AJMC® SUPPLEMENT
THE AMERICAN JOURNAL OF MANAGED CARE®

June 2019
Vol. 25 • No. 6, Sup.

Examining the Application of Immunoglobulin in Multiple Disease States: A Review of Evidence

HIGHLIGHTS

Supplement to *The American Journal of Managed Care®*

Examining the Application of Immunoglobulin in Multiple Disease States: A Review of Evidence

Release date: June 17, 2019

Expiration date: June 17, 2020

Estimated time to complete activity: 3.0 hours

Type of activity: Application

Medium: Print with Internet-based posttest, evaluation, and request for credit

Fee: Free

This activity is supported by educational grants from CSL Behring LLC and Grifols.

IgNS Immunoglobulin National Society

Advancing Ig Nursing and Pharmacy Practice

Pharmacy Times Continuing Education™ acknowledges Immunoglobulin National Society (IgNS) for its contributions to the development of this supplement.

Intended Audience

Pharmacists and managed care professionals

Activity Overview

The administration of immunoglobulin (Ig) has become common practice in the treatment of patients with immunodeficiencies, and, more recently, in other disorders, including inflammatory diseases and autoimmune neuropathies. Patients with these disorders experience significant morbidity and mortality, and the often life-altering consequences of these diseases can also have substantial direct and indirect costs accounting for billions of dollars impacting the US economy. With the continual research into the genetic basis of disease, more data will be forthcoming on the evolving use of Ig in patients with genetic abnormalities. Healthcare professionals require proper training and foundational knowledge on best practices for the use of Ig agents to provide patients with clinically appropriate and cost-effective individualized options for therapy that will improve treatment outcomes and overall quality of life.

Statement of Educational Need

Immunoglobulin (Ig) may be considered the foundation of treatment for patients with some primary immune deficiency diseases and frontline treatment for a variety of secondary immune deficiencies as well as certain autoimmune conditions. Multiple factors beyond costs must be considered in determining proper Ig therapy. Those factors include appropriate clinical application, choice of Ig product, route of administration, adverse effect profiles, patient access to treatment facilities, insurance and financial considerations, patient quality of life, and patient's ability to self-administer, among others. With substantial differences in composition among Ig products, clinicians and managed care professionals need to be cognizant of these differences. To best serve patients, managed care professionals should understand the myriad factors that affect patients who are receiving Ig therapy, the differences among products, and the advantages and disadvantages of intravenous immunoglobulin and subcutaneous immunoglobulin treatment options.

Educational Objectives

Upon completion of this activity, participants should be able to:

- Examine the evidence that supports the use of immunoglobulin (Ig) for immune deficiency and autoimmune diseases.
- Differentiate the characteristics and value of intravenous and subcutaneous administration of Ig for individualized treatment.
- Evaluate healthcare utilization economics of patients using Ig treatments in inpatient and outpatient settings.

Accreditation Statement

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OVERVIEW

Through this supplement to *The American Journal of Managed Care®*, managed care professionals will increase their knowledge of immunoglobulin agents to provide patients with clinically appropriate and cost-effective options to improve treatment and quality of life.

TABLE OF CONTENTS

A Supplement to *The American Journal of Managed Care®* PROJ ACE0132

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EDITORIAL SUPPORT DISCLOSURES

Thomas J. Cook, PhD; Debra Gordon, MS; and **Elizabeth Paczolt, MD, FACNM,** have no relevant financial relationships with commercial interests to disclose.

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Immunoglobulin Use in Immune Deficiency and Autoimmune Disease States

Elena E. Perez, MD, PhD

ABSTRACT

Although immunoglobulin (Ig) has been available since the 1950s for replacement therapy in primary immune deficiency, many other effective uses of this class of biologics have been investigated and evolved over recent decades. Ig administration has become common practice in the treatment of the immunocompromised patient and has recently expanded into the treatment of those patients with an inflammatory disease and autoimmune neuropathies per established clinical guidelines. As research into the genetic basis of disease advances, clinicians should better assess complex data surrounding safe and effective uses of Ig to treat patients who present with B-cell and T-cell deficiencies, along with those harboring gene deletions or genetic anomalies who may potentially benefit from Ig therapy. Evidence-based clinical indications for the use of Ig include idiopathic thrombocytopenic purpura, B-cell chronic lymphocytic leukemia, Kawasaki disease, chronic idiopathic demyelinating polyneuropathy, multifocal motor neuropathy, bone marrow transplantation, and pediatric HIV infection, among others, and have evolved over time. Ig is also often tried in refractory cases that might benefit from its anti-inflammatory effects or empirically in off-label situations. Due to its anti-inflammatory effects, high-dose Ig has been used for numerous off-label indications with varying levels of effectiveness and evidence to support its use. A review of all autoimmune conditions for which Ig has been used is beyond the scope of this article and newer treatments are available for many of these disorders. Here the focus will be on selected conditions in which Ig has clear benefit. Because there is a limited supply of Ig and a need for further research into optimal use, it is important for healthcare professionals to better understand current and developing indications and data/levels of evidence to support Ig therapy as its role continues to evolve.

***Am J Manag Care*. 2019;25:S92-S97**

For author information and disclosures, see end of text.

Overview of the History of the Use of Immunoglobulin

The history of treating disease with antibodies began in the 1800s after tetanus and diphtheria toxins were discovered, leading to the realization that immunity to the infections caused by these organisms could be transferred through immune serum. Results of research determined that antibody proteins could be isolated and used as a defense against infectious disease. The arrival of scientific methods to separate antibodies from plasma for safe human injection was the starting point for development of human gamma globulin for individuals with inherited antibody deficiencies.[1]

However, these early immunoglobulin (Ig) treatments were limited by an intramuscular or subcutaneous (SC) route of administration due to low product purity. Ig was shown to be effective for prophylaxis for those exposed to measles or hepatitis A infections. The standard dose at the time was approximately 100 to 150 mg/kg; however, intravenous (IV) administration of these doses to children with measles resulted in severe adverse effects (AEs), including convulsions, fever, restlessness, chills, and even vasomotor collapse. These reactions limited Ig use to administration via intramuscular or SC routes at that time.[1,2] The desire to deliver larger Ig doses led to changes in manufacturing to produce safe IV injectable formulations. This administration route allowed for Ig to be used for a wider variety of clinical conditions. Treatment with Ig was expanded to allow for larger doses for disease suppression in inflammatory and autoimmune disorders. Further research led to more concentrated Ig formulations that can be injected SC for therapy. In addition, home-based SC infusion methods entered the treatment landscape, allowing for improved and more convenient access for patients who needed Ig therapy.[1]

Immunoglobulins are antibodies produced by differentiated B cells called plasma cells. The Ig molecule has a distinctive structure that has the ability to recognize specific antigenic determinants. Ig formulations are produced from the pooled human plasma of thousands of healthy donors, which allows the Ig formulations to contain a large and diverse antibody repertoire.[3] It is important to understand that the supply of Ig is finite because it depends

on donated plasma. Appropriate administration of Ig can be life-saving, and clinicians must be familiar with how to manage any associated AEs. Clinicians prescribing Ig need to better recognize current clinical indications for Ig therapy and the levels of evidence to support its use in immune disorders.[4]

Disease State Overviews, Place of Immunoglobulin in Therapy, and Evidence for Use

Primary Immunodeficiency Diseases

Primary immunodeficiency diseases comprise a heterogenous collection of genetic disorders that impact distinct elements within the innate and adaptive immune system; these may include macrophages, natural killer cells, dendritic cells, neutrophils, complement proteins, B lymphocytes, and T lymphocytes.[3] Primary immunodeficiencies are relatively uncommon. They are inherited genetic disorders that may occur alone or as part of a syndrome, and heterogeneity may be substantial within each disorder. Primary immunodeficiencies tend to become apparent during infancy or childhood, but many primary immunodeficiencies present in adulthood. The estimated overall incidence of primary immunodeficiencies is 1 per 1200 individuals.[5,6] Originally, a male-to-female ratio ranging from 2:1 to 1.4:1 was reported; however, this ratio was found to be closer to 1:1 in more recent data from a US cohort.[7,8] Recent advances in molecular and cellular characterizations of these disorders have delineated their genetic complexity with an estimated 354 inborn errors of immunity defined as of February 2017.[9]

Agammaglobulinemia

Agammaglobulinemia comprises a class of primary immunodeficiency diseases characterized by absent or very low serum antibodies caused by the absence of B lymphocytes in both blood and bone marrow.[4,10] Although the exact incidence of agammaglobulinemia has yet to be elucidated, it has been estimated overall to affect approximately 1 in 300,000 individuals, with X-linked agammaglobulinemia (XLA), having an estimated prevalence ranging between 1 in 350,000 to 1 in 700,000.[11,12] This disorder is further classified into 3 subclasses: XLA, XLA with growth hormone deficiency, and autosomal recessive agammaglobulinemia.[10] The XLA form of the disorder is caused by a defect in the Bruton tyrosine kinase gene, which is vital to B-cell maturation and development. Because this gene is located on the X chromosome, only males are affected, whereas females are carriers. This form of the disorder comprises approximately 85% of agammaglobulinemia cases.[11]

The major symptoms associated with agammaglobulinemia are frequent and severe bacterial infections due to failures in immune response related to the B-cell defects.[10] They usually manifest as recurrent upper and lower respiratory tract infections and begin within the first few years of life in patients with XLA.[13] The respiratory infections related to agammaglobulinemia are most often caused by bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, *Streptococcus pyogenes*, and *Pseudomonas*. Antibody binding is critical for the clearance of these microorganisms. The recurrence of respiratory infections in young patients creates substantial morbidity during the active illness and may also increase the patient's risk for developing chronic lung disease. Repeated episodes of pneumonia can result in chronic airway inflammation, such as bronchiectasis and scarring.[11,13,14]

Agammaglobulinemia caused by a lack of B cells is the clearest indication for the replacement of Ig.[4] Historical retrospective data of children with agammaglobulinemia have demonstrated that both the number and severity of complications related to infection are inversely correlated with intravenous immunoglobulin (IVIG) dose administrations.[4,15,16] In fact, serious bacterial illness was prevented when immunoglobulin G (IgG) trough levels were maintained above 500 mg/dL.[4,16]

