



Highlights from the IG Living Teleconference, April 5, 2017

Topic: Treating IG Side Effects

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

Guest Speaker: Mark Riedl, MD, MS, board-certified in allergy/immunology and an associate professor of medicine in the division of rheumatology, allergy and immunology at the University of California, San Diego

We don't understand a lot about how immune globulin (IG) works and what causes some of its side effects. Unfortunately, that's the truth for most experts.

IG is a biological product taken from plasma donors. When individuals receive a dose of IG, they are receiving antibodies from thousands of different people whose plasma was pooled from donors across the U.S. That plasma is then put through a rigorous process in which the IgG antibodies are extracted from all the other proteins in the plasma and then purified to make it safe to store and infuse into people. This process has taken many years, and it's been made as safe as can be with current technology. Of course, there's always a plus and a minus to any medicine or treatment, and while there are tremendous benefits from the antibodies infused with IG therapy, there are also possible side effects because of the activity of these antibodies in the body.

Intravenous IG (IVIg)

IVIg is infused directly into the veins directly. We know from a number of studies that up to half of people who receive IVIg treatment will have side effects. The numbers in most studies are typically 30 percent to 40 percent, but we say up to 50 percent can have side effects. Interestingly, while it's almost half of all patients, on an infusion basis, it's more like 10 to 15 percent of infusions. The reason these numbers don't match up is that some people have side effects with some infusions, but have no side effects during other infusions.

Side effects run the gamut from bothersome to life-threatening. Bothersome side effects can include body aches, headaches, rashes, chills and flu-like symptoms. These can be very debilitating, but they are not life-threatening. In contrast, there are a small number of very serious side effects such as kidney failure, blood clots and anaphylactic reactions. That can result in hospitalizations and even death. These occur in 3 to 5 percent of patients.

There's a clear correlation between the rate of side effects and the dose of IG. We know that those who receive high doses (1 to 2 grams/kg) of IG have a much higher rate of side effects compared to those who receive low doses (1/2 gram/kg) normally given to primary immunodeficiency (PI) patients.

We also know that some side effects are common in people who are dehydrated, which is why it's so important to keep hydrated before, during and after the infusion. Usually, that can be done with oral hydration, but sometimes IV fluids are run during treatment. We also know that the rate of infusion is a main cause of side effects. It's pretty clear that most side effects that happen with IVIG occur with fast infusion rates. Everyone is different, and there's no magic number, but typically if infusions are given in less than three to four hours, people will have a much higher rate of side effects. I recommend four hours for a typical PI infusion (30 grams or so). But, again, it depends on the person. Some people have to go at a very slow rate of about six to eight hours. Nobody really likes that, not patients or nurses, but if that's what it takes to reduce side effects, that needs to happen.

The good news is that most IVIG side effects are transient, meaning they're going to resolve, although it may take several hours or several days. Most occur immediately following the infusion. The ones that aren't transient are the side effects that are more serious, which can cause lasting problems. So, if we can manage these during and after the infusion, they don't appear to leave any long-term damages.

Here are some tips to minimize side effects:

- 1) *Necessity*. Make sure that IG is a necessary treatment. The people who tend to have the most side effects are the people who need IG the least. You need to be sure you need it and are benefiting from it, because if you're not, the side effects can be worse than the condition being treated.
- 2) *IVIG vs. subcutaneous IG (SCIG)*. IVIG has more systemic side effects than SCIG. If experiencing a lot of side effects from IVIG, it's worth exploring the SCIG route. Especially for PI conditions, SCIG has become an attractive option.
- 3) *Hydration*. Adequate hydration is a general rule. Make sure to drink a lot of fluids (water, energy drinks, etc.) and, in some cases, IV hydration can help.

4) *Infections.* We think the reason some infusions go better with some people than others is due to infections. When a person has a bacterial or viral infection, the antibodies from the IVIG try to clear out the infection, which actually makes a person feel worse during the infusion. If an infection is present, it's often necessary to delay infusions for a few days and give antibiotics to clear the infection first. Infections are also the reason people have side effects early on with treatment because we think the treatment is trying to clear up the infection. So, sometimes side effects gets better after the first few infusions.

5) *Infusion rate.* Oftentimes, slowing down the infusion rate can decrease side effects. This may mean really dragging out the treatment, but if it reduces side effects, it may be worthwhile.

