# Editorial

## Intravenous Immunoglobulin: A Life-Saving (and Potentially Fatal) Treatment

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In this issue, Drs. Sheehan and Lesher report on the association of deep venous thrombosis and high-dose intravenous immunoglobulin (IVIg) in the treatment of pemphigus vulgaris. IVIg has proved to be a highly effective agent in the treatment of refractory immunobullous diseases and refractory dermatomyositis. Its mechanism of action is not fully known, but it appears to be related in part to catabolism of immunoglobulins.

Increasing use of IVIg has led to the dual realizations that IVIg therapy can be life saving and that it can be fatal. This message hits close to home for me. For one of my patients with severe refractory dermatomyositis and respiratory paralysis, IVIg proved to be a life-saving therapy. I have no doubt that the treatment saved her life. I also have little doubt that her ultimate death from a pulmonary embolism was related to her treatment.

How then do we reconcile the unique effectiveness of this agent with its risks? Minor reactions to IVIg infusions are common, especially headache, which occurs in about 30% of patients.[1] Minor infusion reactions can be reduced by slowing the rate of infusion. Contamination of IVIg with hepatitis virus has occurred with transmission of the virus to the recipient. This problem was identified during the 1990s. The pharmaceutical industry responded rapidly, and the current risk of disease transmission is minimal. Elevations in liver enzymes are still seen commonly but rarely result in discontinuation of therapy.

Severe adverse events occur in fewer than 4% of patients and include thromboembolic events, anaphylactic reactions, and retrosternal pressure mimicking myocardial infarction.[1] Thromboembolic events have included deep venous thrombosis of both the upper and lower extremities, thrombosis of the jugular vein, myocardial infarction, stroke, and pulmonary embolization. Reports of renal failure are strongly linked to products containing sucrose, maltose, glucose and glycine.[2] Patient age and preexisting renal disease are important risk factors.

The average dose of IVIg for the provision of antibodies to immunoglobulin-deficient patients is 400 mg/kg per month. Even at immunoglobulin replacement doses, thromboembolic events have been described.[3] Much higher doses (starting at 1–2 g/kg) are needed for the treatment of autoimmune diseases, and doses of 4 g/kg are used to treat patients with toxic epidermal necrolysis. Thromboembolic events are usually associated with high-dose treatment and rapid infusion. The events may relate to transient increases in serum viscosity, but hypotension and generation of platelet-activating factor also may be involved. Risk factors include underlying prothrombotic conditions such as protein C deficiency, protein S deficiency, factor V Leiden deficiency, or prothrombin mutations. Additional risk factors include immobility, obesity, pregnancy, oral contraceptive use, surgery, trauma, and malignancy.

The report in this issue and a recent report in the *Archives of Dermatology* have focused the attention of dermatologists on the risks of thromboembolic events inherent in IVIg therapy.[4] To minimize the risk of side effects, the infusion rate should be less than 10 g/h.[4] Additional risk factors should be carefully evaluated.

IVIg is a valuable part of our therapeutic armamentarium. We are only beginning to realize its full therapeutic potential and the magnitude of the risks involved with therapy. Clinical trials are

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required to evaluate the role of prophylactic measures. Until then, the level of risk and the possible role of low-dose anticoagulants should be discussed with the patient.

## REFERENCES


1. Stangel M, Kiefer R, Pette M, et al. Side effects of intravenous immunoglobulins in neurological autoimmune disorders—a prospective study. *J Neurol*. 2003;250:818-821.
2. Eibl MM. Intravenous immunoglobulins in neurological disorders: safety issues. *Neurol Sci*. 2003;24(suppl 4):S222-S226.
3. Brown HC, Ballas ZK. Acute thromboembolic events associated with intravenous immunoglobulin infusion in antibody-deficient patients. *J Allergy Clin Immunol*. 2003;112:797-799.
4. Katz KA, Hivnor CM, Geist DE, et al. Stroke and deep venous thrombosis complicating intravenous immunoglobulin infusions. *Arch Dermatol*. 2003;139:991-993.
5. Wittstock M, Benecke R, Zettl UK. Therapy with intravenous immunoglobulins: complications and side-effects. *Eur Neurol*. 2003;50:172-175.