More recently, a study by Orange et al centered on the question of the effect of trough level on the incidence of pneumonia. The investigators performed a meta-analysis of clinical trial studies evaluating trough IgG and pneumonia incidence in patients with hypogammaglobulinemia primary immunodeficiencies. This encompassed 17 studies with 676 total patients and 2127 patient-years of follow-up. Results demonstrated that the incidence of pneumonia declined by 27% with each 100 mg/dL increment in trough IgG level. The pneumonia risk for patients at trough levels of 1000 mg/dL was one-fifth of those whose trough levels were 500 mg/dL. Overall, the findings suggest that pneumonia risk can be progressively reduced by higher trough IgG levels.[4,17,18]

Hypogammaglobulinemia

Hypogammaglobulinemia occurs when Ig levels in the serum decrease or there is a significant lack of IgG antibody response to an antigen vaccine challenge. In these patients, deficient antibody production leads to decreased Ig concentrations and a considerable inability of a patient to have an IgG antibody response to challenge with an antigen. Notable diagnostic factors associated with hypogammaglobulinemia include recurrent infections (*S pneumoniae* or *H influenzae*), infections caused by atypical pathogens, and repeated use of antibiotics for treatment. Primary hypogammaglobulinemia affects young children and adults. Examples of primary immunodeficiencies that fall into this category include combined immunodeficiency disorders, combined immunodeficiency with syndromic features, such as Wiskott-Aldrich syndrome (WAS), hyper-immunoglobulin M (IgM) syndromes, and diseases of immune dysregulation with autoimmunity.[4]

Ig replacement is indicated for patients with recurrent bacterial infections and reduced serum Ig levels who also fail to respond to a protein or polysaccharide vaccine challenge. For example, a patient may be unable to make IgG antibodies against the tetanus

toxoid and/or pneumococcal polysaccharide vaccines. A patient with common variable immunodeficiency (CVID) is a typical example, as CVID is the most frequently diagnosed heterogenous disorder related to antibody deficiency.[4] An international consensus definition of CVID was recently published and includes the following criteria for diagnosis: a low IgG level measured on at least 2 occasions 3 weeks apart (repeated measurement may be eliminated if the IgG level is 100-300 mg/dL), low IgM and/or IgA, impaired antibody response (vaccine responses) to at least 1 type of T dependent or independent antigen, and exclusion of other types of hypogammaglobulinemia.[19] CVIDs are the most common culprit identified in symptomatic primary antibody failure in both children and adults.[20]

Data from a cohort of patients with confirmed CVIDs in a medical center over a 22-year period assessed Ig doses for IVIG therapy, finding that the doses had been adjusted in accordance to infection severity versus treated to any trough IgG level. Trough IgG levels ranging from 5 g/L to 17 g/L were found to prevent breakthrough infection. Doses of replacement Ig used for preventive purposes ranged from 0.2 g/kg/month to 1.2 g/kg/month. There was a strong correlation between baseline serum IgG levels and the increases to IgG levels, at which point patients were free of infection. Complications also played a significant role. Patients with bronchiectasis received higher Ig doses than those without bronchiectasis. In addition, the clinical phenotype of each CVID was an important factor. Patients who had enteropathy, cytopenias, and polyclonal lymphoproliferation needed substantially higher Ig doses to prevent infection than patients with lymphoid malignancies. Results overall hallmarked the importance of Ig therapy in these patients; replacement doses required to keep a patient bacterial infection-free have to be individualized for each patient. This highlights the heterogeneity of the patient population, CVID phenotypes, and the need for individualized management of each patient with CVID and hypogammaglobulinemia who requires Ig replacement.[4,18,20]

Specific Antibody Deficiency

Specific antibody deficiency (SAD), also termed selective antibody deficiency, is a primary immunodeficiency characterized by normal levels of Igs but that is impaired by specific antibody production.[4,6] Patients with SAD have normal IgA, IgM, total IgG, and IgG subclass levels; however, they also have recurrent infections and poor antibody responses to polysaccharide antigens after vaccination. SAD presents complex diagnostic and therapeutic challenges because there is a lack of consensus over both areas. The overall clinical significance of SAD disorders is not well understood.[21] Four phenotypes of SAD have been defined: memory, mild, moderate, and severe. Any of the phenotypes may require antibiotic prophylaxis, Ig replacement, or both depending on the individual patient and actual clinical illness. Patients who can initially mount adequate antibody concentrations against polysaccharide antigens but have a waning response to an antigen challenge over a 6-month period have the memory phenotype.[4,22]

Ig replacement for patients with SAD should be provided if severe polysaccharide nonresponsiveness (against the 23-valent pneumococcal polysaccharide vaccine) has been firmly established along with evidence for recurrent bacterial infections requiring antibiotic therapy for the individual patient.[4,21] Antibiotics are the first-line therapy for infections; however, infection severity and antibiotic prophylactic efficacy are critical to any decision surrounding Ig replacement in patients. Further evidence of infection should be documented, including abnormalities of sinus or pulmonary imaging, elevations in C-reactive protein, and erythrocyte sedimentation rates, which may provide additional evidence to support Ig replacement therapy. In addition, although patients with SAD may receive benefit from conjugate vaccine immunization, Ig replacement is indicated if there is poor antibody response to vaccination.[23,24] Ig replacement is considered appropriate in patients with recurrent and treatment-refractory otitis media who are at risk for permanent hearing loss, bronchiectasis, recurrent infections requiring IV antibiotics, failed antibiotic prophylaxis, and diminished quality of life because of recurrent infections, in addition to any hypersensitivities to antibiotic prophylaxis that may inhibit optimal therapy.[4]

Recurrent Infections Due to Unknown Immune Mechanism

Ig therapy may be the only feasible option for treatment in patients with primary immunodeficiency diseases where the actual mechanism surrounding the individual's inability to prevent recurrent infection has no obvious etiology. In these cases, the patient presents with recurrent episodes of an infection but has normal or near-normal immune function upon assessment. Culprit disorders include hyper-immunoglobulin E (IgE) syndrome with normal IgG, IgM, and IgA but defects in antibody response; WAS with normal total IgG but impaired protein and polysaccharide antigen response; or ataxia telangiectasia (AT) with IgA and IgG2 deficiencies and a documented history of infection susceptibility.[4]

The consensus is that Ig therapy in these disorders is a useful adjunct to therapy. Data have demonstrated that some patients with hyper-IgE syndrome and recurrent respiratory infections have benefited from Ig replacement.[4,25] Use of Ig replacement with prophylactic antibiotics in patients with WAS was supported in a study of 73 centers and 507 patients.[4,26] It has also been estimated that 12% to 15% of patients with AT require Ig therapy.[4]

Secondary Immunodeficiency

A secondary immunodeficiency results from immune system compromise due to a nongenetic factor.[27] Ig replacement therapy

has been utilized in a variety of diseases that lead to a secondary humoral deficiency, including hematologic malignancies, pediatric HIV infections, prematurity, geriatrics, hypogammaglobulinemia associated with solid organ or bone marrow transplantation, and patients who have received B-cell–depleting agents for therapy.[4]

Chronic Lymphocytic Leukemia

The most common complication and cause of mortality in chronic lymphocytic leukemia (CLL), a hematologic malignancy, is infection that occurs in patients with hypogammaglobulinemia, advanced disease, or both.[4] Recurrent infections create substantial morbidity and mortality in patients with CLL, causing 30% to 50% of deaths from the disease.[28-31] Hypogammaglobulinemia is a frequent complication of hematologic malignancies, most commonly seen in CLL and multiple myeloma (MM).[31]

Data from studies of patients with CLL have demonstrated the benefit of Ig replacement therapy to prevent infection. Raanani et al assessed multiple trials of patients with CLL and MM and found that there was a significant decrease in the occurrence of major infections in patients treated with Ig (relative risk, 0.45). Although there was no survival benefit noted in this trial, the investigators concluded that Ig replacement therapy should be considered on an individual basis for patients with CLL and hypogammaglobulinemia.[32]

Clinicians may consider replacement Ig therapy for patients with CLL and recurrent serious bacterial infections whose antibody levels fall below the protective level following the receipt of diphtheria, tetanus, or pneumococcal vaccine.[4] It is important to emphasize that patient selection for Ig treatment should be based on proven antibody production deficit rather than hypogammaglobulinemia alone.[31] In fact, current guidelines for therapy specifically state that hypogammaglobulinemia by itself does not constitute a basis for even initiating CLL treatment.[33]

Multiple Myeloma

Infections are a major factor for increased morbidity and mortality in patients with MM.[34] Early data surrounding approximately 3100 patients with MM demonstrated that 45% of early deaths (within 6 months) in patients with MM were caused by infections.[34,35] A more recent study of 9253 patients found that patients with MM had a 7-fold higher risk of developing any infection versus matched controls.[34]

As noted above with CLL, data from studies of patients with MM have demonstrated the benefit of Ig replacement therapy to prevent infection. Results from multiple trials have shown a significant decrease in the occurrence of major infections in patients with MM treated with Ig.[32] A recent analysis of 47 patients with MM who had a history of recurrent moderate to severe bacterial infections demonstrated that treatment with IVIG resulted in a significant decline in the infection rate following therapy. The rate declined from 17% to 0% in patients with severe infection, 55% to 34% in patients with a moderate degree of infection, and 28% to 21% in patients who were considered to have mild infection.[36] Ig replacement therapy should be considered on an individual basis for patients with MM, hypogammaglobulinemia, and proven antibody deficit.[31,32]

Autoimmune Diseases

Immunoglobulin has been used for therapy in a number of autoimmune disorders, although efficacy in this area varies. Complicating factors exist because this category includes several different autoimmune diseases (eg, hematologic, neurologic, organ-specific) and the treatment approach to these diseases has markedly changed and advanced with the introduction of biologic and immunomodulating drugs for therapy.[4]

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is a demyelinating peripheral neuropathy, specifically a polyradiculopathy, characterized by acute progressive motor weakness that involves the extremities, bulbar and facial muscles, and sensory or autonomic dysfunction in some patients. The disorder is thought to be caused by the immunologic destruction of either myelin or the Schwann cells of the peripheral nervous system.[4] It is a syndrome that occurs post infection, most commonly with *Campylobacter jejuni*, although the Epstein-Barr virus, *Mycoplasma pneumoniae*, and *H influenzae* have also been implicated in the development of GBS. Rapid and progressive weakness is a key feature of GBS and is usually reached within 4 weeks, followed by a plateau phase that can last from several weeks to months.[37]

