

The Nuts and Bolts of Immunoglobulin Treatment for Antibody Deficiency



Richard L. Wasserman, MD, PhD *Dallas, Texas*

Immunoglobulin therapy is a key element in the management of most patients with primary immunodeficiency disease. Allergist/immunologists should be familiar with the appropriate evaluation of candidates for immunoglobulin, the characteristics of immunoglobulin products, and how to use them to provide the best care to their patients. Available immunoglobulin products appear to be equally efficacious, but they are not interchangeable. Minimizing the risk of serious adverse events and controlling minor side effects is important to ideal patient care. Immunoglobulin may be administered intravenously or subcutaneously. Individualizing the choice of immunoglobulin product, mode of administration, and site of care can optimize the clinical outcome and minimize the burden of care. © 2016 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2016;4:1076-81)

Key words: Antibody deficiency; Immunodeficiency; Immunoglobulin replacement

IgG replacement has been a key element in the treatment of primary immunodeficiency disease (PID) since Bruton's reports of brothers with recurrent pneumococcal bacteremia and absent gamma globulins in the early 1950s.¹ Although Bruton treated his patients subcutaneously, later with the addition of a "spreading factor,"² immunoglobulin, intramuscular (IGIM) became the norm in the United States. Immunoglobulin replacement significantly decreased bacteremias, but recurrent respiratory tract infections continued to be a major cause of morbidity and premature mortality because of the low IGIM dose, usually 100 mg/kg every 3 weeks. The introduction, in 1981, of immunoglobulin, intravenous (IGIV) allowed for significantly higher doses, revolutionizing the care of patients

with PID. A dose-response relationship was appreciated almost immediately.³

In the United States, IGIV became the standard of care, whereas immunoglobulin, subcutaneous (IGSC) was routine in Scandinavia. Berger et al⁴ resurrected IGSC in 1982, but this route was seldom used in the United States until a specific IGSC product was approved in 2006.⁵ More recently, hyaluronidase-facilitated IGSC (immunoglobulin, hyaluronidase facilitated [IGHy]) has expanded the options.⁶

WHY SHOULD ALLERGIST/IMMUNOLOGISTS KNOW ABOUT IMMUNOGLOBULIN THERAPY?

Immunoglobulin is among the most complex of the drugs commonly prescribed by allergist/immunologists. To optimize their patients' care, prescribers should understand the indications, modes of administration, the selection of a particular product, and the potential for mild and life-threatening adverse events (AEs). In the absence of this knowledge, the prescribing physician may not make the best choices or, worse yet, may cede the decisions to a health care provider who has little or no knowledge of the patient and who may be influenced by factors other than the patient's best interest. Living with PID is burdensome because of recurrent infections and comorbid conditions.⁷ It is important to individualize immunoglobulin administration to minimize the added burden caused by the treatment and associated AEs.

INDICATIONS

This review only considers immunoglobulin therapy for PID. Because antibody production defects are an element of most PIDs, immunoglobulin replacement is the cornerstone of treatment for these disorders. Although many immunodeficiency phenotypes and approximately 300 immunodeficiency genotypes have been identified, not all patients with infection problems or even those with defined PIDs should be treated with immunoglobulin replacement.

There should be no controversy about immunoglobulin treatment for genetically diagnosed patients with a well-described PID such as X-linked agammaglobulinemia, severe combined immunodeficiency, Wiskott-Aldrich syndrome, or others. The appropriateness of immunoglobulin replacement is less straightforward for those patients whose diagnosis is based on their clinical presentation and nongenetic laboratory evaluation. Patients should be considered for immunoglobulin therapy on the basis of a history of severe, or recurrent, or unusually complicated, or poorly responsive bacterial infections and laboratory evidence of an antibody production disorder.⁸

Most immunologists agree that a minimal antibody deficiency evaluation should include measurement of IgA, IgG, and IgM levels. Many will order an IgE because some patients who are

Medical City Children's Hospital and Allergy Partners of North Texas, Dallas, Texas
This study was supported by Allergy Partners of North Texas.

Conflicts of interest: R. L. Wasserman has consultancy arrangements with Shires, ADMA Biologics, Inc., Bioplasma Laboratories, CSL Behring, Kedrion, Grifols, Therapure, and Prometic; has received 1 or more grants from or has 1 or more grants pending with Shires, Octapharma, Bioplasma Laboratories, and Therapure; has received 1 or more payments for lecturing from or is on the speakers' bureau for Shires and CSL Behring; and has received 1 or more payments for the development of educational presentations for Shires.

Received for publication June 14, 2016; revised September 14, 2016; accepted for publication September 21, 2016.

Corresponding author: Richard L. Wasserman, MD, PhD, Allergy Partners of North Texas, 7777 Forest Lane, Ste B-332, Dallas, TX 75230. E-mail: drichwasserman@gmail.com.

2213-2198

© 2016 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2016.09.011>

Abbreviations used

AE- Adverse event
AUC- Area under the time/concentration curve
IGHy- Immunoglobulin, hyaluronidase facilitated
IGIM- Immunoglobulin, intramuscular
IGIV- Immunoglobulin, intravenous
IGSC- Immunoglobulin, subcutaneous
ISR- Infusion-site reaction
IV- Intravenous
PIDD- Primary immunodeficiency disease

deficient in protective antibody production are able to make allergic antibody that may contribute to symptoms. Neither serum IgD concentration nor IgA subclasses correlate with infection risk and should not be measured. Similarly, IgG subclass determinations have poor sensitivity and specificity as markers of clinically important antibody production defects. Because many patients produce nonfunctional immunoglobulin or are able to generate an antibody response only to some antigens, the evaluation should include measurement of the response to protein and carbohydrate antigens.⁸ Diphtheria and tetanus toxoids are the most commonly tested antiprotein responses, and pneumococcal polysaccharide vaccine (PNEUMOVAX®23) is most often used to test the anticarbohydrate response. The use of vaccines in the diagnosis of immunodeficiency has been reviewed.⁹

The appropriate diagnosis and treatment of patients with an infection history suggestive of an immunodeficiency, IgG concentration that is near normal or normal, and a less than robust response to vaccination are controversial.¹⁰ Although disagreement exists regarding the serum IgG concentration below which treatment is mandated (ie, <500 mg/dL, <400 mg/dL, <300 mg/dL, <200 mg/dL) as well as the definition of a normal response to vaccine, the infection history is the most important data element. These issues are more fully discussed elsewhere.⁸ Nevertheless, it is very important to obtain these studies because virtually all third-party payers will require these data as part of their approval process. Notably, the definition of an appropriate immunodeficiency evaluation has evolved significantly over the past 60 years and will certainly continue to evolve as the understanding of the host defense system deepens.

