IG Brand Differentiation

Primary immune deficient patients and their caregivers must consider many factors when choosing an immune globulin product.

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THE FIRST PRIMARY immune deficiency (PI), X-linked agammaglobulinemia (also known as Bruton's agammaglobulinemia), was identified in 1952. There are now more than 450 PIs recognized by the International Union of Immunologic Societies, affecting more than six million people worldwide.

PIs are a group of conditions in which part of the immune system is missing or does not function properly. People living with PI are at risk of recurrent, severe, prolonged and/or unusual infections that can occur in the sinuses, throat, ears, lungs, skin and, less frequently, in the urinary or intestinal tract, brain or spinal cord. Acute therapies such as antibiotics are used to treat active infections, but the goal of PI management is to prevent infections from occurring. In most cases, infections are prevented with immune globulin (IG) therapy, which normalizes the immune system to prevent infections and helps improve quality of life, increase lifespan and preserve organ function. IG therapy replaces missing or ineffective immune cells known as immunoglobulins (Igs) — proteins made by the body and found in the blood that attach to unwanted pathogens such as bacteria and viruses to destroy and remove them. There are five types of Igs: IgA, IgD, IgE, IgG and IgM. IgG is the most abundant, making up approximately 75 percent to 80 percent of Igs, and it is what is replaced in PI patients with IG therapy.

To produce IG therapies, source plasma is collected from thousands of healthy human donors and then manufactured, or fractionated, into specialized therapeutic products. While many different IG replacement therapy products are available, not all are the same, and choosing the right one for a patient is important for achieving the best outcomes. Choosing an IG product is determined by several factors, including the

patient's indication, other health conditions, stabilizers, concentration, route of administration, peak and trough levels, and patient location and lifestyle. Each factor is important both individually and when taken into account together.

Indications

IG replacement products are indicated for a variety of disorders grouped into a few broad categories:

1) Replacement therapy for immunodeficiencies such as PI and hypogammaglobulinemia

2) Immunomodulatory therapy for autoimmune disorders, rheumatic inflammatory conditions and neurological disorders

3) Hyperimmune therapy to protect against specific infectious agents

For immunodeficiencies, the indication is one of 450 different types of PI. Serious forms of PI are typically found in infancy, while others are diagnosed in older children and adults. And, some mild forms of PI may not be diagnosed for years until a pattern of recurrent infections occurs.

Other Health Conditions

Other health conditions can play a crucial role in determining product choice and route of administration (subcutaneous or intravenous):

- Patients with volume concerns such as fluid restrictions, renal (kidney) impairment or failure, cardiac (heart) or pulmonary (lung) insufficiency and a history of thrombosis (blood clots), as well as neonatal and geriatric patients, require special considerations.
- Patients with IgA deficiency require products with a low IgA content due to the potential for anaphylaxis (a severe allergic reaction).
- Obese patients may require a higher dose of IG since adipose (fatty) tissue has poor blood supply. And with higher doses, adjusted dosing may be required initially to decrease the risk of adverse events.
- Patients with non-O blood types are at risk for hemolysis/hemolytic anemia (destruction of red blood cells) when administered with high doses of IG, so products containing the lowest anti-A and anti-B antibody titers are preferred.
- Males of reproductive age should consider products that do not contain PH20 (hyaluronidase), which has a potential cross-reactivity with the natural PH20 expressed in adult male sexual organs (testes, epididymis and sperm).
- Patients with arthritis or conditions affecting coordination may struggle with preparing or self-administering products, so the intravenous route of administration may be more appropriate.

Stabilizers

Since IG is a blood product, stabilizers are added to prolong its usability. Stabilizers are the substance(s) in IG products added to help keep the product intact and protect it against environmental stress. They preserve the function and activity of proteins to prevent aggregation (clumping together) of the product and prolong shelf life, keeping the product usable for a longer period of time.

Stabilizers can be added alone or in combinations and include glycine, polysorbate 80, maltose, d-sorbitol, glucose and L-proline. The choice of stabilizer impacts which product should or should not be prescribed for many people. For instance, sugar-based stabilizers such as d-sorbitol and maltose can affect glucose control and are not a good choice for diabetics. D-sorbitol should also be avoided by individuals with hereditary fructose intolerance, a metabolic disease that causes severe low blood sugar and the buildup of substances in the liver. Proline is an amino acid or protein building block in the blood. Individuals with hyperprolinemia (too much proline) should avoid products with L-proline as a stabilizer.

