

Considerations for the Optimal Use of Immunoglobulin

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The purpose of this supplement is to educate managed care practitioners and decision makers about the appropriate and optimal use of immunoglobulin G (IgG). It reviews the use of IgG in immunodeficiency syndromes, discusses differences in IgG products (eg, formulations and routes of administration), and describes practical challenges related to IgG use for payers, practitioners, and patients. The advent of numerous intravenous and subcutaneous formulations of IgG presents new opportunities impacting patient preferences, site of care, and costs. The content of this supplement is based on a review of scientific literature and discussions from an expert roundtable panel consisting of clinicians and managed care professionals.

Immune Globulin Products

Immunoglobulins (Ig) are large Y-shaped proteins produced by B-cells and plasma cells that are used by the immune system to identify and neutralize foreign objects such as bacteria and viruses. There are 5 Ig isotopes—IgA, IgD, IgE, IgG, and IgM. The majority of antibody-based immunity to pathogens involves IgG. As a result, people with low IgG levels are at greater risk of infections. This was well documented in 1952 when Dr Ogden Bruton treated an 8-year-old boy with a 3-year history of unrelated but continuous serious infections and illness.

After numerous attempts to understand the etiology of the child's illness, it was determined that he had agammaglobulinemia, an inherited disorder in which there are very low levels of Ig. Once the diagnosis was established, Dr Bruton subcutaneously administered human serum globulin (containing 3.2 g of gamma globulin) to the child. Following treatment, he had no further illnesses.¹

Following Dr Bruton's discovery and published results, numerous Ig preparations were developed with different routes of administration. An initial attempt to use an intravenous (IV) formulation proved to be unsafe, as severe anaphylactic reactions were documented.² This was followed by attempts to administer Ig intramuscularly.³ Unfortunately, intramuscular preparations had unique challenges, including pain at the injection site, difficulty in delivering large doses, highly inconsistent absorption, and limited duration of action.⁴

In the late 1970s and early 1980s, improvements in IVIg production led to the development of several preparations.³ These

Abstract

Immunoglobulins are large Y-shaped proteins produced by B-cells and plasma cells that are used by the immune system to identify and neutralize foreign objects such as bacteria and viruses. Immunoglobulin G (IgG) preparations are approved by the US Food and Drug Administration for the treatment of primary immunodeficiency disease, idiopathic thrombocytopenic purpura, Kawasaki disease, chronic lymphocytic leukemia with frequent infections, bone marrow transplantation, to prevent infection in pediatric human immunodeficiency virus, and chronic inflammatory demyelinating polyneuropathy. However, IgG products are frequently used off label in many autoimmune conditions. The advent of numerous intravenous and subcutaneous formulations of IgG presents new opportunities impacting patient preferences, site of care, and costs. The appropriate and optimal use of IgG is reviewed based on discussions from an expert roundtable panel and review of the scientific literature. Clinicians and payers should consider patient preferences, evidence-based guidelines, and policies when selecting an IgG product.

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For author information and disclosures, see end of text.

■ **Table 1.** Primary Immune Deficiencies⁷

Immune deficiencies normally treated with IgG therapy (most to least common)

- Common variable immunodeficiency
- Immunoglobulin G defects
- X-linked agammaglobulinemia
- Severe combined immunodeficiency
- Wiskott-Aldrich syndrome
- Hyper immunoglobulin M
- Antibody defect

Immune deficiencies not normally treated with IgG therapy (most to least common)

- Immunoglobulin A deficient
- DiGeorge syndrome
- Transient hypogammaglobulinemia
- Neutropenia
- Hyper immunoglobulin E
- Candidiasis
- Complement deficiency
- Chronic granulomatous disorder
- Leukocyte adhesion deficiency

IgG indicates immunoglobulin G.

products inspired the World Health Organization (WHO) to establish minimal requirements for IVIg preparations, including⁵:

- IVIg should be obtained from a pool of at least 1000 donors.
- The Ig should be free of prekallikrein activator, kinins, plasmin, and preservatives or other potentially harmful contaminants.
- The preparations should contain at least 90% intact IgG without immunoglobulin fragments, and the IgG should be biochemically modified as little as possible to maintain opsonins, complement-binding, and other biologic activities.
- All IgG subclasses should be present in proportions similar to those found in normal pooled plasma.