GBS can be treated with a combination of IVIG, corticosteroids, and plasma exchange.[4] IVIG is administered at 2 g/kg body weight, usually in 0.4 g/kg doses for 5 consecutive days.[37] Data from randomized trials have suggested that IVIG started within 14 days from the onset of GBS symptoms accelerates recovery as much as plasma exchange (plasma exchange is considered superior to supportive care alone). IVIG therapy has been found to be more likely to be completed versus plasma exchange because of its enhanced convenience and greater availability, in addition to fewer AEs.[37,38]

Kawasaki Disease

Kawasaki disease (KD), also termed Kawasaki syndrome or mucocutaneous lymph node syndrome, occurs in children. It is hallmarked by fever, rash, hand and foot swelling, red and irritated eyes, mouth and throat inflammation, and swollen lymph nodes in the neck. Acute disease tends to be self-limiting and not serious, although long-term cardiac complications can occur in some patients if not diagnosed and treated early.[39]

The administration of IVIG and aspirin in the acute phase is considered the standard of care in children with KD to prevent

the development of cardiac complications, specifically coronary aneurysms.[4,40] Standard first-line therapy for KD centers around a recommended dose of 2 g/kg of IVIG in combination with 80 mg/kg to 100 mg/kg oral aspirin administered within the first 10 days when the illness is evident. This regimen has shown significant efficacy in preventing coronary aneurysm development. However, approximately 15% to 20% of patients treated with this regimen will require a second IVIG treatment to control inflammation. The addition of corticosteroids to therapy is undergoing continued investigation, with some Japanese studies demonstrating additional therapeutic benefit.[41]

Immune Thrombocytopenic Purpura

Immune thrombocytopenic purpura (ITP) is a hematologic disorder characterized by isolated thrombocytopenia caused by low levels of platelets. The disorder affects both adults and children, with pediatric patients accounting for half of the diagnoses of ITP.[42,43] Although ITP can occur without signs or symptoms, typical symptoms include easy and excessive bruising, superficial bleeding into the skin that appears as petechiae and nosebleeds, and gum bleeding.[43,44]

Treatment of ITP is usually indicated in children who are at the highest risk of complication from bleeding and patients with chronic refractory disease.[4] Current standards of care outline that corticosteroids are the cornerstone of treatment for ITP. IVIG and anti-D Ig (for patients with Rh-positive blood type) have also been recommended for first-line therapy. IVIG can rapidly increase the platelet count and is the preferred therapy for those patients with active bleeding. IVIG is usually administered as a single dose that can be repeated as needed based on platelet increase response that is expected within 24 to 48 hours in up to 85% of those who are treated, although further use of IVIG after the initial dose is dependent on clinical response to the initial dose.[45-48]

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a neurologic disease that manifests as progressive weakness in the arms and legs along with an impaired sensory function in the extremities. The disorder occurs from damage to the myelin sheath over the peripheral nerves. Most common in young adults and in men, CIDP often begins with symptoms of tingling or numbness that initiates in the fingers and toes, extremity weakness, areflexia, and feelings of abnormal sensations. This disorder is closely related to GBS and is often referred to as a clinical counterpart of that neurologic disorder.[49] However, the progression of CIDP is less acute and often takes weeks or months.[4]

Immunoglobulin has become part of the therapy regimen for CIDP over the past 2 decades along with corticosteroids and plasma exchange. Approximately 50% to 70% of patients with CIDP will respond to IVIG therapy.[50] The IVIG in CIDP Efficacy Trial (ICE) studied 117 patients with CIDP who received either IVIG or placebo using the Inflammatory Neuropathy Cause and Treatment (INCAT) criteria and assessed improvement in the INCAT disability score for the analysis over 24 weeks. Those who showed improvement could then be reassigned in a 24-week extension trial. Results demonstrated that 54% of patients treated with IVIG had an improvement in an adjusted disability score versus 21% of those who received placebo, and that was maintained to week 24. This was a crossover trial, and results were similar during the crossover period. The investigators concluded that this trial demonstrated the short- and long-term efficacy of IVIG to treat patients with CIDP.[50,51] With the evolving treatment landscape, home-based SC infusion for immunoglobulin agents have proved to be another option as well, allowing for improved and more convenient access for patients. It should also be a consideration for patients with poor venous access, cardiovascular risks, and systemic IVIG-related AEs.

Conclusions

Ig therapy is now essential and standard for the treatment of many different immune and inflammatory diseases and has also been determined to be useful in other disorders, not limited to the diseases discussed here. As noted earlier, appropriate use of Ig can reduce disease morbidity and even save lives. With the growing list of indications for Ig administration, it is imperative for healthcare professionals to fully comprehend the optimal use of this therapy. Ig therapy needs to be applied where it is supported by well-researched evidence and where it will provide the most clinical benefit. Data surrounding best practices in Ig use will continue to evolve, providing more treatment options for patients that may improve outcomes and quality of life for those affected by a variety of both common and rare diseases. ■

Please note that information on the use of Ig in disorders other than the ones covered here can be found in the following review article: Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: a review of evidence. *J Allergy Clin Immunol.* 2017;139(3S):S1-S46. doi: 10.1016/j.jaci.2016.09.023.

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Funding source: This activity is supported by educational grants from CSL Behring LLC and Grifols.

Author disclosure: Dr Perez has the following relevant financial relationships with commercial interests to disclose:

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Consultant – CSL Behring, Genentech, Shire

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Differentiating Characteristics and Evaluating Intravenous and Subcutaneous Immunoglobulin

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Intravenous and Subcutaneous Immunoglobulin Treatment Options

Immunoglobulin (Ig) has provided lifesaving therapy for a range of primary immunodeficiency diseases. With the introduction of subcutaneous immunoglobulin (SCIG) products, treatment options have expanded for patients with several conditions, such as primary immunodeficiency diseases or chronic inflammatory demyelinating polyneuropathy (CIDP), that require Ig therapy. In addition, recombinant human hyaluronidase-facilitated SCIG (fSCIG) is an option with primary immunodeficiency diseases, which allows for easier entry of large volumes of fluid through the extracellular matrix.[1] **Table 1**[2-9] lists the currently available intravenous immunoglobulin (IVIG) and SCIG products. IVIG and SCIG products are manufactured from the plasma of healthy donors. Plasma pools are derived from a minimum of 1000 donors as mandated by the FDA but typically include a larger number.[10] Generally, a batch of Ig will include plasma from approximately 15,000 donors.[11] The volume of the plasma pools in production typically ranges from 2000 kg to 4000 kg.[12] Ig products sold in the United States are derived solely from US donor plasma, although the final Ig product may be manufactured in FDA-approved facilities outside of the United States.[2] These supply factors impose an inherent limit of source material that can cause supply chain issues, such as frequent product shortages, and is reflected in the product cost. The limited supply of product puts a premium on the importance of clinically appropriate therapy, including the decision to use the intravenous (IV) or the subcutaneous (SC) route of administration. SCIG products are currently only approved for the treatment of primary immunodeficiency, with the exception of immunoglobulin subcutaneous (Hizentra), which is also approved for CIDP[13]; IVIG products are indicated for several other disease states (Table 1[2-9]).[2,14] Clinicians and managed care professionals should also be aware that physicians often prescribe Ig products, particularly IVIG, for off-label uses, and payers do reimburse (often denied, and need appeal) for such uses.[15] Although those off-label uses, which may number more than 150,[16,17] are outside the scope of this paper, they represent a very important component of Ig therapy; readers are encouraged

ABSTRACT

Clinicians have a range of options for treating patients with disease states that require the use of immunoglobulin (Ig). Traditionally, intravenous immunoglobulin (IVIG) administration has provided effective therapy for a variety of disease states. More recently, subcutaneous immunoglobulin (SCIG) administration has become available for patients with primary immunodeficiencies and chronic inflammatory demyelinating polyneuropathy (CIDP). Ig is used as replacement therapy in patients with primary or secondary immunodeficiencies and has been shown to reduce morbidity due to bacterial infections associated with antibody deficiency. The mechanism of action for use of Ig in the treatment of autoimmune disorders is complex and partially understood, but immunomodulatory effects have been suggested in CIDP and multifocal motor neuropathy. The available IVIG and SCIG products differ in their pharmaceutical properties (eg, pH, osmolality, IgA content, sodium content, and stabilizer), which can affect safety and tolerability in some patients. The pharmacokinetics of Ig also differ based on the route of administration. With IVIG administration every 3 or 4 weeks, peak concentrations are greater and trough concentrations are lower, which can increase the propensity of systemic adverse effects (AEs) and impact tolerability of therapy. SCIG infusions are typically administered more frequently (ie, biweekly, weekly, and even daily based on patient need), resulting in steady state concentrations with fewer fluctuations in Ig plasma levels. The route of administration plays a major role in the types of AEs seen in patients receiving Ig therapy, with systemic AEs associated with IV administration and local reactions more commonly seen with SC administration. By understanding the differences in IVIG and SCIG products, which are not interchangeable, and the patient characteristics that guide product selection, clinicians and managed care providers can better serve patients with immunodeficiency disorders and other disease states.

