# Highlights from the IG Living Teleconference, Aug. 11, 2016

**Topic: IVIG for Chronic Inflammatory Demyelinating Polyneuropathy, Guillain Barré Syndrome and Myositis**

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

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## What Is Intravenous Immune Globulin (IVIG)?

IVIG are essentially antibodies from healthy people that are intravenously infused into individuals who require IG therapy. In healthy people, antibodies fight bacteria, viruses, funguses, etc. But, in some people, their immune systems go awry and make antibodies that attack their own bodies. This can happen to any organ: kidneys, liver, heart, brain and the ones we'll talk about today, which are nerve and muscle diseases.

When we try to treat diseases that are caused by abnormal antibodies, the immune system has to be corrected to stop it from attacking itself. There are two ways to do this. First is to take medicines that poison the bone marrow so a person's body doesn't make as many antibodies. This sounds great, but there is no way to stop a body from making only the bad antibodies. So by taking these medicines, the level of all antibodies is decreased, weakening the immune system. If the immune system is chronically weakened year after year, problems are created such as the potential for developing cancer later in life. While these medicines are still prescribed, this is a downside to them.

A second way is to block bad antibodies. While we don't know exactly how, this is what IVIG does. Rather than poisoning an individual's bone marrow, it prevents the immune system from attacking itself, which means it doesn't really matter if a person is making bad antibodies. For neuromuscular diseases, IVIG is infused into the body to block the bad antibodies from damaging nerve or muscle. The upside to this is, long term, there are not the same risks as other treatments. Most importantly, the immune system isn't weakened. Instead, IVIG strengthens the immune system. The downside is IVIG only works for as long as it's in a person's blood. And, we know that for most people, that is about 21 days; after that, the IVIG has cleared out of the person's system. So, it doesn't have any long-term effect. This is why most people need the treatments repeatedly.

## Three Main Neuromuscular Diseases

There are three main neuromuscular diseases for which IVIG is effective:

1) Guillain Barré syndrome (GBS) is a disease in which a person gets some type of viral illness, and when their body's immune system tries to fight that virus, it appears to mimic something on their nerves. So, as their body increases its immune system to fight the virus, it attacks the nerves. Over a period of a few days to as long as two weeks, that person develops severe weakness, often in the hospital unable to walk and move. Once the virus leaves the person's system, their body doesn't continue to make those bad antibodies. In essence, GBS is a single event of attacking the nerves.

If GBS isn't treated, the person is going to get better. But, if they are treated during the first two weeks with IVIG, that person is going to get better faster. So we try to treat them when they're very weak. IVIG is a single treatment, with one dose of medicine given, after which the body is left to recover on its own. Sometimes recovery can be very slow, taking six to 12 months or even a couple of years until a person gets close to normal. But, a person doesn't need ongoing treatment because their body's immune system isn't continuing to make the bad antibodies that attack their nerves.

2) In some people, the attack doesn't present quite as quickly. Rather, instead of days, the attack present over months. This is known as chronic inflammatory demyelinating polyneuropathy (CIDP), which is a chronic attack on the person's immune system. This means the person's body will continue to make the bad antibodies that attack their nerves. These people respond very nicely to IVIG, but because their bodies continue to make the bad antibodies, most people will need to stay on therapy for a long time.

3) A third disease, myositis, has many forms, and how we treat them and how long depends upon the type. IVIG treatment is prescribed for three types: polymyositis, dermatomyositis and necrotising myositis. Those three are the only types that actually improve with IVIG. The most common form of myositis in adults is called inclusion body myositis, which does not get better with IVIG, so it is not prescribed. But, again, myositis tends to be a very chronic condition in which people need the IVIG therapy long-term on an ongoing basis.

## Questions

*1) What's new in the research field for CIDP?*

There are a lot of things going on in terms of research, but what most people are looking at are different ways to change the immune system to block the ability of the antibodies to attack the nerve. So, the more state-of-the-art research is being conducted on drugs that have more side effects such the immunosuppressive drugs.

*2) How often should patients get nerve conduction tests once they have a CIDP diagnosis and are on IVIG treatment?*

Doctors do things differently, and there's not really a right or wrong way. My approach is to never conduct nerve conduction tests again. I use them to make a diagnosis of CIDP. But once the diagnosis is made, the treatment, whatever is prescribed, is designed to make patients better. The problem with repeating nerve conduction studies is that, many times, I've seen a person get much better clinically, but their nerve conduction studies don't improve. Or, their nerve conduction studies improve, but clinically, they're not doing any better. For me, I'm treating the patient; I'm not treating the test.

