The Changing Face of Primary Immunodeficiency: Improving Diagnosis and Access to Treatment for All Patients

CMEO Podcast Transcript

Mark Ballow, MD:

Hello, and welcome. On behalf of CME Outfitters, I would like to welcome and thank you for joining us for the CMEO Snack, *The Changing Face of Primary Immunodeficiency: Improving Diagnosis and Access to Treatment for All Patients*. This program is supported by educational grants from Grifols and Takeda Pharmaceuticals. This activity may include discussions of products and devices that are not currently labeled for use by the U.S. Food and Drug Administration (FDA). The faculty have been informed of the responsibility to disclose to the audience if they will be discussing off-label or investigational uses, that is any uses not approved by the FDA of products or devices. Let me start by introducing myself. I am Mark Ballow, part of the Division of Allergy and Immunology, Department of Pediatrics at the University of South Florida Morsani College of Medicine at Johns Hopkins All Children's Hospital in St. Petersburg, Florida. Dr. Azar, do you want to introduce yourself?

Antoine Azar, MD:

Yes. Hi, Dr. Ballow, and thank you for the introduction. Glad to be with you here. I'm Antoine Azar, I'm a faculty physician in Allergy and Immunology at the Johns Hopkins University in Baltimore, Maryland.

Mark Ballow, MD:

Thank you. To frame the discussion today, let me review our first learning objective in which we're going to assess the various presentations of primary immunodeficiency (PI), including atypical presentations that we're seeing more often, and to improve PI recognition and diagnosis. This is a complex slide that shows an overview of PI, some of the important components. So, for example, there has now been described over 559 genetically inherited disorders that make up the monogenetic inborn errors of immunity. We know that these patients present with various clinical presentations, and depending on the type of underlying immunodeficiency, they may have increased susceptibility to certain bacteria, virus, or fungal infections. But many of our patients, as we'll go into a little bit later, also have non-infectious complications including autoimmune, autoinflammatory, allergic, or lymphoproliferative manifestations.

So, this becomes a diagnostic challenge. In fact, even though 559 inherited genetic disorders have been described, every year there are more genetic mutations that have been defined as inborn errors of immunity. The estimated prevalence of primary immunodeficiency is about 1 in 1,200 live births. One of the issues that we'll talk about later is the length of time to make a diagnosis between the onset of symptoms and the actual diagnosis of what's going on with a patient. Now, as opposed to primary immunodeficiencies, we are seeing more patients actually in the adult group with secondary immunodeficiencies. Dr. Azar, do you want to comment on that, since you're in internal medicine while I'm in pediatrics, and you have a fair amount of expertise with secondary immunodeficiencies?

Antoine Azar, MD:

Yes, we are certainly seeing, as you mentioned, Dr. Ballow, more and more patients with secondary immunodeficiency, which can be caused by a variety of reasons. And these are in fact much more common than

primary immunodeficiency disorders, and mostly, secondary immunodeficiency is a weakened immune system caused by a secondary cause. This is often due to medications, a lot of biologics that are currently being used to treat a variety of inflammatory disorders, and it can be caused by malignancy, for example, chronic leukemia, or lymphoma. In addition, there are a lot of new medications over the past few years that have been introduced, such as chimeric antigen receptor (CAR) T-cell therapy and bispecific antibody therapies. All of these have caused a significant and profound secondary immunodeficiency and the rise in the prevalence of secondary immunodeficiency as well.

Mark Ballow, MD:

Thank you. As previously mentioned, there are now over 559 distinct genetic mutations that lead to inborn errors of immunity. On this slide, the left-hand portion of the slide is kind of a cumulative discovery of these genetic monogenetic abnormalities leading to immunodeficiency and autoinflammatory disorders. You can see that it starts in 1980, but it actually goes back prior to that in the 1970s, discovering the first genetic causes for some of the primary immunodeficiencies, and this has increased dramatically over the past 10 years with advances in molecular biology. Every 2 years, the International Union of Immunological Societies (IUIS) meet and they discuss these new genetic discoveries, these new genetics that are associated with a primary immunodeficiency or an autoinflammatory disorder, and they get published in one of the journals.

