or adjunctive therapy.[3]

The dose of replacement therapy is important, as is consideration of the half-life (ca 3 weeks). Giving replacement dose IVIG at monthly intervals is usually less effective because of the reduction in serum levels prior to the next dose. Comparative studies have shown that the trough level of IgG, the serum concentration just prior to the next infusion, is an effective target in preventing infections in primary antibody deficiency.[4] Once a trough IgG level within the normal range is achieved, there is a controversy about whether further increases in the dose of IVIG leads to additional therapeutic efficacy. Asymptomatic progression of bronchiectasis despite optimal IVIG treatment is a problem in a minority of patients.[5]

IVIG immunomodulatory therapy

High-dose IVIG (hdIVIG) is widely used in the treatment of a range of autoimmune and inflammatory conditions (see Ref 6 for detailed review).

Neurological disorders

hdIVIG has become established therapy in a number of neuropathic disorders, including Guillian–Barré syndrome, multifocal motor neuropathy with conduction block and chronic inflammatory demyelinating polyneuropathy. The efficacy of hdIVIG has significantly reduced the need for plasmapheresis in these conditions. Effective responses have been shown in a number of other autoimmune neuropathies, although both the quality of evidence from some trials and the response to therapy within trials have been variable. Many of these conditions are rare, so studies have involved small numbers of patients. Examples of dis-

eases shown to have responses to hdIVIG include refractory dermatomyositis,[7] refractory polymyositis, myasthenia gravis unresponsive to other therapies, Eaton-Lambert myasthenic syndrome, stiff person syndrome and possibly relapsing remitting multiple sclerosis[8] but not secondary progressive MS.[9] The limitation of evidence in these latter conditions suggests that hdIVIG should be used only as second-line therapy. Robust mechanisms should be in place to ensure treatment efficacy rather than placebo effect.

Haematological disorders

The first haematological disease shown to respond to hdIVIG was idiopathic thrombocytopenic purpura,[10] although this is now usually managed with steroids. Other conditions in which IVIG may play a role include acquired haemophilia and reduction of haemolysis in children with haemolytic disease of the newborn. Replacement dose IVIG can be used to prevent cytomegalovirus infection in hypogammaglobulinaemic patients following allogenic stem cell therapy.

Dermatological disorders

A wide range of skin diseases has been treated with hdIVIG. There is good evidence that it should be first-line treatment of children with Kawasaki disease as it reduces the incidence of coronary aneurysms if started within 10 days of symptom onset. The blistering disorders (pemphigus vulgaris, pemphigus foliaceus, bullous and nodular pemphigoid, mucous membrane pemphigoid, gestational pemphigoid, epidermolysis bullosa acquisita and linear IgA disease) are now frequently treated with hdIVIG, although the evidence of efficacy is perhaps greatest for pemphigus vulgaris and cicatricial pemphigoid; double-blind, placebo-controlled trials are needed.

The use of hdIVIG for toxic epidermal necrolysis varies considerably between countries, reflecting the incomplete evidence base and the difficulty in performing large controlled trials with rare conditions. There are also case reports and small series indicating that hdIVIG is effective in atopic eczema, chronic urticaria, scleromyxoedema, pyoderma gangrenosum, pretibial myxoedema, erythema multiforme and psoriasis, although substantially more data will be needed before hdIVIG therapy could be considered routine in these disorders.

Vasculitic disorders

A number of studies have shown that hdIVIG is effective adjunctive therapy in antineutrophil cytoplasmic antibody associated systemic vasculitis (AASV). It has also been used as sole therapy in

