EXPANDING USES OF IVIG

Researchers are taking a closer look at intravenous immune globulin for its potential to stop the progression of multiple complex conditions from lupus to multiple sclerosis.

By Ilana Jacqueline

THE LIST OF conditions that intravenous immune globulin (IVIG) may potentially treat has grown exponentially since its first use to treat primary immunodeficiency disease (PI) in 1952. It is known IVIG protects against infections, modulates the immune system and reduces inflammation,[1] but it's not entirely understood why it works, not only for diseases it is approved to treat, but for many others that have failed to respond to conventional treatments.

To date, the U.S. Food and Drug Administration (FDA) has approved IVIG for only six indications: PI, idiopathic thombocytopenic purpura, multifocal motor neuropathy, B-cell chronic lymphocytic leukemia, Kawasaki disease and chronic inflammatory demyelinating polyneuropathy. And, while the most frequent prescribers of IVIG therapy have been immunologists, today, specialists in neurology, nephrology, rheumatology, dermatology and hematology have all found clinical uses for the treatment.[2] As a matter of fact, it is believed, and in some instances medical evidence has shown, that IVIG may be beneficial for treating many off-label indications, which, according to past estimates, represent 50 percent to 80 percent of total IVIG use.[3] These indications include a host of complex medical conditions, including lupus, multiple sclerosis (MS), Alzheimer's disease, dysautonomia, infertility and many others.

The IVIG Process

The manufacture of IVIG starts with plasma donations. In the United States alone, there were more than 38 million donations of plasma collected in 2016, according to the Plasma Protein Therapeutics Association (PPTA),[4] more than double the 15 million donations collected just one decade ago. Worldwide, the total annual demand for plasma by pharmaceutical companies that manufacture plasma-based therapies is about 38 million liters.[5] To meet this growing demand, most of the world's plasma is collected in about 400 plasma donation centers scattered throughout the U.S., with some of it exported to other countries.

Once collected, plasma — 92 percent water and 8 percent proteins — must go through a fractionation process that separates and collects the individual proteins, of which 64 percent are albumin, 20 percent are immune globulin, 2.5 percent are alpha-1 antitrypsin, less than 1 percent are clotting factors, and 13.5 percent are others such as antithrombin, protein C, C1 esterase inhibitor, etc.

As part of the industry's voluntary international standards program for manufacturers, known as the Quality Standards of Excellence, Assurance and Leadership (QSEAL), all plasma is held in inventory for 60 days before it can enter the manufacturing process. This allows for rigorous testing to identify, retrieve and destruct plasma donation from donors who are disqualified for various reasons such as having received a tattoo or piercing at the time of the original donation or failing to report foreign travel.[6]

Once the plasma is released from inventory, it is ready for fractionation. During the fractionation process, plasma is pooled from multiple

donations, purified and processed in a specific order to extract specific plasma proteins that have a proven health benefit. The steps and regulations required to collect donated plasma and complete the manufacturing process that ultimately results in the final therapies takes between seven and nine months. Between weeks 0 and 4, the plasma is collected. Then, between weeks 4 and 12, it is batched and transported to the fractionation plant, where it is stored from weeks 12 through 16. During this period, "it is the combination of time, temperature, pH and alcohol concentration [that] allows the extraction of the specific therapeutic proteins." At that point, the plasma is inspected and released for production. Production occurs between weeks 20 and 24. Then, between weeks 24 and 28, internal testing of the therapeutic proteins takes place, and the therapies are then released by FDA and shipped between weeks 28 and 32 to the wholesalers and end users.[6]

The IVIG Challenge

In the U.S., there are currently six companies — BPL, CSL Behring, Grifols, Kedrion, Octapharma and Shire — that manufacture and market IVIG products. These include Carimune NF, Flebogamma 5% DIF, Flebogamma 10% DIF, Gammagard Liquid, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam 5%, Octagam 10% and Privigen.

With a half-life between three to four weeks and costs exceeding $100,000 annually, IVIG for off-label (unapproved by FDA) treatment is frequently a burden for providers to present enough scientific evidence to gain approval for the cost of treatment. For those fortunate enough to be treated with IVIG off-label, results are often not instantaneous, but often take several months and several infusions before any benefits are quantified, which can cause disruption in therapy. This was the case for Cece Collins, a patient with dysautonomia who did not respond to typical treatment options. "My doctor has championed the use of IVIG for me, but the insurance process has still been a nightmare," says Collins. "We had to have mountains of documentation, including research articles. The medical director at the institution where I'm receiving treatment wants me to submit a review of my progress after every four infusions. But I won't see results until I have at least six solid months of continuous treatment. Gaps in coverage mean that I'm only on my fourth dose, and I was just rejected from the next round of infusions."

