Myopathies: The Effects of IVIG Therapy

While IVIG is not an FDA-approved therapy for myopathies, many cases illustrate its effectiveness. Still, more research is needed to determine its efficacy and to ensure access.

By Ronale Tucker Rhodes, MS, and Annaben Kazemi

Autoimmune disease affects some 23 million Americans. It's an evolving area of medicine that has scientists puzzled — not just about what causes it but how to prevent it, because once it starts, autoimmune activity can be especially difficult to stop. Many autoimmune disorders, such as myopathies, are extremely rare. While there is no known prevalence of myopathies, they are believed to affect fewer than three to seven out of 100,000 persons each year.[1] There is no cure for myopathies, but they can be successfully treated and managed. In conjunction with other therapies, intravenous immune globulin (IVIG) has been shown to be an extremely effective treatment for two types of myopathies — polymyositis (PM) and dermatomyositis (DM) — which are characterized by muscle weakness due to dysfunction of muscle fiber.[2] Another disorder that has some similarities to myopathies is stiff-person syndrome (SPS), or stiff-man syndrome, for which IVIG has also shown to be an effective treatment.

PM and DM

Myositis, which includes PM and DM, falls under the idiopathic inflammatory myopathies umbrella. It is estimated that there are about 40,000 people in the U.S. who have the disease, 3,000 to 5,000 of whom are children. The disease is characterized by persistent muscle inflammation that develops slowly over weeks to months and years, causing progressive weakening of the muscles. It can range in severity from mild to debilitating, and later in the course of the disease development, muscle wasting or shortening (contracture) may develop. While there is no known cause, it is believed to be caused by an autoimmune response in which the body's immune system turns against its own muscles and damages muscle tissue.[3] Currently, investigators are studying whether the disease is triggered by an allergic reaction, exposure to substance or medicine, another disease such as cancer or rheumatic conditions, or a virus or other infectious agent.[4]

PM is a disease in which the inflammatory cells of the immune system directly attack muscle fibers. The disease affects skeletal muscles (those involved in making movement) on both sides of the body, which causes progressive muscle weakness that leads to difficulty swallowing, speaking, rising from a sitting position, climbing stairs, lifting objects or reaching overhead. Those affected may also experience arthritis, shortness of breath and heart arrhythmias. PM rarely occurs in people under age 18, with most cases occurring in those aged 30 to 60.[4,5]

DM is a disease in which the inflammatory cells attack the small blood vessels that supply blood to the muscles and skin. The disease is characterized by a patchy skin rash, with purple or red discolorations, that typically develops on the eyelids and on muscles used to extend or straighten joints such as the knuckles, elbows, knees and toes. Red rashes may also occur on the face, neck, shoulders, upper chest, back and other locations, accompanied by swelling. The rash usually precedes or occurs simultaneously with progressive muscle weakness; however, sometimes there is no obvious muscle involvement. DM occurs in both adults and children. Adults may experience weight loss or a low-grade fever, have inflamed lungs and be sensitive to light, and the disease may be accompanied by tumors of the breast, lung, female genitalia or bowel. Children more often develop calcium deposits that appear as hard bumps under the skin or in the muscle (called calcinosis), which usually occurs one to three years after disease onset but may occur many years later. However, adults may also develop calcinosis.[4,5]

The initial treatment for PM and DM is high doses of corticosteroids such as prednisone. For those who don't respond well to prednisone, immunosuppressant drugs such as azathioprine, methotrexate and mycophenylate may reduce inflammation. Another therapy option is Acthar (ACTH), which recently received FDA approval for the treatment of both DM and PM. ACTH stands for adrenocorticotropin hormone, which helps the body stimulate the production and release of cortisol, a natural steroid involved in controlling the inflammatory process. IVIG is considered when first-line therapies are ineffective or contraindicated due to other conditions.[5]

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SPS

SPS is considered an interneuron disorder. It is not a disorder of the muscle; rather, the symptoms are due to excessive motoneuron activation, which results in involuntary muscle contraction involving predominantly proximal muscles.[6] Since the disorder presents in a similar fashion to other myopathies, it is sometimes categorized under the idiopathic inflammatory myopathies umbrella. The prevalence of SPS is unknown, but it is estimated to occur in fewer than one in one million persons, and it is believed to be underdiagnosed due to a general lack of awareness of the disease in the medical community.[8]

