Understanding and Treating IG Side Effects

Knowing what side effects, from mild to serious, to expect during and after immune globulin infusions can prepare patients and their caregivers for treatment changes to mitigate their impact.

By Ronale Tucker Rhodes, MS, and Kris McFalls

It makes most people chuckle:
A television commercial touts the benefits of a wondrous new drug; the patient is smiling and laughing, obviously enjoying a newfound healthy lifestyle while spending time with family and friends. Then, the announcement: “Side effects include …” Wow, the viewer thinks, no thanks!
The truth is that there is nothing funny about a drug’s side effects — especially when it comes to a life-sustaining drug like immune globulin (IG). IG patients either undergo the treatments or they forgo them, which brings on far worse consequences than those caused by side effects. Fortunately, many IG patients never experience any effects, and while those who do often think they are having a severe reaction, by definition, the reaction is typically a moderate or mild side effect. And, the good news is that in almost all cases, the effects can be controlled or even eliminated.

Side Effects Defined

Side effects, also referred to as adverse drug reactions (and considered one and the same by the Federal Drug Administration [FDA]), are those that are expected, although undesired, and are listed on the package insert for each medication. Mild or moderate side effects typically occur due to the manner in which the treatment is administered, and they can be managed. Serious side effects, on the other hand, also can be a result of the components of the drug itself and result in hospitalization or prolongation of an existing hospitalization and can be life-threatening.

The Mayo Clinic has an exhaustive list of side effects available at www.mayoclinic.com/health/drug-information/DR601705/DSECTION=side-effects. Most of these effects often can be eliminated by stopping the infusion temporarily and then restarting at a lower infusion rate, and even by switching the treatment modality.

Mild and Moderate Side Effects and Treatments

Mild and moderate side effects of intravenous IG (IVIG) are headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea and hypotension. Headaches and their more severe form, migraines, tend to be one of the more common side effects. Patients can overcome both forms of headaches by treating with antihistamines, NSAIDS and steroids both before and after an infusion. In addition, hydrating before, during and after an infusion can help alleviate some of the discomforts.

Other forms of treatment also can be tried. For example, a patient just beginning IVIG treatments experienced a mild migraine the day following her first treatment. As a further preventative, she increased hydration and took Tylenol before her next two treatments. Regardless, on her third treatment, she experienced a severe migraine lasting three days. For her next infusion, her doctor ordered a small dose of prednisone to be taken the day before the infusion, the day of the infusion and the day after the infusion. In addition, the rate of the infusion was decreased. With these treatment adjustments, the patient still experienced occasional mild headaches, but she no longer had migraines.

In another instance, a patient experienced severe migraines following IVIG infusions. The patient was given Tylenol, Benadryl and steroids, as well as a migraine prophylaxis, prior to treatment, but the headache symptoms persisted. Different formulations of IVIG 5% and 10% were then tried, but the migraines continued. So, the patient switched to subcutaneous IG (SCIG), which has eliminated the problem, and no premedications are needed.

For SCIG patients, the most common side effects include headaches and local irritation (redness, swelling, itching, blanching) at the needle site. Some reactions, especially for patients new to SCIG therapy, are expected, and most decrease with time once the body becomes accustomed to the therapy. Patients bothered by reactions, applying ice or heat to the needle sites can help decrease some of the symptoms. Using a topical anesthetic cream 30 to 60 minutes prior to starting the infusion also can be helpful. Patients with persistent symptoms should explore needle placement as a possible cause. If the needle is not properly placed, it is possible that some of the fluid is leaking into surrounding tissue rather than into the subcutaneous space. A provider experienced in SCIG therapy should be able to help patients troubleshoot and eliminate possible causes to site reactions. However, in some cases, patients are simply unable to tolerate the side effects of SCIG and need to switch back to IVIG treatment.
Serious Side Effects and Treatments

Serious side effects are rare, and most can be reduced by screening the patient for factors predisposing them to complications. Serious side effects can include acute renal failure, thrombosis, Stevens-Johnson syndrome, serum sickness, aseptic meningitis and anaphylaxis. The most severe form of IG-related headache comes from aseptic meningitis, and in fact, patients with a history of migraines appear to be more susceptible to aseptic meningitis. Symptoms, which are severe and similar to meningitis, usually begin a few hours after treatment but can occur up to two days later. They can include severe headache, photophobia, nausea, vomiting, fever and painful eye movement. Although cerebrospinal fluid (CSF) can show increased white blood cells and proteins, cultures are generally negative, thus resulting in the aseptic diagnosis. Treatment to prevent aseptic meningitis includes antihistamines, NSAIDS and steroids both before and after an infusion.

