Immune Globulin: Each Product Is Unique

While all IG products are comparably effective, they also have relevant differences that determine their tolerability by patients.

By Ronale Tucker Rhodes, MS

THE CURRENT AVAILABILITY of multiple immune globulin (IG) products gives providers many choices when prescribing this lifesaving therapy. With the approval of the latest IG product in December 2012, there are now 11 IG products that treat six U.S. Food and Drug Administration (FDA)-approved diseases (primary immunodeficiency disease, idiopathic thrombocytopenic purpura, multifocal motor neuropathy, chronic lymphocytic leukemia, Kawasaki disease and chronic inflammatory demyelinating polyneuropathy), as well as a host of non-FDA-approved conditions.

The benefit of product choice, of course, is that it allows providers to match the best-suited product to the patient. And, this is extremely important because, while all products contain IgG (the most common protein in the body that helps ward off infections) and they all have comparable efficacy, they are not pharmaceutically equivalent. There are relevant differences between the current products on the market, considered third and fourth generation, that have evolved in terms of composition, resulting in decreased risk of infusion-related reactions and other adverse events. Product variations in sodium content, stabilizers, osmolality, IgA content, concentration and pH can affect the tolerability of a product for one patient versus another, based on both clinical conditions and comorbidities.1,2

Adverse effects of IG therapy have been greatly reduced in the last two decades; however, with the new generation of products, there are other serious adverse events that have been observed, including acute renal failure, aseptic meningitis, hemolysis and thrombosis. Some of these events can be attributed to either the size of the dose administered for specific indications, the rate of infusion, the differences between IG products or to characteristics of the patient receiving the treatment.3

When choosing an IG product based on the differences between each, the key factors a clinician considers are the patient’s body type, weight, conditions presenting in addition to the one being treated with IG (such as diabetes, high blood pressure or heart disease), whether they are pregnant or post-menopausal, other medications taken, kidney function, and if there is patient history of blood clots or migraines. This information is particularly important for dosing recommendation and premedication selection, and it helps clinicians tailor patient-specific suggestions for tolerating therapy.4

Following is a review of the key differences among the products’ stabilizers, osmolality, IgA content and concentration, as well as a discussion of infusion rate and route of administration.

Stabilizers

When intravenous IG (IVIG) was originally approved by the FDA in 1981, it contained no stabilizers, and patients often experienced undesirable side effects such as fever, chills, fatigue and chest, hip, joint and back pain, which were believed to be due to the formation of immunoglobulin aggregates. To resolve this issue, stabilizers were added, primarily sugars such as sucrose, maltose, glucose and sorbitol, and in some cases, glycine and albumin.5

The specific stabilizer used can play an important role in a product’s tolerability.7 Today, most IG products are no longer stabilized with a sugar; however, a few still are, which can result in other adverse events. There is a strong association between renal failure and sucrose-containing products, rapid rates of infusion and
diabetes. This is rare, and the cause of renal failure is unknown, but it is believed that it could be due to the fact that sucrose has the highest osmotic activity of the stabilizers in IG products. In addition, since sucrose is metabolized by an enzyme, called sucrase, that is found only in the intestine, when administered intravenously, sucrose is eliminated unchanged in the urine, possibly resulting in osmotic nephrosis. And, while cautious use of IVIG is recommended in patients at increased risk for adverse renal events, including those with renal impairment, diabetes mellitus, age greater than 65 years, dehydration or hypovolemia, sepsis, paraproteinemia or concomitant use of nephrotoxic drugs, they are not contraindicated in patients with renal insufficiency. In fact, screening for IgA deficiency prior to IVIG infusion is not routinely recommended.

The amount of IgA in a given IG preparation may also influence the risk for common reactions that are milder such as fever, malaise, myalgia and headache.

**Concentration**

Today's IG products come in 5%, 10% and 20% solutions. The solution percentage is the number of grams of IgG protein in an IG therapy solution. For instance, a 5% IG product contains 5 grams of IgG protein per 100 mL of solution, a 10% IG product contains 10 grams of IgG protein per 100 mL of solution, etc. The highest-concentration 20% solution can only be infused subcutaneously. Three of the higher-concentration 10% products can be infused subcutaneously, while all of them can be infused intravenously. The lowest-concentration 5% products are approved only for intravenous infusion.

Most of today's products are available as a ready-to-use liquid formulation. However, there are two products that are lyophilized and require reconstitution and pooling into an evacuated container for administration to the patient.