SPS is a neurological disorder with features of an autoimmune disease characterized by fluctuating muscle rigidity in the trunk and limbs and a heightened sensitivity to stimuli such as noise, touch and emotional distress, which can set off muscle spasms. People with SPS often have abnormal posture and appear hunched over and stiffened. They can be too disabled to walk or move, and they may be afraid to leave the house because street noises such as the sound of a horn can trigger spasms and

falls. SPS is often associated with other autoimmune diseases such as diabetes, thyroiditis, vitiligo and pernicious anemia. Sixty percent of people with the disease have anti-GAD (glutamic acid decarboxylase) antibodies. The disease affects twice as many women as men, and symptoms typically begin between ages 30 and 50.[7,8]

Like PM and DM, there is no cure for SPS. However, people with SPS respond to high doses of diazepam, several anti-convulsants, gabapentin and tiagabine. In recent years, several studies have shown IVIG to be effective in reducing stiffness and lowering sensitivity to noise, touch and stress in people with SPS.[8]

IVIG for PM, DM and SPS

IVIG is not an FDA-approved therapy for PM, DM or SPS. However, numerous studies have shown it is effective in many cases as a treatment for all three. It is unknown why IVIG works in treating these autoimmune diseases, but there are many theories about how IVIG provides an immunomodulatory effect, which adjusts an individual's level of an immune response.

One theory is complement fixation. Complement is a protein that is part of the immune system, which works in combination with antibodies to help destroy antigens such as bacteria. The activation of complement is called the complement cascade. In some autoimmune diseases, complement may combine with antibodies and attack a person's own tissues. It is thought that IVIG may bind to complement and reduce the attack on self. Another theory is neutralization, which is similar to that of complement fixation. However, with this theory, IVIG is thought to bind directly to the antibody causing the attack on self rather than interfering with the complement cascade. A third theory is suppression of cytokines. Cytokines are proteins that are necessary for communication between cells. In the case of autoimmune diseases, some cytokines may become overactive. IVIG can bind directly to cytokines, or it can prevent the cytokines from completing their communication or message to other cells by blocking a receptor on the other cells. A final theory is that by receiving a large amount of donor antibodies through an IVIG infusion, that patient's immune system may decrease the production of the destructive antibodies that attack their own tissue.[9]

For PM and DM, the typical starting dose of IVIG is 2 g/kg. At this dose, the improvement in strength has shown to be impressive and becomes noticeable even as soon as 15 days after the first infusion. Repeated infusions every five to eight weeks may be necessary to maintain the

response.[10] In a meta-analysis of 14 articles on the use, effectiveness and adverse effects of IVIG in patients with PM and DM, IVIG was used successfully. The standard dose was 2 g/kg given in two to five individual daily doses, with the course of treatment lasting three to six months. In one double-blind study included in the meta-analysis, patients with refractory DM treated with IVIG combined with corticosteroid significantly improved muscle strength and decreased serum creatine kinase levels, compared with a placebo. And, in many open-label trials in the meta-analysis, the beneficial effect of IVIG in refractory, flare-up, rapidly progressive or severe PM/DM was documented. IVIG was shown to be effective in most PM/DM patients with lung involvement and esophageal involvement. In some patients, IVIG lowered the corticosteroid dose required for maintenance, demonstrating the most effective steroid-sparing effect. And adverse effects were generally tolerable.[11]

For SPS, IVIG is used in both inpatient and home settings, with the usual dose of 2 g/kg administered over two to five days. However, treatment may extend past that period.[12] In a study of 16 anti-GAD antibody-positive patients who were randomized to receive IVIG or a placebo for three months, efficacy was based on the difference in scores of the distribution of stiffness index and heightened sensitivity (spasms) from baseline to the second and third months of the infusions. The stiffness scores in the IVIG-randomized patients declined significantly from month one through month four, but rebounded when they crossed to a placebo. In contrast, the scores in the placebo-randomized group remained constant from month one through month four, but dropped significantly after crossing to IVIG. Eleven

patients who received IVIG became able to walk unassisted, stopped falling and assumed household or work duties. The duration of the benefit of IVIG varied from six weeks to 12 weeks or up to a year. And, the anti-GAD antibody titers declined after IVIG, but not after a placebo.[13]

Of course, IVIG therapy is not successful for all PM, DM and SPS patients. In these cases, other therapies can be tried. For some PM and DM patients, rituximab, cyclophosphamide and tacrolimus have shown to be successful therapies.[10] Because IVIG is not an FDA-approved therapy for DM, PM and SPS, patients may have difficulty with insurance approval for IVIG, and even those who have documented response to therapy while on IVIG therapy may have issues with ongoing reimbursement. The following cases illustrate how treatment with IVIG can be successful, and how each case is different.

