

Immunoglobulin therapy: Methods of delivery

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The goal of immunoglobulin therapy in patients with primary immunodeficiency is to provide adequate broad spectrum antibodies to prevent infections and long-term complications, especially chronic lung disease. IgG preparations are derived from a plasma pool of approximately 10,000 donors by a Cohn ethanol fractionation method. Purification and fractionation processes result in a product that contains 95% to 99% IgG, with varying trace amounts of IgM, IgA, and other plasma proteins. Additions such as sugars, amino acids, or albumin stabilize the IgG molecules from reaggregation. Viral inactivation and viral removal are achieved by various approaches including low pH, solvent and detergent treatment, pasteurization, and nanofiltration.

IMMUNOGLOBULIN INTRAVENOUS THERAPY IN PATIENTS WITH PRIMARY IMMUNE DEFICIENCY

Dosage requirements

Several studies have examined dosage requirements for immunoglobulin intravenous (IGIV) in patients with B-cell immune deficiency. In a randomized crossover study, Roifman et al¹ studied either 600 mg/kg or 200 mg/kg IGIV in 12 patients with antibody deficiency and chronic lung disease. Pulmonary function improved on the higher doses of IGIV therapy. Quartier et al² performed a retrospective study of the clinical features and outcomes of 31 patients with X-linked agammaglobulinemia (XLA) receiving replacement IGIV therapy between 1982 and 1997. IGIV was given at doses of >250 mg/kg/3 wk and achieved a mean serum trough level of 500 to 1140 mg/dL (median, 700 mg/dL). The authors concluded that although achieving a trough serum IgG level of >500 mg/dL was effective in preventing severe acute bacterial infections, these levels did not prevent chronic lung disease. In addition, enteroviral meningoencephalitis still developed in 3 patients. The authors suggested that higher doses of IGIV to

Abbreviations used

IGIV: Immunoglobulin intravenous
SCIG: Subcutaneous immunoglobulin
XLA: X-linked agammaglobulinemia

maintain a serum IgG trough level >800 mg/dL may improve pulmonary outcome. Other studies in patients with common variable immunodeficiency comparing standard doses with high-dose IGIV have shown significant reduction in the number and duration of infections with high-dose IGIV.³ A decrease in number of infections, days missed from school or at work, or hospitalized days may not be sufficient indicators of adequate treatment. Therefore, the improvement or maintenance of pulmonary function is an important measure of the success of therapy. The dosage requirements for patients with XLA and common variable immunodeficiency may be quite different because the risk of enteroviral infections is higher in patients with XLA.

Route of administration: Intravenous

Generally, 400 to 600 mg/kg/mo should raise the trough serum IgG level near the low normal range. On average, peak serum IgG levels increase approximately 250 mg/dL, and trough levels increased 100 mg/kg for each 100 mg/kg of IGIV infused. The target trough level for patients with moderate hypogammaglobulinemia with pretreatment serum IgG levels between 300 to 600 mg/dL should be at least the pretreatment serum IgG level plus 300 mg/dL. Higher trough levels (>800 mg/dL) have the potential to reduce further the incidence of infection and chronic lung disease, as discussed. Ultimately, the dose must be individualized and titrated to achieve clinical benefit for the patient being treated. Variability in the metabolism of IGIV could influence efficacy of therapy. Measurement of preinfusion (trough) serum IgG levels every 3 months until a steady-state is achieved, and then every 6 months if the patients is stable, may be helpful in adjusting the dose of IGIV to achieve adequate serum IgG trough levels. For patients who have a high catabolism, more frequent infusions, such as every 2 to 3 weeks at lower doses, may maintain the serum IgG level in the normal range. The rate of elimination of IgG may be higher during a period of active infection; measuring serum IgG levels and adjusting to higher dosages or shorter intervals may be required.

Initial treatment should be administered in the hospital under close supervision of experienced personnel. The risk of developing adverse reactions in the initial treatments is much higher. In patients with active infection, the dose should be halved to 200 to 300 mg/kg, and the dose repeated 2 weeks later to achieve a full dose. The rate of administration should follow the manufacturer's recommendations. After achieving normal serum IgG levels, adverse reactions are uncommon unless patients have active

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infections. To minimize the cost and inconvenience of in-hospital therapy, studies have been conducted in self-administration and home treatment. For home therapy, patients should be trained under close professional supervision to assure correct techniques; they should be guided on how to recognize and treat adverse reactions; and they must be informed that self-infusions should be done only in the presence of a responsible adult who is ready to assist. Individuals with recurrent, severe adverse reactions with IGIV infusions or those with significant cardiac dysfunction may not be candidates for home infusion therapy. Patients receiving home treatment should be monitored as regularly as patients in hospital-based treatment centers for clinical status, liver function, and serum IgG level. The placement and use of indwelling venous access for IGIV administration should be carefully weighed against the thrombotic and infectious risks inherent to these devices that may be further amplified in immunodeficient patients.