IMMUNOGLOBULIN PRODUCTS

All immunoglobulin products comprise at least 90% to 95% IgG. The US Food and Drug Administration (FDA) terms these products “Immune Globulin X% (Human)” and abbreviates them as IGHy, IGIM, IGSC, and IGIV, relating to the various modes of administration for which a product is approved. Different manufacturers have used synonymous variations such as IVIG and IVIg.

Because there are no prospective studies comparing available immunoglobulin products, comparisons of study reports should be made with caution. Most immunologists regard immunoglobulin products as equivalent, especially with regard to efficacy, but not generic because of differences in the way individual patients tolerate particular products. All immunoglobulins are derived from recovered (ie, blood donations) or source (ie, pheresis donors) plasma from a minimum of 1500 but as many as tens of thousands of donors. Isolation of the IgG component of plasma usually begins with a cold ethanol precipitation

TABLE I. Characteristics of immunoglobulin products

Characteristic	Comments
Concentration IV	One product may be used at 3%, 6%, 9%, or 12%. All others are either 5% or 10%
Concentration subcutaneous	10%-20%
Stabilizers	Carbohydrates such as sucrose or maltose Amphophilic amino acids; glycine or proline
Sodium content	Zero to twice normal saline
Osmolality	Near isosmolal to 1074 mosm
Lyophilized or liquid	Liquid preparations do not require reconstitution
Storage	Most products have some room temperature storage stability
IgA concentration	A few patients with IgA level of <7mg/dL have been reported to make IgE anti-IgA that has caused anaphylaxis. This is a very infrequent occurrence. Products with a very low IgA content are preferred for these patients. Contaminating IgA provides no therapeutic benefit

followed by additional steps to reduce contamination and eliminate or inactivate blood-borne pathogens. The products differ in the isolation process, pathogen removal steps, and excipients or stabilizers (Table I) (for product-specific details, see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). The FDA mandates at least 3 pathogen inactivation/removal steps. There have been no reports of blood-borne infection (including HIV and prion disease) attributed to an immunoglobulin product sold in the United States in more than 20 years.¹¹

IMMUNOGLOBULIN DOSING

The relationship between immunoglobulin dose and clinical outcome has been recognized for at least 30 years.^{3,12} More recently, Orange et al¹³ have shown, using meta-analysis, that increasing the dose of IGIV by 100 mg/kg/mo increases the trough IgG level by 121 mg/dL and decreases the incidence of pneumonia by 27% (Figure 1).

The goal of therapy, however, should be neither the achievement of a particular serum IgG concentration nor the prevention of all infections. Rather, immunoglobulin therapy should minimize serious infections and decrease the rate of all infections to approximately that seen in the normal population.¹⁴ The concept of individualized biologic troughs, initially based on 2 patients whose infections increased when their IgG trough levels fell below a certain level that was different for each patient,¹⁵ and supported by long-term observation of a large cohort of patients with common variable immunodeficiency and X-linked agammaglobulinemia,¹⁴ has become widely accepted.

For decades, immunologists have used IgG trough levels (drawn immediately before a dose of immunoglobulin) as a surrogate marker for efficacy and as a guide to adjust dose. When an IGSC product was developed, the US FDA established a standard requiring that the area under the time/concentration curve (AUC) be at least 80% of the AUC achieved with intravenous (IV) administration (Figure 2). This concept, derived from small molecule pharmacokinetics, posits, in absence of data relating AUC to infection prevention, that the exposure to IgG over time is important to treatment efficacy. Nevertheless, because the IGSC AUC is substantially less than the IGIV AUC,

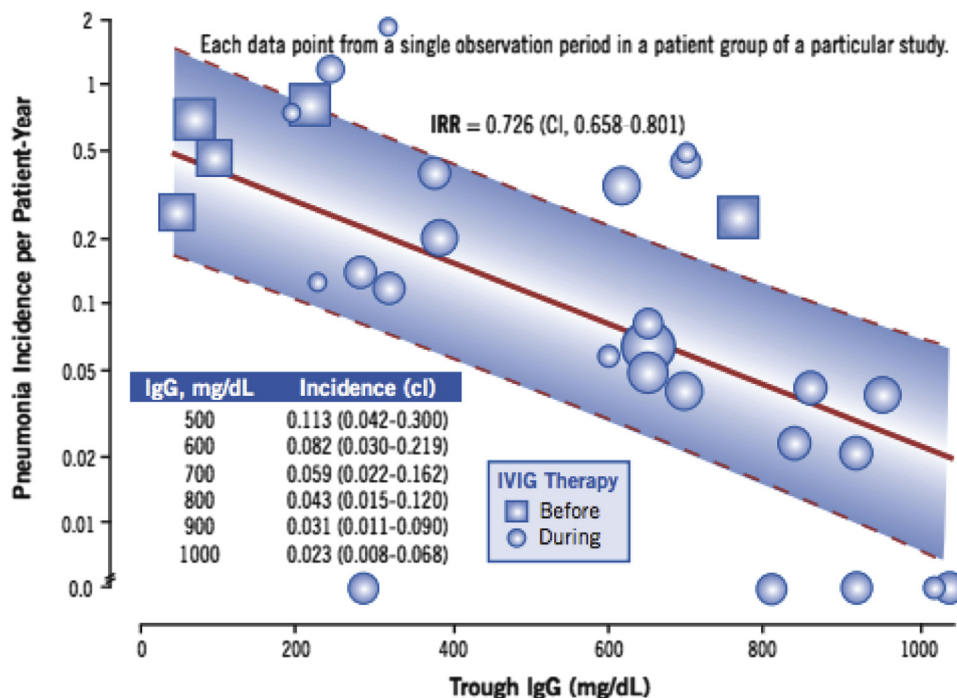


FIGURE 1. Meta-analysis demonstrating a relationship between IgG trough level and pneumonia compiled from published studies of IGIV therapy in patients with PID. Each circle or square represents a single study and the size corresponds to the patient-years of the study. The squares represent the incidence of pneumonia before the start of immunoglobulin therapy. The multilevel model predictions are indicated by the red line and the 95% CI of the meta-regression by the dashed lines. *IRR*, Incidence rate ratio. Reprinted from Orange JS, Grossman WJ, Navickis RJ, Wilkes MM. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: a meta-analysis of clinical studies. *Clin Immunol* 2010;137:21-30,¹³ with permission from Elsevier.