6) *Product.* There are many flavors of IVIG, and they have all been proven to work effectively, but they're not all exactly the same. They all have antibodies, but they may have other components to stabilize and preserve the products. So, while we can't predict what types of reactions people will have, there are certain products that will agree with certain individuals than others. That's why some experts are very insistent about with sticking with the same product if it's working. On the flip side, it's worth it to try another product if there are a lot of side effects.

7) *IgA deficiency.* We know that in some cases, lacking IgA can lead to severe reactions to IVIG infusions. So if a person has zero IgA when testing, there is some evidence that person could be at risk for having a IG-mediated reaction to some of the products. It doesn't happen to everyone, but we do keep an eye on that. That usually occurs when IgA is absent, not just low.

8) *Pre-treatment.* Typically, the recommended regimen for pre-treatment is aspirin or nonsteroidal anti-inflammatory drugs and antihistamines (Benadryl), which help with inflammation and any aches or pains or headaches that might develop. Steroids can also be used before the infusion. While sometimes they are necessary, I am not a big fan of steroids because there can be cumulative side effects of using them over months and years.

We often divide side effects with IG into those that are immediate and those that are delayed. Immediate reactions happen during or immediately after (within a few hours) infusion. These include nausea, vomiting, joint pain, headache, fevers and chills. In rare cases, true anaphylaxis, an allergic reaction to the product itself can occur. People with an anaphylaxis reaction may break out in hives, get really itchy, their heart rate may race or their blood pressure may drop, and they have trouble breathing. This is why it's necessary to have epinephrine or adrenaline on hand, and it is why IVIG needs to be administered by a nurse. This is one of the more serious things we worry about.

Delayed side effects occur in 30 to 40 percent of patients and happen a day or more after the infusion. These can include kidney issues, blood clots, rashes, joint pain, fatigue, headache, etc.), and they are tough because we don't know why people have them — except to say that antibodies are pouring in the body and linking up with bacteria and viruses, but they're also linking up with tissues within the person's cells, and we think that may be responsible for joint pains and headaches. Especially with IVIG, the higher the dose, the bigger that spike of antibody pouring into the system. We think this is one of the reasons SCIG has fewer systemic side effects, the level up of antibodies are pushed up, but very gradually.

Headaches can be an immediate or delayed side effect, and some can be very painful. Some people can get aseptic meningitis, which is not an infection but an inflammation of the lining of the brain. We think this is caused by the IG getting into the brain and causing some inflammation. Again, to lessen this, we recommend slow infusion rates, and pre-treating with aspirin or ibuprofen. Sometimes, steroids help, but you have to weight the risks of these. There's a special medication called cyproheptadine (in pill form), which has some effects on serotonin. There has been some data that shows it can actually prevent headaches in some cases. And, then, migraine medicine can work to head of headaches.

I have a few other comments about serious side effects. Most kidney issues related to IVIG pertain to products used in IVIG such as sucrose. Sucrose has largely been removed from IVIG products. However, there is still one product on the market that has it. The good news is that most kidney problems with IVIG have been significantly reduced. But, it's still important to monitor kidney function in people who are treated IVIG.

As far as blood clots are concerned, we have to be very cautious when treating people with IG who are on high-dose therapy or who have other risks for clots (smoking, high blood pressure, previous clots). Again, to protect against this, we recommend hydration and slow infusion rates. For people who are getting very high doses, we recommend splitting up the infusion over a couple of days or three days.

There are rare cases of people getting anemia or lowered white blood cell counts. This is why most clinicians will measure blood regularly every few months to make sure the IG isn't causing any more of these unusual side effects.

People do still have questions about infectious risks, and rightfully so. This is a blood product, and over the past 20 or so years, this product has been incredibly safe. But, there have been problems in the past. The last cases of hepatitis, for example, were in 1994. Plasma is screened and goes through several steps to purify it to kill off and filter viruses. And, the products themselves are regularly tested for infectious issues. So we feel reasonably confident that we're not missing any major infectious problems. But, I always tell people nothing is ever 100 percent, and this is why it's so important to keep a record of infusions (product and lot number). While it probably won't ever be needed, if there ever is a recall, a person will want to be able to go back to see if they got that product.

SCIG

The upside to SCIG is there is a lower incidence of headaches, body aches, flu-like symptoms, nausea, etc., but a much higher rate of local infections, pain and redness at the site of the infusion. Some people benefit from using antihistamine before the infusion or ibuprofen or Tylenol. And, some of these side effects can be addressed by technique, so it's important to address the needle length, preparation of the needle before infusion, how fast the infusion is going and how much volume is being used at each site. Another trick is to try a different SCIG product. There are a few of them now, and they all have different features.