Adverse Effects of Immune Globulin Therapy

As illustrated by seven patient vignettes, many different common infusion-related adverse effects can occur for a variety of reasons — all of which have treatment options.

By E Richard Stiehm, MD

HUMAN IMMUNE GLOBULIN (IG) is used for replacement therapy in primary and secondary antibody immunodeficiencies for prevention and treatment of certain infections, and as an immunomodulatory agent for autoimmune and inflammatory disorders. IG use is increasing rapidly because of improved diagnosis of immunodeficiency, new indications and expanding use in less-developed countries.

IG is available for use intravenously (IVIG), subcutaneously (SCIG) or intramuscularly (IGIM). The latter route is mostly given as a single small injection for prevention of certain infectious diseases, often as a special hyperimmune globulin (e.g., hepatitis B IG [HBIG] and tetanus immune globulin [TIG]).

IG therapy is not without risk.[1,2] Reactions can be local or systemic, immediate or delayed, and late or potential (Table 1). Local reactions at the infusion sites are particularly common with slow subcutaneous infusions. Local pain and swelling, while rarely serious, occur in up to 75 percent of all SCIG infusions, balanced by the rarity of systemic reactions (1 percent to 3 percent). By contrast, local reactions with IVIG infusions are very rare (e.g., persistent pain, bruising or swelling due to fluid extravasation), but systemic reactions are very common, occurring in 20 percent to 50 percent of patients at least once, and 5 percent to 15 percent of all infusions.

Product factors causing systemic reactions vary considerably among different manufacturers and even among lots of the same brand. These include specific antibodies to cells or tissues, trace quantities of other IGs (e.g., IgA), high molecular weight IG complexes, other serum proteins, microbial antigens, cytokines, factors that activate the patient's own immune system, and procoagulation factors not removed by fractionation (Table 2).

Infusion-related adverse risks include dose, rate, route, premedication, etc. Patient factors include age, past reactions, acute or chronic illness, etc. Patient factors that predispose to thromboembolism are indicated by an asterisk (Table 3).

IG is administered in hospitals, clinics, doctors' offices, infusion centers and at home by health agencies or family members. Because of the risk of side effects, healthcare providers or responsible adults must be able to recognize and treat such reactions and have access to an emergency center that can deal with the occasional serious reactions described below.

Several of the more common adverse reactions are illustrated in the following vignettes.

Patient 1:

A 16-Year-Old Boy with X-Linked Agammaglobulinemia

Jonathan, age 16, has X-linked agammaglobulinemia and has received monthly IVIG at a New York infusion center for the last five years without problems. He takes Tylenol and Benadryl before each infusion. Before attending a 10-week summer camp in New Mexico, the camp made arrangements for his IVIG to be given at a nearby small hospital. He was happy to receive his first infusion there, as he had developed a respiratory infection with a low-grade fever, and the IVIG infusions often help him recover quickly.

The infusion center gave him the same IVIG dose at the same rate as in New York, but the IVIG brand was different. Further, the camp nurse forgot to give him his premedication. Halfway through the infusion, he developed chills, a temperature of 102 degrees, back pain, nausea and malaise. The infusion was temporarily interrupted, Benadryl and Tylenol were given, and the infusion resumed after 45 minutes. He felt achy and feverish for the next 12 hours, relieved by naproxen and additional Benadryl.

Diagnosis: Mild constitutional reaction to IVIG associated with concurrent infection

Comment: Three factors may have contributed to these adverse effects. He had a respiratory infection, he switched brands, and he did not take his premedication (Table 3). Other immediate reactions may include headache, hypotension, urticarial rash or palpitations. These are usually transient and are treated as above with slowing or stopping the infusion, giving antihistamines and nonsteroidals. Intravenous steroids are necessary in some instances.

Patient 2:

A 15-Year-Old Girl with Newly Diagnosed Common Variable Immunodeficiency

Dr. Jones told Susan's parents that the reason their daughter developed sinus problems, bronchitis and, now, pneumonia was that she had hypogammaglobulinemia and poor antibody responses to childhood vaccines and a recent Pneumovax vaccine. But, he told them she would feel better once she started on regular doses of IVIG. The first IVIG dose of 500mg/kg was given with premedication, and except for a slight headache, the infusion was well-tolerated.

That night, two hours after she went to bed, she awoke with a splitting headache, stiff neck and mild nausea. At the emergency room, her temperature was 100 degrees Fahrenheit, and her stiff neck was present but improved. Her white blood count was 12,550 cells/ul. The resident suggested a spinal tap, but the attending physician diagnosed aseptic meningitis secondary to the IVIG infusion; he gave her Vicodin and sent her home with directions to return if she developed a worsening fever or headache.