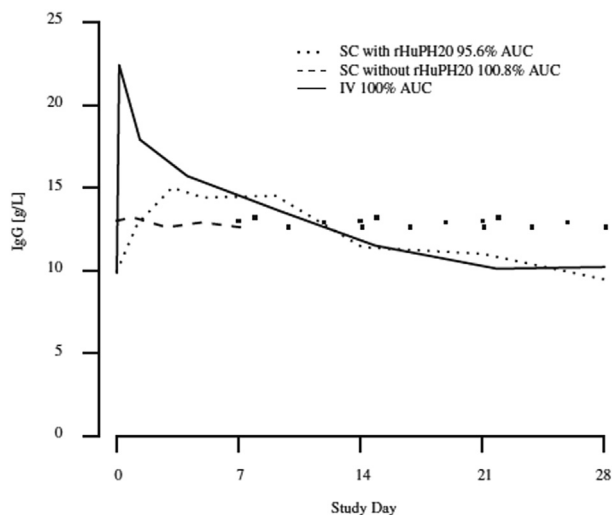


FIGURE 2. Pharmacokinetic curves from one subject comparing a 4-week infusion of IGIV, a weekly infusion of IGSC 10% at 143% of the IV dose with the same data points extended across the 4-week period to facilitate comparison with the other curves, and a 4-week infusion of IGHy at 104% of the IV dose. These curves are typical of pharmacokinetics from other studies of IGIV and IGSC as well as other subjects in this study who received IGHy. Reprinted from Gupta S, Puck J, Engl W. Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency. *J Allergy Clin Immunol* 2012;130:951-7,⁶ with permission from Elsevier.

manufacturers have been required to recommend, in their package inserts, IGSC doses 137% of the comparable IGIV dose. The European Medicines Association has not required a similar dose adjustment factor and many experienced immunologists do not make the dose adjustment.

SERIOUS SIDE EFFECTS

Serious, life-threatening AEs are infrequent among immunoglobulin recipients in general and less common in patients with PID than in those who receive immunomodulatory (higher) doses of immunoglobulin. Although these AEs can occur with any product administered by any route, there are recognizable risk factors¹⁶ and mitigation strategies (Table II). All side effects of immunoglobulin therapy are more common and likely to be more severe when the dose or administration rate is high. Because systemic side effects cannot be predicted, some immunologists administer 50% of the intended first dose and give the remainder the next day. Decreasing the infusion interval so that each infusion will be smaller and slowing the infusion rate should be considered for high-risk patients. Although there may be product-specific serious AE risks,¹⁶ there is a general sense that serious AEs are less frequent with IGSC than with IGIV.

TOLERABILITY

Immunoglobulin tolerability refers to minor (ie, not life-threatening) AEs that occur during or within 72 hours of infusion. Aggregated or denatured IgG, peak IgG level, and mucosal

TABLE II. Serious AE risk factors and mitigation strategies

Serious AE	Patient-specific risk factors	Mitigation strategies
Renal injury/failure	Carbohydrate-containing products, particularly sucrose. Preexisting renal compromise, loop diuretics, age, diabetes	Avoid carbohydrate-containing products in patients with risk factors, ensure good hydration
Thrombosis/embolism	Age, previous thrombosis, recognized general thrombosis risk factor, thrombophilia, hyperviscosity	Measure serum viscosity if indicated, ensure good hydration
Hemolysis	None	No specific recommendation
Aseptic meningitis	History of migraine	Consider pretreatment with a triptan
Transfusion-related acute lung injury	None	No specific recommendations
Heart failure	Preexisting cardiac compromise	Avoid sodium-containing products
Anaphylaxis	The first or second infusion or the first or second infusion after a hiatus of several months	Administer a small test dose of a different product using the subcutaneous route

bacterial colonization have been invoked to explain these reactions but the etiology is not clearly understood. Reactions may be more common when IGIV is administered during an intercurrent infection. IGSC is associated with fewer systemic AEs than is IGIV. IGHy is also substantially better tolerated than is IGIV but is associated with a higher frequency of systemic AEs than is IGSC. Common, nonserious systemic side effects of immunoglobulin infusion include migraine headache, myalgias, malaise, and fatigue. Less commonly, patients may develop fever, diarrhea, rash, chest tightness, and cough or sinus tenderness.

Patients treated subcutaneously may experience infusion-site reactions (ISRs) or local AEs including pain, itch, erythema, and induration. For reasons that are not understood, in each study of IGSC, the frequency of ISRs decreases over the first few months of treatment. It is not possible to define a particular immunoglobulin product as safer or better tolerated than another; however, favorable patient/product pairs occur frequently. That is, a particular patient may tolerate one product better or worse than another.

PREVENTION OF ADVERSE REACTIONS TO IMMUNOGLOBULIN

There are no controlled studies of interventions to prevent or treat immunoglobulin side effects. Some experts premedicate all patients, especially for the first 2 doses. Systemic adverse reactions are treated by prehydration, either oral or IV, slowing the infusion rate, decreasing the dose by shortening the interval between infusions, and administering a nonsteroidal anti-inflammatory drug or acetaminophen, and an antihistamine, diphenhydramine, or hydroxyzine. Glucocorticoids, approximately 1 mg/kg, maximum 40 mg of prednisone, can be given orally 1 to 3 hours before starting the infusion or intravenously immediately before the infusion. Clinicians must, however, be mindful of the total steroid exposure that results from routine premedication. Triptans are useful for headache. Changing to a different product may reduce or eliminate systemic AEs. When systemic AEs are problematic, changing to subcutaneous administration is often the best solution. ISRs are treated with warm or cold compresses (depends on the patient) for discomfort and topical diphenhydramine for itch. Some patients benefit from pretreatment with a topical anesthetic.

TABLE III. Choosing a needle for IGSC administration

Needle length	Patient type
4 mm	Infants, low-BMI toddlers
6 mm	Most toddlers, children, and some lean teenagers and adults
9 mm	Most American adults, BMI < 30
12 mm	Most adults, BMI > 30
14 mm	Obese

BMI, Body mass index.

