Immunoglobulin

Findings from the AMCP Market Insights Program

Meeting Objectives

- Explain what is Immunoglobulin, replacement and treatment
- Understand the indications for Immunoglobulin
- Understand the differences in the available Immunoglobulin products and preparations
- Discuss Pipeline products

Introduction

Immunoglobulin (IG) derived from the plasma of donors is used in the treatment of an array of disorders, including primary and secondary immune deficiency states and a variety of autoimmune and inflammatory disorders.

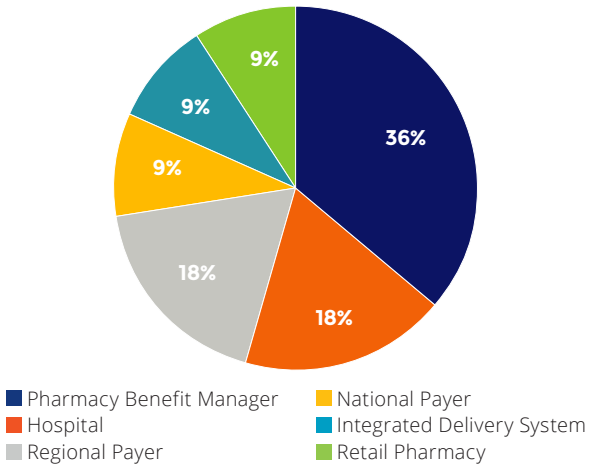
There has been a rapid expansion in the use of immunoglobulin for an ever-growing number of conditions requiring additional understanding and coverage criteria for payers. Payers have numerous options to ensure immunoglobulin is used appropriately for the right patient in the right setting. These include formulary management, site-of-care programs, education for providers and patients, switching preferred products (e.g. IVIG to SCIG), preauthorization policies limit prescribing to select medical specialties, implementation of evidence-based coverage criteria, and shifting coverage from the medical to the pharmacy benefit.

To understand the appropriate and cost effective use of immunoglobulin, AMCP convened an expert panel of managed care stakeholders. Panelists included representatives from national and regional health plans, integrated delivery systems, hospitals, and pharmacy benefit managers. (Figure 1). Participants discussed the changing landscape of immunoglobulin administration, pipeline and distribution dynamics, business considerations, coverage trends and the impact of shortages on formulary management and the delivery of care.

Rising Demand for Immunoglobulins

Today, immunoglobulin is used for a number of chronic and acute conditions, including primary immune-deficiency disease (PIDD), chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN), certain autoimmune conditions and acute inflammatory conditions (Table 1 or Chart 1 option). The use of immunoglobulin is also increasing in the medical specialties of cardiology, dermatology, rheumatology/nephrology, and infectious disease.

Figure 1. Market Insights Forum Participant Mix



"The use [of IG] is inconsistence and we struggle with the variety of indications being requested [for coverage]"
– Regional Health Plan

Additional factors impacting the total immunoglobulin use and cost are increasing diagnoses of primary immunodeficiency and neurologic conditions, the aging population, new indications, the average gram prescribed per patient, and the price per gram.[1]

Immunoglobulin is primarily administered as an intravenous (IVIG) and subcutaneous (SCIG) dose (Table 2). SCIG therapies have emerged in the past decade as a safe and effective alternative to IV administration. The primary difference between these two routes of administration is that SCIG is often self-administered, weekly, at home by patients or caregivers, and require multiple injections to ensure proper dosage, whereas IVIG is most frequently administered, monthly, by an infusion nurse in the home setting or at a healthcare facility. There are different methods of administering immune globulin subcutaneously including traditional and facilitated subcutaneous.

