Answers to Commonly Asked Questions About Common Variable Immunodeficiency (CVID)

Marc 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, was the guest expert at the *IG Living* Readers Teleconference held June 24, during which he answered many commonly asked questions concerning CVID.

Why Is CVID Referred to as "Common Variable" When It Is Not Common?

The prevalence of CVID is about one in 25,000 people, which makes CVID a rare medical condition. However, when looking at the genetic causes of primary immunodeficiency diseases (PIs), CVID is one of the most prevalent. Therefore, in the realm of PIs, CVID is quite common. CVID is referred to as variable because of the symptoms associated with it — infections, gastrointestinal (GI) issues, lymphoma, etc. — that vary from person to person. As such, there are many different symptoms and different clinical courses in people who have the same disorder.

Why Does CVID Take So Long to Diagnose?

Historically, it has been a challenge to get the proper testing for diagnosing CVID because it is a rare condition. According to the most recent studies, diagnoses are being made earlier, but we have a long way to go to get CVID diagnosed quickly after the onset of symptoms in most patients. Older studies showed it took a decade or more to diagnose CVID. Today, on average, it takes about five to seven years to diagnose CVID; however, some patients still aren't diagnosed for 10 to 20 years or more.

There has been a lot of effort to raise awareness about PIs over the years. And, while awareness has improved, CVID is still very rare. So, one reason it takes so long to diagnose is because most physicians and healthcare practitioners are either not familiar with the disease, or they may have heard about it in their training, but have forgotten about it. Therefore, CVID is not something they're thinking about or testing for.

Another reason CVID can take so long to diagnose is that there is a perception that PIs are a pediatric problem — something that is diagnosed at birth or early in life. So, many adults have to battle the myth that it doesn't happen to adults or that they would have already been diagnosed.

In addition, finding the right doctor to diagnose CVID can be a challenge. The symptoms of CVID can be similar to other common conditions: sinus infections, bronchiectasis, bowel issues, etc. These are conditions that a lot of physicians see as run-of-the-mill; but they're not, if they keep recurring. It takes a certain healthcare practitioner to know that recurring infection is not normal. And, while infection is the hallmark of CVID, there are also many other symptoms and complications. For instance, if the primary symptom is GI problems or granulomatous disease, physicians don't equate that to an immune deficiency, and CVID gets overlooked.

Finally, today, doctors specialize in certain areas of medicine, and through no fault of their own, they often don't look at the big picture. As such, individuals have to run into the right specialist or seek out the physician who will look at the big picture of various symptoms and conduct the appropriate testing.

Yet, even when physicians think of CVID as a possible diagnosis, they often don't know what tests to conduct or how to interpret those tests. This is a particular challenge, so physicians who are not familiar with CVID are being encouraged to refer patients to a practitioner who is familiar with the disease. Unfortunately, there is a relative shortage of specialists who have a strong interest in this kind of immunology.

How Is the Time of CVID Diagnosis Calculated?

Studies that look at the time to diagnose CVID base it on the date from when a patient first started to record recurrent infections or presenting symptoms to when they were tested and diagnosed. This is an inexact science, however, because it relies on backward tracking and recollection.

Introducing

HyQvia

[Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase]

For adults with primary immunodeficiency

What is HYQVIA?

HYQVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase] is a liquid medicine containing immune globulin and recombinant human hyaluronidase indicated for the treatment of Primary Immunodeficiency (PI) in adults. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobuliemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

Limitation of Use:
Safety and efficacy of chronic use of recombinant human hyaluronidase in HYQVIA have not been established in conditions other than PI.

HYQVIA is infused under the skin into the fatty subcutaneous (subQ) tissue, in 1 infusion site, up to once every 4 weeks. A second infusion site may be used if needed.

For more information about HYQVIA, talk to your doctor or visit **www.HYQVIA.com**

Detailed Important Risk Information

HYQVIA can cause serious side effects. Call your healthcare professional or go to your emergency department right away if you get:

- Hives, swelling in the mouth or throat, itching, trouble breathing, wheezing, fainting or dizziness. These could be signs of a serious allergic reaction.
- Bad headache with nausea, vomiting, stiff neck, fever, and sensitivity to light. These could be signs of swelling in your brain.
- Reduced urination, sudden weight gain, or swelling in your legs. These could be signs of a kidney problem.
- Pain, swelling, warmth, redness, or a lump in your legs or arms, other than at the infusion site(s). These could be signs of a blood clot.
- Brown or red urine, fast heart rate, yellow skin or eyes. These could be signs of a liver or blood problem.
- Chest pain or trouble breathing, blue lips or extremities. These could be signs of a lung problem.

These are not all the possible side effects with HYQVIA. Talk to your healthcare professional about any side effects that bother you or that don't go away.

What is the most important information that I should know about HYQVIA?

- HYQVIA can cause blood clots.
- Call your healthcare professional if you have pain, swelling, warmth, redness, or a lump in your legs or arms, other than at the infusion site(s), unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body.
- Your healthcare professional may perform blood tests regularly to check your IgG level.
- With your consent, your healthcare professional may provide blood samples to Baxter Healthcare Corporation to test for antibodies that may form against the hyaluronidase part of HYQVIA.
- Do not infuse HYQVIA into or around an infected or red swollen area because it can cause infection to spread.
- Talk to your healthcare professional if you become pregnant. Women who become pregnant during HYQVIA treatment are encouraged to enroll in the HYQVIA Pregnancy Registry by calling Medical Information at 1-866-424-6724.

What are the possible or reasonably likely side effects of HYQVIA?