MODES OF IMMUNOGLOBULIN ADMINISTRATION

IGIV is usually given every 3 to 4 weeks, but some patients are treated every 10 to 14 days. The frequency depends on the patient's schedule, side effects, and end-of-cycle deterioration. Because IGIV requires venous access and many patients require a health care professional to start the IV line, frequent infusions are burdensome for most patients. Home infusion eases the burden but still requires coordination with a health care professional. IGIV bioavailability is 100% and ISRs occur only when the IV infiltrates but systemic AEs are more frequent than with IGSC.

IGSC is most commonly given once a week, but may be given as often as every day or as infrequently as every 2 weeks. Dosing more than once a week (using consequently lower doses) can be very helpful for patients who experience systemic side effects following weekly IGSC infusions. IGSC obviates the need for IV access, rarely requires a health care professional, and is usually self-administered at home.

IGSC bioavailability, however, is 63% of IGIV and, as discussed above, the FDA recommends a dose adjustment of 137% of the IV dose.¹⁷⁻¹⁹ Keeping in mind that the goal of immunoglobulin replacement is infection prevention rather than a specific IgG level target, most experienced immunologists do not apply the dose adjustment factor when converting a patient from IGIV to IGSC. IGSC is recommended for use after at least 1 IV infusion (see package inserts) that serves as a loading dose. If IGSC is dosed weekly without previous IV treatment, it will take 24 weeks to reach a steady-state IgG level.²⁰ The weekly IGSC dose may be given daily for 4 days to provide a loading dose without an IV.

IGHy uses recombinant human hyaluronidase to enhance bulk fluid flow in the subcutaneous space, allowing substantially increased fluid volumes per infusion site and more rapid infusion

TABLE IV. Virtues and drawbacks of modes of immunoglobulin administration

Attribute	IGIV	Conventional IGSC	IGHy
Infusion frequency	Every 3-4 wk	Daily to every 2 wk	Every 2-4 wk
Treatment options	Medical supervision Venous access	Self-administration No venous access	Self-administration or HCP No venous access
Relative dose	100%	137% of IV	100%
Sites (needle sticks)/mo	1	12 (range, 8-20)	1-2
Systemic AEs	Higher than IGSC	Lower than IGIV	Similar to IGSC
Local AEs	Rare	Common	Similar to IGSC

HCP, Health care professional.

rates than does conventional IGSC. In a pivotal trial, patients received up to 600 mL per infusion site at a rate of 300 mL/h/site, allowing the self-administration of a full monthly dose of immunoglobulin in a single site.⁶ In that study, the systemic reaction rate was about 50% of that seen with IGIV and the local ISR rate was comparable to IGSC. Although 18% of subjects developed transient, binding, nonneutralizing antibodies to the hyaluronidase that were not associated with local or systemic AEs, the long-term significance of antihyaluronidase antibodies remains unknown. (For a more detailed discussion of antihyaluronidase antibodies, see this article's Online Repository at www.jaci-inpractice.org.)

TECHNICAL ASPECTS OF IMMUNOGLOBULIN ADMINISTRATION

Most immunologists feel that implanted IV-access devices (Port-a-Cath or similar) are not appropriate solely for IGIV infusions because of the infection²¹ and thrombosis^{22,23} risks. Patients in whom intravenous access is problematic should be treated with IGSC or IGHy. IGIV may be infused using any IV pump or gravity drip. Because of rate-related systemic side effect concerns, infusion rate recommendations begin with a rate of 0.5 mg/kg/min and scale up using several rate changes to a maximum of 8 mg/kg/min.^{24,25} Many patients, however, can tolerate higher infusion rates with fewer rate-change steps. In my experience, most patients prefer shorter infusion times. When a patient has tolerated the IGIV administered according to the package insert for at least 2 infusions, I alter the infusion scheme, one parameter per infusion, by decreasing the steps from starting to maximum rate and increasing the infusion rate maximum by 10% to 20% per infusion as long as there are no systemic side effects. This approach must be individualized because each patient tolerates IGIV differently.

Conventional IGSC is usually infused using a subcutaneous infusion set and pump. Mechanical (wind up) and electromechanical (syringe pumps or peristaltic pumps) are suitable. Because of subcutaneous resistance to bulk fluid flow, conventional IGSC infusions are relatively high-pressure systems. Therefore, IV pumps are not suitable because pressure settings designed to detect IV infiltrates will trigger alarms frequently during IGSC infusion. Although they work well for many patients, mechanical pumps may not generate sufficient pressure for successful infusion in some patients, resulting in unacceptably long infusion times. An IGSC infusion should take about 60 to 90 minutes. Local AEs are common but seldom severe.^{6,17-19} Intradermal infusion is painful and may lead to ulceration and abscess. The most common cause of difficult ISRs is a needle that is too short (see Table III). When prefilling the infusion set, it is important to fill the tubing but not create an immunoglobulin

drop at the needle tip because it will cause pain. If a drop appears, it should be wiped away with an alcohol swab.

"Push" IGSC uses small, frequent (2-7 d/wk) doses pushed by hand with a butterfly needle and syringe. Push is less costly than pumped infusions because the cost of the pump is eliminated and several butterfly needles and 10- or 20-mL syringes cost less than a subcutaneous infusion set. Some patients prefer push because each infusion takes less time than do weekly or biweekly pumped infusions.

When infusing IGHy, the human recombinant hyaluronidase is pushed by hand using a syringe and a high-flow subcutaneous infusion set. Following the hyaluronidase infusion, the immunoglobulin is administered through the same infusion set using a syringe or peristaltic pump with a high-pressure shut-off. Although the hyaluronidase pretreatment results in a low-pressure subcutaneous infusion, the high flow rate causes back pressure within the infusion set and tubing. This problem is eliminated by using a high-flow infusion set; unnecessary pressure shut-offs resulting in very long infusion times may occur if a standard IV pump is used.

CHOOSING/RECOMMENDING A ROUTE IN A NEW PATIENT

When the diagnosis of immunodeficiency is made in an acutely ill patient, I explain the initial choice of a mode of immunoglobulin treatment in a very directive way. In acutely ill, hospitalized patients, I recommend an initial dose of 1 g/kg administered intravenously over 12 to 24 hours. Because the patient is hospitalized, using a long infusion time to minimize side effects is not a problem. If the patient is acutely ill, but not hospitalized, I will administer 500 to 600 mg/kg intravenously following the package insert. The IV route rapidly achieves a high serum IgG concentration that may play a role in recovery from the active illness.