Am J Manag Care. 2019;25:S98-S104

For author information and disclosures, see end of text.

to refer to the findings of a work group of the American Academy of Allergy, Asthma, and Immunology (AAAAI) for their review and categorization of the evidence for the use of Ig for a wide range of disorders.[14]

Choosing the Right Patient for the IV and SC Routes of Administration

The AAAAI established a list of 8 guiding principles to help clinicians make quality decisions regarding IVIG for patients with primary immunodeficiency.[18] These principles provide a framework for the clinically appropriate use of IVIG. Although the AAAAI's principles are directed at IVIG for primary immunodeficiency, many points also translate to SCIG therapy and other FDA-approved indications, such as CIDP or multifocal motor neuropathy. Site of care, route of administration, and product characteristics are principles that apply globally when considering the effective use of Ig. The AAAAI states that the decision to infuse Ig in a hospital, hospital outpatient, community office, or home-based setting must be based on clinical characteristics of the patient and a discussion between the healthcare providers and the patient. Ultimately, the route of administration of Ig should be based on patient characteristics, as the IV and SC routes have demonstrated efficacy based on appropriate dosing regimens.[19] Lastly, Ig is not a generic drug, and Ig products are not interchangeable based on the variability of key components in each product. When making the clinical decision regarding an Ig product, clinicians should be aware that some products may be designed for a single route of administration, whereas others may be approved for multiple routes of administration (refer to Table 1[2-9]). For example, immune globulin (Flebogamma DIF) is approved only for IV administration,[4,5] and immune globulin with recombinant human hyaluronidase (HyQvia) is approved only for SC administration.[20] Other products, such as immune globulin (Gammagard Liquid 10%) and immune globulin injection, caprylate/chromatography purified (Gamunex-C 10%), are approved for IV and SC administration.[21,22]

It is recommended that payers and institutions keep an open Ig formulary because a

TABLE 1. IVIG and SCIG Products and Their Indications[2-9,a]

Product	Indications
IVIG Products	
Immune globulin (Asceniv) 10%	• Primary humoral immunodeficiency
Immune globulin (Flebogamma DIF) 5%, 10%	• Primary humoral immunodeficiency • Immune thrombocytopenic purpura
Immune globulin (Gammagard S/D) 5%, 10%	• Primary humoral immunodeficiency • B-cell chronic lymphocytic leukemia • Immune thrombocytopenic purpura • Kawasaki disease
Immune globulin (Gammaplex) 5%, 10%	• Primary humoral immunodeficiency • Chronic immune thrombocytopenic purpura
Immune globulin (Octagam) 5%, 10%	• Primary humoral immunodeficiency (5%) • Chronic immune thrombocytopenic purpura (10%)
Immune globulin (Panzyga) 10%	• Primary humoral immunodeficiency • Chronic immune thrombocytopenic purpura
Immune globulin (Privigen) 10%	• Primary humoral immunodeficiency • Chronic immune thrombocytopenic purpura • Chronic inflammatory demyelinating polyneuropathy
IVIG/SCIG Products	
Immune globulin (Gammagard Liquid) 10%	• Primary humoral immunodeficiency (IV/SC) • Multifocal motor neuropathy (IV)
Immune globulin injection, caprylate/chromatography purified (Gammaked) 10%	• Primary humoral immunodeficiency (IV/SC) • Idiopathic thrombocytopenic purpura (IV) • Chronic inflammatory demyelinating polyneuropathy (IV)
Immune globulin injection, caprylate/chromatography purified (Gamunex-C) 10%	• Primary humoral immunodeficiency (IV/SC) • Idiopathic thrombocytopenic purpura (IV) • Chronic inflammatory demyelinating polyneuropathy (IV)
SCIG Products	
Immune globulin (Cutaquig) 16.5%	• Primary humoral immunodeficiency
Immune globulin (Cuvitru) 20%	• Primary humoral immunodeficiency
Immune globulin (Hizentra) 20%	• Primary humoral immunodeficiency • Chronic inflammatory demyelinating polyneuropathy
Immune globulin with recombinant human hyaluronidase (HyQvia) 10%	• Primary humoral immunodeficiency

IV indicates intravenous; IVIG, intravenous immunoglobulin; SC, subcutaneous; SCIG, subcutaneous immunoglobulin.

[a]Carimune NF and Vivaglobin have been discontinued in the United States as of the date of publication, although some products may still be available on the market. Bivigam was previously discontinued but has been reapproved as of May 2019.

TABLE 2. Pharmaceutical Properties of Select IVIG, IV/SCIG, and SCIG Products[2,6-8]

Product	Osmolality (mOsm/kg)	Sodium Content	pH	IgA (mcg/mL)	Stabilizer
IV Products					
Asceniv 10%	N/A	100-140 mEq/mL	4.0-4.6	≤200	Polysorbate 80, glycine
Flebogamma DIF 5%	325 ± 4.8	<3.2 mEq/mL	5.6±0.1	<3.1	Sorbitol
Flebogamma DIF 10%	343 ± 6.4	<3.2 mEq/mL	5.5±0.1	<3.1	Sorbitol
Gammagard 5% S/D	636	146 mEq/mL	6.4-7.2	<1	Glycine
Gammagard 10% S/D	1250	292 mEq/mL	6.4-7.2	<2	Glycine
Gammaplex 5%	Not <240, typically 420-500	30-50 mEq/mL	4.8-5.1	<10	Sorbitol, glycine, and polysorbate 80
Gammaplex 10%	Not <240, typically 280-288	≤5 mEq/mL	4.9-5.2	<20	Polysorbate 80, glycine
Octagam 5%	310-380	≤30 mEq/mL	5.1-6.0	<200	Maltose
Octagam 10%	310-380	≤30 mmol/L	4.5-5.0	106	Maltose
Panzyga 10%	240-310	Trace	4.5-5.0	100	Glycine
Privigen 10%	240-440	Trace	4.6-5.0	≤25	Proline
IV or SC Products					
Gammagard Liquid 10%	240-300	None added	4.9-5.2	37	Glycine
Gammaked 10%	258	Trace	4.0-4.5	46	Glycine
Gamunex-C 10%	258	Trace	4.0-4.5	46	Glycine
SC Products					
Cutaquig 16.5%	310-380	≤30 mmol/L	5.0-5.5	≤600	Maltose
Cuvitru 20% solution	208-292	None added	4.6-5.1	80	Glycine
Hizentra 20%	380	Trace	4.6-5.2	≤50	Proline
HyQvia 10% solution (+ hyaluronidase)	240-300	None added	4.6-5.1	37	Glycine

IgA indicates immunoglobulin A; IV, intravenous; IVIG, intravenous immunoglobulin; NaCl, sodium chloride; SC, subcutaneous; SCIG, subcutaneous immunoglobulin.

patient may not tolerate a certain product and may require options based on product and patient characteristics. Specific Ig products need to match with patient characteristics to ensure patient safety; a change of Ig product should only occur with the active participation of the clinicians and other members of the healthcare team.

Another pertinent resource for clinicians is the *Immunoglobulin Therapy Standards of Practice* published by the Immunoglobulin National Society (IgNS), which is in its second edition.[2] The IgNS document comprehensively covers many aspects of Ig therapy, with practice criteria accompanying each standard. Recognizing the collaborative approach that is necessary to properly treat patients who are receiving Ig therapy, IgNS emphasizes the interdisciplinary aspects of patient care that includes prescribers, pharmacists, nurses, and many other healthcare professionals.[2]

Patient Factors and Formulation Factors

The primary and active component of Ig products is immunoglobulin G (IgG). However, formulations of Ig can vary in many different respects: IgG monomer, dimer, and aggregate concentrations; IgA and IgM content; stabilizers; additives; and levels of impurities.[2] When multiple products are being considered for a specific patient, clinicians must weigh the impact of these pharmaceutical formulation factors, as they contribute to differences in safety and tolerability.[23-27]

Osmolality of IVIG, IV/SCIG, and SCIG products ranges from 208 mOsm/kg to 1250 mOsm/kg. Most of the products are within the range of physiologic osmolality of approximately 290 mOsm/kg (**Table 2**[2,6-8]). Products that deviate substantially from physiologic osmolality levels may put the patient at risk for various infusion-related adverse effects (AEs), such as thrombotic events and aseptic meningitis, particularly in elderly or neonatal patients, patients with cardiometabolic impairment, and patients with renal dysfunction.[2,24] Similarly, the same patient populations may be sensitive to the sodium content of Ig products, which is reported in a variety of units (eg, mmol/L, mEq/mL, mg/mL). If the pH of an injectable product is substantially below physiologic levels, localized reactions at the site of injection may result. With the pH of Ig products ranging from a low of 4 to 7.2 (see Table 2[2,6-8]), a slow infusion time

may be advisable for products with pH levels toward the lower end of the range.

Although Ig products primarily contain IgG, they also contain varying amounts of IgA (<1 mcg/mL to ≤200 mcg/mL for IVIG products and 37 mcg/mL to 80 mcg/mL for SCIG products).[2] Early research indicated that rare but severe anaphylactic reactions to Ig products were most likely to occur in patients who were severely deficient in IgA and also had IgE-type anti-IgA antibodies present. However, the administration of a low-IgA product has been shown to be effective in preventing severe allergic reactions in a small number of IgA-deficient patients who have previously experienced such reactions. Because SCIG therapy has a slower release of product into the general circulation, there are also a number of reports in the literature suggesting that SCIG therapy may be used successfully in IgA-deficient patients who experience adverse drug reactions (ADRs) to IVIG products.[2]

Stabilizers are included in the product formulations to prevent IgG aggregation, which may increase the risk of certain AEs, such as anaphylaxis.[19] Glycine is the most commonly used stabilizer, whereas D-sorbitol, glucose, maltose, L-proline, and polysorbate 80 are included in some formulations. Ig products containing glucose should be avoided in patients with diabetes when it is feasible as they can potentially raise serum glucose levels. Furthermore, products that contain maltose as a stabilizer should be used cautiously in patients with diabetes as some blood glucose monitoring systems (glucometers) may return falsely elevated glucose levels, which could lead to the unnecessary administration of insulin and result in hypoglycemia. Fortunately, most glucometers exhibiting this interference have been phased out of the market.[19]

TABLE 3. Advantages and Disadvantages of IVIG and SCIG Therapy[2,32]

	IVIG	SCIG
Advantages	• Less frequent dosing • History of efficacy • Safety profile and risk mitigation strategies are well known • Frequent contact with healthcare professionals during administration can mean better clinical monitoring and early identification of problems	• Self-administration feasible for patients with cognitive and fine motor ability • Smaller infusion volumes allow gradual absorption and steady state IgG levels • No venous access needed • Common AEs are localized at the infusion site
Disadvantages	• Requires venous access • Skilled personnel typically needed for administration • Peaks and troughs of PK profile may affect efficacy and safety • Systemic AEs	• Often requires more frequent infusions and multiple SC infusion sites and needlesticks • Lack of direct patient monitoring when self-administered to evaluate technique • Patient adherence may decrease • Localized site reactions

AE indicates adverse effect; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; PK, pharmacokinetics; SC, subcutaneous; SCIG, subcutaneous immunoglobulin.

TABLE 4. Local Adverse Drug Reactions With SCIG Therapy and Mitigation Strategies[2]

Local Reaction	Mitigation Strategies
Leaking at the infusion site	• Ensure needle placement and security • Ensure adequacy of SC tissue • Ensure appropriate needle length • Ensure appropriate volume infused per site • Ensure appropriate rate of infusion
SCIG: Reaction at the infusion site should be consistent with volume of drug infused and is expected to appear raised and quarter-sized in diameter. fSCIG: Reaction at the infusion site is expected to appear as a soft, diffuse pancake.	If greater reaction is seen, the following may be considered: • Decrease the volume per site • Change site of infusion • Ensure appropriate needle length • Administer lower doses more frequently • Assess sensitivity to adhesive • Consider slowing infusion rate • Ensure good dry priming needle technique in SCIG tubing and needle sets • Consider gentle massage or using a warm or cold compress post infusion

fSCIG indicates facilitated subcutaneous immunoglobulin; SC, subcutaneous; SCIG, subcutaneous immunoglobulin.