**Routes of Administration**

IG can be administered intravenously through a vein (IVIG) approximately once every three to four weeks, or subcutaneously under the skin (SCIG) every other week, once weekly or twice weekly. SCIG is FDA-approved therapy for only primary immunodeficiency, although it has been prescribed to treat other conditions.

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products stabilized with maltose, there is a possible interaction with strips that test for glucose in the blood. The maltose may cause an erroneous reading indicating glucose is high when it really isn’t. However, most test strips have been modified to prevent these erroneous readings when maltose is present.

**Osmolality**

Osmolality is the solute concentration contained in the IG solution; thus, the higher the osmolality, the higher the concentration of the IG solution. Higher osmolality solutions, also known as hyperosmolar, are typically seen with older lyophilized IVIG products. In contrast, today's fourth-generation products have a more physiologic osmolality comparable to that of individuals' blood because they have had amino acids glycine and L-proline added to them to help reduce the overall solute load, which can become elevated with sugars.

Hyperosmolar solutions tend to cause more local venous irritation at the infusion site. They also may be associated with an increased risk of thrombosis. Dehydration also can cause the blood to become hyperosmolar, which is one of the reasons people receiving IG therapy are encouraged to drink a lot of water before, during and after the infusion.

**IgA Content**

All IG products contain varying amounts of IgA (one of the five classes of antibodies found in the blood). IgA is not problematic for most people. However, in patients who are IgA deficient, IgA can cause the formation of anti-IgA antibodies that can cause anaphylactoid reactions upon infusion of IVIG, which would result from the IgE development against IgA. While the risk of anaphylactoid reaction in IgA-deficient patients is anticipated, the incidence is low given the total number of reactions reported compared with the overall number of patients.
Risk-assessment guidelines are important tools when dosing regimens and routes of administration are being considered. Guidelines include evaluation of patient history and physical examination, risk factors, comorbidities and tolerance to appropriately manage potential serious and nonserious adverse events.

SCIG is not appropriate for everyone. For those requiring IG for autoimmune disorders, the SCIG route of administration may not be possible due to the large volume of solution needed for a dose. However, for someone receiving a smaller dose, SCIG administration may be possible. Those with very thin skin don’t tolerate SCIG as well as those with normal or thicker skin. And, very thin patients may not have enough fatty tissue in the space between the skin and the muscle to tolerate the SCIG infusion. Conversely, patients with very small veins or who have difficulty getting an IV started may be great candidates for SCIG.

In the past several years, SCIG has become an alternative method of administration of IG because of its many advantages. For one, SCIG results in a reduction in anaphylactoid reactions due to its slower absorption from the subcutaneous tissue into the systemic circulation. SCIG also eliminates the need for vascular access, stabilizes immune globulin levels and increases patient autonomy. And, notably, it has been used by patients with IgA deficiency with antibodies against IgA without inducing hypersensitive reactions. There is, however, an increased incidence of local reactions such as swelling and redness at the site of infusion.

**Infusion Rates**
Each patient has a maximum tolerated rate of infusion based on his or her risk factors and infusion-related reactions. For all patients, and this is essential for those just beginning therapy, IVIG should be administered slowly initially and titrated as tolerated. In general, primary immunodeficiency patients can be administered IVIG in one day approximately once a month (the half-life of IVIG is approximately 30 to 40 days), and they can be administered SCIG in one day over a matter of hours once or twice a week, or every two weeks as specified in the product labeling. On the other hand, patients with autoimmune diseases are generally administered larger doses of IVIG that, in some instances, may be divided into daily infusions over two to five days.

Slower rates of infusion have been linked to a reduced risk of side effects, including common reactions, acute renal failure, aseptic meningitis and thromboembolic complications. One of the most commonly reported side effects of IG therapy is headache, which has been found to increase with larger doses infused over a shorter period of time. Cases of aseptic meningitis are rare, but when it occurs, it requires discontinuation of IG treatment, and the symptoms typically stop after three to five days. Several causes for this have been proposed, including hyperviscosity that may be the result of rapid infusions of high doses into a volume-depleted hyperviscous bloodstream.

Stopping an infusion at the first sign of reaction tends to be the best way to manage it. After symptoms abate, most patients tolerate continuing the infusion at a slower rate.

**Highly Improved and Tolerated Products**
With advances in manufacturing processes, today’s IG products are safer than ever before. However, every IG product has different pharmaceutical characteristics, and there is even variation from batch to batch of each product. It’s these differences that can influence patient tolerability. But with careful patient screening and understanding of the inherent differences in the products, clinicians can ensure that the most appropriate product is prescribed to the patient.

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**Sources**