When the patient is not acutely ill, the modes of immunoglobulin administration (Table IV) should be explained to the patient to encourage the shared decision making that will lead to a better understanding of the therapy and better adherence. This discussion should include a description of common systemic side effects as well as ISRs that occur frequently so that the patient knows what to expect and knows that the infusion reactions typically decrease in frequency and severity over time.^{25,26}

MONITORING PATIENTS RECEIVING IMMUNOGLOBULIN

Physicians prescribing immunoglobulin should maintain close contact with their patients and, whenever possible, be directly involved in the treatment of their infections. Experts differ on the frequency of visits between monthly and annually. It is important to set high goals for infection control and communicate

those goals to patients with PIDD who often become accustomed to not feeling well.⁷ Each visit should include queries related to interval infections, the immunoglobulin infusion experience, side effects, and end-of-cycle deterioration that suggests the need for a higher dose or shorter interval between infusions. The patient's weight (for both adults and children) and vital signs should be obtained before beginning the infusion. If a reaction occurs during the infusion, vital signs should be repeated frequently until the reaction improves. In my experience, asking the patients how they feel during the infusion is more informative than scheduled vital signs. Complete blood cell count, liver and kidney function tests, and a trough IgG level should be obtained before starting a new product and at least annually after that. Some young patients, treated appropriately at presentation, may experience immune maturation, eliminating the need for immunoglobulin. Young patients should be considered for reevaluation after 2 to 5 years of therapy.

INSURANCE APPROVALS

Immunoglobulin is a costly therapy and therefore most payers require a prior authorization for treatment. Even if the therapy is provided by a specialty pharmacy, the prescribing physician will be required to provide a letter of medical necessity. In my experience, it is possible to identify the elements of a sweet spot in creating such letters. The core components of a letter of medical necessity are a brief summary of the history, the diagnosis, the dose and brand of immunoglobulin (always prescribe immunoglobulin by brand without substitution), the infusion interval, and supporting laboratory studies. Standard letter templates (see this article's Online Repository at www.jaci-inpractice.org) can be incorporated into an electronic medical record and customized. Letters should be as short as possible so that the key information can be readily identified.

SUMMARY

Allergist/immunologists who care for patients with PIDD will provide the best care if they understand the elements of immunoglobulin therapy and individualize immunoglobulin dose, route, and frequency of treatment to optimize patients' outcomes by minimizing the burden of care.

Acknowledgments

I thank the many patients with PIDD and families from whom the proper use of immunoglobulin therapy was learned. Drs Mark Stein and Robert Sugerman provided valuable comments on this manuscript.

REFERENCES

- Bruton OC. Agammaglobulinemia. *Pediatrics* 1952;9:722-8.
- Bruton OC. Agammaglobulinemia: a working concept. *Hawaii Med J* 1956;16:147-9.
- Pirowsky B. Intravenous immune globulin therapy in hypogammaglobulinemia: a review. *Am J Med* 1984;76:53-60.
- Berger M, Cupps TR, Fauci AS. High-dose immunoglobulin replacement therapy by slow subcutaneous infusion during pregnancy. *JAMA* 1982;247:2824-5.
- Ochs HD, Gupta S, Kiessling P, Nicolay U, Berger M. Subcutaneous IgG Study Group. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. *J Clin Immunol* 2006;26:265-73.
- Wasserman RL, Melamed I, Stein MR, Gupta S, Puck J, Engl W, et al. Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency. *J Allergy Clin Immunol* 2012;130:951-7.
- Seeborg FO, Seay R, Boyle M, Boyle J, Scalchunes C, Orange JS. Perceived health in patients with primary immune deficiency. *J Clin Immunol* 2015;35:638-50.
- Bonilla FA, Khan DA, Ballas ZK, Chinen J, Frank MM, Hsu JT, et al. Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; and the Joint Council of Allergy, Asthma & Immunology. Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol* 2015;136:1186-1205.e1-78.
- Orange JS, Ballou M, Stiehm ER, Ballas ZK, Chinen J, De La Morena M, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2012;130:S1-24.
- Gelfand EW, Ochs HD, Shearer WT. Controversies in IgG replacement therapy in patients with antibody deficiency diseases. *J Allergy Clin Immunol* 2013;131:1001-5.
- Centers for Disease Control and Prevention (CDC). Outbreak of hepatitis C associated with intravenous immunoglobulin administration — United States, October 1993-June 1994. *MMWR Morb Mortal Wkly Rep* 1994;43:505-9.
- Roifman CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinemia and chronic lung disease. *Lancet* 1987;1:1075-7.
- Orange JS, Grossman WJ, Navickis RJ, Wilkes MM. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: a meta-analysis of clinical studies. *Clin Immunol* 2010;137:21-30.
- Lucas M, Lee M, Lortan J, Lopez-Granados E, Misbah S, Chapel H. Infection outcomes in patients with common variable immunodeficiency disorders: relationship to immunoglobulin therapy over 22 years. *J Allergy Clin Immunol* 2010;125:1354-1360.e4.
- Bonagura VR, Marchlewski R, Cox A, Rosenthal DW. Biologic IgG level in primary immunodeficiency disease: the IgG level that protects against recurrent infection. *J Allergy Clin Immunol* 2008;122:210-2.
- Sridhar G, Ekezu BF, Izurieta HS, Selvam N, Ovanesov MV, Divan HA, et al. Immune globulins and same-day thrombotic events as recorded in a large health care database during 2008 to 2012. *Transfusion* 2014;54:2553-65.
- Hagan JB, Fasano MB, Spector S, Wasserman RL, Melamed I, Rojavin MA, et al. Efficacy and safety of a new 20% immunoglobulin preparation for subcutaneous administration, IgPro20, in patients with primary immunodeficiency. *J Clin Immunol* 2010;30:734-45.
- Wasserman RL, Melamed I, Kobrynski L, Strausbaugh SD, Stein MR, Sharkhawy M, et al. Efficacy, safety, and pharmacokinetics of a 10% liquid immune globulin preparation (GAMMAGARD LIQUID, 10%) administered subcutaneously in subjects with primary immunodeficiency disease. *J Clin Immunol* 2011;31:323-31.
- Wasserman RL, Irani AM, Tracy J, Tsoukas C, Stark D, Levy R, et al. Pharmacokinetics and safety of subcutaneous immune globulin (human), 10% caprylate/chromatography purified in patients with primary immunodeficiency disease. *Clin Exp Immunol* 2010;161:518-26.
- Rojavin M, Sidhu J, Pfister M, Hubsch A. Subcutaneous immunoglobulin loading regimens for previously untreated patients with primary antibody deficiency. *Clin Exp Immunol* 2014;178:146-8.
- Stein MR. Sepsis masquerading as reaction to gammaglobulin. *Ann Allergy Asthma Immunol* 1998;81:96.
- Benadiba J, Robitaille N, Lambert G, Itaj NK, Pastore Y. Intravenous immunoglobulin-associated thrombosis: is it such a rare event? Report of a pediatric case and of the Quebec Hemovigilance System. *Transfusion* 2015;55:571-5.
- Albisetti M, Kellenberger CJ, Bergsträsser E, Niggli F, Kroiss S, Rizzi M, et al. Port-a-cath-related thrombosis and postthrombotic syndrome in pediatric oncology patients. *J Pediatr* 2013;163:1340-6.
- Wasserman RL, Church J, Stein M, Moy J, White M, Strausbaugh S, et al. Safety, efficacy and pharmacokinetics of a new 10% liquid intravenous immunoglobulin (Bivigam™ IVIG) in patients with primary immunodeficiency. *J Clin Immunol* 2012;32:663-9.
- Jolles S, Orange JS, Gardulf A, Stein MR, Shapiro R, Borte M, et al. Current treatment options with immunoglobulin G for the individualization of care in patients with primary immunodeficiency disease. *Clin Exp Immunol* 2015;179:146-60.
- Wasserman RL. Common infusion-related reactions to subcutaneous immunoglobulin therapy: managing patient expectations. *Pat Pref Adherence* 2008;2:163-6. Available from: <http://www.dovepress.com/common-infusion-related-reactions-to-subcutaneous-immunoglobulin-therapy-peer-reviewed-article-PPA>. Accessed June 5, 2016.