Volume is also a significant consideration when choosing an Ig product, whether it is IV or SC. IVIG products are available as 5% or 10% solutions. One product is available as a lyophilized powder that can be reconstituted into a 5% or 10% solution using sterile water. When considering an IVIG product to select for a patient based on volume, it is very important to keep the clinical picture of the patient in mind. Extra volume could be beneficial in those patients who do not maintain adequate oral hydration and could also help minimize ADRs. In contrast, the extra volume could worsen underlying clinical conditions, such as congestive heart failure, hypertension, and renal dysfunction. Furthermore, the additional volume of low concentrated products may take longer to infuse and increase nursing time. SCIG products are commercially available as 10%, 16.5%, and 20% solutions. Although a 10% product may be better tolerated in some patients,

the greater volume of product that needs to be infused means more SC infusion sites and frequent administrations. The rate of infusion and volume per site is individualized for each product and must be taken into consideration, in addition to patient tolerability.[2-8]

When writing a prescription for Ig, some prescribers may specify a brand, and some payers impose limited formularies that require the use of a specific Ig product. If the prescribed or reimbursed product is not ideal for the patient based on these clinical characteristics, it is incumbent upon the Ig clinician to advocate for other options with the prescriber or payer if warranted.[2] The potential interactions between patient factors and pharmaceutical formulation factors must be considered by clinicians when making IVIG or SCIG product choices and must be assessed on an ongoing basis.

Individual Patient Ability and Preference

Patient preference for one form of administration is an important factor to consider when choosing between IVIG and SCIG. In addition, it is important to understand and consider options that are available for the site of care. Options for the site of care include the following[2]:

- Hospital inpatient with prescriber/nurse supervision
- Hospital outpatient with prescriber/nurse supervision
- Physician office with prescriber/nurse supervision
- Free-standing infusion suite with prescriber/nurse supervision
- Home-based infusion with nurse supervision
- Home-based infusion without nurse supervision (SCIG only)

Patients often prefer the convenience of home-based Ig administration,[28,29] and studies suggest that home administration is feasible for certain patient populations. Factors that must be considered by clinicians when determining the site of care include the patient's medical history and comorbidities, age, ability to travel, home environment, previous experience with Ig, access to emergency medical services or 911, availability of a caregiver, third-party payer restrictions, financial burden, and preference. In addition, when evaluating the appropriateness for SCIG therapy, the Ig clinician must assess the patient's ability to learn how to successfully perform self-administration and to adhere to dosing regimens.[2]

Studies reviewing patient preferences of site of care have revealed a mixed picture; the site of care and route of administration need to be a patient-specific consideration. In the VISAGES study, Bienvenu et al observed that approximately 70% of patients who received hospital-based IVIG preferred hospital-based administration. Of 12 home-based patients who received IVIG, just 1 patient preferred hospital-based administration. All patients who received home-based SCIG preferred that arrangement compared with the option of hospital-based therapy.[30] In a survey study with 300 respondents, Espanol and colleagues determined that a majority of respondents (76%) were satisfied with their current treatment arrangement, either IVIG or SCIG.[28] In a smaller study, Hoffmann et al observed that 92% (n = 22) of adult patients preferred SCIG over IVIG, and 83% (n = 20) preferred home-based therapy over the alternative.[31]

Ig Treatment Options, Risks, and Benefits

Determining the best Ig treatment option for a given patient requires an assessment of the risks and benefits of each product. As outlined previously, patient considerations may dictate a particular route of administration. When an initial assessment has been completed and it is found that IVIG and SCIG would both be feasible for a patient, additional factors, including AE profiles, dosing frequency, and pharmacokinetics (PK), can be considered. **Table 3**[2,32] summarizes the advantages and disadvantages of each route of administration, which are described in detail throughout this paper.

The number of indications for IVIG and SCIG therapies preclude listing all the corresponding dosing recommendations. What follows is a summary of dosing recommendations for common indications. In primary humoral immunodeficiency, the IVIG dose is 300 mg/kg to 800 mg/kg every 3 or 4 weeks, and the SCIG dose is adjusted from the adjusted IVIG dose every 1 to 14 days. For CIDP, an IVIG loading dose of 2 g/kg is given in divided doses over 2 to 5 consecutive days with a maintenance dose of 1 g/kg every 3 weeks administered over 1 day or divided into 2 doses of 500 mg/kg given on 2 consecutive days (modified according to patient response). Alternatively, SCIG may be utilized for maintenance dosing in some patients at 0.2 g/kg to 0.4 g/kg weekly. For immune thrombocytopenic purpura or idiopathic thrombocytopenic purpura, the IVIG dose is 1 g/kg for 1 to 3 doses. Patients with multifocal motor neuropathy would receive a loading dose of 400 to 500 mg/kg daily for 5 days, followed by a maintenance dose of 0.5 to 2.4 g/kg/month based on clinical response.[2] The information provided is from the IgNS Standards of Practice; note that it is not based on the individual package inserts, but includes other dosing recommendations from the published literature. Please refer to individual prescribing information for specific product dosing.

IVIG: Unique Considerations

Besides patient and formulation factors, the choice between IVIG and SCIG often hinges on dosing frequency, which is highly dependent on PK differences between the routes of administration. IVIG introduces Ig directly into the circulatory system via venous access. After IVIG administration, the IgG serum concentration shows an initial sharp rise followed by a rapid decrease for 1 to 4 days after the infusion and then a gradual decrease over the next 21 to 28 days.[33] Steady state is achieved between the fourth and sixth infusion of IVIG in a naïve patient who is usually dosed every 3 to 4 weeks. Once steady state is reached, a pre-infusion trough level can be obtained, but the utility of monitoring trough levels is indication-specific. In primary immunodeficiencies, dose and interval are titrated to

achieve an IgG trough level of greater than 500 mg/dL. For patients with common variable immune deficiency, many prescribers target an initial serum IgG level equal to that of the patient's pretreatment level plus 300 mg/dL. However, as the IgNS Standards of Practice indicate, Ig dosing should be based on a combination of clinical response and appropriate trough levels rather than trough levels alone, which is a clinical practice supported by the literature.[2,34-38] Patients who receive IVIG therapy for immunodeficiencies appear to have an increased risk of infection as IgG trough levels are approached. This phenomenon, sometimes referred to as wear-off, may increase the risk of infection by 26% for patients on a 3-week administration cycle and 55% for patients on a 4-week administration cycle.[39] IVIG dosing in autoimmune disorders is even more variable following the initial recommended starting dose, and it is customarily based on the individual patient's clinical response.

Overall, Ig therapy is safe and well tolerated in most patients. AEs in patients undergoing IVIG therapy tend to be systemic in nature.[40,41] Such AEs are observed more commonly in treatment-naïve patients and may occur up to 34% of the time with the first infusion.[32] Other estimates point to similar (eg, up to 40%) rates of AEs with IVIG infusion. Whenever possible, the goal should be to prevent ADRs from occurring, and this can usually be achieved by proper product selection and administration.[2] If ADRs do occur, it is important to note that many of the systemic AEs associated with IVIG can be attenuated by reducing the infusion rate of IVIG, ensuring adequate hydration, and/or premedicating the patient with nonsteroidal anti-inflammatory drugs, corticosteroids, and antihistamines.[14,19,42,43]

SCIG: Unique Considerations

One of the often-mentioned advantages of SCIG is the option to administer required doses at a time and place of the patient's choosing. Although many patients receiving IVIG can use home infusion services, the option to receive treatment that does not require a skilled healthcare professional is an advantage of SCIG. However, the advantage of home-based administration may be mitigated to some degree by the more frequent dosing schedules often required for SCIG, as well as the need to self-infuse using needle sets, SC infusion pumps, and syringes.[42] With more frequent dosing schedules, patients may be advised to vary the site of injections as well as limit the volume per site based on SCIG product used.[6,13,20-22] The dosing frequency for SCIG is predicated on PK principles and varies between SCIG and fSCIG.

When Ig is administered SC, it must first diffuse through the SC space into the lymphatic system before entering the circulatory system via the thoracic duct.[19] This results in a decreased peak concentration compared with IVIG. With more frequent dosing (eg, daily, weekly, or biweekly), trough levels with SCIG are not as severe as IVIG and a steady state concentration is achieved.[32,44,45] The absorption process inherent with SCIG administration reduces the bioavailability of Ig by approximately 30% to 35%.[46] Based in part on potential differences in bioavailability, the IgNS recommends consulting with the prescriber to determine what conversion factors, if any, are used when switching patients from IVIG to SCIG.[2] This is similar to practices in other parts of the world where dose adjustments between IVIG and SCIG are not typically required but may be individualized for patients based on PK and clinical response.[47] However, fSCIG has some of the properties of SCIG and IVIG regimens, resulting in hybrid PK profiles for fSCIG. Although the bioavailability of fSCIG products is similar to that of IVIG products, peak serum IgG levels are typically lower than those encountered with IVIG infusion; thus, fSCIG retains an AE profile closer to that of SCIG.[1]

Given the PK parameters, SCIG therapy has the advantage of few systemic AEs, which may occur in fewer than 5% of patients who receive SCIG. One meta-analysis determined that the systemic AE rate for SCIG was 0.43%.[42] On the other hand, patients who receive SCIG therapy are more likely to experience local site reactions (eg, erythema, swelling, warmth, induration, and soreness), which may occur in up to 75% of patients.[42] See **Table 4**[2] for a summary of local ADRs that can occur with SCIG products, along with suggested mitigation strategies.

Conclusions

Whether administered via the IV or SC route, successful Ig therapy depends on expert clinical knowledge and experience, as well as a collaborative healthcare environment.[2] IV and SC are both clinically appropriate modes of administering Ig to patients with primary immunodeficiency disorders and other autoimmune disease states. Each mode of administration has advantages and disadvantages but remains a patient-specific choice.[2,32] Many factors must be considered when choosing between IVIG and SCIG, including patient characteristics, pharmaceutical formulation factors, patient preference, and patient lifestyle and abilities, among others. ■

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Funding source: This activity is supported by educational grants from CSL Behring LLC and Grifols.