The process has been frustrating for both Collins and her physician who have had to manage her rapid decline. Unfortunately, the relevant studies have not been enough for insurance to provide continuity of care and to keep her stabilized.

IVIG Possibilities

Despite the challenges, many diseases are being studied for off-label IVIG treatment with varying results. Following is a brief review of a select few.

Lupus. An autoimmune disease that can cause damage to skin, joints and organs, lupus is a chronic condition thought to be caused by a combination of a person's hormones, environment and genetics. The Lupus Foundation of America estimates 1.5 million Americans and at least five million people worldwide suffer from a form of lupus. The disease strikes mostly women of childbearing age, and can cause symptoms of hair loss, extreme fatigue, stroke, rashes and chronic pain.[7]

FDA has approved the use of corticosteroids, antimalarial drugs, monoclonal antibody belimumab (Benlysta), Acthar injections and aspirin to treat lupus. However, because of these powerful immune-suppressing treatments, some patients experience lower antibody levels that can leave them vulnerable to infection. Treating these infections is a primary benefit of IVIG. However, IVIG can also help boost abnormally low platelet or low red blood cell counts. And, the use of IVIG can prevent a patient's white blood cells from destroying platelets, which can cause autoimmune thrombocytopenia and autoimmune hemolytic anemia.

While IVIG is not a first-line treatment for lupus since it is time-consuming and expensive, for some patients, it may be their only hope at successful disease management. A 2015 study at the University of California, Irvine, tested the efficacy of IVIG in lupus erythematosus patients that yielded positive results. In the study, 15 patients were administered 500 mg/kg of IVIG per day on consecutive days up to a total of 2 g/kg per month for three months. IVIG was then discontinued, and the subjects were monitored for an additional six months for a possible relapse. Study results showed IVIG monotherapy achieved rapid and persistent decrease in disease activity, steady improvement of patients' quality of life, low relapse rate and mild nature and short duration of relapses. In addition, since healing was maintained for months after treatment, the researchers concluded it is possible "IVIG triggered molecular events mediating the therapeutic action of IVIG that continued to unfold after the end of therapy."[8]

MS. An autoimmune disease that impacts the central nervous system, MS often impairs the spinal cord, optic nerves and brain.

This chronic, lifelong condition is progressive, meaning it can intensify over time and, in some patients, may become disabling. There is no cure for MS, but there are treatments available to help patients manage symptoms. These include corticosteroids to help reduce inflammation and disease-modifying drugs such as Betaseron, Axonex, Extavia and Plegridy.

While IVIG does not appear to slow the progression of MS, treatments may lengthen the time between relapses for those with relapsing-remitting MS. Doctors have also prescribed IVIG for patients with severe relapses that have not responded to corticosteroids.

In a 2008 meta-analysis of six clinical trials, researchers found results were consistent. While IVIG was well-tolerated, the studies could not substantiate a beneficial effect of IVIG in the studied doses, and the utility of IVIG for relapsing-remitting MS was still in question. However, the results did prove that IVIG can be considered as an alternative therapeutic option, second-line therapy or adjuvant therapy considering its positive beneficial effects.[9]

Alzheimer's disease. Though Alzheimer's disease affects an estimated 5.5 million Americans and is the sixth-leading cause of death in the United States, its cause and cure have eluded scientists since its discovery by German physician Alois Alzheimer in 1906. This fatal progressive disease, which is the most common form of dementia, destroys brain cells and causes challenges with brain function and memory loss.

IVIG therapy for Alzheimer's was thought to be very promising in its early stages. In 2009, the Alzheimer's Association reported studies of medical records of 847 people who received IVIG treatments versus those of nearly 85,000 people who did not. The studies showed people who received IVIG had a 42 percent lower risk of developing Alzheimer's disease over four years.[10]

Discouragingly, in 2013, a more formalized study called GAP (Gammaglobuin Alzheimer's Partnership) was conducted by the Alzheimer's Disease Cooperative Study (ADCS), the National Institute of Aging and Baxter International. The Phase III trial measured the progress of 390 patients in 45 centers in the United States and Canada, and after 18 months of treatment, it failed to prove efficacy in reducing cognitive decline and stabilizing existing functional abilities in patients.[11]

However, while most studies found on clinicaltrials.gov have either been completed or terminated, there are currently two active studies not currently recruiting, and another that began in December 2015 and is currently recruiting that is evaluating the effect of IVIG on brain scans for research purposes only (not for medical treatment). The study is broken down into three parts in which patients receive a single dose or placebo, multiple doses or placebo for up to 24 weeks and multiple doses or placebo for up to 72 weeks.[12]

Interestingly, a new study posted on Oct. 24, 2017, purports to determine if changes in brain amyloid levels are evident three months after infusion of 0.4 g/kg of IVIG every 14 days times five infusions. The study is currently enrolling by invitation, and it is estimated to be completed by May 2019.[13]

Dysautonomia. Presenting in several forms, including postural orthostatic tachycardia syndrome, neurocardiogenic syncope and multiple system atrophy, dysautonomia is an umbrella term used to describe the dysfunction of the autonomic nervous system. It is not a rare condition, as it is estimated to affect (in some form) more than 70 million people worldwide, according to Dysautonomia International. The condition can occur secondary to diseases like diabetes, rheumatoid arthritis, celiac disease, Parkinson's and Sjögren's syndrome.