APPENDIX



Characteristics of Immune Globulin Products Used to Treat Primary Immunodeficiency Diseases Licensed for Use in the United States

BRAND NAME	Gamgarrd S/D		Gamgarrd Liquid	HYQVIA*	Gammaglex	Bivigam	Carimune NF	Hizentra	Privigen	Febogamma DIF	Gamunex - C	Gammaked	Octagam
	5%	10%											
MANUFACTURER	Baxalta Incorporated	Baxalta Incorporated	Baxalta Incorporated	Bio Products Laboratory	Biotech Pharmaceuticals Corporation	CSL Behring	CSL Behring	CSL Behring	CSL Behring	Grifols	Grifols	Kedron	Octapharma
METHOD OF PRODUCTION (Including Viral Inactivation)	Cohn-Onsley fractionation, ion-exchange chromatography, solvent detergent treatment	Cohn-Onsley fractionation, ion-exchange chromatography, solvent detergent treatment	Cohn-Onsley fractionation, ion-exchange chromatography, solvent detergent treatment	IG 10% (human) of HYQVIA; Cohn-Onsley fractionation, ion-exchange chromatography, solvent detergent treatment, 35m nanofiltration, low pH elevated temperature incubation Recombinant human hyaluronidase produced from genetically engineered Chinese Hamster Ovary (CHO) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase PH20	Kidder & Nitschmann fractionation, solvent detergent treatment, DEAE-Sephadex chromatography, solvent detergent treatment, CM-Sephadex chromatography, Virus Filtration (20 nm) Terminal low pH incubation (30°C, 2 weeks)	Cohn-Onsley fractionation, Anion exchange chromatography; Precipitation and removal of fraction III of the cold ethanol process, solvent detergent treatment, 35 nm nanofiltration	Kidder Nitschmann fractionation, pH 4.0, trace pepsin, nanofiltration, TSE Reduction Steps	Cold alcohol fractionation, octanoic acid fractionation, anion exchange chromatography; pH 4 incubation, depth filtration, nanofiltration; TSE reduction steps include octanoic acid fractionation, depth filtration, and virus filtration	Octanoic Acid Fractionation, CHB Filtration, pH 4.0 incubation, depth filtration, Chromatography, Nanofiltration, TSE Reduction Steps	Cold alcohol fractionation, polyethylene glycol precipitation, ion exchange chromatography, pH 4 treatment, pasteurization, solvent detergent treatment, and double sequential nanofiltration through 35 and 20 nm filters	Cohn-Onsley fractionation, caprylic/ chromatography purification, cloth and depth filtration, final container low pH incubation	Cohn-Onsley fractionation, caprylic/ chromatography purification, cloth and depth filtration, final container low pH incubation	Cohn-Onsley cold ethanol fractionation, ultra-filtration, chromatography, solvent detergent treatment
FORM	Lyophilized	Liquid	Liquid	Liquid	Liquid	Lyophilized	Liquid	Liquid	Liquid	Liquid	Liquid	Liquid	Liquid
SHELF-LIFE/STORAGE REQUIREMENT	24 Months (room temperature storage)	36 Months (refrigerated) 24 Months (room temperature storage not to exceed 25°C or 77°F)	36 Months (refrigerated) 3 Months (room temperature storage not to exceed 25°C or 77°F)	24 Months (room temperature storage)	24 Months (refrigerated)	24 Months	30 Months (room temperature storage)	36 Months (room temperature storage)	24 Months (room temperature storage)	36 Months	36 Months	24 Months	
RECONSTITUTION TIME	N/A	None (Liquid Solution)	None (Liquid Solution)	None (Liquid Solution)	N/A	Several Minutes	None (ready-to-use Liquid Solution)	None (Liquid Solution)	None (Liquid Solution)	None (Liquid Solution)	None (Liquid Solution)	None (Liquid Solution)	None (Liquid Solution)
AVAILABLE CONCENTRATIONS	5% 10%	10%	10%	10%	5% 10%	10%	3 to 12%	20% (200 mg/mL)	10%	5% 10%	10%	10%	5%
MAXIMUM RECOMMENDED INFUSION RATE	4 mL/kg/hour 8 mL/kg/hour	5 mL/kg/hour	>40 kg BW: 3mL/shrt <40 kg BW: 2mL/shrt str at 150mL/site	< 40kg BW: maximum 160 mL/site > 40kg BW: maximum 300 mL/site	4.8 mL/kg/hour	3.5 mL/kg/hour	Maximum 3 mg/kg/min (2 mg/kg/min for patients with renal dysfunction or thrombotic risk)	Up to 25 mL/hr/injection site (50 mL/hr for all sites combined)	4.8mL/kg/hour	6.0 mL/kg/hour 4.8 mL/kg/hour	4.8 mL/kg/hour (IV) 20 mL per hour (SC)	4.8 mL/kg/hour (IV) 20 mL per hour (SC)	<4.2 mL/kg/hour
*TIME TO INFUSE 35 gms	Time will vary based on concentration and tolerability	Time will vary based on concentration and tolerability	Time will vary based on tolerability and route of administration	Time will vary based on patient tolerability	125 minutes or 2.05 hours	Time will vary based upon patient tolerability; 145.5 min based on recommended infusion rates	Variable based on patient tolerability	Time will vary depending upon volume and tolerability	Variable based on patient tolerability	1.6 hours 1 hour	Time will vary depending on route of administration	Time will vary depending on route of administration	2.5 hours
SUGAR CONTENT	20 mg/mL glucose	40 mg/mL glucose	No added sugars	No added sugars	5% D-sorbitol (polyol)	No added sugars	1.67 gm sucrose per gram of protein	None	None	None	None	None	100 mg/mL maltose
SODIUM CONTENT	8.5 mg/mL sodium chloride	17 mg/mL sodium chloride	No added sodium	8.5 mg/mL sodium chloride in recombinant human hyaluronidase. No added sodium in IG 10%	30 - 50 mmol/L	0.100-0.140 M sodium chloride	<20 mg sodium chloride per gram of protein	Trace Amounts (<10 mmol/L)	Trace Amounts	Trace Amounts	Trace Amounts	Trace Amounts	<30 mmol/L
OSMOLALITY/ OSMOLALITY	636 mOsm/kg	1250 mOsm/kg	240-300 mOsm/kg	240-300 mOsm/kg	460-500 mOsm/kg	< 510 mOsm/kg	192-1074 mOsm/kg	380 mOsm/kg	isotonic (320 mOsm/kg)	240-370 mOsm/kg	258 mOsm/kg	258 mOsm/kg	310-380 mOsm/kg
PH	6.8 ± 0.4	4.6 - 5.1	4.6 - 5.1	4.6 - 5.1	4.6 - 5.1	4.0 - 4.6	6.4 - 6.8	4.6 - 5.2	4.8	5.0 - 6.0	4.0 - 4.5	4.0 - 4.5	5.1 - 6.0
IgA CONTENT	≤ 1 µg/mL < 2.2 µg/mL	N/A	37 µg/mL	37 µg/mL	Average: <4 mcg/mL (Specification value: <10 mcg/mL)	≤ 200 µg/mL	720 µg/mL	≤50 mcg/mL	< or = 25mcg/mL	Average: <3 mcg/mL (Specification value: < 50 mcg/mL) Average: <3 mcg/mL (Specification value: < 100 mcg/mL)	46 µg/mL	46 µg/mL	<100 µg/mL
APPROVED METHOD OF ADMINISTRATION	Intravenous	Intravenous	Subcutaneous	Subcutaneous	Intravenous	Intravenous	Intravenous	Subcutaneous	Intravenous	Intravenous	Intravenous	Subcutaneous	Intravenous