On the right-hand side, being a pediatrician, of course we see many children in the early-age group, say, age 0 to 5, who present with primary immunodeficiency, and many of these obviously are born with their immunodeficiency. However, it's become obvious that the majority of patients with primary immunodeficiency are actually adolescents and adults. These are the patients who are much more difficult to diagnose because they may present initially not with increased infections, as one usually thinks of with primary immunodeficiency, but some type of dysimmune regulation, as we'll talk about shortly. On this slide is a survey by the Immune Deficiency Foundation (IDF) in 2023 of the types of immunodeficiencies associated with their cohort of patients, and it's pretty similar with the registries from both the United States and Europe, that over 50%, somewhere around 60% to 65%, as a matter of fact, of patients with primary immunodeficiency present has antibody immune deficiencies.

There, of course, are patients who present with combined T- and B-cell immune deficiencies, patients who present with innate immunodeficiency affecting leukocytes or neutrophils, patients who present with complement deficiencies, and patients who present with autoinflammatory disorders. Dr. Azar, I don't know if you want to add anything to your experience in the breadth of the type of patients you see with primary immunodeficiency?

Antoine Azar, MD:

Yes, Dr. Ballow, I agree that the antibody deficiency disorders are, by far, the most common, and this is particularly true in the adult population and, really, any part of the immune system can be affected. I also reiterate that we think about the main presentation of primary immunodeficiency as recurrent infections, severe infections, unusual infections that have an onset in early childhood; however, I will reiterate what you mentioned, that often the presentation can be with autoimmune disease, and that may manifest first before infections, for example, autoimmune cytopenias, idiopathic thrombocytopenic purpura, or immune

thrombocytopenia (ITP). Patients can present with autoinflammatory disease, and children, also severe eczema, severe food allergies, and lymphoproliferative disease or malignancy. It's important to know that these can be the presenting symptoms, and that will make us think when a patient is presenting with such disorders that it should alert us to think about the possibility of the primary immunodeficiency disorder as well.

Mark Ballow, MD:

Thank you. I think we mentioned this before, that particularly adolescents and young adults present with non-infectious presentations of primary immunodeficiency, as you mentioned, autoimmunity, often, different types of cytopenia, and that's where genetic studies are really important in these patients who present with immune dysregulation. The literature suggests that somewhere between 30% and 35% of genetic testing will identify specific monogenetic causes of that primary immunodeficiency. Obviously, this will vary depending on the phenotype presentation of the patient. But this has really been helpful, and obviously as we discover more genetic abnormalities that relate to an underlying immunodeficiency, this will improve dramatically.

This next slide is actually an interesting article from the European Society for Immunodeficiencies (ESID), in which they have a registry of over 16,000 patients. You can see from the diagram on the left-hand part of the slide that even though the most common presentation is infections, as you would expect from patients with an immunodeficiency, 18% of these patients actually presented initially with some type of autoimmune or immune dysregulation. Therefore, these are the patients who may present to our colleagues, the hematologist, the gastroenterologist, the rheumatologist, et cetera, and unfortunately there's often a delay in the diagnosis and presentation to the clinical immunologist with these patients. Now, we'd like to switch a little bit and introduce Ilana. Ilana is a 35-year-old patient advocate and author of *Surviving and Thriving with an Invisible Chronic Illness*. She spent the first 19 years of her life constantly battling with various illnesses, reaffirming the idea that early and definitive diagnosis of PI is critical for improving outcome and health-related quality of life. Let's jump right into a quick video clip of Ilana describing her initial journey with PI.

Ilana Jacqueline:

I'm Ilana Jacqueline, and I have what we in the patient community call lucky girl syndrome, as in due to my social determinants of health, I was lucky enough to get diagnosed, far sooner than many patients with PI, which might be a bit confusing, to point out. As you can see on this slide, I was not diagnosed with my disease until I was 19 years old, and in the general health sphere, this would seem extremely unlucky. However, beyond being a patient, I have also worked as a patient advocate for the last decade in the rare disease community. And if there's one thing that I've come to realize, it's that most patients do not have the resources, the finances, the connections, or the simple physical ability to endure what I had to endure to get this diagnosis. So, my story starts like this: I was born sick, constantly dealing with infections, mostly lung, bronchitis, mucosal, sinus, strep, and viruses, and they would not improve, not without aggressive intervention, and oftentimes without hospitalizations.

I was fortunate in that I had a mother who was a great advocate for me but who endured many instances of medical gaslighting where she was told she was being overprotective and paranoid, and that some children were just sickly children. Before the age of 18, with great insurance and access to a university hospital just 1 hour from my home in South Florida, I would see pediatricians, pulmonologists, allergists, and have many hospitalists

who would look over my care and assess me as a patient, but none that would make the diagnosis, and I slipped through the cracks.