Diagnosis: Aseptic meningitis due to IVIG

Comment: Aseptic meningitis is a not an uncommon complication of IVIG, usually occurring 6 hours to 12 hours after a high-dose IG infusion.[3] Spinal fluid shows both lymphocytes and granulocytes; cultures are sterile. Patients with a history of migraine are more susceptible to this complication. Symptoms usually subside in 48 hours. Recurrences are common and can be minimized by steroid premedication, smaller and divided IVIG doses and slower rates of infusion.

Patient 3:

A 50-Year-Old with Chronic Lymphocytic Leukemia and Antibody Deficiency

William, a 55-year-old carpenter, was receiving chemotherapy for chronic lymphocytic leukemia for the last several years. After several bouts of sinusitis and a second case of pneumonia, his immune system was evaluated. Despite normal IG levels, he had no antibodies to 22 of the 23 pneumococcal serotypes following a pneumococcal polysaccharide vaccine (Pneumovax). An antibody deficiency was diagnosed, and he was started on IVIG. Ten minutes after the start of his first IVIG infusion, he developed tightening of his chest, wheezing and an urticarial rash. His heart rate increased to 120 beats per minute, and his blood pressure fell to 100/60. The infusion was stopped, adrenalin was given and intravenous Solu-Cortef was started. After one hour, he was improved and was able to go home with instructions to continue Benadryl and oral steroids. Blood drawn before the infusion showed that he had an IgG antibody to IgA and selective IgA deficiency.

Diagnosis: Anaphylaxis to IVIG associated with an IgG anti-IgA antibody

Comment: Anaphylaxis with IVIG is a very rare complication, but it is why IVIG should be administered at a facility with trained personnel. Anaphylaxis is sometimes associated with an antibody to IgA acquired during a prior exposure to IG.[4] Patients with selective IgA antibody are more likely to have such antibodies; these are usually IgG antibodies rather that IgE antibodies. Most individuals with these antibodies, including those with selective IgA deficiency, do not develop anaphylaxis. Thus, testing for IgA deficiency or IgA antibodies is not recommended prior to an IVIG infusion. Patients experiencing such a reaction should wear a medic alert badge, use an IVIG product low in IgA or receive SCIG.

Patient 4:

A 10-Year-Old Girl with Intestinal Lymphangiectasia and Painful SCIG Infusions

Evelyn, age 10, has a long history of low-grade diarrhea, mild abdominal pain and slow growth — symptoms that were ignored by her doctor-averse rural parents. When seen in an ER for cough and fever that was diagnosed as pneumonia, symmetrical pitting edema of the legs was noted. Blood tests revealed lymphopenia (700 cells/ul), low albumin (2.5 g/dl) and hypogammaglobulinemia (IgG 215 mg/dl). Intestinal biopsy disclosed intestinal lymphangiectasia. Protein loss through the stool was confirmed by the presence of alpha-1 antitrypsin in the stool.

IVIG was given for the hypogammaglobulinemia. Yet, despite high doses, a therapeutic IgG level could not be achieved. She was switched to weekly 20% SCIG infusions using three abdominal wall sites, which corrected the hypogammaglobulinemia. However, she developed pain, redness and swelling at the infusion sites for several days after the infusion. The IG dose at each infusion site was decreased by using five sites and giving the half doses biweekly.

Diagnosis: Local pain and swelling with SCIG

Comment: Local reactions of persistent pain, redness and swelling to subcutaneous IG are common and usually subside within 24 hours.[5] The same site can be used repeatedly, and often, over time, these doses are better tolerated (site-related tolerance). Many patients find that the 10% SCIG is better tolerated than the 20% formulation. Some patients prefer smaller doses given daily without the need of an infusion pump. Conversely, some patients tolerate larger infusions given every two weeks. (Recently, the U.S. Food and Drug Administration approved a 10% solution with human hyaluronidase with a dosing regimen requiring only one infusion up to once per month [every three to four weeks] and one injection site per infusion that promotes rapid absorption from the infusion site.)

