

Addressing the Challenges to Immune Globulin Access

Understanding the factors contributing to shortages of immune globulin products can help to mitigate a crisis that threatens critical consequences for patients.

By Ronale Tucker Rhodes, MS

ACCORDING TO THE University of Utah Drug Information Service, as of Dec. 31, 2020, there were 129 active drug shortages in the U.S., down from 166 during the same period in 2019 and 186 in 2018.¹ While the number of shortages is down these days, all drug shortages can have a significant impact on patient care. Notably, when “medically necessary” medicines such as immune globulin (IG) that treat rare, serious, genetic and life-threatening illnesses and have few to no alternative treatment options are in short supply, the result for patients includes chronic debilitation, permanent physical damage and even death. After experiencing two IG shortages in the U.S. since the mid-1990s, many patients and their caregivers are concerned we may be headed for another due to the COVID-19 pandemic. To better address these shortages, it helps to understand their causes and what can be done to respond to them.

IG Access: A History Lesson

Since the landmark development of the U.S. Food and Drug Administration (FDA)-approved intravenous IG (IVIG) product in 1981, the first major shortage of IG experienced in the U.S. was caused by product recalls, manufacturing-standards violations and product export.

It began in 1995, when FDA issued recommendations that plasma products made from pools later found to include a donor with a fatal and little-understood disease known as Creutzfeldt-Jakob disease (CJD) be withdrawn from the market, which resulted in recalls and voluntary

withdrawals. By 1997, four manufacturers that produced the vast majority of IG — Bayer, Baxter Healthcare, Alpha Therapeutic and Centeon — had recalls and withdrawals totaling approximately 7 percent of the total IVIG supply. This part of the shortage was addressed when a review of data from FDA, the National Institutes of Health and the Centers for Disease Control and Prevention suggested the risk for transmission of CJD by blood products, if it existed, was considerably lower than the risk for harm to public health from CJD-related quarantines and withdrawals, causing the Surgeon General to recommend plasma derivatives, including IVIG, be withdrawn only if the blood donor developed new-variant CJD.

Shortly after its recommendation to withdraw IVIG due to CJD, FDA doubled its inspections of plasma products manufacturers and discovered serious violations of manufacturing standards. While every manufacturer received warning letters citing numerous deficiencies, FDA allowed them to continue operating while addressing the problems. Yet, although some companies decided to continue operations, others opted to stop release and distribution of IVIG and shifted resources to compliance correction. Centeon, in particular, decided to shut down production and didn't distribute product at all in 1997, accounting for just over half of the 20 percent shortfall. At the same time supply was diminishing, demand was surging because of newly approved indications and an increase in off-label (non FDA-approved) uses. In fact, the Immune Deficiency Foundation

and physicians across the country estimated 50 percent to 70 percent of IVIG was being prescribed off-label.

Another contributing factor to the shortage was export of IVIG. FDA reported exports accounted for up to 29 percent of distributed product, depending on the manufacturer. And, the International Plasma Products Industry Association reported exports from the major U.S. fractionators increased from 1996 to 1997, accounting for approximately 20 percent of their marketed IVIG products.²

As demand for IG products substantially increased, a second shortage of IG products spanned from April 2019 through April 2020, resulting in treatment for some patients either being limited or stopped altogether. Unfortunately, while manufacturers and distributors of IG products have always contracted with one another to deliver product based on historic usage and future projections to curtail shortages, production capacity was inadequate to keep up with the increase in demand. In fact, since FDA approved the first IVIG product in 1981, IG has experienced a sustained record of near-continuous demand growth. According to Grand View Research, which forecast IVIG use until 2022, the global IVIG market size “was estimated at \$9.09 billion in 2016 and is anticipated to grow at a CAGR (compound annual growth rate) of 7.1 percent over the forecast period.” North America accounts for more than 45 percent of the IVIG global market and is expected to maintain this high market share through 2022.⁶

According to Keith Berman, MPH, MBA, a blood products expert and editor of *International Blood/Plasma News*, “The clinical utility of IG across an ever-broadening spectrum of serious or life-threatening autoimmune, inflammatory, immunodeficiency and other immune-mediated disorders continues to be documented in patient studies and case reports now numbering in the thousands.” In addition, Berman says, there is a trend toward more aggressive treatment with high-dose IG in autoimmune neurologic diseases in particular; a steadily increasing proportion of patients being treated with long-term IG; and a growth in worldwide demand for IG products. For instance, there is a surge in IG demand in many countries in Southeast Asia, accounting for 18 percent of the market in 2014, and worldwide demand growing at an average rate of 9 percent between 2008 and 2016.⁷