Treatments for dysautonomia are varied. There is no cure, but patients may improve with treatment for an underlying cause of the disease. Treatment is often prescribed per symptom and can include responses to combat orthostatic hypotension. Patients are instructed to elevate the head of their bed, eat a high-sodium diet and can be prescribed drugs such as fludrocortisone and midodrine. Doctors are also exploring the use of intravenous saline therapy.

Jill Schofield, MD, a researcher on the topic of antiphospholipid syndrome and the use of IVIG in refractory autoimmune dysautonomia patients, describes these patients as having an underlying autoimmune disease, a family history of autoimmune disease and progressive worsening of dysautonomia symptoms over time, despite typical treatment. She has been prescribing a unique dose of IVIG to these patients: high-dose (1 to 2 gm/kg monthly) given slowly with aggressive hydration to reduce the risk of aseptic meningitis and thrombosis. On average, 88 percent of patients have responded to treatment within 5.7 weeks. "IVIG is highly efficacious in patients with refractory autoimmune dysautonomias," says Dr. Schofield. "And, it is a fairly safe and well-tolerated treatment in these patients when given with pre- and sometimes post-hydration." Dr. Schofield plans to release the results of her findings later this year.

Infertility. Pregnancy and autoimmune conditions can lead to a multitude of complications, including miscarriages. It is not understood why IVIG works for women with recurrent pregnancy loss, but it has been found to lower the incidence of

miscarriage. One theory is that IVIG combats natural killer cells (NK). Women who have never given birth and have high levels of NK cells in their peripheral blood have higher chances of pregnancy loss.[14]

With infertility affecting nearly 12 percent of women in the United States, it can be troubling to many who find themselves excluded from what some physicians feel is an ineffective treatment with a high price tag. The American Society for Reproductive Medicine and the American Congress of Obstetricians and Gynecologists claimed that after reviewing five studies in the 1990s, IVIG simply did not show enough evidence to suggest it could treat or prevent miscarriages. Still, some doctors vouch for its impact, and many fertility clinics still offer the treatment to couples in distress, as long as they're willing to pay for it out of pocket.[15]

Alzahra Hospital Tabriz in Iran is currently recruiting for a study on immunomodulatory effects of IVIG on pregnancy rate or patients with recurrent pregnancy loss. A similar study on unexplained primary recurrent miscarriage and the use of IVIG is being conducted in Tokyo.[16]

Other disease states. There are currently more than 90 clinical trials recruiting patients to study the use of IVIG in different conditions, including:

- Small fiber neuropathy
- Kawasaki disease
- Chronic inflammatory demyelinating polyneuropathy
- Influenza
- Toxic shock syndrome
- Autoimmune epilepsy
- Spinocerebellar ataxia
- Demyelination in diabetes mellitus
- Sickle cell disease
- Post-polio syndrome
- Graft-versus-host disease
- Antibody positive psychosis
- Idiopathic inflammatory myopathy
- Sarcoidosis
- Dermatomyositis
- Myasthenia gravis
- Alloimmune thrombocytopenia

Looking Forward

Numerous researchers believe IVIG holds promise for treating many more diseases than those currently FDA-approved. And, clinical trials are key to uncovering its potential. According to Lilly Stairs, who serves on the board of the American Autoimmune Related Diseases Association and heads patient advocacy at Clara Health, patient participation in clinical trials is what truly makes or breaks awareness, availability and coverage of a new treatment. "Patients are key stakeholders in the clinical trials process and absolutely have the power to both improve and expedite them," explains Stairs. "When sponsor companies include patients in the clinical trials design process, it exponentially improves enrollment, speed and outcomes because the trial is tailor-made to accommodate the needs of the patient."

To help in expediting the process, it is critical that physicians make patients aware of clinical trials and the power of breakthrough research. "We need to work together to demystify clinical trials, which are often stigmatized and considered a 'last resort,'" adds Stairs. "All patients deserve to know that clinical trials are a treatment option and can provide access to cutting-edge therapies. Greater awareness and participation will result in faster enrollment and ultimately a quicker pathway to approval." ❖

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