Jackie's Story: PM

Jackie is a retired teacher who can remember experiencing symptoms long before she was diagnosed with PM. Simple tasks like hanging laundry on a line or carrying bags of groceries up the stairs became increasingly difficult. She couldn't sit through a movie because at the end, she wouldn't be able to get up out of her chair. For five years, she rationalized away her symptoms until one year when she was on vacation in Hawaii. During a hike, she became so short of breath, she couldn't keep up with the group, despite considering herself in relatively good shape. "I knew then that I couldn't rationalize away my symptoms," she explains.

Jackie made an appointment with her physician, who examined her, drew blood to look for numerous disease factors and ran a battery of other tests. When a blood test showed increased levels of creatine kinase (a muscle enzyme), she underwent a muscle biopsy. It was a frustrating few months while her doctor searched for answers, but the muscle biopsy confirmed her doctor's suspicions, and she was diagnosed with PM.

Her treatment began with prednisone, which caused her to gain a tremendous amount of weight, further limiting her mobility. She also was prescribed methotrexate, azathioprine, cyclosporine, mycophenolate and cyclophosphamide, all of which failed to reduce her creatine kinase levels or increase her muscle strength. She took a leave from teaching as she fought to cope with her physical symptoms, as well as with depression. Despite her treatments, she still struggled with symptoms and felt so weak that she was unable to keep up with normal daily activities. At her lowest point, she ended up in the hospital for several weeks with respiratory failure.

Because her treatments failed, her doctors suggested a course of IVIG while in the hospital, which resulted in her creatine kinase levels decreasing by half. She is now receiving IVIG therapy every four to six weeks in addition to high doses of prednisone, and she has continued to see a drop in creatine kinase levels with each dose of IVIG, usually leveling off around 1,000. "I can feel the benefits of an IVIG infusion after a few days," says Jackie. "They last about three weeks and then slowly wear off a bit in the last week before the next infusion." Jackie receives her IVIG in an outpatient clinic over two consecutive days, and each session takes about six hours. "I sit in a La-Z-Boy-type recliner, and usually I sleep, although sometimes I read a bit or listen to music," says Jackie. She takes acetaminophen and pseudoephedrine when the IVIG starts and again before bed to help minimize the headaches and body aches that she experiences afterwards. She also says eating a banana and drinking plenty of water help with the side effects of IVIG.

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Since her diagnosis, Jackie has had to give up two of her loves: teaching and piano playing in her church choir. However, she tries to stay active and to not allow her disease to cripple her. There are times of remission when she feels great and her life resembles the more active lifestyle she used to enjoy. But when the disease acts up and her medications increase, she mourns the loss of her old life. Her advice: "Take things one day and one problem at a time, and try to do things you enjoy on the good days — even if it is something really small. Missing your old life is normal as you try to redefine a good, but different life."

Daniel's Story: DM

Two years ago, at age 20, Daniel was attending a university in the San Francisco Bay area. He was working part time in a restaurant and began noticing that it was difficult to lift the trays of food. After he played a casual game of basketball, he found his legs were weak and he was exhausted beyond normal. He chalked it up to the flu. Under a lot of pressure as exams neared, he began losing even more strength in his arms and legs, and he developed a rash around his eyes and on his knuckles and elbows. At first he thought it was stress, so he went to the school health clinic. The nurse suggested mononucleosis or shingles and told him to see his regular doctor while on break.

IVIG is an experimental treatment in these diseases, and the amount and duration of therapy differs depending upon the patient.

Within three weeks of going home at break, he could no longer stand up, sit down or raise his arms above his shoulders. After seeing his family practitioner, he was referred for further testing at a major medical center. "It was frightening not knowing what was going on," says Daniel. "We were stumped … until my mom did some research and suggested it could be dermatomyositis." Daniel ended up spending several nights in the hospital, and after a skin and muscle biopsy confirmed his diagnosis, he was started on prednisone. "I was told my condition was rare, but what was even more uncommon was my age when symptoms appeared," explains Daniel. "I was told most people are either diagnosed before age 10 or after age 40."

In those first months after diagnosis, he was unable to go to school, unable to work and had to move back home, relying heavily on his parents. He became depressed and felt isolated. The prednisone caused mood swings and diarrhea, and with the weight gain, he was in danger of developing diabetes. Six months after beginning treatment with prednisone and methotrexate, Daniel still experienced severe muscle pain and fatigue. His physician recommended starting a course of IVIG, after which Daniel demonstrated both improved muscular and cutaneous involvement scores that were significantly better than his pretreatment scores. Today, Daniel receives his infusion every two months over a five-day period at a clinic near his parents' home, and he feels the positive effects up to a month after each dose. He has begun to see improvements physically; he can dress himself, walk the family dog and has even begun to enjoy spending time out with friends again.