Mark Ballow, MD:

I have also seen patients with this long period before a diagnosis is made, and one patient comes to mind. This is a 40-year-old woman who actually had ITP and was treated with rituximab. She did fine. Her ITP did actually great and it went into remission. But some years later, in fact 7 years later, she started to have infections. Her hematologist did an initial immune workup, and she had almost no B cells. So, he referred the patient to us. And, in fact, indeed, she had an underlying primary immunodeficiency disease. Just remember this, she had ITP, she had a couple of good years after her ITP when she went to remission, then started to have recurrent infections like 7 years later, until we finally made a diagnosis of primary immunodeficiency disease. And, in fact, she did have a monogenic defect of CTLA-4 haploinsufficiency. Dr. Azar, I'm sure you've had similar patients who have had a long period between onset of symptoms and actual diagnosis.

Antoine Azar, MD:

It is sometimes unfortunate that it takes such a long time, like with Ilana going through years and years of illnesses and infections that were not explained, until finally, years later, a testing was done and immunodeficiency diagnosis was made. There's really the significant delay, and it's important to try to shorten that delay, recognize, and screen for immunodeficiency earlier when we suspect it. So, how do we suspect it? There's a variety of resources that are available for all clinicians, whether immunologists, primary care physicians, or any specialists, that will help alert them to the early warning signs and symptoms of an immunodeficiency. For example, there are the 10 warning signs of the Jeffrey Modell Foundation that have been around for a while, have been available and published for a while, and these include, for example, recurrent ear infections, sinus infections, serious infections, pneumonia, family history of immunodeficiency, a variety of warning signs that should alert us to the need to screen these patients.

In pediatrics, failure to thrive is an important indicator as well that should alert us to think about immunodeficiency. More recently, there have been similar warning signs, also by the Jeffrey Modell Foundation, for adults, and these are in many ways similar to what you see in the pediatric population as well and consist of a variety of frequent or unusual infections. And another reminder for us, whether we are talking about the pediatric age group or the adult age group, these immunodeficiencies, worse, can occur at any age. It's really important to have a low index of suspicion to help people like Ilana get diagnosed sooner. Well, this brings us to our first audience response question, which I'm going to read. Which of the following reflects an atypical presentation of PI? A, a child with severe combined immunodeficiency at birth, presenting with failure to thrive; B, a child with severe eczema and multiple food allergies who develops recurrent skin infections; C, an adult presenting with recurrent pneumonia and sinus infections since childhood, requiring frequent hospitalizations; D, a child experiencing recurrent viral upper respiratory infections while attending daycare; and E, I don't know. Dr. Ballow, would you like to discuss the correct answer and why?

Mark Ballow, MD:

Well, we're talking about an atypical presentation, and obviously for patients with severe combined immunodeficiency, it's a typical presentation of presenting a failure to thrive soon after birth and as well as recurrent infections. That's not really atypical. Let me go down to C, which is an adult presenting with recurrent infections and sinus infections requiring frequent hospitalizations. Again, that may be a patient with an underlying immunodeficiency, clearly, and it may suggest an antibody immunodeficiency. Again, not really an atypical presentation. Of course a child with recurrent viral upper respiratory tract infections in daycare is a frequent presentation scenario that we see almost every day of patients referred to us by pediatricians to roll out immunodeficiency, and in fact they don't. They just have increased exposure to viruses in daycare. That brings us to B, which is a child with severe eczema, food allergies, who are developing infections, particularly, recurrent skin infections. This is really an unusual presentation. If I had to put my thinking hat on, this is the type of patient we would get early genetic screening for because it fits very nicely into a monogenetic defect of a primary immunodeficiency called DOCK8 deficiency, which is an autosomal recessive immunodeficiency that commonly presents in the pediatric age group. So in this case, B is the correct answer.