In addition to many disease states now being treated

with IG therapy, one of the chief drivers of heightened IG demand is secondary antibody deficiencies (SAD). According to an article in *Frontiers of Immunology*, the prevalence of SAD is estimated to be 30 times more common than primary immunodeficiency diseases (PI), the disease for which the first IVIG product was approved and for which all IG products on the market today are indicated. Common causes of SAD include hematological malignancies such as CLL or multiple myeloma and their treatments, as well as side effects of many immunosuppressive agents and procedures involved in solid organ transplantation. According to the article’s authors, “It is becoming increasingly important to address the unmet [treatment] needs of this growing patient population,” which is progressively being treated with IG therapy.⁸

Another key driver of increased IG therapy demand is the growing geriatric population, which is prone to antibody deficiency disorders due to weakened immune systems. According to the U.S. Census Bureau, the number of people aged 65 years and older in the U.S. was approximately 46.2 million in 2014, and their numbers are expected to reach 98 million by 2060.⁹

During the period April 2019 through April 2020, IG was in short supply, resulting in treatment for some patients either being limited or stopped altogether.

To address this demand growth, Berman says, IG manufacturers must 1) forecast and invest in plasma collection facilities to ensure sufficient additional donor plasma is available to process into IG products, and 2) plan, invest and provide adequate lead time to construct and secure regulatory approval to operate new or expanded fractionation (how plasma is manufactured into IG products) and related IG production facilities.⁷

The Reasons Behind Drug Shortages

Since 1999, FDA has been working with the healthcare industry and patients to prevent and mitigate shortages of medically necessary drugs. FDA considers a drug medically necessary if it “is used to treat or prevent a serious disease or medical condition and for which no acceptable drug

alternative is available in adequate supply.”

The top reason for drug shortages involves quality concerns caused by manufacturing issues of delays/capacity (64 percent), but a lack of raw material (27 percent), boost in drug demand (5 percent) and lack of financial incentive to continue production (2 percent) can also affect drug availability.³ Clearly, the reasons behind previous IG shortages lend credence to these statistics.

IG Shortage: What’s Available?

Currently, there are 16 IG products marketed by seven manufacturers: Asceniv (IVIG 10%), Bivigam (IVIG 10%), Cutaquig (subcutaneous IG [SCIG] 16.5%), Cuvitru (SCIG 20%), Flebogamma DIF (IVIG 5% and IVIG 10%), Gammagard Liquid (IVIG 10% and SCIG 10%), Gammagard S/D (IVIG 5%, low IgA), Gammaked (IVIG 10% and SCIG 10%), Gammaplex (IVIG 5% and IVIG 10%), Gamunex-C (IVIG 10% and SCIG 10%), Hizentra (SCIG 20%), Hyqvia (SCIG 10%), Octagam (IVIG 5% and IVIG 10%), Panzyga (IVIG 10%), Privigen (IVIG 10%) and Xembify (SCIG 10%). These products — manufactured by ADMA Biologics, BioProducts Laboratory, CSL Behring, Grifols, Kedrion, Octapharma and Takeda — are deemed medically necessary drugs to treat many diseases for which it is the only therapy.

IVIG and SCIG are approved by FDA to treat these diseases: chronic inflammatory demyelinating polyneuropathy, chronic lymphocytic leukemia (CLL), immune thrombocytopenic purpura, Kawasaki disease, multifocal motor neuropathy and PI. But, as mentioned previously, IG products are also prescribed to treat a host of off-label diseases and conditions, including autoimmune disorders, neurological diseases and SAD, among others.

A Need for More Plasma

According to Berman, “More than 90 percent of the global supply of plasma for fractionation comes from ‘source plasma,’ which is typically collected from remunerated donors in dedicated licensed centers that use automated apheresis equipment to perform plasmapheresis to separate and retain only the plasma portion of donor blood. The balance of the plasma supply comes from ‘recovered plasma’ separated from whole blood donations that is not needed for direct transfusion into hospital patients.”¹⁰

Once collected, plasma (comprised of 92 percent water, 7 percent proteins and 1 percent other solutions) must go through a fractionation process that separates and collects

the individual proteins, of which 64 percent are albumin, 20 percent are IgG, 2.5 percent are alpha-1 antitrypsin, less than 1 percent are clotting factors, and 13.5 percent are others such as antithrombin, protein C, CI esterase inhibitor, etc., to produce plasma therapies such as IG, clotting factor, etc.