For replacement therapy in patients with primary immune deficiency, all brands of IGIV are equivalent, although there are differences in viral inactivation processes and possibly tolerability. The choice of brands may be dependent on the hospital or home care formulary, and the distributor availability and cost. The dose, manufacturer, and lot number should be recorded for each infusion to perform look-back procedures for adverse events or other consequences. It is crucial to record all side effects that occur during the infusion. It is also recommended to monitor liver and renal function tests periodically, approximately once or twice yearly.

Route of administration: Subcutaneous

The subcutaneous route may also be helpful in patients who experience severe rate-related types of adverse reactions, catabolize the IGIV faster than normal, or want the convenience of self-administration (Table I). The subcutaneous immunoglobulin (SCIG) replacement therapy is safe, well tolerated, and effective in achieving adequate serum IgG levels. In a safety and efficacy study, Ochs et al⁴ reported that the most frequent treatment-related adverse event was infusion site reactions that decreased over time. No treatment-related serious adverse events were reported. Although anaphylactoid and severe adverse reactions are very uncommon, such reactions can occur even with SCIG.

Berger⁵ has detailed the dosage calculations and techniques for SCIG administration. In brief, the calculated monthly dose—for example, 400 to 600 mg/kg/mo—is converted into grams for weekly administration. Depending on the concentrations of the IgG product, such as 10% to 16%, the weekly dose in grams is converted to milliliters of SCIG product. Clinical studies with an approved IgG preparation for the subcutaneous route, such as Vivaglobin 16% (CSL Behring GmbH, King of Prussia, Pa), indicated that a dose of 137% of the intravenous dose may be needed to achieve comparable metabolic rates when administered by the subcutaneous route. Generally, adult patients tolerate 15 to 20 mL per infusion site depending on the amounts of subcutaneous tissues (children can be given 5-10 mL per site; a general guideline is 0.1-0.25 mL/kg/site/h). The number of bottles of SCIG needed per week has to be determined, and teaching the patient to self-administer needs to be arranged. Subcutaneous infusions require a small portable syringe-driver-type pump together with a 10-mL to 20-mL syringe and an infusion set with a specialized subcutaneous 25-gauge to 27-gauge needle. The length of the needle may have to be adjusted for the thickness of the

TABLE I. Comparison of routes of administration of IGIV

Intravenous route	
Advantages	
	Achieve rapid plasma levels
	Can use this route in patients with bleeding disorders
	Intervals of 3-4 wk
Disadvantages	
	Need intravenous access
	Interrupt patient's schedule for period of 3-5 h
	Patient often needs to come to a hospital or infusion center
	Side effects may be more frequent in some patients
Subcutaneous route	
Advantages	
	Intravenous access not needed
	Poor venous access
	Eliminate trough levels
	Achieve a stable serum level of IgG
	May eliminate fatigue of 3rd to 4th wk before next infusion
	Less systemic adverse effects than intravenous route
	More flexibility for patient's (parent's) schedule
	Distance from infusion center or hospital
	Young adults going to college
Disadvantages	
	Minor local reactions at the site of infusion
	Patient reliability
	Need for a pump

subcutaneous tissue of each patient. Before each infusion, the line needs to be checked to ensure that there is no blood return. The SCIG schedule should be started 1 week after the last IGIV infusion, or a new patient should be loaded with 5 to 6 SCIG doses.

Local tissue reactions include swelling, soreness, redness, induration, local heat, itching, and bruising. Infusions need to be given weekly at multiple sites or more often if needed to maintain adequate serum IgG levels. Infusion sites are usually on the abdominal wall and lateral thigh. Before home treatment, patients need to be instructed on the correct technique and the recognition of possible side effects. Because smaller amounts are given more frequently, the serum levels of IgG reach a more steady state compared with the peaks and troughs of the intravenous route. This may have implications in the treatment of autoimmune disorders that require high-dose IVIG therapy. A few recent anecdotal case reports have described success in treating patients with autoimmune neuromuscular diseases with SCIG as maintenance therapy.

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