Today, Ig products are prepared from plasma pooled from at least 3000 to 10,000 healthy blood donors and contain a broad range of antibodies against pathogens and foreign antigens.³ These products also adhere to the International Union of Immunological Societies/WHO principles listed above and include a broad range of IgG subclasses in proportions similar to those observed in healthy blood (ie, IgG1, 60%-70%; IgG2, 20%-30%; IgG3, 0%-6%; IgG4, 0%-4%).⁶

The risk of infectious agent transmission is reduced by processing the plasma in a series of purification steps, including an array of precipitation, centrifugation, filtration, and other techniques, with specific steps such as solvent detergent treatment and pasteurization. Each manufacturing step can be monitored for its potential to inactivate specific viruses.³

Because of the number of available IgG preparations and the increasing number of immune deficiency disorders (Table 1), IgG preparations (and dosing schedule) appropriate for individual patients and their immunodeficiency should be utilized.⁷

Indications and Uses for IgG Products

IgG preparations are approved by the US Food and Drug Administration (FDA) for the treatment of primary immunodeficiency disease (PID), idiopathic thrombocytopenic purpura (ITP), Kawasaki disease (KD), chronic lymphocytic leukemia (CLL) with frequent infections, bone marrow transplantation (BMT), to prevent other infections in pediatric human immunodeficiency virus (HIV), and chronic inflammatory demyelinating polyneuropathy (CIDP).⁸

PIDD

PIDD is a group of inherited, heterogeneous disorders of the immune system that result in increased rates and severity of infections. Patients may have immune dysregulation associated with autoimmune diseases, and an increased risk of developing malignancies.⁹ All IgG products are approved for treating PIDD (Table 2).

ITP

ITP is an acquired autoimmune disorder caused by inadequate production and increased destruction of platelets.²⁰ The disease was originally classified as acute (lasting ≤ 6 months) or chronic (lasting > 6 months), but these terms have recently been replaced by new categories: (1) newly diagnosed; (2) persistent (present for 3-12 months); and (3)

chronic (present for 12 months or longer).^{21,22} Infectious triggers of ITP include HIV, hepatitis C virus infection, and *Helicobacter pylori*.²⁰

Patients with ITP can display a wide array of symptoms, and some patients may be asymptomatic. However, the most commonly reported symptom is mucocutaneous bleeding, which manifests as purpura, epistaxis, or menorrhagia. Other forms of bleeding such as gastrointestinal or intracranial hemorrhage may also be observed.²⁰ Approximately half of the available IgG products are FDA-approved for ITP (Table 2).

KD

KD is one of the most common causes of acquired heart disease in children. Although typically self-limited, it can result in coronary artery aneurysm, myocardial infarction, congestive heart failure, and arrhythmias.²³

CLL

Patients with CLL can develop hypogammaglobulinemia and impaired cell-mediated immunity and opsonisation. Prophylactic use of IgG can reduce the risk of infections, which are the major cause of morbidity and death in patients with CLL.²³

BMT

Patients undergoing BMT are at great risk of developing infections. Several controlled trials have found that prophylactic IVIg decreased the rates of cytomegalovirus infection, interstitial pneumonia, and graft-versus-host disease in allogeneic BMT recipients.²⁴

Pediatric HIV

Children infected with HIV are prone to infections

Table 2. FDA-Approved IgG Products¹⁰⁻¹⁹

	PIDD	ITP	CIDP	KD	CLL	BMT	HIV
Intravenous products							
Lyophilized powder							
Carimune NF, nanofiltered	X	X					
Gammagard S/D	X	X		X	X		
Liquid							
Flebogamma 5% DIF	X						
Flebogamma 10% DIF	X						
Gammagard Liquid, 10%	X						
Gammaked, 10%	X	X	X				
Gammaplex, 5%	X						
Gamunex-C, 10%	X	X	X				
Octagam (5%) and Octagam 10%	X						
Privigen, 10%	X	X					
Subcutaneous products							
Hizentra, 20%	X						
Gammaked, 10%	X						
Gamunex-C, 10%	X						
Gammagard Liquid, 10%	X						

BMT indicates bone marrow transplantation; CIDP, chronic inflammatory demyelinating polyneuropathy; CLL, chronic lymphocytic leukemia; FDA, US Food and Drug Administration; HIV, human immunodeficiency virus; IgG, immunoglobulin G; ITP, idiopathic thrombocytopenic purpura; KD, Kawasaki disease; PIDD, primary immunodeficiency disease.

despite normal or even elevated levels of total serum IgG. It is recommended that these patients receive Ig therapy. The use of Ig therapy in adults with HIV has not been shown to be effective.^{23,25}

