Highlights from IG Living Teleconference December 10, 2015

Topic: Safety, Efficacy, Tolerability, Advantages and Disadvantages of Intravenous and Subcutaneous Immune Globulin Therapy

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[This is an edited version of a live teleconference presentation.]

Historical Perspective of Immune Globulin

The very first patient in the U.S. diagnosed with a primary immunodeficiency (PI) disorder was an 8-year-old boy in 1952 with X-linked agammaglobulinemia (XLA), one of the most severe forms of PI. He was treated by Dr. Bruton at Walter Reed Army Hospital with an intramuscular immune globulin (IMIG) product that was successfully delivered subcutaneously (SCIG).

Until the early 1980s, only IMIG products were available. However, in the late 1970s, a publication described the first subcutaneous administration of an IMIG product in a pregnant woman that allowed her to deliver a baby to term. The IMIG product was delivered subcutaneously because she couldn't tolerate the amount of product she required through IM injections. This case was the first historical precedent for SCIG. (IMIG products can't be delivered intravenously because they contain fragments and clumps of IgG.)

When an intravenous immune globulin (IVIG) product was introduced in 1981 and additional products came on the market through the 1980s, IVIG was felt to be the easier option. It was manageable in the clinical setting and relatively safe. Therefore, development of an SCIG product didn't go forward in the U.S., whereas it did go forward in Europe. In Scandinavia, in particular, SCIG products were introduced in the 1970s, and over the years, have become very popular for treatment options for PIs.

It wasn't until 2006 that CSL Behring introduced the first SCIG product in the U.S. called Vivaglobin 16%. Five years later, Vivaglobin was replaced by Hizentra 20%. Along the way, three 10% concentrated IVIG products — Gammagard Liquid,

Gamunex-C and Gammaked — were all approved for SC administration. Today, in addition, we have HYQVIA 10% from Baxalta (previously Baxter) that is essentially Gammagard Liquid with an accompanying product called hyaluronidase, which enables patients to extend treatment intervals from every two weeks to every four weeks. Soon, in addition to Hizentra, there will be another 20% SCIG product from Baxalta.

Differences Between IVIG and SCIG

Both IVIG and SCIG products are intended to get into the blood stream. The difference between the two is that when IVIG is administered, there is a very rapid spike in serum IgG, whereas with SCIG, there isn't. The big spike from IVIG is often the cause of adverse effects that we don't see as commonly with SCIG. When given subcutaneously, IG is taken through the lymphatic system and gradually enters the circulation, which results in a more consistent serum IgG level. Given equivalent SCIG doses of IVIG over time, individuals have a slightly higher serum IgG level on average. Yet, interestingly enough, when looking at the overall volume of IgG that is circulating (called the area under the curve), IVIG results in more total IgG that is circulating over time. What does this mean clinically? There's no evidence that either product is better than the other in terms of efficacy. Both provide similar protection against bacterial infection. Even though the dosing starts higher with SCIG, over time after titration, the dose is very similar to IVIG. So, both products get the job done. So why would you use one versus the other?

Advantages of SCIG

With SCIG, there is a much lower rate of nonserious systemic adverse reactions such as headache, fever, chills, nausea, vomiting and itching. While these reactions are nonserious, they are still very troubling reactions that can be a real problem for patients, in particular for those newly starting IG therapy.

Studies to date have shown that the rate of nonserious systemic adverse reactions with SCIG is about one-third to one-half the rate with IVIG therapy in PI patients. Very recently, a study conducted in Denmark documented a rate of headache and nausea following treatment with a high-dose SCIG versus IVIG in patients who need much higher doses than are typically used in PI, such as chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN) and post-polio syndrome. When looking at headache and using a visual analog scale, those who were treated with SCIG had a peak value of an average of 1 on a 1-to-100 scale with a range of 1 to 13. So, the worst patient treated with SCIG had a 13 on a scale of 100. When looking at the IVIG group, the average was 11. But, very importantly, the range went all the way up to 96. So, there were patients on IVIG who had really severe headaches. None had severe headaches on SCIG. Again, this study tested high-dose IG. But, the results show that by avoiding the spike in serum IgG, a lower frequency of adverse reactions is experienced. The study showed a

similar story with nausea. The SCIG group had a value of 0 with a range up to 21 versus a value of 3 with a range up to 90 in the IVIG group.

Related to this are more serious systemic adverse events: anaphylaxis, aseptic meningitis, hemolytic reactions and venous arterial thrombosis (blood clots), all of which are serious and potentially life-threatening. Fortunately, these types of serious events are very rare, but they do occur with IVIG, which is why a warning label identifies these problems. With SCIG, these more serious systemic adverse reactions are exceedingly rare and have virtually never been documented in clinical trials.

A third category of moderate reactions has also been described in some studies. One study in Scandinavia, for example, looked at more than 33,000 SCIG infusions in 155 patients with PI who experienced just six moderate systemic adverse events and no serious systemic adverse events. IVIG can't match that record. On the other hand, those who have never had a serious adverse event more likely never will. And, those who stay on the same product and follow the same protocol likely won't have a serious event. In fact, most people don't experience serious adverse events, so it's not a concern. But for those who are treated with IVIG and who do experience these events, SCIG is an option to consider since the likelihood of experiencing another serious event is much higher.

Venous access is another advantage of SCIG. For those who have very low blood pressure, poor veins or some difficulty with venous access, SCIG eliminates these issues. Venous access can be an issue for anyone, but especially for young children and people who are frail. Another option other than SCIG for those with venous access issues is a portacath; however, these external catheterization devices introduce the risk of infection themselves.

