Highlights from the IG Living Teleconference, Sep 2, 2015

Topic: Immunology Q&A

Guest Speaker: Following is an edited version of the IG Living Teleconference with guest speaker Dr. Marc Riedl.

I'm a board certified allergist and immunologist, and I'm also certified in internal medicine and clinical pharmacology. I've done some investigation of drugs and other treatments over the years. But, mostly, I deal with adult patients with primary immunodeficiencies (PIs), and my specific interest has been with common variable immunodeficiency (CVID), which is one of the most common PIs. When we speak of PIs, we're talking about the intrinsic or inherent function of the immune system to fight infection, but also to regulate some of the usual functions of immunity and control some of the other bodies' important systems. As an immunologist, it's a very humbling experience because I spend a lot of my time saying "I don't know" when I get asked questions. The immune system is incredibly complex and incredibly resilient, which is why human beings are able to live with all the insults everyday from toxins and bacteria to viruses and other things. But the truth is that our understanding of the immune system is pretty basic.

Overview of the Immune System

We break up the immune system into a few different arms:

Arm 1: At the center of this arm are T cells, which are the brains behind the operation (the quarterback or coach) that are telling the immune system what to do. T cells are critical to survival. Without them, we don't live very long because infection will overwhelm us. That's called cellular immunity. In most of the adult PIs like CVID, the T cells still work reasonably well. They may not be entirely normal, but T cells still work and they're important for directing the immune response and for fighting viruses and fungal infections, as well as directing the B cells.

Arm 2: Outside of T cell function, there is the antibody arm, which is made up of B cells that turn into plasma cells that crank out antibodies. Antibodies are the proteins that are primarily important for fighting bacterial infections but also play a role in defending against viruses. Many of the most common PIs are antibody deficiencies. These include CVID, hypogammaglobulinemia (X-linked and Bruton's), specific antibody deficiency and IgG subclass deficiencies, which are all types of antibody problems, and they are clearly the most common immunodeficiencies we run into in practice when we see patients with infections. So, the B cell issues are very common, and that's where intravenous immune globulin (IVIG) therapy comes in — to help boost that side of the immune system.

Arm 3: Another arm is called the innate immune system, which is the oldest part of the immune system if you look at other organisms evolutionarily. The innate immune system includes 1) the complement system, a series of proteins that punch holes in bacteria and help prevent infection, and 2) toll-like receptors (on cells that recognize patterns that are seen in the cell walls of bacteria and certain types of fungal elements) that get triggered and send a signal to cells to get an immune response. The innate immune system is not where we usually find problems, but it is possible. This is also a part of the system we can test if there are issues with infections or other immune problems.

These arms all talk to each other, which is part of what's interesting but also what's confusing about the immune system. The signaling happens through receptors between cells, so T and B cells talk to each other through receptors but also through chemical signals called cytokines, which come in lots of different flavors such as interleukin 1 or 4 or tumor necrosis factor. You may recognize these names because there are now drugs developed to target some of the cytokines or some of these protein signals that go between the immune cells for things like rheumatoid arthritis and certain other autoimmune problems. These cytokines are used as targets for drug developers if there is dysregulation or inflammation.

Q &A (these questions were posed by callers)

Question: How can one have CVID where antibodies either aren't produced or don't operate and have autoimmune dysregulation where the body attacks itself?

Answer: This is one of the paradoxes of CVID. The primary issue is that the body isn't making enough antibodies, and those antibodies aren't functioning very well. That's why the principal problem with CVID is recurrent infections, which is how most people present and, in most cases, is the biggest danger. The second biggest problem is autoimmune conditions. Depending on the study, 25 to 30 percent of CVID patients also carry an autoimmune diagnosis, which may include rheumatoid arthritis, lupus, anemia, low platelets and GI issues.

The best way I can explain it is that CVID is not just an issue with protecting against infection, but it's rather the immune system in chaos. The most recognized problem of CVID is infectious risk. But the chaos also includes autoimmune conditions. The truth is we don't know exactly why that happens. There is evidence that T cells (the brains behind the operations) in some CVID patients don't work properly. They may still be able to direct some traffic and fight off some of the really bad infections, but they don't do a great job of regulating the immune system or keeping it from attacking the body in some fashion. In some people with CVID, the regulatory T cells (the police officers who the put the breaks on the immune system) are dysfunctional or deficient so they don't stop the immune system from recognizing and attacking certain tissues in the body. Again, we don't really know the reasons why this happens.