There are good studies that show no correlation between the changes in nerve conduction studies and a person's clinical response. About the only time I would repeat a study is if I thought the person had CIDP and I treated them, but they failed to get better. In that instance, I would question whether I was wrong about the diagnosis.

It is important with CIDP in particular to know that there is no test for it. Myositis can be diagnosed with a muscle biopsy. And, GBS is a very easy to diagnose clinically. But, CIDP is very tricky, and many different pieces of the puzzle have to be placed together to make that diagnosis. So even though I see many CIDP patients, I am never convinced I am right about my diagnosis until I treat them and they get better. The response to IVIG will tell me if I was right.

*3) Is inclusion body myositis treated with IVIG?*

Although inclusion body myositis is placed in the same category as polymyositis and dermatomyositis, it doesn't belong in that category because there is no evidence that it is caused by the immune system. It's much more of a degenerative disease in which the muscles are dying, but they're not dying as a result of the immune system. People have tried to treat inclusion body myositis with many different forms of immunomodulatory drugs (IVIG, chemotherapy, prednisone, etc.), and none have really worked. So most of us believe it's not an immune disorder, and we don't prescribe IVIG.

With other forms of myositis, however, we do prescribe IVIG. But, truthfully, the data is not that great. In fact, some insurance companies have started to point to the fact that there is no good data that shows IVIG works to treat myositis. Yet, many of us who do a lot of work with myositis believe it works. That's why I'm in the process of working with one of the manufacturers to conduct a large clinical trial to prove it works and the insurance companies should pay for it.

Right now, the American Academy of Neurology has concluded that there is no benefit to IVIG treatment for inclusion body myositis and polymyositis, but for dermatomyositis, there might be a benefit. That's the most data-driven review there has been. So, with polymyositis and dermatomyositis, we start with steroids, then move to the second line of therapy which is one of the immunosuppressant drugs, and if patients are still refractory, we start IVIG.

*4) Can too high of an IgG level be dangerous?*

Yes, but the IgG level has to be very high. A normal person might have 1 gram of IgG in their blood per deciliter. Someone with hypogammaglobulinemia, a low immune system, might have a level of ½ gram or even lower in some cases. Someone with CIDP who has a normal immune system and who has been given a dose of IVIG might have 1½ grams. So, while this level is increased, it doesn't seem to be harmful.

In certain forms of cancer such as multiple myeloma a person will make a lot of IgG — maybe 3 or 4 grams at baseline because the cancer cells are producing IgG. In those cases, we are worried and don't prescribe IVIG because we don't want to push their IgG levels even higher. In the worst cases, we worry about hyperviscosity syndrome that could lead to clots that lead to strokes, heart attacks or other serious medical issues. So, if a person's IgG level is high to begin with, we will sometimes avoid giving them IVIG. If it's normal or low, we think it's fine.

*5) What kind of reactions do people experience from IVIG?*

While IVIG is safe, many people have bad side effects. I describe it like a transfusion reaction because the infusion is with a blood product that is coming from a lot of other people.

The most common side effect is a headache (in our infusion centers, headaches occur in about 40 percent of people). In most cases, the headaches aren't terrible and can be regulated by the rate of infusion. The faster the infusion, the worse the headache will be. But a headache on day two or three following infusion is pretty common.

Other effects such as nausea, chills, rash and feeling run down are not as common. That occurs about 5 percent or 10 percent of the time. Most of the time, we can manage those with the rate of infusion or by treating with Tylenol or Benadryl or, in bad cases, steroids.

Some people will have terrible side effects after each infusion. Managing those effects is an art, not necessarily a science.

For these, we do a lot of things:

a. There are many brands of IG, and they are all produced slightly differently. So, for most people, the side effects are not so much due to the IVIG but the preservatives or the way they're prepared. For instance, some people have a terrible rash to brand A and when switched to brand B, they have no rash. The easiest thing to do if someone has a side effect more than once or twice is to try to change the brand.

b. Sometimes, it's the total dose of IVIG. Infusions tend to be given in one or two consecutive days, with IG remaining in the bloodstream for the rest of the month. But, side effects can be reduced by breaking up IVIG infusions in smaller doses in smaller increments, say on a weekly basis. The goal is to infuse the same total number of grams of IG to the person in a given month. We are also trying to get people who have bad side effects to IVIG to switch to subcutaneous IG therapy, which can be given in much smaller doses more frequently, even daily.