Author disclosure: Dr Ness has no relevant financial relationships with commercial interests to disclose.

Authorship information: Concept and design; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

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REPORT

Managing Cost of Care and Healthcare Utilization in Patients Using Immunoglobulin Agents

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Introduction

Primary immunodeficiencies are a heterogenous group of immune-related conditions in which individuals exposed to pathogens risk severe and often life-threatening infections. The first patient with primary immunodeficiency was treated with subcutaneous human immunoglobulin (Ig) in 1952, transforming the outlook for these patients.[1] The use of Ig has since been shown to reduce the risk of infection, antibiotic use, and hospital admissions, while leading to improved growth in pediatric populations and the maintenance of normal pulmonary function, thus dramatically improving quality of life and prognosis.[2,3]

Today, Ig is also used on- and off-label for the chronic and acute treatment of numerous other conditions, including chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN); to prevent bacterial infections in patients with certain hematologic malignancies, pediatric HIV, chronic lymphocytic leukemia, or following bone marrow transplantation; to increase platelet count in patients with idiopathic thrombocytopenic purpura; for certain autoimmune diseases, such as myasthenia gravis, immune-mediated inflammatory myopathies, immune-mediated blistering diseases, stiff person syndrome, and others; and to treat immunologic deficiencies in patients receiving B-cell–depleting targeted therapies.[4,5] Ig is primarily used in its intravenous (IVIG) and subcutaneous (SCIG) formulations. Both can be delivered via an infusion pump; this often provides greater ease and convenience for patients and their families.[4]

Igs are one of the most complex specialty drugs for payers to manage. There are several reasons for this, including the large number of products currently on the market, which all have various doses, formulations, and indications; off-label uses; and adverse effects (AEs). Other important factors include patient and family education, the administrative support required, and site-of-care issues related to product delivery.[6,7]

The use of Ig is also increasing as diagnoses of primary immunodeficiencies and neurologic conditions increase, the population ages, and new uses are identified.[8,9] For instance, the number of Medicare beneficiaries with primary immunodeficiencies receiving IVIG grew

ABSTRACT

The introduction of human immunoglobulin (Ig) therapies 40 years ago reduced the risk of often life-threatening infections for individuals with one of several immune-related conditions known as primary immunodeficiencies. Since then, the use of Ig has expanded to numerous other conditions. However, even though less than 1% of covered lives under Medicare or commercial insurers require Ig, it is in the top 5 drug categories in terms of annual spending. The cost of Ig is directly related to the type of delivery method used and the site of care. Numerous studies attest to the efficacy and cost savings of shifting Ig to the home setting, as well as shifting patients from intravenous Ig (IVIG) to subcutaneous Ig (SCIG). In addition, surveys find that patients with primary immunodeficiencies prefer home delivery, with patient evaluations also finding a preference for SCIG. Payers have numerous options to ensure Ig is used appropriately for the right patient in the right setting. These include formulary management, site-of-care programs, education for providers and patients on the possibility of switching from IVIG to SCIG, preauthorization policies that restrict the use of Ig to certain specialties for specific indications, implementation of evidence-based coverage criteria, and shifting coverage from the medical to the pharmacy benefit.

***Am J Manag Care*. 2019;25:S105-S111**

For author information and disclosures, see end of text.

60% between 2010 and 2014, with 25% of patients being younger than 65 years.[10] In 2016, the Jeffrey Modell Foundation reported a 19% global increase in the number of patients receiving Ig between 2013 and 2015, with a 7% increase in those receiving IVIG and a 100% increase in those receiving SCIG. In the United States, the number of people with primary immunodeficiencies receiving Ig increased 11.5% during that time, with a 10% increase in IVIG administration and a 39.3% increase in SCIG administration.[11] However, primary immunodeficiencies still remain undiagnosed, underdiagnosed, or misdiagnosed. Not only does this increase the risk of mortality for patients, but it also results in higher costs for payers.[11,12]

Economic Burden of Chronic Immunodeficiency Diseases

A 2017 report from the Jeffrey Modell Foundation that used the IMS database containing medical and pharmaceutical claims for more than 60 million patients from 90 US health plans found that annual treatment costs for patients with primary immunodeficiencies declined from $111,053 per patient before diagnosis to $25,271 per patient after diagnosis, even before Ig treatment.[13] Even accounting for an annual $30,000 per patient cost of Ig, total cost savings post diagnosis were $55,882 (**Table 1**[13]).

A retrospective analysis of a large commercial database identified 1388 patients undiagnosed with primary immunodeficiencies for at least 5 years (84 for at least 10 years). Patients had a mean 39% increase in pneumonia, 20.4% in sinusitis, 20.2% in bronchitis, and 14.2% in otitis in the 10 years before diagnosis. In addition, there was a 29.1% average annual increase in hospitalizations, 10.5% in outpatient visits, and 5.3% in outpatient drug utilization.[14]

Other studies highlight the costs of other conditions for which Ig is used. One analysis of 31,451 medical records estimated the cost of hospitalizations for CIDP between 2010 and 2012 at $2.1 billion. Each CIDP hospitalization cost an average of $68,231, which was higher than that of a matched cohort, although the authors did not specify the cost of hospitalization for controls. The patients with CIDP also had lengths of stay 50% longer than controls.[15]

Cost of Immunoglobulin

In 2016, commercial payers spent an average of $2.00 per member per month (PMPM) on Ig (average claim $4154), a 16% increase

TABLE 1. Costs of the Most Frequent Conditions Affecting Patients With Primary Immunodeficiencies in the Year Before and After Diagnosis[13]

Condition	Pre-Dx Average No. of Episodes	Pre-Dx Cost per Episode	Pre-Dx Annual Cost	Post-Dx Average No. of Episodes	Post-Dx Cost per Episode	Post-Dx Annual Cost	Post-Dx Average Annual Savings
Persistent otitis media	4.2	$528	$2217	1.6	$528	$845	
Serious sinus and upper respiratory infections	4.6	$1125	$5175	2.1	$1125	$2362	
Viral infections	3.7	$1275	$4717	1.4	$1275	$1785	
Acute bronchitis	3.1	$1700	$5270	0.8	$1700	$1360	
Bacterial pneumonia	2.8	$3552	$9945	0.6	$3552	$2131	
Chronic obstructive pulmonary disease and bronchiectasis	4.3	$3165	$13,609	1.4	$3165	$4431	
Hospitalization days	19.8	$2480	$49,104	3.1	$2480	$7688	
Physician/ED visits	70.8	$180	$12,744	11.7	$180	$2106	
Days on antibiotics	1662	$10	$1662	72.8	$10	$728	
School/work days missed	33.9	$195	$6610	8.9	$195	$1735	
Total cost annually per patient without IgG			$111,053			$25,171	$85,882 annual savings per patient per year without IgG
Average annual cost of IgG						$30,000	
Total cost savings annually including 100% on IgG (actual total 25.6%)							$55,882 annual savings per patient per year without IgG

Dx indicates diagnosis; ED, emergency department; IgG, immunoglobulin G.
The cost of the most frequent conditions affecting patients with primary immunodeficiencies pre- and post-diagnosis, and the post-diagnosis average annual savings. Reprinted by permission from Springer Nature: Springer, *Immunologic Research*, "Modeling strategy to identify patients with primary immunodeficiency utilizing risk management and outcome measurement," Modell V, Quinn J, Ginsberg G, et al © 2017.

over the previous year. The category represented the third highest drug category for payers at 8% of total drug spending, even though fewer than 1% of members (0.41 per 1000) required Ig treatment.[16]

Ig represents the fourth highest drug spending for Medicare Advantage plans, with an average PMPM of $2.82 in 2016 and an average cost per claim of $3282, representing 6% of overall Medicare Advantage prescription drug spending that year. The number of Medicare Advantage beneficiaries utilizing Ig, although higher than the commercial population, is still less than 1% (0.97, per 1000).[16]

Site of Care

When it was first approved, IVIG was typically delivered in the hospital setting as that was considered a safer place to manage AEs. Today, however, IVIG and SCIG may also be delivered in the home or physician office setting.[17] The Jeffrey Modell Foundation estimated that 38% of US patients with primary immunodeficiencies received IVIG in a clinic setting in 2015 and 30% received IVIG in the home setting, whereas 28% of patients received SCIG (**Table 2**).[11] Since then, many payers have instituted site-of-care policies, so these percentages are likely higher.[18,19] Guidelines from the American Academy of Allergy, Asthma and Immunology note that the decision as to where to infuse the drug should be based on clinical considerations, including patient experience, patient comorbid conditions, and circumstance.[20]

In 2015, 48% of IVIG covered by commercial payers was delivered in the home or specialty pharmacy setting, 30% in the hospital outpatient setting, and 24% in the physician office setting, which represents a slight decline in hospital setting delivery from 2014 (33% to 30%). Under Medicare Advantage, 36% was delivered in the home or specialty pharmacy setting, 38% in physician offices, and 26% in hospital outpatient settings. This represents a significantly higher decline in hospital outpatient delivery between 2014 and 2015 (35% to 26%) in the managed care Medicare environment.[21]

The outpatient hospital setting can be the most expensive site for delivery of IVIG for commercial payers (**Figure 1**).[17] This is because reimbursement is typically based on a percentage of billed charges plus a facility fee. Reimbursement in physician offices and nonhospital-owned clinics, however, is based on the cost of the drug plus an administrative fee, whereas home infusions are typically paid at average wholesale price minus any discounts or average sales price plus a percentage, plus equipment and nursing reimbursement.[22] It is important to keep in mind that there are multiple reimbursement scenarios in each site of care (hospital, hospital outpatient, physician office, home), which vary based on the payer and the route of administration.