*0.5 g/mL for a 70 kg adult = 35 gms; 5% Concentrations: 1g = 10 mL.
 *Time will vary depending upon volume and tolerability. Using 35 grams as monthly dose, calculate weekly dose: 6.75 grams/55 mL, infused into 4 sites @ rate up to 20mL/hr/site, which can range from 45 mins. To 3 hrs.
 *No longer sold in the U.S.
 *HYQVIA is a dual unit containing 10% IgG (100 mg/mL) and 150 U/mL recombinant human hyaluronidase.
 *Shorter room temperature shelf life of HYQVIA (3 months) compared to Gamgarrd Liquid (24 months) is due to the recombinant human hyaluronidase component of HYQVIA.
 *The time to infuse is based on the maximal infusion rate. Check product label for storage temperatures, which vary among immunoglobulin brands. Check package insert for detailed prescribing information. Information for each of the products listed above has been provided directly to IDF by the manufacturer of that product.

Immune Deficiency Foundation
 110 West Road, Suite 300, Towson, MD 21204
 Phone: 800-296-4433 | E-mail: idf@primaryimmune.org | Website: www.primaryimmune.org

FIGURE E1. Characteristics of immunoglobulin products used to treat PIDDs licensed for use in the United States.

CONSIDERATIONS IN CHOOSING PARTICULAR IMMUNOGLOBULIN PRODUCTS

The following section presupposes that product price and insurance company preferences play no role. Clinicians should weigh the increased risks of low-frequency side effects against financial considerations that may impact the patient's ability to get immunoglobulin therapy. This section is based primarily on the author's 35-year experience with IGIV and addresses issues that have never been subject to prospective controlled trials.

Among immunoglobulin products, both IV and subcutaneous, there are no efficacy differences. The choice of a particular product should be guided by considerations of risk for serious, life-threatening AEs and tolerability. In this section, I offer comments on the clinical relevance of product differences. An important difference among the products is how the immunoglobulin molecules are treated during isolation. This difference may account for some of the tolerability difference.

Carbohydrate and saline—stabilized versus amino acid—stabilized IGIV products

There is a clear association between carbohydrate-stabilized IGIV and renal injury. Although the strongest association is with sucrose, there is some concern about other carbohydrates as well. Other risk factors for IGIV-associated renal injury are preexisting renal compromise, age, hypertension, and diabetes. Because carbohydrate-free products are available, many clinicians

choose to avoid adding a risk factor to a patient already at increased risk of renal compromise.

Osmolality and sodium content

Patients such as those with abnormal cardiac or renal function may develop fluid overload when infused with products high in osmolality or sodium content. There are particular concerns for those with compensated congestive heart failure and sick neonates. Some clinicians believe that infusion-related headache, the most common side effect of IGIV, is caused by fluid shifts. If infusion headache is a concern, a low-sodium, near-isosmolar product is preferred.

Concentration

All products except for one are either 5% or 10% in IgG concentration. Obviously, using 10% cuts the fluid load in half.