Question: What is autoimmune dysregulation?

Answer: Autoimmune dysregulation means that the immune system is recognizing your own tissues as a foreign antigen. It's mounting an attack on some part of your body tissue (whether it's the blood cell, joint, etc.). This attack usually involves both T and B cells, with T cells being the brains and telling the B cells to attack that tissue. Of course, in CVID, antibodies aren't made very efficiently, so the autoantibodies may not be as important in CVID. As many of you know, a lot of lab tests for autoimmune conditions look for autoantibodies against human tissues, which is one of the challenges in CVID patients who have autoimmunity. Looking at those antibodies in a lab test may not be very accurate because, with CVID, 1) one doesn't make a lot of these antibodies, and 2) if you're getting IG treatment, your system is flooded with those antibodies, which means the tests won't give an accurate measurement of an autoimmune reaction. So, it's this self-reactivity that causes autoimmune problems and the regulatory cells that are failing at some level.

Question: How does inflammation and pain play a role in autoimmunity?

Answer: Inflammation causes upregulation of certain chemicals and cells that cause irritation and increase blood flow, and that will cause the nerve endings to get activated. Most inflammation is associated with some pain; the nerve endings get activated to cause pain. That could be painful joints, painful intestines or painful skin. Wherever the inflammation is, you'll have pain associated with that.

Question: What causes autoimmune flare-ups, and what can be done to prevent them?

Answer: We don't know what causes flare-ups. We think this is a programmatic failure of the immune system, meaning it's not controlling its reactivity; its recognizing the own body and attacking it. There are certain triggers. Some people experience flare-ups with infection or certain types of stress. The reasons for that aren't clear. But if you aggravate the immune system with stress or infection, then we think there's an overexaggerated response that can lead to autoimmune problems.

Sadly, at the moment, there is no known way to prevent these conditions from developing. We think a lot of autoimmunity is genetically programmed, along with some environmental insults over the years that may trigger things. But most of the treatments are not preventive — they're basically to treat the symptoms as they're happening and to stop the process from causing pain and disability and, ultimately, damage to the tissues. It's unfortunately a very reactive way of going about things. That's one reason to work with your specialist to monitor for the development of these systems.

Question: Why isn't fatigue listed as a common symptom of CVID?

Answer: I would agree that fatigue is something we see in a lot of patients with CVID. The reason I think it's not listed as a primary symptom is that there are a lot of causes of fatigue. Fatigue is a very nonspecific thing; there are literally hundreds of reasons why people can feel tired. In this field, we've been a little hesitant to blame the immunodeficiency for everything. I think there are people whose fatigue is directly related to CVID, but it's a mistake to jump to that as the explanation. There is a long catalog of things that should be looked at before we blame fatigue on CVID, including getting enough sleep, eating well, having a working thyroid, having normal blood counts and no endocrine problems. We also don't talk about fatigue a lot as a symptom because nothing has been proven effective to treat it. As such, it's a very frustrating circumstance.

Question: At what stage is stem cell replacement for CVID?

Answer: Stem cell transplant currently means that you can take healthy cells and put them into a body to regenerate the immune system. But this is a problem at the moment for people with CVID because their existing immune system has to be wiped out with chemotherapy drugs first in order to have a chance to engraft or live in the body with the relatively normal T cell function we see in CVID. This is the real problem with transplantation, and this is where all the risk lies; we haven't figured out how to make that happen without endangering peoples' lives. If you wipe out the immune system completely, you're at major risk of dying from infections very quickly.

There was a paper published not too long ago reporting the experience at several big research centers with stem cell transplant for CVID. I don't know if the results were encouraging or not. The data show that about half of the people who got the transplantation died. So, there's a 50-50 proposition of surviving stem cell transplant currently with CVID based on that study. And those are heavy odds, so it's not something we are ready to prescribe just for anyone. The good news is that for the 50 percent who lived, most were cured of the associated complications with CVID. These are people who had severe autoimmune problems, severe granulomatous disease, gastrointestinal issues — all the things we know can be really devastating with CVID. These were very sick people — people who probably had a very short life expectancy if they didn't undergo this procedure.