"Historical approach has been managing the indications, it is agnostic to [IG] product... they are viewed as clinically comparable."
– National Payer

Table 1. Common Uses and Dosing for IVIG[9-11]

Disease	FDA Approved Indication	Goal of Therapy	Dosing (slide 68)
Acute Disseminated Encephalomyelitis (ADEM)			2 gm/kg over 5 days, then 0.4 gm/kg every 4 weeks Duration depends on clinical condition
B-cell Chronic Lymphocytic Leukemia (CLL)	yes	Prevention of bacterial infections due to hypogammaglobinemia	0.4 g/kg every 3-4 weeks
Bone Marrow Transplantation	yes	Prevention of infections, pneumonitis, and acute graft-versus-host disease (GVHD) following bone marrow transplantation	
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	yes	To improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse	2 gm/kg over 3-5 days, then 1 gm/kg every 3 weeks
Dermatomyositis/ Polymyositis	No Evidence: IIa Recommendation: B		2 gm/kg over 2-5 days every 4 weeks
HIV Infection	yes	Reduction of serious bacterial infection in pediatric patients infected with HIV	
Idiopathic Thrombocytopenic Purpura (ITP, CITP)	yes	Increase platelet count in ITP to prevent or control bleeding	
Kawasaki Disease	yes	Preventing coronary artery aneurism associated with kawasaki disease	
Multifocal Motor Neuropathy (MMN)	yes	Modulating immune inflammatory condition, improve muscle strength and disability in adult patients	
Multiple Sclerosis (RRMS)			2 gm/kg over 3-5 days, then 0.4 gm/kg every 3-6 weeks
Myasthenia Gravis (MG)			2 gm/kg over 2-5 days
PemphIgus			2 gm/kg over 2-5 days every 4-6 weeks
Primary Immunodeficiency Disease (PIDD)	yes	To protect against frequent and/or severe infections (bacterial and viral)	IVIG: 0.3 to 0.6 g/kg, every 4 weeks SCIg: 0.1-0.2 g/kg every 4 weeks

Adapted from Perez J Allergy Clin Immunol 2017;139:S1-46, Bonilla FA. Ann Allergy Immunol 2005; 94; S1-S63, Wasserman, R. MD PhD Lecture "Immunoglobulin (Ig) Therapy 8/2020

Preferred Product Considerations

Immunoglobulins are one of the more complex specialty drugs for payers to manage. Panelists identified several reasons for this, including the large number of products on the market, various doses, formulations, indications, off-label uses, and adverse effects. Other important factors include the administrative support required and site-of-care issues and time related to product delivery.

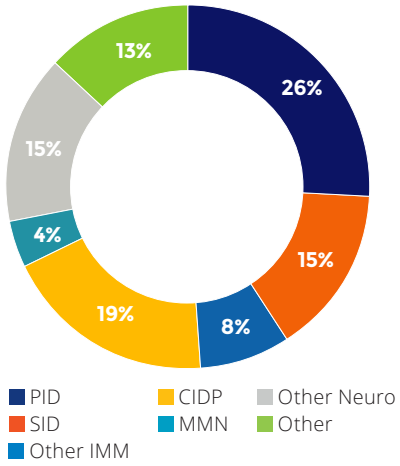
"There is a lot of parity within the Ig class among the majority of the disease states"
– *Integrated Delivery System*

"We would like to see more subcutaneous administration, as long as the physician supports it."
– *Hospital*

The IV route has historically been the preferred route because of the larger volumes that could be administered. SCIG is gaining popularity compared with IV administration. Participants recognized that SCIG offers several benefits for patients who receive immunoglobulin therapy. The primary benefit is convenience, as the patient may be trained to self-administer SCIG or be able to have a caregiver trained to administer at home.

Although both routes of immunoglobulin administration have been deemed safe and effective, selection of a

Chart 1: United States Immunoglobulin Use by Disease State 2017[12]



Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Multifocal Motor Neuropathy (MMN), Primary Immunodeficiency Disease (PID)

preferred agent can be predicated on multiple factors, such as contracting, indications, site of care, safety, and possible adherence concerns with SCIG. Panelists listed the numerous factors (Table 3) they take into consideration when selecting a preferred IG product; and most state their preference is to have more than one preferred agent available on formulary.

"You want to have a preferred [IG] product, but also you want to have some secondary [IG] products."
– *Integrated Delivery System*

Comprehensive Payer Management

Panelists emphasized that payers use a variety of approaches to manage the cost and appropriate use of immunoglobulins. Payers are most likely to use prior authorization (PA) as a management strategy, followed by preferred product formulary status and limit prescribing to certain medical specialties, with allergy, immunology, oncology and neurology as the most commonly cited specialties. The use of restricted formularies and prior authorization are important programs for managing immunoglobulin utilization and cost, with coverage commonly limited to FDA-approved indications, and exception processes in place for coverage requests related to off-label indications, acute conditions and special populations (e.g. geriatric or neonates).

