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Intravenous immune globulin in primary immunodeficiency

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SUMMARY

The development of safe and effective intravenous preparations of immune globulin (IVIG) represents a major advance in the treatment of patients with severe antibody deficiencies. Such therapy is expensive, few trials have been performed to compare one type of IVIG preparation with another under equivalent conditions, and published studies have been of relatively short duration. The overall consensus is that high-dose IVIG (at least 400/mg/kg/month) is superior to lower doses and most clinicians aim to maintain trough IgG levels above an arbitrary level of 5 g/*l*. Adverse reactions, usually mild, are common in antibody-deficient patients during the first few infusions, but severe, anaphylactoid reactions are extremely rare other than in patients with antibodies to IgA. IVIG is not associated with transmission of human immunodeficiency virus or hepatitis B, but there remains a small but definite risk of transmission of non-A, non-B hepatitis, including hepatitis C. Self-infusion of IVIG in the patient's home is a realistic alternative to hospitalization. In the UK, guidelines for home therapy have been approved by professional medical bodies and by the Department of Health. Home therapy has proven to be both safe and cost-effective.

Keywords antibody deficiency IVIG immunoglobulin replacement home therapy

INTRODUCTION

The lives of patients with antibody deficiency have been improved dramatically by the availability and efficacy of immune globulin replacement therapy [1–4]. Initially, IgG formulated for intramuscular injection produced a marked decrease in the prevalence of infections; however, the injections are painful, the amount of IgG that can be given is limited, and anaphylactic reactions are relatively common [5].

The introduction of preparations that can be safely infused intravenously has overcome these problems. Such preparations are well tolerated and effective in most patients and adverse reactions are so infrequent that self-administration of intravenous immune globulin (IVIG) at home is a safe and acceptable form of therapy [6–9].

INDICATIONS FOR IMMUNE GLOBULIN THERAPY

The clearest indication for immune globulin replacement therapy is antibody deficiency [10]. Such deficiencies range from virtually complete absence of all major immunoglobulin classes to more selective disorders, but not all require treatment since they vary in their clinical severity. The most common forms of primary antibody deficiency are common variable immunodeficiency [11] and X-linked hypogammaglobulinaemia [12]. However, patients with IgG subclass deficiencies and specific antibody defects are increasingly recognized [13]. It must be stressed that impaired antibody production, following test immunization if necessary, and not a somewhat low level of an immunoglobulin isotype or subclass, is the key indication for replacement therapy. Consequently, patients with primary immunodeficiency diseases other than exclusively antibody deficiency may benefit: these include disorders such as severe combined immunodeficiency, Wiskott–Aldrich syndrome and ataxia telangiectasia [10].

The availability of immune globulin replacement therapy has greatly reduced the morbidity due to bacterial infections associated with major forms of antibody deficiency [3,14]. This has made early identification of all patients with primary antibody deficiency especially important. Unfortunately, early diagnosis is the exception rather than the rule [15,16]: in the North West of England the average diagnostic delay in primary antibody deficiency was 2·5 years in children and 5·5 years in adults [16], illustrating the poor awareness of this condition. One reason for the lack of awareness, especially in adults, is the widespread but erroneous belief that all forms of primary antibody deficiency present in childhood, whereas 95% of patients with common variable immunodeficiency present after the age of 6 years [11].

IMMUNOGLOBULIN REPLACEMENT

Immunoglobulin replacement therapy can be given via intramuscular, subcutaneous or intravenous routes. Preparations intended for intramuscular or subcutaneous routes must not be given intravenously.

Intramuscular immune globulin

Intramuscular immune globulin (IMIG) has been available for more than 40 years but has now been largely superseded by IVIG. IMIG preparations do not transmit virus infections,

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such as hepatitis B, hepatitis C or human immunodeficiency virus (HIV), but the injections are painful, it is difficult to maintain serum IgG levels above 2 g/*l* and the risk of a severe adverse reaction is significant: up to 20% of patients have an anaphylactoid reaction at some time [5].