Antoine Azar, MD:

Thank you, Dr. Ballow, for the thorough explanation of these presentations and reiterating the atypical presentation that we have to think about, which leads us also to think about, like I mentioned earlier, other specialists being involved in this journey of diagnosis, such as pulmonologists; ear, nose, and throat (ENT) physicians; rheumatologists; hematologists; and oncologists. They often see these patients who are presenting to them, and this collaboration between the specialists, the pediatrician, the internist is really important to improve the diagnostics and early initiation of therapy. We can think about several stages of testing for PI. Of course, there's a newborn screen which screens for every newborn for a severe combined immunodeficiency (SCID), there's recognition of the early symptoms in the primary care clinic based on the patient's presentation and the family history, and then there's a specialized non-immunological secondary care that occurs for these patients by a variety of specialists and specialized referral units or immunology centers or immunologists where the diagnostics, the therapeutics are done and initiated. So, it's really a combination effort across different specialties in order for us to really diagnose these disorders earlier.

Mark Ballow, MD:

Thank you. Let's talk about the laboratory evaluation. I stress this all the time with my fellows, that the history and physical exam are really important in constructing a laboratory evaluation. For example, if the patient is presenting with recurrent sinopulmonary tract infection, obviously you want to target the humeral or antibody immune system. And the initial evaluation is pretty straightforward, quantitative serum immunoglobulins, complete blood count (CBC) with differential, and then looking at functional antibodies. These functional antibodies are most easily measured by looking at vaccine responses. In adults, you can also look at isohemagglutinins, which is anti-ABO (blood group), red blood cell antigens. Initially going further than that, at least by health care providers or primary care providers, that's probably enough.

Then if something comes up, they should actually refer the patient to a clinical immunologist expert because the tests that we look at subsequently include cellular immune function tests, flow cytometry. Looking at tumor

mutational burden (TMB) cell phenotypes is a little bit more sophisticated and is also an expensive laboratory test, and it requires a lot of interpretation when you get the results back as well. If the patient doesn't present with what we think is a humoral immune defect, that's where the history of physical exam comes in. So, for example, if the patient presents mainly with skin infections, then we may want to gear our workup more towards a neutrophil abnormality. There are approaches there as well that start with a CBC, and differential is a good place to start, but, again, a more sophisticated workup requires probably a clinical immunologist. Let's bring up our second video clip of Ilana.

Ilana Jacqueline:

I started to see every specialist I could get into, every single one, and we ran so many tests and I had so many doctors who just couldn't wrap their heads around what it was that I was experiencing. And I started to feel like I was crazy. I got to a point where I did not want to keep seeking answers, but I was also too sick to live like this. So, one day, my stepfather went to synagogue and asked his congregation to pray for me out loud. And after he did that, one of the men in his temple introduced himself as an infectious disease doctor, lucky, and he told him to bring me to his office and that he would try to figure me out. My parents dragged me to that appointment, I mean dragged. I was so scared to have another doctor gaslight me and make me feel silly and paranoid for being so sick.

But he didn't. He took my history for over an hour, he looked through all of the blood tests and scans that had already been performed, he did his own exam, and he said, "I think I know what's wrong with you." I didn't want to get my hopes up because I'd heard that before, but this time just seemed different. Not long after that, we went home and we waited for results, and he called and he said, "Hey, you have this disease, you have something called hypogammaglobulinemia, and your levels are critically low, and you need to go to the hospital right now and start intravenous immunoglobulin (IVIG)."

Mark Ballow, MD:

Ilana had basically lost all hope and exhausted any potential of receiving any answers from numerous specialists as to why she was always sick. She truly nailed down the point that it can be an excruciating long road to receiving an actual diagnosis, which is evident here in this slide describing the extensive path to diagnosis that so many adolescents with PI face. These experiences further underscore the importance of an early and an accurate diagnosis of PI, if it is suspected, so that we can truly improve outcomes for these individuals.

Antoine Azar, MD:

Dr. Ballow, I want to reiterate that common variable immunodeficiency (CVID), some patients have what we call an infection-only phenotype where the main presentation is infections, and some patients present or develop non-infectious complications. And this shows you the prognosis in patients who develop these non-infectious complications, whether it is autoimmune disease, liver disease, lymphoma, lung disease; all of these place the patient at significantly increased risk for morbidity and mortality. In fact, the risk of death is 11 times higher in patients who develop these non-infectious complications. That's another reason for us to sum up this part of the Snack, which is to reiterate that recognizing early, recognizing the presentations by a variety of specialists, and making a diagnosis early are really important for long-term favorable outcomes.

Mark Ballow, MD:

Yes, and let me just add to that because this is where genetic testing is so critically important, because if we can identify a monogenetic cause of the underlying immunodeficiency disorder, there may be targeted precision approaches and treatment for these patients, which will change their course of existence and of survival. This is a very exciting area of our discipline, not only defining these new genetic causes but actually applying new either biologics or small molecules as precision therapy to try to enhance their well-being.