ANTIHYALURONIDASE ANTIBODY SAFETY

There are no data-based questions regarding the impact of antihyaluronidase antibodies on fertilization. The target of these antibodies is expressed only in postpubertal males, never in females of any age (including fetal) and not in prepubertal males. Approximately 5% of the general adult population tests positive for antihyaluronidase antibodies. Having antihyaluronidase antibodies does not appear to correlate with infertility or past pregnancy complications.

In addition, animal studies in mice, rabbits, and nonhuman primates (in whom antihyaluronidase antibodies are neutralizing and, because the recombinant human hyaluronidase is xenogenic, have much higher titer) have failed to reveal any abnormalities of fertilization, reproduction, or pregnancy outcome. In the absence, however, of fertility studies in humans, the effect of antihyaluronidase antibodies on human fertility is unknown.

In actuality, "unknown" means unknown, not further defined.

SAMPLE LETTERS OF MEDICAL NECESSITY

These letters are structured to be incorporated into an electronic medical record. They include the common PIDD diagnoses for which immunoglobulin therapy is prescribed and the products most often used in our patients. They are designed so that the physician will highlight and delete diagnoses, products, and dosing intervals that are not relevant to the individual patient and will customize the text and dose.

IGIV initiation of therapy

Medical Director

Patient Insurance Company

RE: Patient

DOB:

ID:

GROUP:

Dear Doctor:

I am writing to request authorization of immunoglobulin supplementation therapy for the above-referenced patient with a disorder of antibody production. I have recommended intravenous immunoglobulin therapy for this patient.

This patient had a long history of recurrent bacterial respiratory tract infections. An immunologic evaluation demonstrated disorder of antibody production (laboratory studies attached). The specific diagnosis is listed below. Because his infections could not be controlled with the most aggressive conventional therapy, this patient needs immunoglobulin supplementation therapy.

Large studies of immunoglobulin therapy in immunodeficiency patients have shown that a statistically significant therapeutic response is seen after 1 year of therapy. Therefore, I request authorization to treat this patient for at least 1 year. His need for this therapy, however, will be lifelong.

Primary diagnosis:

D80.0—X-Linked agammaglobulinemia, autosomal-recessive agammaglobulinemia, hypogammaglobulinemia

D80.6—Antibody deficiency with near-normal immunoglobulins or with hypergammaglobulinemia

D80.9—Immunodeficiency with predominantly antibody defects

D83.0—Common variable immunodeficiency with predominantly B-cell abnormalities

D83.1—Common variable immunodeficiency with predominantly T-cell abnormalities

D83.2—Common variable immunodeficiency with predominantly B- or T-cell autoantibodies

D83.8—Common variable immunodeficiency, other

D83.9—Common variable immunodeficiency, unspecified

D82.1—DiGeorge syndrome

Drug: Bivigam J1556

Drug: Gammagard J1569

Drug: Carimune J1566

Drug: Gamunex/Gammaked J1561

Drug: Privigen J1459

Drug: Octagam J1568

Dose: grams

Interval: every 3–4 weeks

Duration of therapy: requesting 1 year, will need it for life

Thank you for your prompt attention to this matter. If you require further information, please contact me.

Sincerely,

Transition from IGIV to IGSC

Medical Director

Patient Insurance Company

RE: Patient

DOB:

ID:

GROUP:

Dear Doctor:

I am writing to inform you that I have recommended replacement of intravenous gamma globulin supplementation therapy with subcutaneous gamma globulin infusion for this patient. This change is recommended to reduce the risk of thrombosis, because of difficult venous access, because of unacceptable side effects, and because of increased risk of thrombotic complications and renal failure due to age, obesity, diabetes, and hypertension.

Because of the decreased bioavailability of subcutaneously administered immunoglobulin, the FDA recommends adjusting the dose of subcutaneous immunoglobulin to 137% of the monthly IV dose.

Primary diagnosis:

D80.0—X-Linked agammaglobulinemia, autosomal-recessive agammaglobulinemia, hypogammaglobulinemia

D80.6—Antibody deficiency with near-normal immunoglobulins or with hypergammaglobulinemia

D80.9—Immunodeficiency with predominantly antibody defects

D83.0—Common variable immunodeficiency with predominantly B-cell abnormalities

D83.1—Common variable immunodeficiency with predominantly T-cell abnormalities

D83.2—Common variable immunodeficiency with predominantly B- or T-cell autoantibodies

D83.8—Common variable immunodeficiency, other

D83.9—Common variable immunodeficiency, unspecified

D82.1—DiGeorge syndrome

Dose: grams

Interval: more frequently than weekly, weekly, biweekly

Duration of therapy: requesting 1 year, will need it for life

If you require further information, please contact me.

Sincerely,

Transition from IGSC to IGHy

Medical Director

Patient Insurance Company

RE: Patient

DOB:

ID:

GROUP:

Dear Doctor:

I am writing to inform you that I have recommended replacement of conventional subcutaneous immunoglobulin

supplementation therapy with enzyme-facilitated subcutaneous immunoglobulin infusion using HyQvia for this patient. This change is recommended because of infusion-site reactions, because of the large number of infusion sites, and because the high frequency of conventional subcutaneous infusions interferes with adherence to the treatment regimen.

Note that in contrast to conventional subcutaneous immunoglobulin infusion, no dose adjustment is recommended for HyQvia when compared with intravenous immunoglobulin.

Primary diagnosis:

D80.0—X-Linked agammaglobulinemia, autosomal-recessive agammaglobulinemia, hypogammaglobulinemia

D80.6—Antibody deficiency with near-normal immunoglobulins or with hypergammaglobulinemia

D80.9—Immunodeficiency with predominantly antibody defects

D83.0—Common variable immunodeficiency with predominantly B-cell abnormalities

D83.1—Common variable immunodeficiency with predominantly T-cell abnormalities

D83.2—Common variable immunodeficiency with predominantly B- or T-cell autoantibodies

D83.8—Common variable immunodeficiency, other

D83.9—Common variable immunodeficiency, unspecified

D82.1—DiGeorge syndrome

Drug: HyQvia J3490

Ramp up schedule will comprise the following:

Week #1: grams

Week #2: grams

Week #4: grams

Week #7 and every 4 weeks thereafter: grams

Duration of therapy: requesting 1 year, will need it for life

Thank you for your prompt attention to this matter. If you require further information, please contact me.

Sincerely,

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.