When people can live through the chemotherapy part of transplantation, they actually can be cured of many of the terrible complications of CVID. On the flip side, only about one-third of them got off their IG treatments, which tells us that we can repair some of the T cells or other issues, but it's more difficult to replace the B cells sufficiently so people can stop IG treatments. We need safer ways to get the stem cells to implant and do what they're supposed to, because 50 percent mortality is not something we're going to recommend to very many patients. It's just too dangerous right now. But, there are newer types of chemotherapy, and there are newer ways that we're looking at this. We have to continue to look at research studies and clinical trials to make it more viable.

Question: Is CVID linked to a specific genome, or does it vary from person to person?

Answer: We don't know the specific genetic mutation in most people who have CVID. We are able to identify a known genetic mutation that leads to this deficiency in only 5 percent to 10 percent of people. It's highly variable from person to person. In the other 85 percent to 90 percent of people, we don't know what the genetic problem is that's causing this deficiency.

This is another area in which there's lot of research going on. There are some big groups looking at exome sequencing where you can sequence the entire genetic code and you can look at people with and without CVID and find the spots where there are big changes in the genetic code. And that has started to yield some hot spots — areas where we think the action might be in terms of causative mutations leading to CVID. But this is still very complex and very slow going. The human genome is basically equivalent to taking volumes of War and Peace (a huge 500-page book), piling those books until there is an eight-story building, taking that paper from all those pages and putting it a paper shredder, and then trying to piece it back together into sequence to find which word is misspelled. That's how much data is in the human genome, so that's the project we're looking at when searching for a mutation that might cause CVID. The good news is that technology is allowing this process to go faster and faster, but you still have to shatter the DNA and put it back to together to figure out where the problem is.

Another complication is that CVID is probably not just one mutation in a lot of people. It's probably a sequence of different mutations in different areas that add up to a problem making antibodies. So, the answer is: It's highly variable, and while we're making progress, we still have a ways to go in identifying where the genetic breakdown is in any given person. It's still very important because once we have that information, we can work toward gene therapy or gene editing that might allow us to repair the genetic code if we can figure out where the problem lies. But it will be years yet before we feel competent about being able to repair genetic defects.

Question: Is there a way to increase IgG levels through diet, exercise or drugs?

Answer: No. If so, it would be a lot easier than some of the treatments we currently have to use. There is no scientific evidence that doing anything other than IG replacement therapy does anything to improve IgG levels. The cellular factory that cranks out the antibodies is broken, and you can't fix that by eating or exercising in a certain way. You have to replace those proteins because the body is not capable of making them at the levels it needs to.

Question: Am I negatively affecting my doctor's ability to help me if I don't tell him/her every symptom I have because I don't want to be seen as a hypochondriac?

Answer: With PI or any complex medical condition, there are a lot of things that can and will go wrong. I think it is important to let your physician and specialist know about the symptoms you're experiencing. Withholding information can sometimes cause problems because we don't get the whole story and can't get the big picture. That said, you are right on point that these things happen to normal people, too. So, I do sometimes caution my patients with PI that they're allowed to have "normal" stuff like a cold and bronchitis, and it may have nothing to do with PI because they're normal people, and these things happen to normal people. We can't blame everything in the world on PI or autoimmunity. It's not that simple, and it's a mistake to lump everything into that bucket. But, it's still important to report symptoms. And it's important to find good doctors who you trust and know they're listening to you and using good judgment. That said, if there are a lot of different symptoms, it is important to prioritize what you discuss with your doctor.

Question: Can a child outgrow an antibody deficiency?

Answer: This is an interesting issue in children who have been diagnosed with low antibody levels, also known as hypogammaglobulinemia. There is something called transient hypogammaglobulenimia of infancy or childhood. And, there has been a study that has looked at this. Most small children who have low antibody levels when born will outgrow it by 1 to 2 years old.

But, there is another group of children that has B cell memory problems, meaning their antibody levels start out low, then improve over time (sometimes up to a decade, age 10 or so) but the function is a little sluggish. This means that if their receive a vaccine, they may or may not respond to it very well, and if they do respond to it, it may wear off after a while. These kids actually do gain their B cell memory slowly but over time, and that is a good sign. And, these kids have a normal immune function by the time they're 10 or 12 years old, and they won't need IG replacement therapy.