Antoine Azar, MD:

Yes, absolutely. I absolutely agree, Dr. Ballow. Speaking of therapy, we'll switch gears and jump into the second section of this talk, where we'll talk about the different types of immunoglobulin replacement therapies that are currently available for the treatment of primary immunodeficiency. When you look at immunoglobulin replacement therapy, I'll go over some names and how we refer to them, we refer to immunoglobulin replacement therapy (IgRT). We have the intravenous immunoglobulin, which is IVIG, the subcutaneous immunoglobulin (SubQ IG or SCIg), and the facilitated subcutaneous immunoglobulin (fSCIg). This is a variety of terminologies for different immunoglobulin products. I'll start talking about IVIG first and pass it on to Dr. Ballow to talk about SubQ IG as well.

IVIG has been around for a very long time and is very effective at reducing serious bacterial infections. Most patients tolerate IVIG very well. Most of the adverse effects tend to be more mild and tend to be more systemic; these include headaches, fevers, myalgia, chills, nausea. Often, adjustments to the infusion, like the infusion speed or pre-medications, can help significantly with these adverse effects. In general, IVIG is started at a dose of 400 to 600 milligrams per kilograms that are provided every 3 to 4 weeks intravenously, and then the dose is adjusted down the road based on the patient's clinical course and the patient's serum immunoglobulin levels to make sure that they're getting adequate replacement. Dr. Ballow, would you like to talk about the subcutaneous version?

Mark Ballow, MD:

Yes. With subcutaneous, we talk about two different types of subcutaneous immunoglobulin replacement therapy: one is conventional and the other is facilitated, which I'll talk about in a few minutes. Conventional subcutaneous immunoglobulin therapy is very straightforward. We put small amounts of immunoglobulin, purified immunoglobin (IgG), underneath the skin in a subcutaneous space. We try to shoot for every other week in order to get an adequate replacement therapy of the patient's hypogammaglobulinemia. But the nice thing about subcutaneous immunoglobulin therapy is the flexibility. You can do it daily, you can do it every 3 days, you can do it weekly, you can do it bi-weekly, and it has many less systemic side effects in contrast to IVIG, although some patients do have some obviously local reactions—mild reactions of either redness, some itching, some swelling—that usually resolves in 3 or 4 days, and this tends to go down the longer the patient is on subcutaneous immunoglobulin therapy.

For facilitated subcutaneous immunoglobulin therapy, that is designed actually to administer the dose of immunoglobulin that's calculated monthly, actually, every 3 to 4 weeks, and in which you use recombinant hyaluronidase to open up the spaces in the subcutaneous space in order to get larger amounts of immunoglobulin in the subcutaneous space at one time. So, for example, with conventional, usually you can

only get anywhere between 25 and 30 mL maybe, depending on the product, 60 mL at one particular site. With facilitated subcutaneous immunoglobulin therapy, the way it's designed with the hyaluronidase opening up the subcutaneous space, you can actually get 300 mL at one subcutaneous site. I usually don't do that. I usually divide it up into two sites on a monthly dose, which makes it a little bit easier for the patient.

Antoine Azar, MD:

Yes. There are several advantages and disadvantages of intravenous and subcutaneous, which is really good because it offers our patients a variety of options. As I tell my patients, "We're going to be able to give you immunoglobulin one way or the other, whether it's intravenous, SubQ, or facilitated SubQ, depending on your situation and profile." I would summarize and highlight some of the advantages and disadvantages of IVIG. IVIG is given less frequently, typically every 4 weeks, sometimes every 3 weeks. You can give a large volume intravenously, and there's a rapid increase in the serum IgG level. Some of the disadvantages is that patients often have to travel to an infusion center. Home infusions can occur but require also some coordination. It requires a venous access and medical supervision to be done on a regular basis, and it has a higher systemic side effect profile compared to SubQ IG.

The SubQ on the other hand is flexible. It can be done in the home setting by the patients themselves once they're trained, it does not require venous access, and it provides more steady-state serum IgG level, but it requires a more frequent dosing. And like you mentioned, Dr. Ballow, several infusion sites are often required and require some dexterity and ability of the patient to self-infuse. So, there are pluses and minuses, and these are things that we discuss with every patient every time to make sure we are choosing the best product that the patient will be able to receive because they're going to be on this therapy for a lifetime. Dr. Ballow, would you like to comment also on the wear-off effect that we see with IVIG therapy and how that compares with SubQ IG?