Patient 5:

A 20-Year-Old Boy with Immunodeficiency and Inflammatory Bowel Disease

Jamel has common variable immunodeficiency and has recently been diagnosed with Crohn's disease. When his IgG levels decreased from 600 mg/dl to 380 mg/dl, his IG dose was increased from 400 mg/kg per month to 600 mg/kg per month. A blood test conducted three days after the higher dose revealed that his hemoglobin had fallen from 12.5 grams to 9.8 grams. A direct Coombs' test was positive, and the indirect bilirubin (a brownish yellow substance found in bile) and the reticulocyte (immature red blood cells) count were slightly elevated. His blood group was A positive.

Diagnosis: Coombs' positive hemolytic anemia associated with IVIG administration

Comment: All IGs have low titers of antibodies to red cells usually directed against blood types A and B. These antibodies, termed isoagglutinins, coat A, B or AB red cells present in all individuals except those who have blood type O. The coated cells are phagocytized in the spleen and destroyed (hemolyzed), resulting in a mild, usually asymptomatic anemia. If the administered IG has a high titer of isoagglutinins or is given in large amounts, the hemolysis may result in significant anemia, with a fall of hemoglobin of up to 5 gm/dl.

Contributing factors to this complication include non-type O blood group, female sex, splenomegaly or an underlying inflammatory disease. The latter was present in the above patient, resulting in enhanced reticuloendothelial activity of the spleen.

Patient 6:

A 58-Year-Old Man with Myasthenia Gravis and Leg Pain

Tom has had myasthenia gravis for 10 years, and despite neostigmine, prednisone and azathioprine, muscle strength was decreasing. He was started on IVIG 1 g/kg monthly, which improved his muscle strength. Three days after an uneventful infusion, he took an airplane flight from Los Angeles to Boston. One day after arrival, he developed pain and swelling in his right calf. An ER physician diagnosed a deep vein thrombosis and treated him with anticoagulants.

Diagnosis: Venous thrombosis after IVIG and air travel

Comment: Thrombotic complications of IVIG can be mild as in the above or very serious, including heart attack, stroke, pulmonary embolism and veno-occlusive disease in transplant patients.[7] Most (70 percent) are arterial thrombosis occurring hours or days after infusion, or venous thrombosis (30 percent), which may be delayed for several weeks after the infusion. Risk factors are multiple, including both patient factors and product factors (Table 2). Certain IG lots were withdrawn from the market because of residual procoagulant activity following fractionation. The U.S. Food and Drug Administration has added a black box warning to IG because of this risk. Most such events occur in adults receiving high-dose IVIG, but children and patients receiving SCIG have also been affected. Preventive measures are listed in table 4.

Patient 7:

A 60-Year-Old Man with Hepatitis C Undergoing Liver Transplant

James received a liver transplant one week ago for liver failure due to hepatitis C. Since both he and the donor were cytomegalovirus (CMV) seropositive, he has received postoperative IVIG every other day to prevent CMV reactivation. Two weeks post-transplant, he developed decreased urinary output, mild proteinuria and an increase of his BUN (blood urea nitrogen) and creatinine levels. IVIG was discontinued, fluids were restricted and drugs excreted in the kidney were stopped. The renal failure corrected after one week.

Diagnosis: Impression renal failure associated with IVIG

Comment: This patient recovered spontaneously, but other patients have required dialysis. A black box warning of the risk of renal failure with IVIG has been added to the package inserts.[8] Risk factors include large doses, prior renal disease and sucrose- or maltose-containing products. Most of the latter products have been removed from the market.

Summary

The above vignettes highlight the more common major side effects of IG therapy that have occurred in multiple patients. Less common reactions are listed in table 1. In addition to these sporadic complications, IG therapy will obscure the diagnosis of antibody immunodeficiency, negate the value of serologic tests for current or past infectious diseases, and inhibit the antibody response to many vaccines.

Most adverse reactions to IG are minor, but severe reactions can occur. Thus, careful attention should be given to the choice and route of product, the patient's past response to infusions and past or present illness, and the availability of persons that can recognize and manage adverse events. ■

Table 1. Adverse Effects Associated with Human Immune Globulin Use

Mild Adverse Effects (common, usually immediate*)

- Infusion site pain, swelling, erythema*
- Headache*
- Myalgia, back pain, arthralgia*
- Fever, chills, flushing*
- Anxiety, malaise, fatigue*
- Nausea, vomiting*
- Hypotension, hypertension, tachycardia*
- Hyponatremia**
- Neutropenia**
- Direct Coombs' positivity**

Moderate Adverse Effects (less common, usually delayed)**

- Persistent headache**
- Aseptic meningitis**
- Hemolytic anemia**
- Serum sickness/arthritis**
- Dermatologic complications**
- Interference with vaccine effectiveness and/or immunodiagnosis***