Another advantage of SCIG is a sense of patient autonomy. Patients don't have to go to an office or a medical appointment. They can schedule their infusions when they want to: after school, after work, evenings. And, studies document very clearly that there are fewer lost days from work and school with SCIG therapy than with IVIG therapy in persons with PI.

Advantages of IVIG

First, with IVIG, patients have to infuse only every three to four weeks, so there are fewer treatments. With SCIG, patients have to more frequently, typically every week HYQVIA is an exception to this, as is Hizentra, which offers the option of infusing every two weeks with more needle insertions and more needle sites. In addition, patients don't have to deal with local infusion site reactions (redness and swelling). Roughly half of patients who start SCIG therapy experience local infusion site reactions, but those always tend to decline over time and then tend to be transient. The reactions tend to moderate, but in certain patients, they may remain an issue. Finally, with IVIG, there is no need for training. And, there are no needle sticks that

have to be performed by the patient and other caregivers who may be adverse to providing this type of treatment. With IVIG, patients go to their appointment, and the nurse manages their infusion.

Published Reports about Patient Preferences

There are a number of published studies asking patients who started with IVIG and switched to SCIG which administration option they prefer. In a U.S. and Canadian study in 2006, 80 percent of patients preferred SCIG over IVIG, whereas 19 percent preferred IVIG. In a study in Sweden in 2008 of 12 patients, all preferred SCIG. More recently, in a European study of 82 patients, 92 percent preferred SCIG and only 8 percent preferred IVIG. So, it does appear that once patients try SCIG, the vast majority seem to like it.

Those with other than PI disorders — autoimmune or neuropathic (i.e., dermatomyositis, CIDP, MMN, myasthenia gravis) — who are on high-dose therapy should be aware that a number of European studies have documented that SCIG seems to be effective. It's not definitive at this point that SCIG is equally effective as IVIG because there are not large enough studies. However, there is one multinational study nearing completion by CSL Behring evaluating two different weekly dosing levels of Hizentra in 350 patients to see if they can increase the dosing above the levels normally used with IVIG therapy. That study should be completed soon.

One of the things particularly appealing about SCIG for patients who receive high-dose IVIG (as much as 1 g/kg in a single session, which is two to three times higher than dosing for PI) is that the higher the dose of IVIG, the more likely one will experience serious adverse events. Although rare, the risk does increase with a high dose, and in particular, the risk of thrombosis has been documented. This is particularly important for patients with neuromuscular diseases who tend to be in the higher risk groups for thrombosis to begin with, which include older age, cardiovascular disease and certain other risk factors. So, in the near future, it's likely that physicians in the U.S. will offer patients the option of SCIG in lieu of IVIG for high-dose indications.

Pre-Submitted Questions

1) How do antibodies work in the body?
Essentially, antibodies bind to an antigen or a target protein on the bacterium or virus. Once they bind to that protein, phagocytes (eating cells) grab hold of the antibody and bacterial complex and destroy them. So, the antibody's main function is to attach and identify the bacteria or other pathogen so that the cellular immune system can destroy it.

2) Why are antibodies typically used up in 21 days, requiring another infusion of IG?

This is called catabolism. Essentially, antibodies degrade and are removed through the liver, but over time, the protein structure degrades and is removed and recycled as a new protein. Antibodies last on average about 21 days, which is why IG has to be periodically dosed.

3) Has anyone ever contracted a serious bacterial infection from IG products?
To my knowledge, no. These products go through an incredible series of steps to screen out potentially infectious donor plasma, and the processing itself essentially destroys anything that might have gotten through. In a 35-year history of IVIG and a 60-year history of IMIG, I'm not aware of a single infectious episode. Nevertheless, there is a warning label that references Creutzfeldt-Jakob disease (CVJ), and there are theoretical warnings of other possible pathogens. But the term is theoretical because it has never happened in millions of infusions. But we are dealing with human plasma, and the warning exists because of the theoretical risk.

4) What is the difference between Hizentra 20% and Gammagard 10%?
The advantage of patients infusing a 20% solution is they only have to infuse half the volume of product, which means they have the opportunity to infuse every two weeks versus every week. Or, if patients prefer every week, they can infuse with fewer needles or a smaller volume in each infusion site. A higher percent infusion just means less discomfort, fewer needle insertions or less frequent dosing, or some combination of the three. The real obvious advantage to a 20% solution is that skin doesn't like to have fluid pushed into it in large volumes, so that's why there is a restriction on product volume per infusion site.

5) What is the difference in filtering or processing of IG products?
Each product goes through a slightly different process, which results in some of the components in the final container product, such as stabilizers, being different. Or, one product may introduce some contaminant or protein or other element that another product doesn't have so much of. This is the reason, in some cases, patients may experience minor adverse reactions to one product versus another. In those instances, a physician may recommend switching to a different product to see if it will work better.

6) How safe is the blood supply?
It's extremely safe, and it's never been safer. Twenty-five years ago, there was a real risk of contracting hepatitis B or C from a blood transfusion. No longer. Screening methods are so good now that even getting whole blood or red blood cells or plasma directly from a single donor is extremely safe. That safety is enhanced further when talking about SCIG or IVIG because of all the steps manufacturers take to separate or inactivate potential viruses or other pathogens. There's very little be concerned about in terms of safety of these products.

7) How long is it OK to keep receiving IG?
As long as a physician feels it is necessary. There are no long-term effects of IG. IG contains human antibodies, which are good for us; they're part of what our bodies'

create. IG is part of our blood. As opposed to certain types of drugs that can have adverse effects with cumulative dosing, this is not one of them. It is a natural human antibody, and patients can stay on the drug indefinitely. In fact, people with PI remain on it for a lifetime.