"That is the challenge, having your PAs match the data…years ago we crossed that threshold where it is not just [FDA] label but level of evidence."
– *National Payer*

Infusion site of care advantages were discussed (Table 4) and the outpatient hospital setting was noted to be the most expensive site for delivery of IVIG for commercial payers. 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.[2-4]

"We have had a lot of success in offering home site-of-care whenever it is appropriate. And we have looking for more opportunities to move IG to the home."
– *Regional Payer*

Panelist underscored the importance of having expert clinical teams in place to review medical and social situation to determine the best treatment location and support needed. Moving from the hospital setting to the physician office to the home there is a decrease in the cost of delivering treatment and an increase in convenience for patients. Safe delivery of infusions guidance remains a critical component in site-of-care policies. Given the lower cost of at-home IG administration (either IVIG or SCIG)[2], many payers have introduced sites-of-care policies related to infusions which encourage patients and prescribers to choose less-expensive sites of care. However panelists also noted it is important to keep in mind that there are multiple reimbursement scenarios (e.g. capitation) in each site of care (hospital, hospital outpatient, physician office, home), which vary based on the payer and the route of administration.

Panelists discussed the impact of immunoglobulin pharmacist dose-optimization programs. These programs include pharmacist-led interventions to recommend dose-optimization based on adjusted body weight instead of actual body weight and creating standardize dosing sets in electronic medical record (EMR) systems. Some programs also conduct follow-up immunoglobulin levels and adjust maintenance doses as clinically appropriate. Trough level doing of immunoglobulin was also discussed as an area of interest given the inverse relationship between trough IG levels and pneumonia in patients with PIDD.5 Several payers are looking for real world evidence (RWE) to help support the value of dose-optimization programs, including trough dosing, as recent evidence suggests that alternative dosing weights reduce waste without compromising clinical outcomes but trough-based dosing may only be appropriate

Table 2. Product Comparison Table[13]

	IVIG	SCIg	SCIgFAC
Administration	Intravenous Health care provided-administered	Subcutaneous Self-administered	Subcutaneous Self-administered two part infusion with hyaluronidase
Injection Site	1	4-30 (max 2 oz. per site)	1-2 (max 20 oz. per site)
Frequency	Every 3-4 weeks	Daily, every other day, weekly, biweekly	2-4 weeks
Infusion Time	2-4 hrs.	5 min-2 hrs.	1-2 hrs.
Site of Care	Home infusion, in office, infusion center	Home or physician office or infusion center	Home or physician office or infusion center
Bioavailability	100%	62%	92%
Pre-medication	Required	Seldom needed	Seldom needed
Side effects	Systemic: headaches, malaise, muscle aches, flu like symptoms Local adverse reactions: rare	Systemic: rare, local reactions are common(redness, swelling, itching, discomfort)but decreases over time	Systemic: less than IVIG Local reactions similar to SCIg

Loraine Anderson, M, Immunoglobulin Clinical Considerations Presentation. October 28, 2020

for some patients. Panelist noted that dose-optimization programs are based upon clinical response to IG products.

"We know that ideal body weight is just as effective as actual body weight for IG dosing, we were able to use IBW to decrease consumption and costs by approximately 5%."
– *Specialty Pharmacy*

Panelists stated that payers sometimes use "grandfathering" programs, which do not require that patients established on a non-preferred immunoglobulin treatment be switched to the formulary preferred formulation. And several payers noted the considerable resource investment required to run product switching programs, inducing building EMR order sets, pharmacist time to educate and switch patients and operational costs. Because of the significant financial opportunity and resources, payers would like more RWE around switching data, specifically around moving from IV to SC, and related outcomes around ease of administration, persistence, adherence and clinical outcomes.