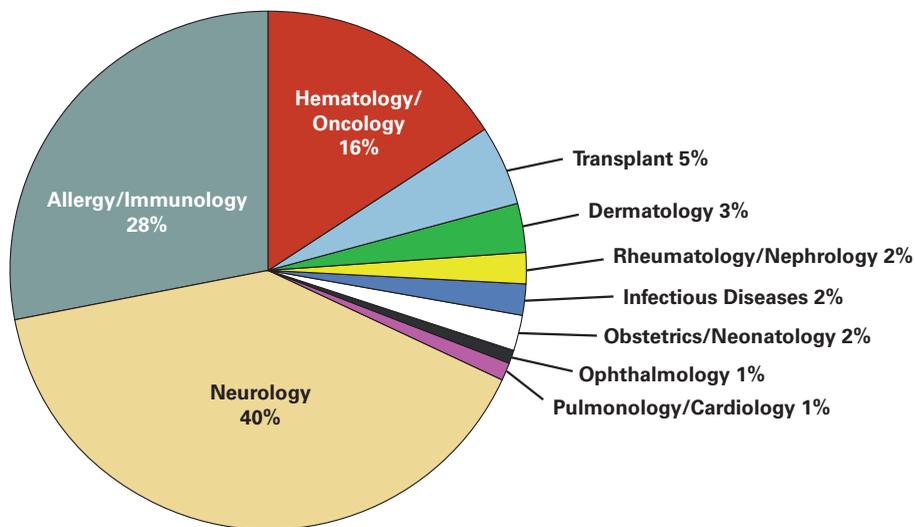
CIDP

The first neurologic indication for IVIg, CIDP, was granted in 2008. CIDP is a distinct acquired demyelinating polyneuropathy characterized by the slow onset (over weeks to months) of weakness, areflexia, and impaired sensation.²⁶ Ig therapy is the first-line therapy for patients with CIDP.²⁵ The ICE (IGIV-C CIDP Efficacy) study supported the short-term and long-term efficacy and safety of IVIg (10% caprylate chromatography purified) in CIDP.²⁷ Proper diagnosis is essential to insure a good response to treatment.²⁸

In addition to FDA-approved indications, IgG is frequently used off label and within numerous medical specialties (Figure 1).²⁹

The most common off-label indications for IgG include multiple sclerosis, graft-versus-host disease in transplant recipients, prevention of antiphospholipid syndrome in miscarriage, and Guillain-Barré syndrome.³⁰ IgG therapy may be useful in numerous conditions, but evidence supporting its efficacy is mixed (Table 3).

■ **Figure 1. IgG Use by Medical Specialty in 2012^{a,29}**



IgG indicates immunoglobulin G.

^aPercentage of total grams of immunoglobulin products.

Reprinted with permission from Marketing Research Bureau. IVIG/SCIG 2017. A Forecast of the Polyvalent Immune Globulin Market (IVIG/SCIG). Market in the United States from 2012-2017. The Marketing Research Bureau, Inc: Orange, CT; November 2011.

Intravenous and Subcutaneous IgG

IgG products are formulated for IV or subcutaneous (SC) administration. The main advantages and disadvantages of each formulation are listed in [Table 4](#).³²

Characteristics of IgG Preparations

Most IgG preparations are administered IV. The numerous IgG products reflect the ways in which their composition can differ. For example, IgG products may vary with respect to:

Sidebar: Is Off-Label Use a Factor for Payers?

Because IgG therapies are often used off label, many insurance providers cover IgG use in numerous immunodeficiency and autoimmune disorders. Most providers work with clinicians, thought leaders, and regulators to ensure that data support its use in a given condition. Drs Fenrick and Pezalla indicated that there is not 1 source or specific compendium used for information. Instead, payers and decision makers refer to product labels, compendia, literature, expert opinion, and insurance provider policies.

- **Product preparation and formulation.** Some preparations are prepared using the Kistler-Nitschmann method, whereas others use the Cohn-Oncley method or cold ethanol fractionation. Further purification methods also vary with each product^{3,33,34}
- **Liquid.** Most preparations are liquefied but 2 are lyophilized.

Sidebar: How Are IgG Product Characteristics Monitored in Clinical Practice to Avoid Associated Risks?