After HYQVIA infusion a temporary, soft swelling may occur around the infusion site, which may last 1 to 3 days, due to the volume of fluid infused. Mild or moderate pain, redness, swelling or itching may occur at the site of infusion and generally go away in a few hours. Local reactions are less likely after the first few infusions. The most common side effects of HYQVIA are headache, fatigue, nausea, fever, and vomiting. Antibodies to the hyaluronidase component of HYQVIA were formed in some patients taking HYQVIA. It is not known if there is any long term effect. In theory, these antibodies could react with your body's own PH20. PH20 is present in the male reproductive tract. So far, these antibodies have not been associated with increased or new side effects.

What is HYQVIA?

HYQVIA is a liquid medicine containing immune globulin and recombinant human hyaluronidase. HYQVIA contains IgG antibodies, collected from human plasma donated by healthy people. The antibodies help your body to fight off bacterial and viral infections. The hyaluronidase part of HYQVIA helps more of the immune globulin get absorbed into the body to fight infection.

Before starting HYQVIA, tell your healthcare professional if you have or had any kidney, liver, or heart problems, a history of blood clots, because HYQVIA can make these problems worse. Also tell your doctor if you have IgA deficiency or a history of severe allergic reactions to immune globulin (IgG) or other blood products, or are pregnant, trying to become pregnant or are breast feeding.

How should I take HYQVIA?

HYQVIA is infused under the skin (subcutaneously) up to once every 4 weeks. You can get HYQVIA at your healthcare professional's office, clinic, or hospital. You can use HYQVIA at home. You and your healthcare professional will decide if home self-infusion is right for you. Do not use HYQVIA at home until you get instructions and training from your healthcare professional.

Who should not take HYQVIA?

Do not take HYQVIA if you are allergic to IgG, hyaluronidase, or other blood products, or have IgA deficiency with antibodies to IgA.

To report suspected side effects, contact Baxter Healthcare Corporation at 1-866-888-2472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Brief Summary of HYQVIA Prescribing Information on following page, including Boxed Warning.

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Baxter

Brief Summary of Prescribing Information
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What is the most important information that I should know about HYQVIA?

- HYQVIA can cause blood clots.
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Does CVID Run in Families, and Is There Genetic Testing for It?

Even though it is believed CVID is caused by genetic mutations, only about 10 percent of diagnoses are clearly familial. Ninety percent are sporadic, which means the disease shows up in only one person in the family. Therefore, only a small minority of patients have inherited CVID. The problem with such testing, though, is that a genetic mutation can be identified in only about 15 percent of all CVID cases. In the other 85 percent, the genetic mutation is unknown. Genetic testing is relatively expensive, so without a high rate of success, it is often not clinically useful outside of the research setting. Much more research needs to be conducted to understand the genetics related to CVID.

What Is the Difference between Hypogammaglobulinemia and CVID?

Hypogammaglobulinemia is a nonspecific diagnosis. Basically, it describes a laboratory value that shows antibody levels are low, but gives no other information on the condition. CVID, on the other hand, has specific criteria: low IgG plus low IgA and/or IgM levels. Therefore, hypogammaglobulinemia is a general diagnosis, whereas CVID is a more specific diagnosis.

It's possible for children to have transient hypogammaglobulinemia, which means their IgG levels are low, but they become normal as they age. This sometimes occurs in children under 5 years old because the development of the immune system is delayed. Therefore, because it could be transient, physicians generally don't like to diagnose children with CVID until they're older than 5 years. In most patients, CVID is diagnosed after puberty.

What Is the Risk of Serious Disease with CVID, and What Can Be Done to Prevent It?

Historically, the major risk of CVID is overwhelming infection (bacteria in the bloodstream, meningitis, etc.). The good news is that infections have dramatically been reduced in patients who are diagnosed and properly treated with immune globulin (IG). And, these days, serious complications such as chronic lung disease (which occurs in 25 percent to 30 percent of patients) resulting from bronchiectasis may be prevented or slowed with IG therapy.

But, there are other conditions, like granulomas and lymphoma, that aren't likely related to infection and cannot be prevented with IG treatment. There are also autoimmune diseases (ADs) associated with CVID, ranging from low blood cell counts and arthritis to lupus. Additionally, 20 percent of CVID patients also have serious GI problems, ranging from irritable bowel disease, Crohn's disease, ulcerative colitis, malabsorption, giardia, etc. A final serious complication occurs with the spleen and lymph nodes. A third of CVID patients will develop problems with the spleen and lymph nodes, but these problems are largely benign. Approximately 8 percent of the time, these problems can result in lymphoma. Unfortunately, we don't have any way to prevent any of these conditions; we can only recognize them early and treat the symptoms as they arise.

In short, infectious problems can be treated with IG; other conditions can't. Therefore, it's important for CVID patients to have regular follow-up with their physician to identify any other conditions that may arise and treat them early.

Can CVID Patients Have an Autoimmune Disease but Test Negative for It?

One of the challenges in dealing with CVID and its associated complications is that patients don't make antibodies well. This includes autoantibodies, and because ADs are typically diagnosed based on autoantibody assays, CVID patients may have all the signs and symptoms of an AD, but their autoantibody lab tests may be normal. In addition, IG therapy may interfere with the lab tests that look for autoimmunity, which can make them unreliable for CVID patients. Therefore, these patients need to find a rheumatologist who will conduct a comprehensive physical examination for an AD and recognize that the lab tests won't necessarily test positive for it.

Are CVID Patients Treated with Medications Other Than Immune Globulin?

IG is the primary treatment for CVID. It is the only proven treatment for preventing infectious complications. However, there are a lot of other medications that might be used to treat complications of CVID. These include antibiotics (although chronic prophylactic antibiotics are not commonly prescribed), immunosuppressant drugs to treat ADs, GI problems or lung problems, and chemotherapy to treat lymphoma, which rarely occurs. ■