It was discussed that some clinicians are encouraged to write non-branded prescriptions for immunoglobulins (i.e., IVIG or SCIG). However, our panelists did not think there were a lot of non-branded prescriptions today, and that brand/preferred agent prescribing was driven primarily by payer policies, utilization management programs and specific patient needs including, indication, risk factors, product differences and dosing. It was also noted that if there is interest in moving away from branded prescriptions, there is a growing number of collaborative practice agreements in other therapeutic areas that could be adopted in the immunoglobulin space to better support physicians to prescribe immunoglobulins generically and allow the pharmacy to select the preferred agent to be administered or dispensed.

Panelists are also using benefit design to better manage immunoglobulin costs, such as specialty channel management programs that shift IVIG coverage from the medical to the pharmacy benefit. However, it was also noted that this could shift more of the cost to the patients depending on their copayment/co-insurance which many payers take into consideration when making benefit changes. Several panelists mentioned that their organization either offers patient assistance or their specialty pharmacy supports finding patient assistance programs for their patients.

Self-insured employers and plan sponsors are showing a growing interest in options to carve out infusion products, like IVIG, with the goal of ensuring proper administration, improving adherence, and reducing hospitalizations resulting from disease exacerbations. PBMs are meeting this interest by offering specialty pharmacies programs staffed by pharmacists and clinicians who have the knowledge and resources to meet the complex disease-specific needs of patients. Although IVIG carve-outs have not gained broad traction, the concept of a carve-out has become an acceptable approach among employers and payers as a way to manage the high costs medications and to improve patient management.

Mixed Contracting Strategies

When establishing a contract for IVIG acquisition, the purchase route is also considered as it varies among manufacturers. Purchases can be made directly from the manufacturer, via a group purchasing organization (GPO), and/or through special pharmacy distribution networks. The chosen method of purchase can have a significant impact on pharmacy budgets. Moreover, if a payer or hospital has more than one product on formulary, the purchasing method may be different for each product depending on the manufacturer.

Table 3. Considerations for Preferred Immunoglobulin Product Selection

Considerations	
Clinical	Evidence
	Expert consensus, key opinion leaders (KOLs)
	Indications
	Off-label uses
	Patient population (indication coverage)
	Safety
Contracting	Exceptions for use of other IG agents during shortage or non-covered indications
	Guarantees during shortage
	Pricing per gram
	Purchase price for IDNs
	Rebates
	Value-based contracting - especially for an IDN where both the medical and pharmacy data is available
Distribution	Data collection for outcomes based contracts
	Open access vs. limited distribution
	Specialty pharmacy network
Financial	Covered benefit (medical vs. pharmacy)
	Patient assistance programs
Patient	Adherence
	Patient ability to self-administer
Product Characteristics	Infusion time
	Route of administration
	Side effects (SCIG < IVIG)
	Site of care
	Stabilizers
	Sucrose load
Utilization	Current utilization and market share
	Limit switching for patients

Participation in the 340B drug pricing program often presents significant cost saving opportunities for covered entities, and IVIG is a good example where particular savings can be obtained. However, the purchase of plasma products at 340B prices is not as straightforward as with other pharmaceutical products. Manufacturers may restrict distribution of drugs at 340B prices because of actual or anticipated shortages. Panelists reported different organizational policies around distribution of 340B savings; some share savings with health plans and others use the 340b savings to support eligible patients with more comprehensive services.

Panelists debated the role for value-based contracting (VBC) with immunoglobulins, which involves payment or reimbursement based on indicators of value, such as patient health outcomes, efficiency, and quality. Some panelists felt that due to the lack of head-to-head comparison studies for immunoglobulins, that VBC could be an important tool for expanding access. Most agreed that the collaborative effort inherent in VBC agreements was seen as promising, as it demonstrates the willingness of health care stakeholders to engage in innovative approaches.

The opposing view was that VBC are best used in clinical areas where there are questions of efficacy, safety or value. And since immunoglobulins have a strong evidence base to support their efficacy and safety across multiple disease states, risk-sharing or flat/percent discounts would be preferred contracting options. In addition, challenges remain for identifying appropriate outcomes/metrics of a VBC due to the high number of conditions that are treated by immunoglobulins. This is especially challenging for PBMs, who typically do not have ready access to medical claims and therefore contracting based on an adherence outcome/metric would be preferred. A capitated arrangement based on utilization may also be of interest for some payers and could be presented as a reasonable option during negotiations.