In the past, product specifics were more variable and made a significant impact on how a clinician would select an IgG product. Today, most IgG preparations are developed to fit the formulary and, as such, pH, osmolality, sodium content, and other characteristics are very similar, and concerns for adverse events are approximately the same for each preparation.

Dr Ballow noted that the newer IgG preparations are fairly similar in that they have low sodium levels, physiologic osmolality, and are in liquid form. These characteristics make selection of an IgG product less complicated and reduce the risk of adverse events, especially in patients with underlying risk factors. That said, there are idiosyncratic differences with regard to tolerability among products.

ilized (Carimune NF, Gammagard S/D)^{11,14,35}

- **IgG concentration.** IgG concentrations range from 3% to 12% (with 5% and 10% common) in the various products.³⁵ However, SC products may have a concentration as high as 20%¹⁹
- **Stabilizer and sodium content.** In most IgG products, amino acids have replaced sugars (eg, sucrose) (due to the potential for renal toxicity) as the stabilizer. IgG products contain very little sodium to reduce the risk of adverse events (especially in those with renal or cardiac disorders)^{3,35,36}
- **Other**
 - Osmolality; most products are isosmotic³⁶
 - pH; most products are formulated at a physiologic pH³⁵
 - Maximum infusion rate³
 - Volume load; the administration of large-volume infusions may not be well tolerated in patients with heart failure, renal dysfunction, hypertension, or vascular disease.³⁵

Pharmacokinetics

The pharmacokinetics of IVIg and SCIg preparations are affected by infusion rate and frequency of administration, with characteristic differences in steady state levels and trough levels. With IVIg preparations, IgG levels in the blood peak as soon as the infusion is finished and can be 2-fold higher than those observed prior to infusion (trough levels) (Figure 2).³⁷ With SCIg preparations, peak serum IgG levels occur approximately 48 hours after the injection.³² Further, peak serum IgG level with SCIg is approximately 61% of that observed with IVIg.³² These pharmacokinetic factors tend to favor the use of SCIg preparations, especially in patients at risk of adverse events associated with high IgG levels.

Practical Perspectives for Managed Care on IgG Use

Evidence-Based Guidelines

There are numerous national and international treatment guidelines for the various conditions requiring IgG

■ **Table 3. Off-Label Use of Immunoglobulin Therapy**^{26,31}

Efficacy confirmed in randomized controlled trials
Guillain-Barré syndrome in adults
Multifocal motor neuropathy
Probable effectiveness
Polymyositis
Dermatomyositis
Autoimmune uveitis
Stiff-person syndrome
Myasthenia gravis
Guillain-Barré syndrome in children
Toxic epidermal necrolysis (Lyell’s syndrome) and Stevens-Johnson syndrome
Possible effectiveness
Severe persistent asthma
Post-transfusion purpura
Autoimmune hemolytic anemia
Autoimmune hemophilia
Autoimmune neutropenia
Lambert-Eaton syndrome
Multiple sclerosis
Connective tissue diseases and systemic vasculitis
Churg-Strauss syndrome
Autoimmune blistering diseases
Chronic urticaria
Systemic lupus erythematosus
Neonatal alloimmune thrombocytopenia
Doubtful effectiveness
Inclusion body myositis
Antiphospholipid antibody syndrome in pregnancy
Chronic fatigue syndrome
Immunodeficiency associated with adult HIV infection
Miller Fisher syndrome
Recurrent spontaneous abortion
HIV indicates human immunodeficiency syndrome.

therapy. Unfortunately, the large variance in patient characteristics often requires guidelines to be generalized. For example, the American Academy of Allergy, Asthma & Immunology (AAAAI) developed 8 guiding principles for IgG use in PIDD to optimize patient care. These are an excellent set of guidelines for physicians and payers (Table 5).³⁸

In clinical practice, guidelines are an important consideration when selecting the most appropriate treatment. Payer policies tend to be based on a variety of sources (eg, expert

■ **Table 4.** Advantages and Disadvantages of IV and SC IgG³²

Intravenous	Subcutaneous
Advantages	
(1) Ability to give a large volume per infusion allows intermittent dosing (every 3-4 weeks)	(1) Lack of requirement for venous access
(2) The immediate rise in IgG levels may be helpful in some cases	(2) Slow administration or gradual adsorption reduces the incidence of adverse effects associated with peak levels
(3) Office-based infusions facilitate patient monitoring and follow-up	(3) Maintenance of more consistent IgG levels eliminates low trough levels, which may decrease “wear-off” effects common with IVIg
	(4) Facilitates self infusion, increasing patient autonomy—may improve patient’s self-image and sense of control
Disadvantages	
(1) Requires venous access and trained personnel in most situations	(1) Relatively small volume per infusion and requires frequent dosing—at least once a week in most cases
(2) Large shift in IgG levels during dosing interval may cause adverse effects at or just after peak, and with low trough levels (“wear-off” effects)	(2) Ability to self-infuse requires a reliable patient and monitoring of adherence