To try to meet the current demand for IG products, industry is growing the number of plasma collection facilities. Between 2004 and 2014, the global supply of plasma intended for fractionation doubled to nearly 40 million liters. And, in the U.S., there were 737 plasma collection centers in 2018 versus just 478 in 2014,¹¹ at which more than 48 million donations of plasma were collected.¹²

Yet, despite this growth in plasma collection, Berman says, “IG product supplies here in the U.S. and internationally were — and continue to be — tight, as plasma raw material supply and IG products manufactured from it just manage to keep pace with worldwide demand growth.”⁹ In fact, he says, to keep pace with demand will require new and expanded plasma collection centers, as well as additional equipment and staff. For instance, it was calculated that an additional three million plasma donations were needed just in 2018.⁷

But now, with the COVID-19 pandemic, even more collection centers, equipment and staff may not be enough to keep up with demand. On Nov. 4, 2020, PPTA, which represents more than 860 human plasma collection centers in the U.S. and Europe, issued a statement warning of an urgent need for plasma donation. “Reports vary, but plasma collectors experienced significant declines in collections due, in part, to the impacts of social distancing measures and other mobility restrictions caused by the COVID-19 pandemic,” the statement reads. “Considering the complex manufacturing of plasma-derived therapies can take seven to 12 months, any decline in plasma donations could impact patients’ ability to access their lifesaving therapies. This sharp decline in plasma collections currently being experienced could cause more significant challenges in the months to come.”¹³

Optimizing IG Production

Even if plasma collection returns to normal and continues to increase, there is a need for increased production of IG products, which is a very complicated, costly and lengthy process. After plasma is released to manufacturers, it must go through a fractionation process in which plasma that is pooled from multiple donors is processed to extract specific therapeutic proteins, which are then subjected to various purification methods and viral inactivation and removal

processes to ensure their safety and efficacy. As PPTA mentioned, the steps and regulations required to collect donated plasma and complete the manufacturing process that results in the final therapies take between seven and 12 months. This, says PPTA, is what “sets the production of plasma protein therapies apart from chemical pharmaceuticals and other biologics whose manufacturing processes are much more condensed and whose direct manufacturing costs are a significantly smaller portion of the overall cost.”¹⁴

But, despite the increase in additional plasma collection centers, IG manufacturers have been thrown another curveball: the COVID-19 pandemic.

It should be noted that IG manufacturers are stepping up to the plate. They have been investing substantially in research and technologies to increase the quality of proteins extracted from plasma, known as the “yield,” to create new and more effective therapies.¹⁵ The original Cohn fractionation process developed in the 1940s resulted in a significant loss in IgG-containing donor plasma. But, since the 1990s, manufacturers’ modifications to their purification processes improved the yield of IgG per liter of plasma. According to Patrick Robert, PhD, of the Marketing Research Bureau, “Over the last 25 years, plasma processing advances have improved IgG yield by roughly 60 percent on average, from 2.5 grams per liter to 4 grams or more per liter today.”⁷ Efforts continue on behalf of manufacturers to invest in new production capacity to keep ahead of forecasted future IG demand growth. And, as stated previously, the number of IG products on the market has almost doubled today compared to just 10 years ago as a result.

Meeting Patient Needs

The growing number of illnesses IG treats (PPTA reports a 66 percent increase in distribution of IG therapy between 2012 and 2018 across North America and Europe), less-than-optimal plasma supply and the complicated manufacturing process will continue to contribute to a possible IG shortage. Therefore, the healthcare industry will need to continue to take steps to

optimize limited supplies for patients, including lowering doses, delaying treatments, prioritizing based on medical need and using alternative therapies when those exist.¹⁶

On another front, several organizations are making efforts to improve the current situation. PPTA continues to work with some manufacturers to assist healthcare providers obtain specific products needed by patients. FDA is helping manufacturers mitigate the supply situation. It is exploring ways to improve the manufacturing yield of IG products, as well as encouraging healthcare providers, hospitals and medical systems to prospectively devise an evidence-based approach to deciding which patients will receive priority treatment.⁴ And, on the supply side, organizations such as PPTA, the Immune Deficiency Foundation and the Immunoglobulin National Society are leading the cause to encourage plasma donations during this pandemic. 