Severe Adverse Effects

- Anaphylactic/anaphylactoid reaction*
- Renal complications**
- Pulmonary complications**
- Thrombosis/embolism***
- Colitis**
- Blood-borne infectious diseases (e.g., hepatitis, parvovirus, prion disease)***

** Immediate reaction—within 6 hours from onset of infusion*
*** Delayed reaction---6 hours to 1 week after infusion*
**** Late reaction—weeks to months after infusion*

Table 2. Adverse Factors in Some IG Products Associated with Adverse Effects

- Microbial contamination (viruses, bacteria, endotoxins)
- IgG immune complexes
- Trace amounts of IgA
- Low pH
- Sugars: glucose, maltose, sucrose
- High osmolality
- High levels of sodium
- Vasoactive enzymes; kallikreins, others
- Erythrocyte antibodies; Anti-A, -B, -D, -Kell; other
- Antibodies to human leukocyte antigens
- Antibodies to neutrophil or platelet antigens
- Pathogenic autoimmune antibodies (e.g., antiphospholipid antibodies)
- Procoagulant factors (Factor Xla)
- Preservatives (thimerosal)

Table 3. Risk Factors for IG Adverse Effects

Infusion factors

1. Prior history of infusion reaction
2. Switch to a new product
3. No premedication
4. First infusion
5. Larger dose
6. Rapid dose
7. Longer interval from prior infusion
8. No pre-infusion or post-infusion hydration

Patient Factors

1. Fever/infection at time of infusion
2. Autoimmune/inflammatory disease
3. Older age*
4. Immobility/air travel*
5. Hypertension
6. Present or past cardiovascular disease*
7. Diabetes*
8. High lipids/cholesterol*
9. Elevated serum proteins/gammopathy**
10. Smoking*
11. Prior/current thrombosis**
12. Estrogen use*
13. Hereditary hypercoagulable state (factor V Leiden, prothrombin mutations, protein C, S, or antithrombin III deficiencies)**
14. Permanent indwelling venous catheter (i.e., Portacath)

** High risk for thromboembolism*
*** Very high risk for thromboembolism*

Table 4. Minimizing Risk of Thromboembolism with IVIG Infusions

1. Limit daily IVIG dose to 400-500 mg/kg. If larger dose is needed, give repeat dose(s) on a subsequent day(s)
2. Consider pre-/post-infusion hydration
3. Use slow infusion rate (e.g., 50 mg/kg for first hour, 100 mg/kg per hour thereafter)
4. Avoid "as tolerated" dose escalation
5. Premedicate with ASA or heparin/enoxaparin in high-risk patients
6. Test for hypercoagulable tests/viscosity/dysproteinemias
7. Do Doppler tests for clots in bedridden patients

E RICHARD STIEHM, *MD, is professor of pediatrics at the David Geffen School of Medicine at the University of California, Los Angeles.*

References

1. Stiehm, ER. Adverse effects of human immunoglobulin therapy. *Transfusion Medicine Reviews*, 2013; 27: 171-8.
2. Bonilla, FA. Intravenous immunoglobulin: adverse reactions and management. *Journal of Allergy and Clinical Immunology*, 2008;122:1238-9.
3. Sekul, EA, Cupler, EJ, and Dalakas, MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy; Frequency and risk factors. *Annals of Internal Medicine*, 1994; 121;259-62.
4. Rachid, R, and Bonilla, FA. The role of anti-IgA antibodies in causing adverse reactions to gamma globulin infusion in immunodeficient patients: a comprehensive review of the literature. *Journal of Allergy and Clinical Immunology*, 2012; 129;628-34.
5. Chapel, HM, Spickett, GP, Ericson, D, Engle, W, Eibl, MM, and Bjorkander, J. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. *Journal of Clinical Immunology*, 2000; 20:94-100.
6. Daw, Z, Padmore, R, Neurath, D, Cober, N, Tokessy, M, Dejardins, D, et al. Hemolytic transfusion reactions after administration of intravenous immune (gamma) globulin: a case series analysis. *Transfusion*, 2008; 48:1598-601.
7. Huang, L, Kanellis, J, and Mulley, W. Slow and steady: reducing thrombotic events in renal transplant recipients treated with IVIg for antibody-mediated rejection. *Nephrology*, 2011; 16:239-42.
8. Centers for Disease Control Prevention. Renal insufficiency and failure associated with immune globulin intravenous therapy-United States, 1985-1998. *Morbidity and Mortality Weekly Report*, 1999; 48:518-21.