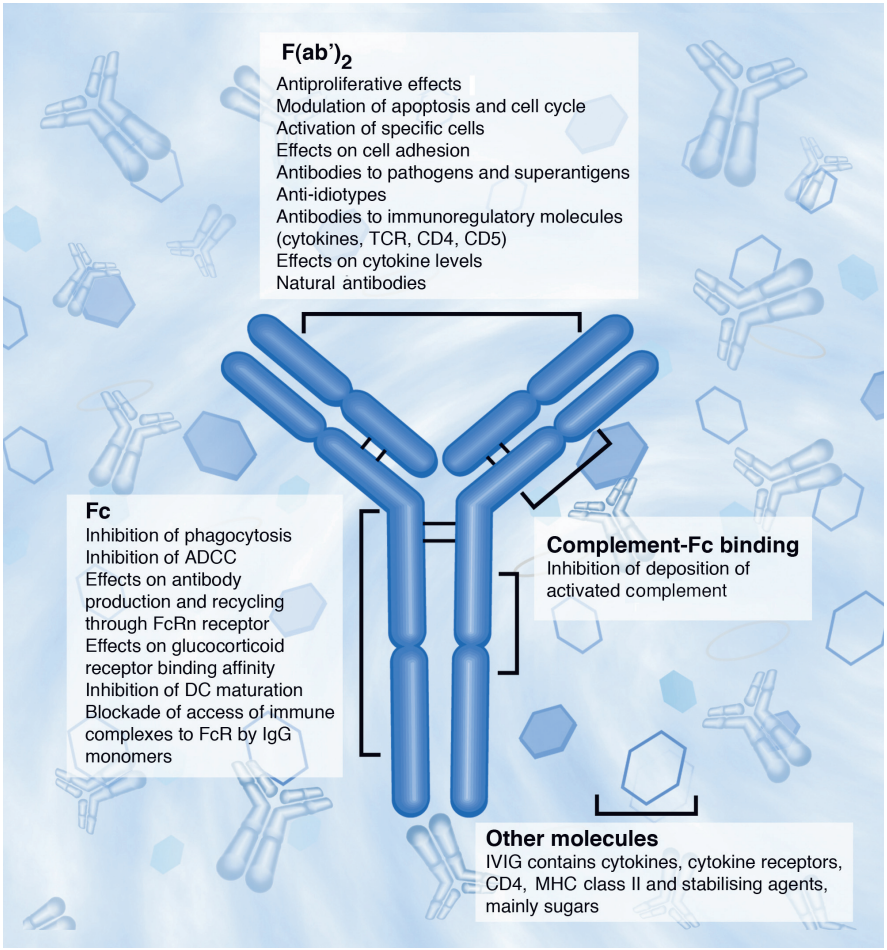

Fig 1. Mechanisms of action of intravenous immunoglobulin (IVIG). To aid understanding, they may be thought of comprising four separate components: actions mediated by the variable regions $F(ab')_2$; actions of Fc region on a range of Fc receptors (FcR); actions mediated by complement binding within the Fc fragment; immunomodulatory substances other than antibody in the IVIG preparations (eg cytokines, soluble cytokine inhibitors, soluble CD4 and major histocompatibility complex (MHC) class II, together with various sugars used as stabilising agents). Not all the potential mechanisms of action fit perfectly into the groupings and several mechanisms may act concurrently. ADCC = antibody-dependent cellular cytotoxicity; DC = dendritic cell; TCR = T cell receptor.

Table 1. Properties of intravenous immunoglobulin preparations currently available in the UK.

Product	Formulation	Manufacturing procedure	Additional antiviral 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	No	720	Sucrose
Sandoglobulin NF	Liquid	pH4	Nanofiltration	<15	None
Vigam Liquid	Liquid	Ion-exchange chromatography	Yes	5	Sucrose

Note: the manufacturing process for all IVIG products has proven in-built antiviral procedures, but some manufacturers have introduced an additional step.
BTS = Blood Transfusion Service; DEA = diethanolamine; NF = nanofiltration; PEG = polyethyelene glycol; SD = solvent detergent.

AASV but not yet in patients with major organ damage. Systemic lupus erythematosus and proliferative lupus nephritis have also responded to hdIVIG in open studies, although randomised controlled trials are lacking, and there are reports of efficacy in birdshot retinochoroidopathy and streptococcal toxic shock syndrome.

Practicalities of IVIG therapy

All patients receiving IVIG should give informed consent. IVIG is a blood product so there should be specific discussion with them about the risks of:

- transmissible infections (including viruses and prions)
- side effects of over-rapid infusion
- anaphylaxis.

There are significant differences in donor pools, stabilisers and additives and production processes between IVIG products. IVIG must therefore always be prescribed by brand name not as generic 'human immunoglobulin'. Having started on one brand, patients should receive that brand in the future and not change to another brand without expert advice, for several reasons:

- limiting exposure to a minimum donor pool reduces the risk of infections
- changing products is associated with a higher risk of reactions[11]
- reducing multiple product exposure facilitates assessment of risk if exposure to a contaminated batch occurs (this may be required only many years after treatment).