RONALE TUCKER RHODES, MS, is the editor of *IG Living* magazine.

References

1. American Society of Health Professionals. Drug Shortages Statistics. Accessed at www.ashp.org/Drug-Shortages/Shortage-Resources/Drug-Shortages-Statistics.
2. Rhodes, RT. Immune Globulin: Controlling Supply and Demand. *BioSupply Trends Quarterly*, Winter 2015. Accessed at www.bstquarterly.com/assets/downloads/BSTQ/Articles/BSTQ_2015-01_AR_Immune-Globulin-Controlling-Supply-and-Demand.pdf.
3. Drugs.com. Drug Shortage Statistics in the U.S. and the FDA Response. Accessed at www.drugs.com/drug-shortages/stats.
4. U.S. Food and Drug Administration. Information About Immune Globulin (Human) Product Shortage, Aug. 12, 2019. Accessed at www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-about-immune-globulin-human-product-shortage.
5. American Society of Health Professionals. Immune Globulin, Intravenous or Subcutaneous, Sept. 27, 2019. Accessed at www.ashp.org/drug-shortages/current-shortages/drug-shortage-detail.aspx?id=527.
6. Sussman, R. Growth in Demand for Intravenous Immune Globulin (IVIg) and Conservation Strategies. *Acurity*, February 2019. Accessed at www.gnyha.org/wp-content/uploads/2020/06/Growth-in-Demand-for-Intravenous-Immune-IVIg-and-Conservation-Strategies.pdf.
7. Berman, K. Plasma Fractionation: The Challenge of Keeping Pace with Global IG Demand. *BioSupply Trends Quarterly*, Summer 2018. Accessed at www.bstquarterly.com/assets/downloads/BSTQ/Articles/BSTQ_2018-07_AR_Plasma-Fractionation-The-Challenge-of-Keeping-Pace-with-Global-IG-Demand.pdf.
8. Patel, SY, Carbone, J, and Jolles, S. The Expanding Field of Secondary Antibody Deficiency: Causes, Diagnosis, and Management. *Frontiers in Immunology*, Feb. 8, 2019. Accessed at www.frontiersin.org/articles/10.3389/fimmu.2019.00033/full.
9. U.S. Intravenous Immunoglobulin (IVIg) Market Size, Share & Trends Analysis Report By Application (CIDP, Congenital AIDS), By Route of Administration (IV, Subcutaneous), By Distribution Channel, and Segment Forecasts, 2018-2025. Accessed at www.grandviewresearch.com/industry-analysis/us-intravenous-immunoglobulin-ivig-market.
10. Robert, P, and Berman, K. Feeding China’s Growing Appetite for Human Albumin. *BioSupply Trends Quarterly*, Summer 2018. Accessed at www.bstquarterly.com/assets/downloads/BSTQ/Articles/BSTQ_2019-07_AR_Feeding-Chinas-Growing-Appetite-for-Human-Albumin.pdf.
11. Statista. Number of Blood Plasma Collection Centers in the U.S. from 2014 to 2018. Accessed at www.statista.com/statistics/1055323/plasma-collection-centers-in-the-us.
12. Plasma Protein Therapeutics Association. United States Total Collections 2009-2018. Accessed at www.pptaglobal.org/images/Data/Plasma_Collection/2009-2018_US_TC.pdf.
13. Shaw, G. Pandemic-Related IVIG Shortage Has Not Happened — Yet. *Specialty Pharmacy Continuum*, Jan. 22, 2021. Accessed at www.specialtypharmacycontinuum.com/Covid-19/Article/01-21/Pandemic-Related-IVIG-Shortage-Has-Not-Happened-Yet/62333.
14. Plasma Protein Therapeutics Association. Plasma Manufacturing. Accessed at www.pptaglobal.org/plasma.
15. Data on file. The Marketing Research Bureau, Inc.
16. FDA Letter Confirms IG Product Shortage. *Pharmacy Times*, Sept. 29, 2019. Accessed at www.pharmacytimes.com/news/fda-letter-confirms-ig-product-shortage.