Early studies on IMIG by the Medical Research Council demonstrated that the dose given influenced the frequency of infections: patients receiving 50 mg/kg/week developed fewer infections than those treated with the standard dose of 25 mg/kg/week [5].

Subcutaneous immune globulin

Subcutaneous immune globulin infusions have been used in both adults and children. A multi-centre European study to compare the efficacy of subcutaneous infusions with IVIG in adults is about to start, although Gardulf *et al.* [17] have already shown that subcutaneous immune globulin can be administered safely and rapidly.

Intravenous immune globulin

IVIG is the route of choice for most patients with antibody deficiency. At least 17 different preparations have been approved for use by various international regulatory bodies. All are well tolerated and effective, but show individual differences in immunoglobulin subclass distribution and antibody content [18,19].

INTRAVENOUS IMMUNE GLOBULIN THERAPY

World Health Organization criteria

Nearly all IVIG preparations are isolated initially from normal plasma by the Cohn alcohol fractionation method or a modification of it. The World Health Organization [20] established the following production criteria: each lot should be derived from plasma pooled from at least 1000 donors; it should contain at least 90% intact IgG, with the subclasses present in normal ratios; its IgG molecules should maintain biological activity, such as complement fixation; it should be free of prekallikrein activator, kinins, plasmin and preservatives; and it should be free of infectious agents.

In practice, all plasma donations are now screened for hepatitis B surface antigen, and antibodies to HIV and hepatitis C. Commercial lots are produced from plasma pooled from 3000–6000 donors and so contain a broad spectrum of antibodies. Each pool contains adequate titres of antibodies to common antigens, such as tetanus and measles, but there is no standardization of titres of antibodies to other important organisms such as *Streptococcus pneumoniae* or *Haemophilus influenzae*.

Efficacy

The major goal of IVIG therapy is the effective prevention of repeated lung and sinus infections. Few clinical trials have been performed to compare one type of IVIG preparation with another under equivalent conditions, and published studies have been of relatively short duration. The absence of comparison groups has made cross-over studies a common alternative but, unfortunately, many studies have had flaws in design [21].

The efficacy of IVIG was first studied in a cross-over trial [22] comparing the standard intramuscular dose (100 mg/kg/month) with the same dose of an intravenous preparation, and followed by studies in which standard intramuscular treatment was compared with progressively larger doses (150–600 mg/kg/month) of IVIG [23–25]. These studies established that IVIG was superior to IMIG. The efficacy of high-dose (600 mg/kg) versus low-dose (200 mg/kg) replacement regimens was clear when comparing subjective criteria, X-rays, pulmonary function or rates of major or minor infections, and maintenance of a trough serum IgG level greater than an arbitrary level of 5 g/*l* appeared to be of clinical benefit [14].

The efficacy of IVIG in IgG subclass deficiencies is more debatable [13]. For significant IgG1 and/or IgG2 deficiency, coupled with distinct antibody deficits, the use of IVIG is justified. For IgG3 and IgG4 deficiency, the data are less clear-cut [13] because no placebo-controlled trials of therapy in symptomatic children or adults have been published.

Dosage

The optimal dose of IgG for antibody replacement has not been studied prospectively, although comparisons of 100 versus 250 mg/kg/month [26], 150 versus 500 mg/kg/month [27], or 200 versus 600 mg/kg/month [14] all reported improved symptom scores at the higher doses, with much higher trough serum IgG levels. Although these studies were not performed blind, the overall consensus is that high-dose IVIG is clearly superior to low-dose IVIG [4,14,28].