The important properties of currently available UK IVIG products are summarised in Table 1.

IVIG administration

Administration of IVIG should be undertaken by experienced staff. In larger centres, immunology specialist nurses can be helpful in assisting with the practicalities of commencing a patient on IVIG. The rate of administration of IVIG is extremely important. A range

Table 2. Adverse effects of intravenous immunoglobulin (IVIG) therapy.

Immediate infusion-related*	• *Mild to moderate*: headaches, backache, chills, nausea and muscle pain occur (ca 1% of infusions) Largely rate-related or due to infusing patients with coexisting infections (IVIG should never be given to patients with active sepsis) • *Severe*: very rarely anaphylaxis may occur in IVIG recipients with high titres of anti-IgA antibodies
Transmission of infective agents*	• *Hepatitis C*: several outbreaks to date Additional antiviral step introduced by most manufacturers following last outbreak in 1994 • *? Prions*: potential risk; no documented cases to date
Consequences of increasing serum Ig**	• *Renal*: reversible renal impairment (most cases), acute renal failure in mixed cryoglobulinaemia • *Haematological*: cerebral and coronary thromboses, acute haemolysis, neutropenia • *Neurological*: acute aseptic meningitis • *Dermatological*: eczema, urticaria, erythema multiforme, cutaneous vasculitis

* may occur with either low or high-dose IVIG; ** predominantly associated with high-dose IVIG.

of side effects can develop rapidly if there is not adherence to manufacturer's guidelines for administration speed. A classification and summary of the more important and frequent IVIG-induced adverse effects are shown in Table 2.

Given the potential for transmission of blood-borne infections via IVIG, it is essential that batch numbers and quantity of IVIG received by the patient are both carefully documented, preferably electronically, so that recipients of suspected contaminated batches can be rapidly identified and risk assessment undertaken in the future.

Several best practice guidelines for IVIG administration are available on the UK Primary Immunodeficiency Network website (www.ukpin.org.uk).

Conclusions

IVIG remains a safe and effective therapy for a wide range of rare disorders. Demand for unlicensed use remains high. This, combined with the potential for greater profits from sales abroad, has resulted in a world shortage of IVIG which particularly affects the UK. Responsible use of IVIG therefore remains a priority for UK physicians.

Acknowledgements

We would like to thank Lesley MacNeill and Joe Brock for expert graphical help. This review summarises information which is described in greater detail in Ref 6.

References

1 Sewell WA, Jolles S. Immunomodulatory action of intravenous immunoglobulin. *Immunology* 2002;107:387–93.
2 Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants. Review. *Cochrane Database Syst Rev* 2004;(1):CD000361.
3 Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. Review. *Cochrane Database Syst Rev* 2004;(1):CD001239.
4 Roifman CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease. *Lancet* 1987;i:1075–7.
5 Kainulainen L, Varpula M, Liippo K *et al.* Pulmonary abnormalities in patients with primary hypogammaglobulinemia. *J Allergy Clin Immunol* 1999;104:1031–6.
6 Jolles S, Sewell WA, Misbah SA. Clinical uses of intravenous immunoglobulin. *Clin Exp Immunol* 2005;142:1–11.
7 Dalakas MC, Illa I, Dambrosia JM *et al.* A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med* 1993;329:1993–2000.
8 Sorensen PS, Fazekas F, Lee M. Intravenous immunoglobulin G for the treatment of relapsing-remitting multiple sclerosis: a meta-analysis. *Eur J Neurol* 2002;9:557–63.
9 Hommes OR, Sorensen PS, Fazekas F *et al.* Intravenous immunoglobulin in secondary progressive multiple sclerosis: randomised placebo-controlled trial. *Lancet* 2004;364:1149–56.
10 Imbach P, Barandun S, d'Apuzzo V *et al.* High-dose intravenous gamma globulin for idiopathic thrombocytopenic purpura in childhood. *Lancet* 1981;i:1228–31.
11 Ameratunga R, Sinclair J, Kolbe J. Increased risk of adverse events when changing intravenous immunoglobulin preparations. *Clin Exp Immunol* 2004;136:111–3.