IgG indicates immunoglobulin G; IV, intravenous; SC, subcutaneous.
Adapted from Berger M. *Curr Opin Allergy Clin Immunol.* 2011;11(6):532-538.

opinion, government reviews, Cochrane reviews) and not just clinical guidelines (see [Sidebar](#) on S75).

PIDD

The Importance of Early Diagnosis

From a health and financial perspective, the earlier a

patient with PIDD is properly diagnosed, the better. An economic impact study from 118 medical centers determined that the cost of PIDD is significantly higher in patients who are not properly diagnosed. It was estimated that the average annual cost of healthcare for an undiagnosed individual with PIDD was \$102,736, compared with \$22,696 for a diagnosed patient.³⁹ These numbers show the great cost savings that can occur if patients are diagnosed earlier. This is especially important because the National Institutes of Health estimated there are at least 500,000 cases of undiagnosed PIDD in the United States.³⁹

The Importance of Individualized Care

IgG replacement therapy in patients with PIDD is complex, requiring an individualized approach to determine the most appropriate and effective dosage, frequency of infusions, route of administration, and frequency of monitoring to ensure optimal patient outcomes.^{7,40,41}

ITP

In children with ITP demonstrating thrombocytopenia and mucosal bleeding, IgG therapy can be used as the initial treatment.²³ The recommended initial dosing of IVIg for children with ITP ranges from 0.4 g/kg/d for 5 days to 0.8 to 1.0 g/kg/d for 1 or 2 days.^{42,43} These dosages are considered safe, but up to 75% of children report side effects following IgG therapy (eg, nausea, vomiting, fever, and headache/aseptic meningitis).²¹ In adults with ITP, IgG is usually not given unless the patient’s condition is chronic. Oral corti-

Sidebar: Bioavailability of SCIg and IVIg

According to Dr Ballou, for the design of clinical trials, the FDA has enforced the concept of total area-under-the-curve bioavailability of SCIg versus IVIg. “That translates...to a conversion factor so that all the FDA-approved trials with SCIg have a recommendation for a conversion factor that actually increases the dose of the SCIg,” and thus the resulting levels of serum IgG. “For example, for some products the conversion factor is 1.37 and [for another] product...[it is] 1.53. In Europe, they dose SCIg at 1:1 with the IVIg dose. Their regulatory agency didn’t require them to look at this bioavailability question...and therefore, most of the European physicians dose the SCIg equivalent to the IVIg dose. Physicians in Canada dose the SCIg this way as well.” Importantly, efficacy results from US and European studies are similar.

corticosteroids and anti-RhD immunoglobulin are the preferred treatments in newly diagnosed patients.

Other Indications and Off-Label Use

Numerous guidelines are available for various conditions requiring IgG therapy. Clinicians are encouraged to consult with guidelines as well as payer policies regarding the correct preparation and dose for each autoimmune syndrome. In many cases, such as CIDP, fairly high doses of IgG may be required to achieve good outcomes.^{28,44}

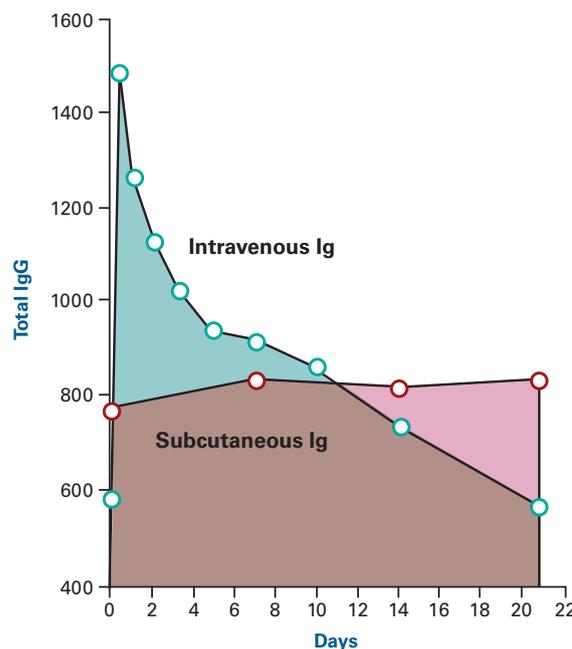
Barriers to Treatment and Issues Related to Compliance