The dose of IVIG needed to keep a patient symptom-free depends on the severity of the antibody defect and the catabolic rate of infused IVIG. Post-infusion serum IgG levels increase by about 2–2·5 g/*l* for each 100 mg/kg infused. Most investigators aim to maintain trough IgG levels above 5·0 g/*l* and this is achieved in most patients by the administration of about 0·4 g/kg/month, usually at 2–3 weekly intervals [4]. Adjustment of both the dose and the infusion interval is empirical.

Metabolism of IVIG

Elimination of radiolabelled IgG depends on the serum concentration. This was shown in studies in which large quantities of IgG were infused into antibody-deficient patients [29]. About half the IgG is redistributed to the extravascular compartment during the first 3–5 days after intravenous infusion.

In normal individuals, the half-life of IgG is 18–23 days but shows subclass variation: IgG1, IgG2 and IgG4 all have half-lives close to this range but the half-life of IgG3 is shorter (7–9 days) [29]. The half-life of serum IgG is variable in patients with antibody deficiency, but most IVIG preparations show half-lives of 30–40 days for IgG, IgG1, IgG2 and IgG4, and 20–24 days for IgG3 [30,31].

Infusion rates

Adverse reactions are common in antibody-deficient patients during the first few infusions; these should be given especially slowly under medical supervision [4]. Although newer IVIG preparations are tolerated much better than first-generation preparations, manufacturers have been cautious in recommending a corresponding increase in standard infusion rates. These rates are 0·01–0·02 ml/kg/min initially, with progressive increases of up to 0·1 ml/kg/min. This results in a maximal rate of 150–300 mg/kg/h. However, carefully selected patients can tolerate very rapid infusion rates [32]. This has the advantage of lessening the duration of hospital attendance for treatment.

Adverse reactions: non-anaphylactic

Adverse reactions may be mild, moderate or severe [4,33]. Mild reactions usually begin within 30 min of the start of the infusion and are characterized by back pain, flushing, chills and myalgia. Mild reactions rarely require the infusion to be stopped but the rate should be slowed until symptoms have subsided. Some investigators advocate pretreatment prophylaxis with aspirin, antihistamines or hydrocortisone but others feel that reactions should not be masked until alternative reasons for such reactions have been excluded. Moderate reactions, such as bronchospasm, wheezing, vomiting, or progressing 'mild' symptoms unresponsive to slowing the infusion, require the infusion to be stopped and appropriate emergency treatment instituted. Severe, anaphylactoid reactions are extremely rare with the present generation of IVIG preparations [1,2,4].

Some patients get delayed symptoms, particularly fatigue and headaches, within 24 h following an infusion. These are usually mild but can last for several hours.

Non-anaphylactoid reactions are usually rate-related and seen most often in newly treated patients or those with active infections. The frequency of reaction falls once infections have been controlled with antibiotics and regular IVIG therapy.

Adverse reactions: anaphylactic

True anaphylactic reactions to IVIG are rare. Signs and symptoms begin seconds to minutes after starting the infusion and typically consist of flushing, facial swelling, dyspnea and hypotension. Such reactions are most commonly due to antibodies to IgA [34] in patients with absolute selective IgA deficiency with or without IgG subclass defects, although IgA antibodies can occur in patients with common variable immunodeficiency. These antibodies are usually of the IgG class [35], although IgM and IgE anti-IgA antibodies have also been reported [34]. Patients with anti-IgA antibodies can successfully and safely receive replacement therapy with those IVIG preparations free (or virtually so) of trace IgA. It should also be remembered that apparent anaphylactic reactions may be self-induced [36].

Immunomodulation

Although IVIG has proved remarkably safe when given to large numbers of antibody-deficient individuals, its poorly understood immunomodulatory properties—a major theme of this symposium—must be borne in mind when considering treatment in patients with debatable indications.

Virus transmission

Fortunately, the cold-ethanol fractionation process substantially reduces the amount of hepatitis B virus present in plasma products and inactivates HIV. Experiments in which donor plasma was spiked with HIV-1 showed that the fractionation process reduced the level of HIV-1 to 10^{-15} of the initial dose [37]. Consequently, there have been no reports of HIV transmission via IVIG even though batches of IVIG were unintentionally prepared from plasma of HIV-infected donors in the early 1980s.