Mark Ballow, MD:

Yes. The Immunity Deficiency Foundation, in a telephone survey, found that patients on IVIG, intravenous immunoglobulin, about 35% to 40% of patients had this phenomenon called wear-off, and that is right before the next infusion, like at week 3 if they're on every 4 weeks. They had kind of lethargy, fatigue, maybe they had symptoms of runny nose, cough, and in fact, they could even have infection during that period of time, that wear-off period. In the old days, what we used to do is we used to chase that. We used to decrease the infusion from every 4 weeks to every 3 weeks, and that would work temporarily where they would not have this wear-off effect, and then they would have this wear-off effect again.

I tell patients that if they have this, if they have these symptoms in the week before their next infusion, that that is a good reason to switch to SubQ IgG. It's probably related to the very high protein peaks of the intravenous IgG that we're giving them and the decline thereafter. And with SubQ IgG, or the facilitated subcutaneous, you get a much more even trough, or what we call steady-state serum IgG level, which I think is important not only in reducing the systemic side effects but removing this issue of wear-off effect.

Antoine Azar, MD:

This brings us to our second audience response question, and I'll go ahead and read it. Which of the following strategies is most effective for reducing IG-associated adverse reactions during an IVIG infusion? A, switch to another immunoglobulin product; B, slow the infusion rate; C, add a high-dose corticosteroid; D, start antibiotics; and E, I don't know. Dr. Ballow, would you like to tackle it?

Mark Ballow, MD:

Well, certainly, starting antibiotics is not appropriate, but one could argue that A, B, or C could be fine. I don't agree with C, starting corticosteroids, although in the old days, when we used lyophilized IVIG, where we did not have subcutaneous immunoglobulin, we had to use steroids to dampen the side effects. But luckily, we don't have to do that now, one, because we have liquid IVIG products, and two, because we have alternatives, which are subcutaneous or facilitated subcutaneous products. You could switch to another immunoglobulin product. We see patients who have adverse reactions to one product and maybe not another. But if it's actually a reaction during an infusion, the best thing to do is just obviously slow the infusion rate, and that's to get an immediate resolution of the adverse effects that are happening at that period of time. So, B is the correct answer.

Antoine Azar, MD:

Yes. Thank you. And yes, I think slowing the infusion rate would be my first step, and often it does result in improvement for resolution of the adverse effects. I agree with you that in the era of having a variety of options, including subcutaneous options, I would really avoid the reaching stage where I'm adding a high-dose steroid before every infusion. So, this is the point where I'll just switch to subcutaneous infusion instead and avoid doing that.

Mark Ballow, MD:

Yes. So, we have more than just immunoglobulin replacement therapy in patients with primary immunodeficiency disease. The first bone marrow transplantation actually dates back to 1966, in which there was a human leukocyte antigen (HLA) identical sibling used in a patient with severe combined immunodeficiency disease. We've come a long way since the 1960s in using stem cell bone marrow transplantation and the use of adjunct therapy in order to make bone marrow transplantation successful. Gene therapy is something that's on the horizon. There are several active groups in the United States who are actually doing gene therapy for a variety of monogenetic inborn errors of immunity. And I would say that we are going to see advances in this area quite quickly now since we have solved some of the initial issues that were initially present with gene therapy.

For patients with adenosine deaminase deficiency, which is another type of patient who presents a severe combined immunodeficiency, we have enzyme replacement therapy as a possibility. There are many approaches to either treatment or even correcting these patients with primary immunodeficiency, particularly if we can identify a monogenetic cause. Do you want to discuss the secondary immunodeficiencies, because this is an area of your expertise, Dr. Azar?

Antoine Azar, MD:

Yes. For secondary immunodeficiencies, of course there are very broad categories of secondary immunodeficiencies. One of the most important ones is secondary hypogammaglobulinemia, that is also caused by either malignancy or, very often, the therapeutics that we are using that can cause really a very profound reduction in serum immunoglobulin levels, and this can increase the infection risk and really lead to poorer outcome in a variety of patients. Immunoglobulin replacement therapy is primarily indicated for primary immunodeficiency disorders. It is often used also for patients who develop a significant secondary hypogammaglobulinemia along with frequent infections.