   If side effects continue to be terrible, a person may decide IVIG is not the best treatment. The goal is to improve quality of life, so if they're sick one to two weeks of the month and only feel good one to two weeks, it might not be a good tradeoff. Then, other treatment options may be considered.

*6) Is IVIG something I have to be on for life?*

Excluding GBS, the traditional thinking for CIDP and myositis is that once you have them, you have them for life. The largest trial for CIDP, the ICE trial, was completed seven years ago. After completion, when people got better, they randomized them to stay on therapy or stop. Of the people who stopped therapy, 50 percent did not have a relapse.

Ten years ago, my answer was always yes, IVIG treatment is for life. And, the majority of time, once a person goes on therapy, they're going to be on it for a very long time. But, these days, I always try to stop it. If a person feels better for a year or two and there's not much variation in symptoms, one of the most important things I tell them is: Before your next infusion, tell me if you feel much worse. If the drug is wearing off considerably, I have no chance of stopping the medicine. If it doesn't seem to be wearing off, I'll phase the person off of it. For instance, I'll prescribe therapy every five weeks or every six weeks until, eventually, it's stopped.

The other thing I try to do is taper the dose. Sometimes, a person can get away with much less of the drug than is thought they need. It's hard because there is no test to tell us how much treatment is needed. The only way to know is to slowly reduce it and see what happens with the symptoms. My goal is to always try to get the person treated with the least amount of the drug, because the lower the dose, the lower the side effects.

*7) Can IVIG be used alone for long-term therapy?*

Yes. If I think a person has CIDP, I prescribe them three months of IVIG, which is enough time to see improvement. I look at that as short-term treatment. Then, I ask: What do we want to do long-term? That is up to the patient. If they did well with the IVIG, I'm happy to just prescribe the IVIG. If the person is active and doesn't want to be tied to the infusions or has side effects, then my goal is to get them off of the infusions, which means introducing immunosuppressant medicines for three to six months during which time the IVIG dose is slowly lowered in hopes of the oral immunosuppressants picking up the slack. Either is fine. We don't have any data that one treats patients better than another. Our goal is to make patients' quality of life better.

*8) Is there a dosing schedule that should be tailored to each person?*

Definitely. We've conducted a number of large studies looking at how neurologists treat with IVIG. There are a lot of different ways, and there are no data that one is better than another. First, we consider three months an adequate trial of IVIG. If they're not better after three months, it's not working. Second, we consider whether there is a good dosing schedule. The dose in those three months needs to be between 1.3 grams per kilogram of body weight and 2 grams per kilogram of body weight. I tend to err on the high side of 2 grams per kilogram per month because that's the maximum dose. How a physician does that varies. I break it up into two days back-to-back. The goal is to get the same dose in in a manageable way. Last, once a person improves, they need to be put on maintenance therapy that is tapered to the lowest dose possible without reducing its effectiveness.

*9) What are the long-term side effects of IVIG?*

Very few. With prednisone, everybody has side effects, and they get worse the longer a person is on it. Oral immunosuppressant drugs can affect the kidney and liver and cause cancer. IVIG has fewer long-term side effects than those drugs. The few serious side effects are the risk of blood clots (but that doesn't seem to have anything to do with length of therapy) and kidney disease, which I tend to think we underestimate a bit. Because the IVIG is a lot of protein that has to go through the kidneys, we see a reasonable number of patients (say 10 percent that are on it for years and years) in which it does start to damage the kidneys a bit. It's rare, but it should be watched for. That's why I think changing to subcutaneous infusions seems to be better for the kidneys than infusing intravenously in large quantities. Other than that, IVIG long-term is very safe.

*10) What is the average length of time a person can go between treatments?*

It varies. In the ICE trial, 1 dose per kilogram of body weight was infused every three weeks, which is a nice place to start with maintenance therapy. If a person gets to every six weeks and there's no wearing-off effect, then they probably don't need it. On average, most people who actively need IVIG infuse every three to four weeks. But it's reasonable to try to stretch it out.

*11) Why does IVIG stop working sometimes?*

First, autoimmune diseases are complicated. We see people with certain diseases (myasthenia gravis, myositis, CIDP) in which they do well for a certain number of years, but then the disease gets worse. That's the nature of these diseases. So sometimes it 's not so much that the IVIG isn't working; it's that the disease is getting worse.