In contrast, several preparations have been associated with major and minor outbreaks of severe, non-A, non-B hepatitis; transmission was related to particular batches of IVIG [38–41]. Current manufacturing processes are on the margin of safety as regards inactivation of non-A, non-B viruses, including hepatitis C, so transmission was probably due to the size of the inoculum. All manufacturers now test all donations for hepatitis C antibodies, as well as for hepatitis B surface antigen and HIV antibodies, and some IVIG products include a heat treatment or detergent solvent step in the manufacturing process specifically to inactivate viruses. Until these steps are shown to prevent hepatitis C infection, potential transmission of this and other unknown viral agents [42] remains a small but definite risk of IVIG therapy.

MONITORING

Monitoring IVIG therapy

The benefits of IVIG therapy can take up to 4–6 months to become apparent, but once a steady state is reached, serum IgG is regularly checked prior to infusion to ensure that target levels for trough serum IgG (about 5–6 g/*l*) are being maintained or exceeded. In children, it is important to ensure that the dose is adjusted as they grow.

Monitoring liver function

Liver function, especially serum transaminase levels, should be measured regularly (every 3 months or so) to exclude subclinical, passively transmitted hepatitis [4]. It has been argued that serum transaminases should be measured at every IVIG infusion in order both to detect a transmission event and to be able to pinpoint the batch of IVIG responsible, so permitting its recall [43]. Batch numbers of preparations infused into individuals must be recorded in the patient notes.

Monitoring infections

A structured monitoring programme is advisable when administering IVIG. Personalized, patient-held, symptom diaries can be used to record the number, duration, site and severity of all infections, all antibiotic usage and any other relevant clinical information.

Monitoring disease progression

Chronic lung disease is the most common cause of death [3] and regular expert review of pulmonary function and structure is an essential component of the long-term management, and crucially important in any studies of efficacy of IVIG therapy. Even with optional antibody replacement therapy, chest damage may progress insidiously unless full ancillary chest treatment is instituted.

HOME THERAPY

The life-long requirement for frequent IVIG infusions is a major inconvenience to the patient with antibody deficiency. Self-infusion of IVIG in the patient's home is a realistic alternative to hospitalization [6–9]. In the UK, guidelines for home immune globulin therapy have been approved by professional medical bodies and by the Department of Health but patients must be trained formally in a recognized centre [4]. Up to July 1993, 248 patients had been trained and registered on home therapy in the UK (V. M. Brennan and H. M. Chapel, personal communication).

The selection of patients is important: they must have received 4–6 months of IVIG therapy without adverse effects;

they must be well motivated; and they must have a parent, partner or caregiver to help them. The patient or helper has to be able to reconstitute the material, perform venepuncture (using a butterfly needle), control the rate, and recognize and treat any adverse reactions.

Self-infusion at home is much more convenient for the patient who avoids travel to and from hospital, as well as time off school or work. The greater involvement of patients in their treatment increases their understanding of the condition, and improves their self-esteem and confidence. In the North West Region of England, over 85% of antibody-deficient patients are now on home therapy and express a high level of patient satisfaction with the programme. Home therapy is also safe: of 50 patients who have received 1480 infusions among them, none has had a serious reaction, and there have been only one moderate and 22 minor reactions (1·5%).

Home therapy is also cost-effective. The average contract price of the different preparations available in the UK ranges from £10–12/g, although there are significant price variations world-wide. Thus, the annual cost of IVIG at a dose of 0·4 g/kg/month is about £4500 for a 70 kg adult and about £650 for a 10 kg infant. Home therapy offers a saving in the added costs of out-patient hospitalization: for a typical patient the saving is about £800/year in the UK [8], and about $2400–3600/year in the USA [7,9].

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