Mark Ballow, MD:

The IDF on their website has a very nice table in which they show the different immunoglobulin replacement therapy types, IVIG, subcutaneous, and facilitated. And it's a nice table to use to present to patients because part of the process is educating patients. It's a joint decision between the patient and the physician or health care provider of what are the benefits, what are the positives, what are the negative aspects of each of the different types of immunoglobulin replacement therapy. This table nicely summarizes all of the quantification, qualifications of the different types of immunoglobulin replacement therapy. Dr. Azar, do you want to talk about switching between IV and SubQ, or vice versa?

Antoine Azar, MD:

Yes. Like I mentioned, Dr. Ballow, making the correct choice, and the shared decision-making, starting patients on the appropriate therapy are really key and that's an important discussion every time we are starting therapy. However, there are situations where patients end up switching also between IVIG and SubQ IG, which is okay, because at the end of the day these are very similar products that are just delivered in a different mechanism, intravenously, subcutaneously, or more frequently or less frequently. So, we do see often patients who end up switching from one therapy to the other. Often, the switch from IV to SubQ occurs because adverse effects with IVIG do not resolve some of the measures we mentioned earlier, that wear-off effect you mentioned earlier the fourth week following the infusion, the difficulties with venous access for patients, especially those who have been receiving IVIG for a very long time, and those patients who really ask for more flexibility, ability to self-infuse, take their immunoglobulin product with them as they're traveling or going on vacation.

On the flip side, there are some patients who switch from SubQ to IVIG as well. This can be due to frequent local side effects with the subcutaneous infusions, patients who prefer less frequent infusions or really prefer to go to an infusion center and have a health care provider provide the infusions, and sometimes patients need to be supervised during the infusion side. All of this reiterates the shared decision-making, regular follow-up, and discussion of all the options that we can provide our patients, again, because this is something they're going to be on for a very long time.

Mark Ballow, MD:

Yes. Let me just emphasize this. There was a very nice paper published by the Italian group in which they had a cohort of patients for whom they did extensive education during the first 6 months of their initiation of immunoglobulin replacement therapy. During this first 6 months, they had a chance to switch to different

modalities, either IVIG to SubQ, or SubQ back to IVIG. They found that this educational process, this shared decision-making, this initial period was so important when naive patients were started on immunoglobulin therapy, that it really resulted in the best quality of life and compliance. That's key, compliance, particularly with subcutaneous immunoglobulin therapy, which is done at home. So, yes, this patient caregiver experience, shared decision-making, is a key consideration definitely.

Well, this brings us to our third and final learning objective, which we kind of touched on a little bit already to stress the importance of implementing multidisciplinary team–based strategies and shared decision-making in optimizing quality of life and outcomes for patients with PI. Dr. Azar, this is kind of a Venn diagram that we've seen frequently, and you touched on this previously, that many of our patients are so complex that it takes other disciplines in order to satisfactorily take care of the patients, whether it's a rheumatologist, a hematologist, or a gastroenterologist. Perhaps you can amplify this as well.

Antoine Azar, MD:

Yes, absolutely. Complex patients with the complex disease, especially those patients who have developed these other organ complications, whether lung disease, which is one of the most common complications in patients with CVID, or gastrointestinal (GI) disease, or other autoimmune disease. That's why a multidisciplinary approach is often needed for immunodeficiency patients. And of course there's a significant role for the patient's primary care, the pediatrician, the internist, as well as a variety of other specialists who often need to really get together to provide optimal care.

Mark Ballow, MD:

Yes. And so we kind of just touched on shared decision-making and this educational process. I like to think of it as parts of a puzzle. If you look at all of the aspects of starting someone on, let's just say immunoglobulin replacement therapy, you have to decide on is it IVIG, is it SubQ, is it facilitated? Where is it going to occur? Is it going to occur at home or is it going to occur in an office space or an infusion center? If it's SubQ, where are you going to put it in the SubQ? Where in the body? The issues about finances: is it going to be covered by their insurance? Are they going to have a co-pay? So, there are a lot of pieces to the puzzle, and that all amounts to optimizing the best for the patient that will fit into their lifestyle as well as with their financial resources as well. I don't know if you have anything to add to that, Dr. Azar?

Antoine Azar, MD:

I totally agree that a number of things are to be taken into consideration, the patient is at the center and the patient's own preferences, but of course, what's the scientific evidence? What's the best therapy? What are the social drivers of health? It’s a combination of all of these. And then it really brings an important discussion with the patient, again, because this is a chronic illness and would have to be managed for a very long time.