Anaphylaxis, a rapidly progressing, life-threatening allergic reaction, can be a side effect of both IVIG and SCIG. Anaphylactic reactions may require administration of corticosteroids and antihistamines, and in very severe cases, administration of epinephrine.

A case in point: One patient who experienced anaphylaxis is a child named Julia. At 7 months old, Julia was diagnosed with pertussis, despite having been vaccinated. Julia’s health deteriorated so rapidly that she was sent by ambulance to a hospital where she stayed for nearly three weeks. At age 5, she was diagnosed with a primary immune deficiency, and at age 6, IVIG treatments were started. Unfortunately, her infusion days rarely went smoothly. From the beginning, Julia was plagued with flu-like symptoms, and by age 9, she experienced severe migraines lasting three days. Doctors treated Julia with Benadryl and prednisone prior to her infusions, as well as with intravenous Benadryl during her infusions. In addition, the rate of infusions was slowed down so much that they took eight hours to complete.

When she turned 10, Julia’s doctors decided to try another brand of immune globulin, hoping to shorten infusion time and decrease side effects. Unfortunately, Julia’s side effects worsened. During the infusion, Julia felt her chest tightening and told her mother she was having trouble breathing. Overcome by an anaphylactoid reaction, Julia went into respiratory arrest, so the doctors quickly stopped the infusion and administered valium and epinephrine. At this point, Julia’s parents considered halting all treatments; it seemed their daughter’s life was threatened with or without IG. But, after weighing the risks and benefits, doctors successfully resumed therapy with the original brand of IVIG. When Julia was 13, doctors suggested subcutaneous infusions in hopes of giving Julia her life-saving IG without risking her life. This worked; Julia was soon free of the side effects that plagued her with every treatment.

Anaphylactic and anaphylactoid reactions (both referred to as anaphylaxis) are life-threatening events that
result from an overreactive and misdirected immune response to a substance that is viewed by the body as foreign (an antigen). An anaphylactic reaction is an acute fatal, or potentially fatal, hypersensitivity reaction that requires the patient to be sensitized and their reaction mediated through immunoglobulin E (IgE) antibodies. An anaphylactoid reaction doesn’t need the presence of IgE antibodies for a hypersensitivity reaction to occur. Thus, an anaphylactic reaction occurs only after the patient has been previously exposed at least once to the antigen and is sensitized. And, it can occur following a single, first-time exposure to certain agents in nonsensitized patients.4

Anaphylactic and anaphylactoid reactions to IVIG therapy are relatively rare, but they can occur in any patient at any time. Some IgA-deficient patients produce certain IgA antibodies that can increase the potential for anaphylaxis. For those patients, it is prudent to use an IVIG product that has a very low IgA content. Alternatively, many patients who experience anaphylaxis have had good success by switching their route of infusion from intravenous to subcutaneous.4

The purpose of documenting and reporting these effects is to prevent future injuries for patients. Of particular importance to the FDA are suspected adverse drug reactions for a new drug (i.e., within three years of entry to market) and suspected severe adverse drug reactions for any drug, no matter when the drug entered the market.5

The FDA also requires many manufacturers of newly licensed drugs to perform post-marketing risk management (pharmacovigilance studies) to collect information on adverse reactions in a more proactive manner. Additional information on serious adverse drug reactions and instructions for reporting an adverse drug reaction to the FDA can be obtained at www.fda.gov/Safety/MedWatch/HowToReport/default.htm.

**Benefits Outweigh Risks**

IG is one of the safest biological products available, and although severe side effects have been reported, they are rare. The good news is that almost all side effects can be safely controlled and often eliminated altogether. And, with the growing number of diseases being treated today with IG, as well as the stringent testing and reporting standards mandated by the FDA, patients who rely on this life-saving treatment can rest assured that they can be safely treated. □

**Sources**

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