In the case of CIDP in which there is a lot of nerve damage, a person can recover and the nerves will regrow as much as they can, but they won't regrow completely. In fact, very often with CIDP, most people don't get to 100 percent of normal, but rather 80 percent. Unfortunately, some people perceive that when they've been treated for two years with IVIG therapy and they plateau in recovery, the IVIG isn't working anymore. But, in reality, it's that the nerves just aren't able to recover any more. With both myositis and CIDP, IVIG doesn't repair the muscles or nerves that have been damaged (the body has to do that on its own), it blocks the damage from happening anymore.

For nerve diseases, I tend to use two years as a good measure. If someone has CIDP, what they're left with two years after treatment is the permanent damage (pain and/or weakness) that happened before CIDP was treated with IVIG. We call this burnt-out disease, and we see it in muscle disease a lot. If the muscle is severely damaged, it is replaced by fat, and that muscle can never grow back. The muscle can get fatter again, say by working out, but the muscles that are completely dead can't ever regrow. Nerves are a little different because nerves can regrow, but they may not regrow quite as well as wanted.

*12) Is IVIG beneficial for Amsan (acute motor-sensory axonal neuropathy)?*

GBS differs from CIDP because it is an acute immune-mediated attack on the nerves, which means is requires only a single course of treatment, whereas CIDP needs ongoing treatment. Amsan is another form of GBS, but rather than damaging the myelin as it does with GBS, it damages the axon, the wire inside the myelin. The bad news is that with the wire being damaged, it is harder to regrow the nerves, whereas with GBS, the nerves do a better job of repairing themselves.

*13) Are myositis and CVID connected?*

No. In CVID, patients have levels of antibodies that are too low, which means a lower level of the immune system. Myositis is an autoimmune disease, which causes an overactive immune system. It's possible that the immune system is not regulated correctly, and could be decreased in one area and increased in another. But, for the most part, we don't think there is any relationship

*14) Is there any long-term pain management for these diseases?*

There are two types of nerves: motor and sensory. With damage to the sensory nerves, two things can happen. The nerve can be killed, which causes numbness. Or the nerve can be sick, which gives off abnormal discharges that can be perceived by the brain as stabbing, stinging, etc. That is called neuropathic pain. There are three types of therapies for this: 1) Seizure medications decrease the amount of electrical signals that those nerves can send; 2) Antidepressants (which are used not because we think the person is depressed) increase certain neurochemicals in the brain and spinal cord called serotonin and norepinephrine that decrease the perception of pain. For instance, seizure drugs work at the feet to decrease the signals that are sent, and antidepressants work at the brain to decrease the perception of pain. And, if those categories of drugs are not enough, there are 3) narcotics. A lot of emphasis is placed on trying not to use narcotics. Most literature says they don't work, meaning in the long run, a person will still have pain. But, most of us believe there is still a place for narcotics. I have a lot of patients who are able to function relatively normally because of narcotics when nothing else worked.

*15) If there is a slow recovery with GBS, is it because there is damage to the axons versus myelin?*

All IVIG does is speed up recovery. GBS can take a couple of years to recover from. After initial treatment, there is no data that retreating accomplishes anything. So, it is sometimes very slow and frustrating. Yes, the slower the recovery and the more severe the weakness, the more it indicates the axons were damaged, and it will take longer to get better. I don't think it means it can't get better. I've seen people quadriplegic and on a ventilator, and two years later, they are close to normal. It's a very scary and frustrating disease because of how quickly it comes on and how impotent one feels, but it's a matter of letting the nerves recover.

*16) Can CIDP affect balance or eyes?*

Generally, CIDP does not affect the eyes. In severe cases, it affects facial muscles making a person unable to blink normally. CIDP absolutely affects balance. Walking is a huge issue because leg strength is diminished. And, when walking, sensory nerves send signals to the brain very quickly, and if those nerves aren't sending the right signals, the person won't know where their feet are and the feet won't know where to go. Sometimes, people will notice that when it's dark, symptoms are much worse because they lose their visual input in addition to losing the input from their feet.

*17) Is IVIG anti-inflammatory?*

Not really in the way we talk about anti-inflammatory. Drugs that are anti-inflammatory are nonsteroidal drugs (ibuprofen, naproxen, etc.) and steroids, which are probably the best anti-inflammatory drugs. But IVIG doesn't have that effect. It doesn't help with joints or swollen areas in the body. What IVIG does is block the immune system, so it's anti-autoimmunity more than it is anti-inflammatory.