Mark Ballow, MD:

Yes. The other factor that we need to discuss is disparities and delivery of healthcare and where the patients live, whether they live, for example, in an urban area or out in a rural area where they may not have the expertise of physicians like a clinical immunologist. Luckily, we have ways to overcome some of this. This is, for

example, where subcutaneous route is an advantage, because if they live out rurally, they may not have an infusion center that's capable of giving IVIG, and that's where SubQ route comes in handy. We also have other mechanisms for reaching out to the patients in the rural areas with telehealth, which we actually employ quite frequently since patients live sometimes 2 hours away from our clinic in St. Petersburg, Florida. So, there are still some barriers that need to be overcome, and most of these relate to insurance. I'm sure you've also seen some issues, those so-called barriers to providing appropriate care with patients in your patient population as well.

Antoine Azar, MD:

Absolutely. And you highlighted some really important factors. Of course, the insurance, the location, where the patients live, the literacy level, all of these can be sometimes significant barriers and they can be quite challenging.

Mark Ballow, MD:

That's part of this shared decision-making. There are some tools that you can use in that initial encounter with patients, as I said, that educational process of asking patients what they would like to see with their treatment. In this case, we're talking about immunoglobulin replacement therapy, not bone marrow transplantation or gene therapy, and that will help with the shared decision-making and help the physician to know what the needs are of our patients. Let me give you an example of that. When I was in private practice in Sarasota, many of our patients were elderly and they did not want to do subcutaneous immunoglobulin because they thought it was too complex, the tubing, and they had difficulty withdrawing the very thick IgG from the vial. They just wanted to go to Sarasota Memorial Hospital, put out their arm, and get IVIG. For them, it was partly a social event, too, because with other patients were the nursing staff. That's where we have to sit down and ask what's best for the patient and what best fits with their lifestyle.

I want to put another plug in here, and that is not only shared decision-making, but afterwards determining what the quality of life is. There are both generic as well as very specific quality-of-life instruments to evaluate how patients are doing after they're on immunoglobulin replacement therapy. One such validated quality-of-life instrument is the PADQOL-16, or primary antibody deficiency quality of life, which is made up of 16 questions and is very easy to do. It's designed for adults with antibody deficiency. You could really use this survey instrument as a way of determining how patients are doing and what problems they're encountering during their immunoglobulin replacement therapy. I don't know if you have anything to add to that, Dr. Azar?

Antoine Azar, MD:

Yes, I'll add this one tool that consists of a series of questions, which is convenient. It can be provided to the patient often after seeing them in clinic. You give them a questionnaire to fill with the number of questions, asking them about their preferences in terms of, Do they like to use one needle every time? How often they like to get infusions? How long? Is it once a week, once a month? Patients can just read through this for a few minutes, answer the questions, and it will give you an output of what are really the highest priorities for patients themselves. So, you can look at that and compare it to what are your priorities as a physician in terms of how you want to treat, what kind of immunoglobulin therapy. It can be really helpful and a nice set of questions that allows patients to think about what their priorities are, because, remember, this is an overload of information.

They just received a new diagnosis, for example, with CVID. They just learned that they're going to be on infusions for a very long time. So, it allows them to think about it and prioritize what's most important for them.

Mark Ballow, MD:

Great. So let's summarize our SMART goals: specific, measurable, attainable, relevant, and timely. Let me just read these. Identify key benefits of newborn screening for PI and counsel families, especially those with a parental diagnosis, on current guideline-recommended testing and follow-up. Identify typical and atypical presentations of PI in both pediatric and adult populations. Follow diagnostic pathways to confirm PI. Utilize shared decision-making approaches to treatment selection with consideration for patient/caregiver preferences, resources, access, and health literacy. Evaluate and compare current immunoglobulin replacement strategies (IVIG, conventional SubQ IG, or facilitated subcutaneous IG) for PI to guide individualized treatment choices and improve patient outcomes and quality of life.

For additional resources, you can follow the prompts CME Outfitters has provided on the following slides. To receive credit for today's activity, you'll need to complete the post-test and evaluation online. Thank you, Dr. Azar, for joining me today in this discussion on how to optimize the identification, diagnosis, and treatment of patients with primary immunodeficiency diseases.

Antoine Azar, MD:

Thank you very much, Dr. Ballow. It was a pleasure having this discussion with you.