"Real world outcomes are huge to us, especially as the future is going to be with value-based contracts."
– Integrated Delivery System

Payers are looking for innovations in ancillary devices and products to improve the delivery of immunoglobulin to support improved adherence and ease of use for patients. Payers stated VBC may be of greater interest if innovative delivery systems and devices come to market, especially if the device is digitally-connected to support disease management, monitoring and adherence.

Reaction to Shortages

Unfortunately, immunoglobulin supply disruptions have been fairly common over the last few decades. The U.S. Food and Drug Administration (FDA) announced on August 12, 2019 that the demand for immunoglobulin products has increased resulting in an ongoing shortage of IVIG and SCIG in the United States.[6] The coronavirus disease 2019 (COVID-19) pandemic has introduced additional stress on the plasma supply. The main issue stems from a drop in plasma donation across the nation that has occurred since the inception of the COVID-19 pandemic. The plasma fractionation process takes months, and supply disruptions are expected to become apparent by early 2021.

Traditional market dynamics have led some stakeholders to a concern that stockpiling will protect their patients in the event that their pipeline of immunoglobulin dries up. In reality, this often exacerbates shortages for the entire health system and further disrupts the supply chain.

Table 4. Infusion Center vs. Homecare Considerations

	Infusion Center	Homecare
Advantages	Safety – Trained staff and equipment available if patient has negative reaction Reassuring – Controlled environment makes nervous patients feel better	Convenient for the patient Comfortable for the patient Less risk of infection
Patient Types	Patients prone to adverse reactions Patients whose home environment is not conducive to administering therapy	Young, active patients Elderly or homebound patients Patients who live far away from infusion centers

"The manufacturing and business model of a plasma manufacturer that uses human blood is dramatically different than a chemical-based pharmaceutical manufacturer. Raw material availability, safety and purification processes - can double manufacturing costs and extend total production time up to 12 months."
– Specialty Pharmacy

Many hospitals and physicians have already developed evidence-based approaches for the use of IVIG and proactively identified priority patient populations for treatment. Additional strategies have included lowering of doses, extension of time between treatments, and use of alternative therapies where those exist. Payers are also implementing clinical management programs to limit access by indication, review off-label prescribing, increase the number of immunoglobulin products that are available to patients on formulary, and establishing guaranteed supplies through pharmaceutical contracting. Panelists stressed the need for educating both physicians and patients about the shortage and the differences in available immunoglobulin products. Ongoing public education on increasing plasma donations may also help.

"There's likely going to be some hoarding of Ig supply as patients recall their difficulties with previous shortages."
– Integrated Delivery System

Ultimately, drug shortages create uncertainty for a range of stakeholders: patients, hospitals, manufacturers, pharmacists and payers. Especially in cases of shortages for lifesaving drugs efforts are needed to ensure the patients that need it will have access to their medication.

Patient Support

Panelists reviewed an online patient support tool which was developed to help patients better understand the differences between IG products and identify their preferences to support patient-physician shared decision making for immunoglobulin treatments. Panelists recognized the value in supporting shared decision making around IG products, but also questioned how the data from the tool would be used beyond the survey tool. Some panelists would require better visibility in to the tool algorithms if the tool was to be used by their patients and providers.

Patient advocacy groups, such as the Immune Deficiency Foundation (IDF) and Jeffrey Modell Foundation (JMF) were also recognized as valuable resources for patients and physicians. Their role primarily being to help patients through unique issues related to their disease state and to support clinicians with patient resources. However, few of the payer panelists had experience working directly with advocacy groups on pipeline information or utilization management programs.

Pipeline

Convalescent plasma and hyperimmune globulin have been investigated as means of providing passive immunity in several notable viral outbreaks. In light of the recent COVID-19 pandemic there has been a rush to develop therapeutics to combat COVID-19, including using convalescent plasma as a possible treatment for severe COVID-19 patients. Hyperimmune globulin is prepared from convalescent plasma and has the potential to provide passive antibody-based immunity to previously unexposed individuals to reduce the risk of disease or to lessen its clinical impact.[7] Convalescent plasma is not routinely available, nor is it a licensed FDA product; it can be made available at times of disease epidemics or pandemics. During the COVID-19 pandemic, over 100,000 units of convalescent plasma have been administered as part of an expanded access program, emergency use authorization, or clinical trial.[8] The COVID-19 pandemic is further stressing the plasma supply by increasing demand for investigational therapies, such as hyperimmune globulin, which could exacerbate the shortage of immunoglobulin.

