ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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The Hypercoagulability of Intravenous Immunoglobulin

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H&O What is intravenous immunoglobulin?

MM Intravenous immunoglobulin (IVIG) is a solution of human plasma–derived immunoglobulin containing an extensive range of immune antibodies that may protect against human pathogens or antigens. It has been in use for more than 2 decades, for conditions such as idiopathic thrombocytopenic purpura, chronic lymphocytic leukemia, and HIV infection. The number of diseases that are being treated with IVIG continues to increase (Table 1). Shortly after the introduction of IVIG agents, they were found to be effective in the treatment of autoimmune and inflammatory disorders. IVIG can sometimes achieve a cure in patients who do not respond to first-line therapies.

The mechanism of action of the underlying immunomodulatory effect of IVIG has not yet been identified, but there are several hypotheses. The mechanism of action may vary according to the disease and the IVIG preparation. One of the hypotheses is that IVIG blocks the reticular endothelium system via reversible binding of the Fc (fragment, crystallizable) region of monomeric immunoglobulin G (IgG) into the macrophage FcyR. IVIG may also protect platelets, megakaryocytes, or both from platelet antibodies. Another hypothesis is that IVIG causes subversion of natural killer cell selectivity, which decreases platelet antibody synthesis and increases platelet production and release.

H&O What are the adverse events associated with this treatment?

MM There are many adverse events. A patient may experience a phlogistic reaction presenting as an acute infection, with fever, flushing, myalgia, nausea, vomiting, nuchal rigidity, and headaches. The symptoms may result from interactions between the newly delivered antibodies and antigens already present in a patient with a chronic infection. Headaches and neurologic side effects of IVIG are common in both adults and children. The symptoms begin during administration or after initiation of the infusion; initial symptoms can also appear as late as 24–48 hours after IVIG administration. Although most headaches resolve in 24 hours, there are reports of headaches lasting 72 hours. Migraine and septic meningitis may occur, particularly in patients with a history of migraine. Migraines may be accompanied by photophobia or nausea; they typically begin after the infusion is com-

Table 1. Diseases Treated With Intravenous Immunoglobulin

Conditions Included in the FDA Indication
- Chronic inflammatory delineating polyneuropathy
- Chronic lymphocytic leukemia
- Graft versus host disease (prevention)
- Hepatic thrombocytopenic purpura
- HIV infection
- Immunodeficiencies (primary and secondary)
- Kawasaki syndrome

Off-label Use
- Agammaglobulinemia (primary)
- Antifactor VIII autoantibodies
- Autoimmune neutropenia
- Common variable immunodeficiency
- Congenital hypergammaglobulinemia (primary)
- Guillain-Barré syndrome
- Idiopathic thrombocytopenic purpura
- Isoimmune thrombocytopenia
- Kawasaki disease
- Lupus
- Myasthenia gravis
- Nephropathy
- Parvovirus B19 infection
- Severe combined immunodeficiency
- Thrombotic thrombocytopenic purpura
- von Willebrand disease
- X-linked agammaglobulinemia
- X-linked immunodeficiency with hyper
- IgM and IgG subclasses deficiencies

FDA=US Food and Drug Administration; IG=immunoglobulin.

pleted. Severe headaches are more common and frequent in patients who receive high doses of IVIG, such as 1–2 g/kg. Headaches tend to diminish after the first few infusions, although some patients develop a recurrent pattern of symptoms. The risk of this reaction can be reduced with slower infusion of IVIG.

Another type of adverse event mimics anaphylaxis and anaphylactoid reactions. These reactions may include tachycardia, chest pain and tightness, hypertension or hypotension, urticaria, dyspnea, lower back pain, nausea, vomiting, sudden anxiety, and a sense of impending doom. These reactions often occur in the middle or near the end of IVIG administration.

Both types of reactions are common after the first infusion of IVIG. Adverse reactions in the next infusion can be avoided by changing the formulation of IVIG and reducing the flow infusion rates. Gradual, stepwise increases are suggested in patients who have experienced adverse events.

Another complication to consider is anaphylaxis in the IgA-deficit patient. Anaphylaxis can occur in those patients who have formed antibodies against IgA because most IVIG preparations contain at least trace amounts of IgA. The presence of preformed IgE against IgA is extremely rare; it is a true anaphylaxis and can be life-threatening.

There are also reactions related to concurrent infection. Some patients experience chills, rapid onset of fever, and flu-like symptoms, including myalgia and arthralgia. This reaction may be particularly pronounced in patients with chronic sinus or lung infection who have not recently been treated with antibiotics, particularly those patients who are receiving IVIG for the first time. The symptoms resemble those that accompany the onset of the infection, although they can be more severe. When possible, preexisting infection should be treated with an antimicrobial before IVIG is administered for the first time or after a lapse of several months. However, the initiation of IVIG should not be delayed. More rare adverse reactions include retinal complications, acute kidney injury, and sepsis.

There are several hematologic complications associated with IVIG infusion, including Coombs-positive hemolytic anemia and severe intravascular hemolysis. IVIG can contain erythrocyte alloantibodies like anti-E, anti-A, and anti-B, which code recipient red cells. Significant intravascular hemolysis can produce reduced serum haptoglobin, and hemoglobinuria and may occur following high-dose infusion. Risk factors for hematologic complications include a high cumulative dose of IVIG, female sex, blood type A or B, a positive inflammatory serologic marker, a positive direct Coombs test, and thyrocytes on blood smear. An acute hemolytic reaction is most likely to occur in patients with active inflammatory disorders. Patients receiving high-dose IVIG should undergo a Coombs test before infusion and be monitored for signs of hemolysis or anemia. Transient neutropenia can occur after IVIG infusion. Risk factors for the development of neutropenia are not known, and it is not common practice to monitor neutropenia after infusion of IVIG.

Regarding the thrombotic complications, studies show that high concentrations of IgG can raise the viscosity of serum and whole blood. Local thrombosis can occur in the site of IVIG infusion and can extend to larger veins, producing thromboembolic events. There are also transient ischemic attacks, as well as stroke and myocardial infarction, which may follow standard replacement as well as high-dose IVIG infusion (particularly when given rapidly). Thromboembolic complications may be attributed to increased viscosity caused by protein load, hypertonic conditions created by a large amount of sugars, or other osmotically activated stabilizers in some IVIG formulations.

H&O What are the risk factors for thromboembolic complications?

MM Risk factors for thromboembolic complications include older age, dehydration, high-dose therapy given in a short period of time, hyperviscosity syndromes, and hypervalinemia. Increased risk is also seen in patients with underlying cardiovascular disease, those with extremely elevated lipid protein concentrations and hypertension, and those who experienced previous thromboembolic events or who are immobilized or bedridden. Thrombosis occurs more often with high-dose IVIG (1–2 g/kg).

H&O How can thromboembolic complications be prevented?

MM For patients at risk, proper hydration is essential. In addition, the IVIG formulation with the lowest osmolarity production should be used. The rate of infusion should be slow, such as 3 g/hour or 50 mg/kg/hour. Clinicians should consider the use of prophylaxis with low-dose aspirin, clopidogrel, or other antiplatelet drugs in a patient with risk factors or thrombocytosis.

Suggested Readings

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