SCIG products may be more expensive than IVIG agents when considered on a per-gram basis. Although this is important to factor in, there are various considerations to examine when analyzing cost-effectiveness. Several analyses discuss substantial savings when IVIG administration shifts to the home setting and/or when patients switch from IVIG to SCIG formulations. A French analysis of IVIG costs in 24 patients (9 with MMN, 8 with CIDP, and 7 with Lewis-Sumner syndrome) found 1-year costs of $54,914 for patients treated in the home versus $104,608 for those treated in the outpatient hospital setting (P <.0001). The authors estimated that 20% of current patients with CIDP could benefit from the switch, with the number as high as 80% among stable patients.[23]

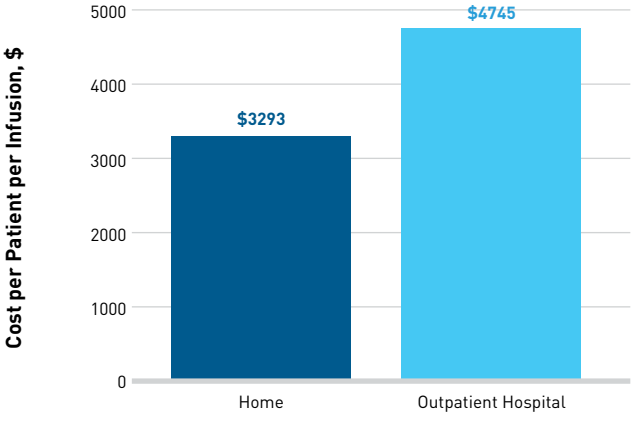
Another retrospective review of a claim database covering nearly 43 million participants in a commercial health plan also found lower overall costs for home infusions, with the cost per infusion per patient to be 31% less in the home setting than in the outpatient setting ($3293 vs $4745; P <.0001) (Figure 1).[17] Overall, the investigators estimated that delivering IVIG in the home setting could provide annual savings of $18,876 to $26,136 for each patient receiving 13 to 18 infusions per year. The analysis also found lower non-Ig costs

TABLE 2. US Patients With Primary Immunodeficiencies Receiving Ig by Site of Care[11]

Type of Ig and Setting	Number of Patients	Percentage of Patients
IVIG at clinic	3098	38%
IVIG at home	2415	30%
SCIG (setting varies)	2272	28%
Other (setting varies)	380	5%

Ig indicates immunoglobulin; IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin.
Adapted from Modell V, Quinn J, Orange J, Notarangelo LD, Modell F. Primary immunodeficiencies worldwide: an updated overview from the Jeffrey Modell Centers Global Network. *Immunol Res.* 2016;64(3):736-753.

FIGURE 1. Mean Cost per Patient per Infusion by Setting[17]



Cost adjusted for baseline Deyo-Charlson Comorbidity Index score, and converted to 2010 US dollars.
P <.0001 home versus outpatient hospital.

(Table 3[17]) and improved adherence in patients who received home infusions (47% vs 22%; P <.001) based on the recommended 13 to 18 infusions per year. A significantly greater number of patients with fewer than 7 infusions per year were in the outpatient hospital versus the home setting (39% vs 29%; P <.0001).[17]

Ye et al used a large commercial claims database to identify patients with at least 3 months of continuous IVIG and compared costs of care among the home, outpatient hospital, or clinic setting. Eighty-three patients switched their IVIG site between clinic and home, and 79 switched between outpatient hospital to home. Switching from the outpatient hospital setting to the home setting led to significantly lower median costs ($6916 vs $4188; P <.0001), although there were no significant differences in costs between the clinic and home setting.[24]

A study by Wasserman et al used data from a large, US-based commercial database to identify outcomes related to IVIG site of service. Of the 1076 patients with primary immunodeficiencies included in the analysis, 51% received IVIG at home and 49% at a hospital-outpatient infusion center. Patients receiving home-based infusions had significantly lower rates of pneumonia (0.102 vs 0.216; P = .0071) and bronchitis (0.150 vs 0.288; P <.0001) independent of prophylactic antibiotic treatment.[25] The differences were significant in the first 3 weeks after the first infusion with no significant difference following the fourth infusion, suggesting, the authors noted, that the setting itself may be a factor in the infection rate. The findings are particularly significant given that recurrent lower respiratory infections eventually lead to the long-term pulmonary disease that is a major cause of morbidity and mortality in these patients.[25]

Given the lower cost of at-home or physician office administration, many payers have introduced sites-of-care policies related to infusions.[18,26,27] This includes removing reimbursement incentives between sites of care; encouraging patients to choose less-expensive sites of care through education, communication, and financial incentives; and restricting settings based on medical necessity or specific patient issues.[28]

In a survey of 59 commercial health plans representing more than 76 million covered lives, there was a 135% increase in plans using site-of-care programs between 2013 and 2017 (26% to 61%). More than half of those without a site-of-care program in 2017 planned to implement one in the next 12 months. Of those with site-of-care programs, 89% have one for IVIG, making it the top therapeutic area with site-of-care programs.[29]

The majority of Medicare fee-for-service IVIG (and other infusions covered under Part B) are delivered in the hospital-owned outpatient setting, physician offices, or skilled nursing facilities, primarily because of financial issues.[30] Traditional Medicare has not, until now, reimbursed supplies and administration for in-home IVIG outside a current pilot program, although it does provide a bundled payment for SCIG.[10,31] A 2014 report from Avalere Health estimated Medicare could save $80 million in infusion services between 2015 and 2025, or 12.6% of overall infusion costs, by encouraging a shift to home infusion.[30]

In 2012, Congress established a 3-year Patient Intravenous Immunoglobulin Access Demonstration project, designed to enroll up to 4000 beneficiaries with primary immunodeficiencies. The demonstration required Medicare to provide a bundled payment to providers for items and services required to administer in-home IVIG, including services provided by a skilled nurse.[10,31] It is important to note that the Demonstration project has been extended beyond the initial 3-year period and results have not yet been published.

TABLE 3. Mean Non-IVIG Costs per Patient per Year Based on Infusion Setting[17,a]

	Hospitalization	Emergency Department	Pharmacy	Office Visits
Home setting	$17,538	$589	$7091	$3277
Outpatient hospital	$20,135	$438	$9663	$4523

IVIG indicates intravenous immunoglobulin.
[a]2010 US dollars.

IVIG versus SCIG

There is a movement to shift patients from IVIG to SCIG given numerous studies demonstrating clinical equivalence between the two with lower overall costs and improved patient satisfaction with SCIG administration. SCIG drugs may be more expensive per gram and that is important to take into consideration. When additional costs are factored in, including administration fees and site-of-care fees, several studies found lower overall costs.

Fu et al conducted a 12-month prospective observational study that analyzed overall costs for 30 patients receiving IVIG and 27 receiving SCIG. Patients on SCIG received training from a nurse during a single visit, then infused the product on their own at home; in contrast, those on IVIG therapy spent 2 to 3 hours in a hospital-based setting receiving the infusion.[32] Total costs to the hospital and health-system costs in the SCIG group were $1836 and $1920, respectively, compared with $4187 and $4931, respectively, for the IVIG group (Figure 2).[32] The lower costs were due to fewer physician and hospital visits and shorter total nursing time required for the infusion (Figure 2).[32]

Moreover, a German cost-minimization analysis on the effects of switching patients with primary immunodeficiencies from hospital-based IVIG to home-based SCIG over 3 years found that SCIG cost $35,438 per patient the first year and $30,441 in subsequent years compared with $34,638 per year for IVIG, resulting in a total savings of $7592 per patient over 3 years, even given additional

costs for equipment and patient training.[33] These are based on a CHF (Swiss currency) to USD conversion (of note, the USD used to have a stronger value than Swiss franc until April 2019; now the Swiss franc is stronger than the USD).

In addition, an analysis of direct medical and indirect costs in 25 pediatric patients who received either SCIG or IVIG in a pediatric clinic also found significantly lower medical costs in the SCIG cohort, as well as nonmedical costs, including travel expenses and parental time (P <.001 for both) (4706 vs 2131; P <.001). Although the study was conducted in Canada, the authors noted that it "could easily be applicable to most healthcare systems in the Western world."[34]

In France, analysts used a cost-minimization analysis with a simulation model to compare hospital costs and transportation in the outpatient and home setting for IVIG and in the home setting for SCIG. Authors concluded that direct medical costs ranged from $22,211 for home-based IVIG to $29,164 for hospital-based IVIG, with home-based SCIG at $28,445. A patient satisfaction questionnaire demonstrated greater satisfaction in terms of convenience with SCIG as well as greater satisfaction with either home SCIG or IVIG versus hospital-based.[35]

Finally, Canadian researchers conducted a cost-minimization and budget-impact model to evaluate the economic benefits of replacing IVIG with rapid push SCIG in Canadian patients with primary immunodeficiencies over 3 years.[36] Under the cost-minimization model, rapid push SCIG was $1487 vs $5800 (USD) for IVIG, reducing per-patient healthcare costs in Canada by 74% ($5765 for IVIG vs $1478 for SCIG) over 3 years, primarily as a result of fewer hospital staff required. The authors estimated that if half of eligible patients switched to SCIG, the cost savings for the healthcare system would be $977,586. If 75% of patients switched, that figure reached $1.47 million. The model applied 85% of the total cost to the Ig itself.[37]

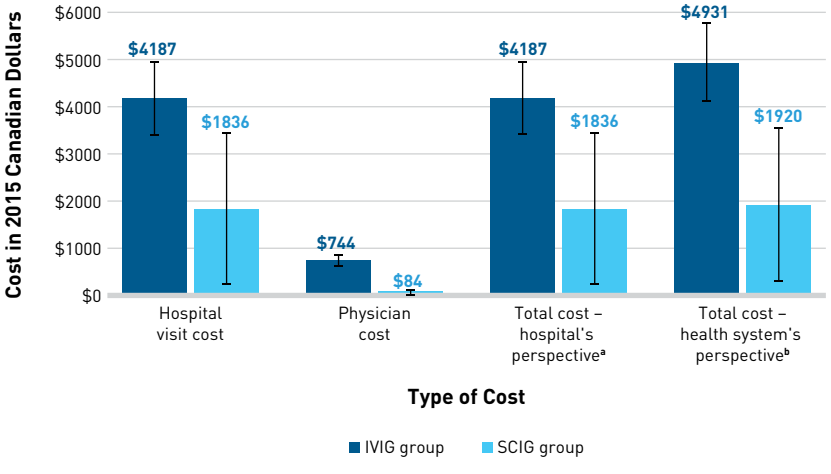
There is good evidence that patients much prefer infusions in the home environment. One systematic review of the literature found that home infusion care provided safe, clinically effective care with improved quality of life and reduced overall healthcare costs.[36,38] In addition, patient satisfaction with SCIG was demonstrated in a recent analysis from the Polyneuropathy and Treatment with Hizentra (PATH) study, which is the largest trial ever to compare relapse rates in patients with CIDP. Investigators randomized 172 IVIG treatment-dependent patients to weekly infusions of placebo or low- or high-dose SCIG. As expected, patients in the SCIG groups had significantly fewer rates of relapse than those in the placebo group. More importantly, the rates of relapse in the SCIG patients were similar to those experienced while on IVIG. Patients preferred the weekly SCIG treatment to monthly IVIG because of a gain in independence and fewer AEs. The results, the authors wrote, suggested that SCIG may be an alternative option as a maintenance therapy for patients with CIDP.[39]