Summary

Immunoglobulin is used most often as a treatment for primary immunodeficiency. However, it is also used for several other chronic and acute indications, which is increasing total utilization. Growing geriatric population, rising prevalence of immunodeficiency diseases, increasing adoption of IVIG treatments, and rising indications are the key drivers of utilization and cost trends. Total cost of

Table 5. Route Considerations

Intravenous (IVIG)	Subcutaneous (SCIg)
Venous access required.	No venous access required
Convenient and well tolerated by most patients	Convenient and well tolerated by most patients.
Peak levels or rapid shifts in IgG level may result in adverse event; Patient may need medications to manage side effects before or after infusions; Ability to give large volumes per infusion allows intermittent dosing (every 21-28 days)	Slow administration and gradual absorption reduces severe headaches and other adverse events; Smaller volumes per infusion requires more frequent dosing (usually weekly)
Variability in IgG level or "Wear off " effect may result in fatigue between infusions	Maintains more consistent IgG levels and eliminates low troughs
Patients may need to travel to receive infusion therapy or have trained healthcare professional in the home	Facilitates self or home infusion, increasing patient autonomy – may improve patient's self-image and sense of control
Intra-infusion adverse effects are possible including chills, rigors, nausea, subjective sense of dis-ease, back ache. Post infusion adverse effects can include headache, malaise, and fatigue. May require pre and post medications to prevent adverse effects	Systemic side effects are rare, but local reactions including redness, swelling and itching are frequent. Pre and post medications are not usually required

immunoglobulin therapy depends on the type of delivery method used and the site of care. Payers are interested in the safety, efficacy and cost savings of shifting IVIG to the home setting, and in shifting patients from IVIG to SCIG. Payers have numerous options to ensure that immunoglobulin is used appropriately for the right patient in the right setting. They have well established site-of-care programs, switching programs, preauthorization policies that restrict the use to certain specialties for specific indications, and shifting coverage from the medical to the pharmacy benefit. But there is growing priority for better channel management and dose optimization programs for immunoglobulins. Payers believe the immunoglobulin class is manageable, and they are looking for collaborative partnerships for additional channel management opportunities. Payers acknowledge that challenges remain around structuring value-based agreements for this class, and therefore are seeing risk-based or flat/percentage discount contracts. Payers also see the need for supply guarantees and preferred product flexibility due to ongoing shortages.

Disclosures

This Market Insights Summit was supported by CSL Bering and Takeda.

Acknowledgments

This summit was moderated by Dana Regan, Eversana Life Science Services. This proceedings document was developed by Terry Richardson PharmD, BCACP, Principal, Rx8Consulting.

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How Will This Impact Your Current and Future Decisions?

• The large number of products, various doses, formulations, and indications makes it one of the most complex classes for payers to manage. However, payers have numerous options to ensure that IG is used appropriately for the right patient in the right setting.

• Growing geriatric population, rising prevalence of immunodeficiency diseases, increasing adoption, and rising indications are the key drivers of utilization and cost trends.

• Better channel management, dose optimization, supply guarantees and preferred product flexibility are needed due to ongoing shortages. Opportunity to generate and use RWE to demonstrate safety, efficacy and cost savings of shifting IVIG to the home setting, shifting patients from IVIG to SCIG, channel management and dose optimization programs.

• Payers believe the immunoglobulin class is manageable, and they are looking for collaborative partnerships. Collaborative partnerships for innovative contracting arrangement will need to be flexible around supply guarantees and additional channel management opportunities.

• Challenges remain around structuring VBC, payers are seeking risk-based, adherence based or flat/percentage discount contracts. Multiple strategies are likely needed and will be based on the specific payer (e.g., commercial, Medicare) and contracts type (e.g., VBC, capitated, adherence-based).

• Use innovations in device and delivery systems to improve patient adherence.