Concentration and Volume

The concentration of products varies by manufacturer, required dose and intended route of administration. Concentration is the amount of IG per volume of fluid and directly relates to the amount of fluid the patient receives. An example of concentration would be to think of IG as the number of peas in a bowl of vegetable soup. A higher concentration (more peas per cup) allows for a smaller volume to be given to obtain the amount of IG (or peas) needed, whereas a lower concentration (fewer peas per cup) results in a larger volume. Patients need more cups of soup with a lower concentration of peas to get the same number of peas in a soup with a higher concentration.

Patients who require large volumes of IG may need to divide it by administering it in smaller doses over multiple days. This is important in those with fluid overload, existing kidney issues or who are at risk for blood clots or kidney problems. Large volumes can also be a concern in newborns and the elderly, as well as those with heart and lung issues.

IG products come in various gram sizes depending on the manufacturer and how much product is needed. Choosing the right size can make the administration process easier and

Table. IG Brand Differential Elements[2]

Brand	Manufacturer	Route	Concentration	Indication	Stabilizer	IgA Content	Sizes
Asceniv	ADMA Biologics	IV	10%	PI (age ≥12 years)	Glycine, Polysorbate 80	<200 mcg/mL	5 g
Bivigam	ADMA Biologics	IV	10%	PI	Glycine, Polysorbate 80	<200 mcg/mL	5 g, 10 g
Cutaquig	Octapharma	SC	16.5%	PI (age ≥2 years)	Maltose	≤600 mcg/mL	1 g, 1.65 g, 2 g, 3.33 g, 4 g, 8 g
Cuvitru	Takeda	SC	20%	PI (age ≥2 years)	Glycine	Average 80 mcg/mL	1 g, 2 g, 4 g, 8 g, 10 g
Flebogamma DIF	Grifols	IV	5%	PI (age ≥2 years)	D-sorbitol	<50 mcg/mL	0.5 g, 2.5 g, 5 g, 10 g, 20 g
Flebogamma DIF	Grifols	IV	10%	PI; Chornic ITP (age ≥2 years)	D-sorbitol	<100 mcg/mL	5 g, 10 g, 20 g
Gammagard Liquid	Takeda	IV, SC	10%	PI (age ≥2 years); MMN (adults)	Glycine	Average 37 mcg/ML	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
Gammagard SD	Takeda	IV	N/A	PI (age ≥2 years); Chronic ITP (adults); Prevention of bacterial infections in hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell CLL; Kawasaki disease (pediatrics)	Glucose, Glycine, Polysorbate 80	5%: <1 mcg/mL; 10%: <2 mcg/mL	5 g, 10 g
Gammaked	Grifols (distributed by Kedrion Biopharma)	IV, SC	10%	PI (age ≥2 years); CIDP (adults); ITP (adults and children)	Glycine	Average 46 mcg/mL	1 g, 2.5 g, 5 g, 10 g, 20 g
Gammaplex	Bio Products Laboratory	IV	5%	PI (age ≥2 years); Chronic ITP	D-sorbitol, Glycine, Polysorbate 80	<10 mcg/mL	5 g, 10 g, 20 g
Gammaplex	Bio Products Laboratory	IV	10%	PI (age ≥2 years); Chronic ITP (adults)	Glycine, Polysorbate 80	<20 mcg/ML	5 g, 10 g, 20 g
Gamunex-C	Grifols	IV, SC	10%	PI (age ≥2 years); CIDP (adults); ITP (adults and children)	Glycine	Average 46 mcg/mL	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
Hizentra	CSL Behring	SC	20%	PI (age ≥2 years); CIDP (adults)	L-proline, Polysorbate 80	≤50 mcg/mL	Vial: 1 g, 2 g, 4 g, 10 g; Prefilled syringe: 1 g, 2 g, 4 g
HyQvia	Takeda	SC	10% (IgG component)	PI (adults)	Glycine	Average 37 mcg/mL	2.5 g, 5 g, 10 g, 20 g, 30 g (based on IgG component)
Octagam	Octapharma	IV	5%	PI	Maltose	Not more than <200 mcg/mL	1 g, 2.5 g, 5 g, 10 g, 25 g
Octagam	Octapharma	IV	10%	Chronic ITP (adults); Dematoyositis (adults)	Maltose	Average of 106 mcg/mL	2 g, 5 g, 10 g, 20 g, 30 g
Panzyga	Octapharma (distributed by Pfizer)	IV	10%	PI (≥2 years); CIDP (adults); Chronic ITP (adults)	Glycine	Average of 100 mcg/mL	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
Privigen	CSL Behring	IV	10%	PI; Chronic ITP (age ≥15 years); CIDP (adults)	L-proline	≤25 mcg/mL	5 g, 10 g, 20 g, 40 g
Xembify	Grifols	SC	20%	PI (age ≥2 years)	Glycine, Polysorbate 80	Average ≤70 mcg/mL	1 g, 2 g, 4 g, 10 g