Other Cost-Management Approaches

In addition to site-of-care policies, payers use a variety of other approaches to manage the cost and appropriate use of Ig, as shown in **Table 4**.[16] In 2016, one-third of commercial payers used product preferencing for IVIG compared with just 17% for SCIG. In contrast, 53% of Medicare Advantage medical benefit administrators used product preferencing for IVIG compared with 20% for SCIG in 2016.[16] This use of restricted formularies or fail-first policies are important options for managing Ig utilization and cost. However, requiring that patients switch to a different formulation from the one they are currently taking could lead to AEs.[40]

Care management can provide substantial economic and clinical benefits. Makanji et al reported on the impact of an Ig utilization-management and dose-optimization program in a regional health plan covering approximately 700,000 lives. The program involved comprehensive medical criteria with steps through alternative therapies when clinically appropriate, along with pharmacist-led interventions to recommend dose optimization based on adjusted body weight instead of actual body weight in obese adults. It also included pharmacist-led education and outreach to physicians.[41-44]

FIGURE 2. Unadjusted Average Costs for IVIG versus SCIG[32]



IVIG indicates intravenous immunoglobulin; SCIG subcutaneous immunoglobulin.
Error bars represent the standard deviation for each variable and group
[a]Hospital's perspective included costs to the hospital (eg, nursing time, overhead, general supplies, and patient-specific supplies).
[b]Health system's perspective included physician fees in addition to hospital costs.
Adapted from Fu LW, Song C, Isaranuwatchai W, Betschel S. Home-based subcutaneous immunoglobulin therapy vs hospital-based intravenous immunoglobulin therapy: a prospective economic analysis. *Ann Allergy Asthma Immunol.* 2018;120(2):195-199.

TABLE 4. 2016 Utilization Management Tools for IVIG and SCIG[16]

	Commercial (percentage of payers; n = 49) 109 Million Covered Lives		Medicare Advantage (percentage of payers; n = 8) 32 Million Covered Lives	
	IVIG	SCIG	IVIG	SCIG
Care management	24%	16%	25%	13%
Clinical pathways	8%	4%	0%	0%
Differential provider reimbursement by drug in therapy class	4%	0%	NA	NA
Dose optimization	16%	8%	NA	NA
Patient adherence program	4%	4%	NA	NA
Post service claim edits	14%	12%	13%	13%
Prior authorization	88%	84%	75%	75%
Site of service	22%	12%	13%	13%
Step-edit requirements	6%	4%	NA	NA
None	2%	14%	25%	25%
Other	4%	2%	NA	NA

IVIG indicates intravenous immunoglobulin; NA, not available; SCIG, subcutaneous immunoglobulin.

In the first year, the program produced a 17% overall reduction in total Ig spend, which translated to an estimated savings of approximately $1.4 million annually ($0.17 PMPM). Dose optimization led to an 8% savings ($606,235) over 1 year, primarily due to dosage changes in obese patients. Overall utilization also declined, and the paid amount for inappropriate indications decreased by 77%.[41]

One study of a care management program for 242 patients who received "high-touch" IVIG clinical management through a home infusion specialty pharmacy found a significantly lower rate of serious bacterial infections in the intervention group compared with a control group (n = 968) (4.13% vs 7.75%; P = .049). Patients received IVIG infusion in their homes or in ambulatory infusion suites. They also received a preinfusion risk assessment by a pharmacist to identify any comorbidities that might increase the risk of AEs; infusion monitoring by an Ig-specialized registered nurse, including individualized infusion rate protocols and patient education; regular clinical follow-up with a pharmacist to assess adherence and AE management; and financial counseling.[45] There were no significant differences in treatment-related AEs or nonserious infections. There was, however, a 20% reduction in annual adjusted total medical costs ($109,476 vs $135,998; P = .002), primarily due to a shift in the site of care from outpatient to home.[46]

Payers are also using benefit design to better manage Ig costs. A study presented at the Academy of Managed Care Pharmacy's 2018 annual meeting described the outcomes of a specialty channel management project that shifted IVIG coverage from the medical to the pharmacy benefit in a Medicaid managed care plan in Pennsylvania. Investigators analyzed claims data from July 1 to October 26, 2017, identifying 135 claims for different IVIG medications for 17 members. The data showed a significant cost-saving benefit of 70.2% (P = .014) when IVIG was managed under the pharmacy benefit.[47] Of course, this could simply shift more of the cost to the patients depending on their copayment.

As noted earlier, Ig is often used off-label. Although many of those uses are clinically appropriate, some are not. For instance, a cost-minimization analysis of financial data related to treating patients with Guillain-Barré syndrome with IVIG or therapeutic plasma exchange (TPE), both of which have been found to be equally effective, found direct costs of IVIG therapy to be more than twice that of TPE ($10,330 vs $4638.)[46]

Finally, preauthorization requirements are nearly always used for Ig. These may include restricting Ig coverage to certain providers in certain specialties, such as immunology, oncology, and neurology[19]; restricting its use for specific indications with limited approval for off-label indications or acute conditions; and longer term approval for chronic conditions such as primary immunodeficiencies.[48]

Conclusions

Immunoglobulin accounts for the third greatest drug spend in commercial plans and the fourth under Medicare, despite the fact that less than 1% of the population covered requires it. It is used most often as a lifelong treatment for primary immunodeficiencies, a heterogenous class of immune-related conditions whose prevalence is increasing. However, it is also used for several other chronic and acute indications, some off-label. The total cost of Ig infusion depends on the type of delivery method used and the site of care. There are factors to be considered for both IVIG and SCIG. Numerous studies attest to the efficacy and cost savings of shifting IVIG to the home setting, and even shifting patients from IVIG to SCIG. In addition, surveys find that patients much prefer home delivery, with patient evaluations also finding a preference for SCIG. Payers have numerous options to ensure that Ig is used appropriately for the right patient in the right setting. These include site-of-care programs, education for providers and patients on the possibility of switching from IVIG to SCIG, preauthorization policies that restrict the use of Ig to certain specialties for specific indications, and shifting coverage from the medical to the pharmacy benefit. ■

*Please note that currency has been converted to US dollars where necessary.

Author affiliation: Chief Operations Officer, NuFACTOR, Temecula, CA.

Funding source: This activity is supported by educational grants from CSL Behring LLC and Grifols.

Author disclosure: Ms Vaughan has the following financial relationships with commercial interests to disclose:

Advisory Board: Grifols

Employment: NuFACTOR

Authorship information: Drafting of the manuscript; critical revision of the manuscript for important intellectual content; and administrative, technical, or logistic support.

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Medical writing and editorial support provided by: Debra Gordon, MS.

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POSTTEST

Examining the Application of Immunoglobulin in Multiple Disease States: A Review of Evidence

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Sample of Online Posttest

Choose the best answer for each of the following:

1. What is the preferred trough level of immunoglobulin G that should be achieved with immunoglobulin (Ig) therapy to reduce risk of pneumonia in patients with agammaglobulinemia or hypogammaglobulinemia?

A. 500 mg/dL
B. 1000 mg/dL
C. 1500 mg/dL
D. 2000 mg/dL

2. Ig replacement is recommended for patients who have which of the following hematologic malignancies and recurrent bacterial infections with low antibody levels?

A. Chronic lymphocytic leukemia
B. Multiple myeloma
C. Chronic lymphocytic leukemia and multiple myeloma
D. Ig is not recommended for use in either of these malignancies.

3. Which of the following agents can be administered both intravenously and subcutaneously?

A. HyQvia
B. Gamunex-C
C. Panzyga
D. Cutaquig

4. EM is a 46-year-old man who is being treated for primary humoral immunodeficiency with IVIG (Gammaked 10%). After 6 months of IVIG treatment at a local infusion center, the patient, in consultation with and approval of his physician, decides to change to subcutaneous immunoglobulin (SCIG) administration at home. Given the difference in bioavailability, how will EM's dose of Gammaked change with SCIG administration according to the prescribing information?

A. Dose will remain unchanged.
B. Gammaked dose will be decreased by 37% to 30%.
C. Gammaked dose will be increased by 30% to 37%.
D. Gammaked is not indicated for SCIG therapy.

5. Which of the following statements is TRUE regarding IVIG and SCIG treatments?

A. IVIG cannot be administered in the home environment.
B. SCIG is only administered in the home environment.
C. Home administration of IVIG does not require a healthcare provider to be present.
D. After initial training, SCIG does not require a healthcare provider to be present.

6. Adverse effects (AEs) can occur with any type of pharmacologic therapy. Which of the following statements is TRUE regarding AEs with IVIG?

A. The most common AE with IVIG is anaphylaxis.
B. Local AEs are more common with IVIG administration than systemic AEs.
C. Proper premedication, appropriate infusion rate, and adequate hydration can mitigate the risks of many AEs with IVIG administration.
D. IVIG administration has a lower risk of AEs than SCIG.

7. With current exception, Ig products that are only approved for the subcutaneous route are exclusively indicated for primary humoral immunodeficiency. Which of the following SCIG products has an additional indication for chronic inflammatory demyelinating polyneuropathy?

A. Cuvitru 20%
B. Hizentra 20%
C. HyQvia 10%
D. Privigen 10%

8. Which is TRUE about the pharmacokinetics of Ig administration?

A. IVIG exhibits lower peak concentrations than SCIG.
B. The absorption process in SCIG increases bioavailability compared with IVIG.
C. Facilitated SCIG exhibits hybrid pharmacokinetic properties of both IVIG and SCIG.
D. SCIG exhibits higher peak concentrations than IVIG.

9. Ig represents what level of cost for commercial payers?

A. Fifth highest drug category for payers and 8% of total drug spending
B. Third highest drug category for payers and 8% of total drug spending
C. Fifth highest drug category for payers and 10% of total drug spending
D. Third highest drug category for payers and 43% of total drug spending

10. A retrospective analysis of participants in a commercial health plan noted improved adherence when the patient received:

A. Home infusion of IVIG
B. Inpatient hospital infusion of IVIG
C. Physician office infusion of IVIG
D. Hospital outpatient infusion of IVIG

NOTES

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