Access to IgG Products

Payer-directed barriers may impede a physician’s efforts to provide optimal therapy in PIDD. For example, some payers require trough-level monitoring every 3 months. Although this can help guide treatment in some patients, it may result in unnecessary costs that can impede future therapy.⁴⁵ Another payer-directed barrier may be requests for a trial of therapy cessation. However, in a genetically based disorder such as PIDD, the underlying reason for requiring IgG will not change, and patients will require treatment for the remainder of their lives.⁴⁴

Occasionally, there may be a shortage of Ig preparations, and that can impede continuity of care. Fortunately, due to the number of available IgG products, shortages have not occurred in the past decade.⁴⁶

■ **Figure 2.** Pharmacokinetics of IVIg and SCIG³⁷



Ig indicates immunoglobulin; IgG, immunoglobulin G; IV, intravenous; SC, subcutaneous. Adapted from Berger M. *Clin Immunol.* 2004;112(1):1-7.

Patient Preference

SCIG and IVIg are associated with similar efficacy (often defined in clinical trials as the incidence of serious bacterial

■ **Table 5.** AAAAI’s Guiding Principles for the Use of IVIg in PIDD³⁸

- (1) **Indication.** IVIg therapy is indicated as replacement therapy for patients with PIDD characterized by absent or deficient antibody production. This is an FDA-approved indication for IVIg, for which all currently available products are licensed.
- (2) **Diagnoses.** There are a large number of PIDD diagnoses for which IVIg is indicated and recommended. Many have low total levels of IgG, but some have a normal level with documented specific antibody deficiency.
- (3) **Frequency of IVIg treatment.** IVIg is indicated as continuous replacement therapy for primary immunodeficiency. Treatment should not be interrupted once a definitive diagnosis has been established.
- (4) **Dose.** IVIg is indicated for patients with PIDD at a starting dose of 400 to 600 mg/kg every 3 to 4 weeks. Less frequent treatment, or use of lower doses, is not substantiated by clinical data.
- (5) **IgG trough levels.** IgG trough levels can be useful in some diagnoses to guide care but are NOT useful in many and should NOT be a consideration in access to IVIg therapy.
- (6) **Site of care.** The decision to infuse IVIg in a hospital, hospital outpatient, community office, or home-based setting must be based upon clinical characteristics of the patient.
- (7) **Route.** Route of administration must be based upon patient characteristics. The majority of patients are appropriate for IV therapy, and a subset is suited for subcutaneous therapy.
- (8) **Product.** IVIg is not a generic drug and IVIg products are not interchangeable. A specific IVIg product needs to be matched to patient characteristics to insure patient safety. A change of IVIg product should occur only with the active participation of the prescribing physician.

AAAAI indicates American Academy of Allergy, Asthma & Immunology; FDA, US Food and Drug Administration; Ig, immunoglobulin; IV, intravenous; PIDD, primary immunodeficiency disease. Reprinted with permission from American Academy of Allergy, Asthma & Immunology. Eight guiding principles for effective use of IVIg for patients with primary immunodeficiency. <http://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Resources/IVIg-guiding-principles.pdf>. Updated December 2011. Accessed May 15, 2012.

Sidebar: How Can Earlier Diagnoses of PIDD Be Achieved?

Because the symptoms of PIDD are easily confused with those of a cold or infection, symptoms may be addressed for years without the clinician suspecting PIDD as the cause. According to Dr Ballow, diagnosis used to take approximately 10 years; now, he estimates about 5 years. Education is needed to diagnose PIDD, and education should not be limited to general practitioners. “I think a lot of it is through physician education, both at the primary care level as well as at the specialty level, because these patients may present to the pulmonologist. They may also present to the gastroenterologist....about a third of those patients may actually present with chronic gastrointestinal symptomatology, and not necessarily pulmonary tract infections.”