Daniel did develop an unusual type of eczema when he first began IVIG, but switching the brand of IVIG eliminated the reaction. "It's been a long and painful road, but with the IVIG infusions, I'm starting to regain strength and be able to do things for myself again," says Daniel. "I don't know why it's working for me … but with no cure for this disease, I'm truly grateful for any improvements." Daniel has regained hope for his future, and with continued improvement, he plans to return to the university and resume his studies in engineering.

Julie's Story: SPS

Julie first noticed symptoms of SPS in elementary school, although at the time, the symptoms were vague. She had aches, pains and stiffness here and there, and she also tired easily when playing sports, but her parents assumed she just didn't want to play. After years of frustration and a visit to a neurologist, she turned to friends for help. The wife of a childhood friend worked with a local neurologist, a well-known director of neurology at local hospitals, with whom she consulted. The neurologist performed several lab tests, an electromyogram and a nerve conduction study, and after a second opinion with a rheumatologist, she was diagnosed with probable SPS. Several months later when she needed oral surgery, she was given dexamethasone to ease the swelling, which also caused her spasms to stop completely. At the prompting of her dentist, she shared her experience with her neurologist, and her diagnosis was confirmed in her mid-30s.

Julie was prescribed the standard medications for SPS patients (a high dose of diazepam, tiagabine and several anti-convulsants), which helped some, but they only slowed her SPS progression. She was forced to stop working because of her illness. She had a small daughter, volunteered in her spare time and had several hobbies, but due to her illness, these things also slipped out of her reach. Eventually, she and her husband and daughter had to move in with family due to a lack of resources after a year

on state disability.

The rarity of SPS made it important for Julie to find a doctor willing to conduct research and try new things. While her neurologist had treated SPS before, it wasn't common for him to recommend IVIG. Luckily, after conducting research and finding information about the disease, which she provided to her neurologist, Julie was prescribed IVIG twice a month, which she received for a little over two years. During that time, she was able to have another successful pregnancy, but only with close monitoring and a substantial additional amount of IVIG.

Out of everything Julie has tried, she found IVIG the most helpful. Her spasms were less frequent, she was not as rigid and her response to stressors was not nearly as exaggerated. "At first, I didn't realize how IVIG was helping," she says. "The effect was gradual. I felt a little better with the first cycle. The second cycle even better. I was able to walk a little further at the grocery store without needing a mobility scooter. I didn't worry about going out in public. I could walk into Home Depot and not have spasms knock me down when I went past the paint mixer."

Unfortunately, Julie's husband was laid off from work, and Julie lost coverage for IVIG treatments. The first two months after stopping IVIG were the worst. As she transitioned to life without IVIG, her stiffness slowly returned, and depression set in. She was wracked with daily spasms and migraines, and she had a serious fall in the shower requiring an ambulance to get her to the ER.

While she worked to regain insurance coverage, Julie's symptoms stabilized, and she has now come to terms with her new reality: not being able to get IVIG treatment. She is focused on making it through just one day at a time. Julie says helping others who are newly diagnosed keeps her motivated. Her advice to those newly diagnosed is to learn. "Learn as much as you can about the disease, the treatment options and your symptoms," she says. "Get copies of your medical records, ask for test results and keep those records in a binder that is easily accessible. More importantly, make sure you are comfortable with your physician. It is very difficult to find a neurologist who has seen stiff person syndrome before."

Living with a Myopathy

Myopathies continue to be a puzzle for scientists, but more and more is being discovered about these diseases, resulting in quicker diagnoses and improved treatments. As these cases illustrate, IVIG can cause a significant turnaround in patients' muscle function and deterioration, yet the amount and duration of therapy differ depending upon the patient. Even so, IVIG therapy is still experimental, and many more studies are needed to determine its effectiveness across the vast range of myopathic and similar disorders. And, because IVIG is not an FDA-approved therapy, access can often be a challenge. However, it is hoped that as more research is conducted to show the efficacy of IVIG treatment, more myopathy patients will be helped by this miracle drug.

RONALE TUCKER RHODES, *MS, is the editor of* IG Living *magazine, and* **ANNABEN KAZEMI** *is the magazine's patient advocate.*

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