decrease waste. The ideal choice is one that is available in a size that offers the needed dose in a single bottle. However, if multiple bottles are required, either the patient or the person administering it must be able to mix the required amounts. And since those with arthritis or conditions affecting coordination might struggle with this, they may want to consider prefilled syringes, infusions at a facility or home infusions.

Route of Administration

After considering the preceding factors, either the subcutaneous (SC) or intravenous (IV) route of administration must be chosen. IVIG infusions are administered directly into the blood through a vein with a needle or small tube. IV administration allows for larger volumes at one time and less-frequent infusions, and infusions are generally administered in an infusion center or hospital. With SCIG infusions, fluids are injected into the fatty layer between the skin and muscle through small needles. As a general rule, SCIG is infused in smaller volumes and performed more frequently. SCIG infusions can be self-administered at home after receiving instruction. Patients with poor venous access (difficulty starting an IV) are often good candidates for SCIG infusions. Only one SCIG product allows for larger volumes to be infused less frequently, but it requires premedication with hyaluronidase.

Peak and Trough Levels

Peaks and troughs represent the levels of IgG in the body. Peak concentration is the maximum amount of IgG available for the body to use, which is highest just after an IG infusion. Trough levels are the lowest amount of IgG available before the next IG infusion. An example of peak and trough levels is filling a glass of water and taking out a little bit every day. The peak level is how much is available when the glass is full, and the trough level is how much water is left before refilling the glass. It's important for patients to not let the glass reach empty because they won't have adequate IgG levels to fight infections. Peak and trough levels are much larger when receiving monthly IVIG infusions than when receiving weekly SCIG infusions. Large differences in peak and trough levels can increase the chance of adverse effects and negatively affect how well patients tolerate infusions, whereas smaller differences result in fewer fluctuations in IgG levels.

Patient Lifestyle and Preference

Patient preference and lifestyle should be taken into account when choosing the product and route of administration since both can impact medication compliance. Patients who have very busy lifestyles or travel a lot may have a hard time scheduling time to go to an infusion center and may benefit from the flexibility that SCIG self-administration allows. Those living in rural areas or who do not have easy access to an infusion center may also benefit from therapy at home, whether self-administered or with a home health nurse.

However, patients who self-administer SCIG infusions must possess the mental and physical ability to do so. For instance, a few products need to be reconstituted, which means dehydrated IG products must be mixed with a saline (salt water) or dextrose (sugar water) solution. In addition, there are patients who merely prefer a once-a-month infusion and don't want to think about their infusions the rest of the month. If it is difficult for patients to fit infusions into their schedule or if they have issues self-administering, it is much more likely they will miss doses and not get the full benefit from treatment.

Choosing the Right Product Is Important

PIs are disorders of the immune system that leave patients at risk for recurrent, severe, prolonged and/or unusual infections. The goal of IG replacement therapy is to prevent infections and provide protection against diseases, improve quality of life, increase lifespan and preserve organ function. Many different IG products are available, and choosing the right one is important to achieve the best result. The indication, other health conditions, stabilizers, concentration, route of administration, peak and trough levels, and patient location and lifestyle should all be considered when making the decision.

Resources

1. American Academy of Allergy, Asthma and Immunology. Eight Guiding Principles for Effective Use of IVIG for Patients with Primary Immunodeficiency. Accessed at www.aaaai.org/Aaaai/media/Media-Library-PDFs/Practice%20Management/Practice%20Tools/IVIG-guiding-principles.pdf.
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6. U.S. Food and Drug Administration. Immune Globulin Intravenous (Human). Accessed at www.fda.gov/vaccines-blood-biologics/approved-blood-products/immune-globulins.

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