Early identification of PIDD is essential, as recurrent infections produce lung damage. Once a patient develops bronchiectasis, the damage is permanent, and nothing can be done to reverse this condition.

infections).³² Patients tend to prefer SCIg treatment, and most who use SCIg will generally not return to IVIg preparations.⁴⁷ This is likely because many patients prefer receiving treatment at home.⁴⁸ Studies have reported improvements in health-related quality of life with SC administration of IgG (compared with IVIg), but additional research is needed to confirm these results in larger study populations. Although differences in safety and tolerability profiles have been

Sidebar: Dosing IgG Therapy

Dr Ballow stated that there are several recent studies that indicate that the best approach for dosing IVIg, or even SCIg, is on an individual basis. The goals are to treat the patient’s symptoms and their underlying problem. Furthermore, he revealed that the old standard of limiting the dose has been proved to be inadequate. For example, “20 years ago or so we used this magic trough level, 500 mg/dL, as a number to shoot for. And we now realize that for many patients, a 500 mg/dL serum total IVIg level is not adequate. It’s not adequate to keep them infection free and it’s not adequate to keep them from getting chronic lung disease. So, the push now by clinical immunologists is really to treat on an individual basis and dosing to keep the patient infection free, whether that may require a trough level of 500 mg/dL in some patients versus 750 mg/dL in other patients, or as much as 900 mg/dL in other patients.”

observed in patients who switch from IVIg to SCIg, a properly designed, direct comparative study between the 2 preparations has not been performed.

A study by Wasserman et al demonstrated that local reactions in patients receiving SCIg decreased over time, most likely due to the patient becoming more experienced with administration.⁴⁹

Cost of IgG Therapy

Cost of supplies for SCIg is usually higher than for IVIg due to frequent dosing; however, these costs are greatly offset by the costs associated with IVIg administration (eg, nursing staff, facility fees, pump rental).³² As such, most consider SCIg to be the more economical therapy.

Site of Care

Each IgG treatment is unique and the site of care is dependent on the patient’s preferences and health. Generally, SCIg preparations are preferred because they are less expensive and administration is less time-consuming. However, SCIg preparations should not be used if the patient prefers IVIg preparations, or if the clinician

Sidebar: Policies Concerning Off-Label Use of IgG

Off-label use of IgG is very common because in the majority of cases, it is determined to be medically necessary. The plethora of data available on IgG use has allowed most payers to develop policies. However, payers try to work with clinicians when an IgG use (or a particular dosage) is questionable. Dr Fenrick noted that off-label use is one area where there are some challenges. “Payment is based on our policy, and sometimes the requested doses do not align with the evidence that supports the use of the product.” To resolve the issue, the insurance provider will have a discussion with the ordering physician and, if necessary, appropriate experts will be brought in for peer-to-peer discussion.

Dr Ballow added that the AAAAI offers its services to review guidelines from third-party payers. They are happy to extend this invitation to medical directors out there who are trying to sort out some of the evidence-based areas of IVIg utilization, especially because this can be very complicated.

thinks the patient is at risk of nonadherence. SCIg allows patients to perform administration on their own and at home. Most patients prefer this situation, but it does require them to be very diligent in maintaining a treatment schedule.

For elderly patients who have transportation difficulties, SC administration can enable transition to home-based care.⁵⁰ If IVIg is the patient's preferred method, cost can also vary depending on where the IVIg is administered (eg, home, doctor's office, infusion suite, or hospital).³⁷

Sidebar: The Importance of Treatment Guidelines in IgG Therapy

Payer Perspective

Dr Pezalla indicated that "For immunoglobulin therapy we now have 208 different citations from the world literature on this. We use Cochrane Reviews, as well as reviews from various government agencies, both in the United States and overseas [from] a number of different sources. We don't publish treatment guidelines for physicians but we do look at treatment guidelines where they exist."

He added, "We also publish online our clinical policy bulletins, which are basically guidance for what we're going to pay for and what we consider medically necessary versus what we consider experimental.... All of our clinical policy bulletins are reviewed once a year and are updated continuously as new things are published or new indications are approved and different things like that happen in the marketplace."

Clinician Perspective

While payers view guidelines as only one of many

sources to determine policy, Dr Ballow noted that guidelines are a very important part of a clinician's decision-making process. Dr Ballow indicated that "The American Academy of Allergy, Asthma & Immunology published guidelines in 2006 that are evidence-based. We are in the process of updating that, so hopefully, in 2013, we'll have an updated evidence-based publication on the use of IVIg in a number of different areas, not only as replacement therapy, but also in autoimmune and inflammatory disorders." Dr Ballow also mentioned that dermatological societies and other professional organizations have published evidence-based guidelines for skin disorders with an immune component. The American Academy of Neurology recently published evidence-based guidelines for IgG therapy. Also, there are Canadian evidence-based guidelines on the use of IVIg for a number of different autoimmune and inflammatory conditions.

Sidebar: Formulary Decisions and Product Switching

IgG products are reviewed by the appropriate pharmacy and therapeutics committee to determine which should be included in the formulary. Efficacy and safety are the primary considerations; cost plays a smaller role in formulary decisions. Often, there are no preferred products, and there's open access to the available products. Dr Fenrick stated that "Among home infusion providers and our specialty pharmacy providers... upwards of 75% of the orders that come in [have] no specific product identified. So it becomes a discussion between the dispensing provider and the prescribing provider as to the appropriate product to be used based on the unique needs of the individual member in question."

Due to a better supply chain and improved understanding of which products can be more readily

switched, IgG product shortages are seldom a concern. According to Dr Pezalla, "When there are problems with distribution or shortages of the medications, then there's this question about how interchangeable [IgG products] can be in patients with certain circumstances. And it's less of a problem now than it has been in the past as they become more purified." However, Dr Ballow stated that "Even though a lot of the newer products are very similar with regard to their composition, there is a difference with regard to tolerability. In fact, several studies [indicate that] about 15% to 18% of adverse reactions occur when you switch from one product to another." This is an important consideration when selecting a different product.

Sidebar: What Patient-Related Factors Should Be Considered When Selecting an SC or IV IgG Product?

Dr Ballow stated, “If there’s a patient that has an issue with compliance, and we know who those patients are, we would never put them on SC because I know what’s going to happen. They’re not going to be vigilant and give themselves weekly infusions of the SC product.”

However, he noted that other factors come into play. For an IV product, venous access and systemic side effects are a consideration, and tend to be less of an issue with an SC route of administration. SC IgG is only FDA approved as replacement therapy for patients with PIDD. “There are a few small studies in the literature about using SCIg as kind of maintenance therapy in patients with neurologic diseases like CIDP....and an ongoing study looking at...patients in remission with the IV route [and]...maintain[ing] [remission with] the SC route.”

Conclusion

The plethora of IgG preparations and the list of on-label and off-label uses continue to expand. As more data become available, clinicians and payers should continue to consider patient preferences, evidence-based guidelines, and policies when selecting the appropriate treatment.

Some areas of IgG therapy warrant further study, including assessment of efficacy. For example, the FDA uses a major outcome measure of incidence of serious bacterial infections for product approval. While this is important, it would be ben-

Sidebar: Pharmacoeconomics of IgG Therapy

There are several pharmacoeconomic studies comparing IV and SC IgG. One was conducted in Canada. Some have been conducted in locations outside of North America, such as Germany. According to Dr Ballow, a good pharmacoeconomic study is needed in the United States. Most studies thus far indicate that the overall cost of SC IgG is less than IVIg because it is not associated with a hospital facility cost.

Sidebar: How Does the Site of Care Impact a Patient’s Expenses?

The site of care can impact cost. Dr Fenrick noted that IVIg preparations tend to be under medical benefits, while SCIg is more likely under pharmacy benefits (if they are self administered). Depending on the patient’s plan, this may determine the therapy they receive. For example, if the product is SC and under that pharmacy plan, typical copays run in the \$30 to \$35 (preferred) to \$50 to \$55 (non-preferred) range. “On the medical benefit side of the house, the member cost share varies based on the plan that they’re in. If there is any deductible, and then coinsurance, and maybe out-of-pocket maximums.”

Sidebar: What Happens if a Patient Cannot Afford Care or Care at a Given Site?

According to Dr Fenrick, “They (care nurses) do help members with respect to identifying if there is a difference in the member cost share based on the site of service to help them with that or to get them in touch with patient assistance programs if appropriate.”

eficial to assess the efficacy of various IgG products in other types of infections (eg, gastrointestinal, upper respiratory tract infections).

Other areas of research include optimal dosing and specific outcome measures, such as the impact of product characteristics on patient satisfaction with treatment and quality of life.

Although the 8 guiding principles from the AAAAI were developed for IVIg use in PIDD, they are an excellent set of guidelines for physicians and payers to use to optimize the care of patients requiring treatment for other autoimmune disorders. SCIg can be less expensive and a more convenient means of administration, but only if it is appropriate for the patient’s condition and preference. Maintaining open access to all preparations and routes of administration allows clinicians to select the IgG preparation appropriate for each patient’s circumstance.

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