

INTRAVENOUS IMMUNE GLOBULIN

Intravenous immune globulins (IVIGs) are antibodies produced in response to antigen stimulation that are used for therapeutic purposes. These therapeutic immunoglobulins (IGs) are polyvalent and are derived from pooled plasma from thousands of human donors. Hyperimmune IGs have directed specificity towards single antigens or infectious agents. The more recent engineered IGs with monoclonal specificity are used for targeted immunotherapy.

IVIG preparations have been a mainstay for the treatment of primary immunodeficiency syndromes—where immunoglobulin replacement can prevent or ameliorate bacterial infections. IVIG use has expanded beyond simple replacement therapy for humoral immunodeficiency to a number of other arenas, including hematological, infectious, and neuroimmunological disorders, and immunomodulation.¹ The exact mode of action of IVIG has not yet been determined, mostly because of its polyclonal nature.

THERAPEUTIC STRATEGIES: The therapeutic use of IVIG is based on two fundamental strategies: *replacement therapy* for primary or secondary humoral antibody deficiency and *immunomodulation* for autoimmune or certain infectious diseases.

Replacement Therapy: The benefits of the use of IVIG in primary immunodeficiency patients with hypogammaglobulinemia (total IgG <400 mg/dL) are well established. Patients with these conditions are at significant risk of developing serious and often life-threatening invasive infections. In patients with primary hypogammaglobulinemia, antibody replacement using IVIG is necessary to minimize complications associated with chronic sinusitis, bronchiectasis, and recurrent episodes of pyogenic pneumonia.

IVIG is a complex immunological product that contains neutralizing and opsonizing antibodies. This may increase antibactericidal activity by stimulating the phagocytic activity of leukocytes. Replacement therapy aims at maintaining an adequate level of serum IGs and consequently, humoral immunity. Optimal levels usually are >500 mg/dL (IgG total) and are the subject of recent investigation.² Testing strategies and replacement frequency are titrated according to serum levels.

Immunomodulant Therapy: IGs impact various immunological responses, ranging from neutralizing foreign agents to immunomodulation. Infusion elicits an array of biological and immunological responses. Like natural IGs, IVIG can bind complement factors and prevent tissue damage mediated by the complement cascade.³

IVIG can modulate the immune activity of both CD8+ and CD4+ cells. This has been attributed to the presence of antibodies directed against several T cell surface molecules such as T-cell receptors, CD4, and the major histocompatibility complex. Immunomodulatory activity also has been attributed to the presence of anti-idiotypic antibodies found in IVIG and is thought to down regulate B-lymphocyte activity⁴ and

TABLE 1. Dosage of IVIG for various disorders

| Allergic Disorders | Dosing Reference |
|---|--|
| Asthma | 2gm/kg/month |
| Hematologic | |
| * Idiopathic thrombocytopenia | 0.4gm/kg/day x 5 days or 1gm/kg/day x 2 days |
| * Chronic lymphocytic leukemia | 0.4 gm/kg |
| Parvovirus B-19 induced anemia | 0.4 gm/kg every 28 days |
| Infections | |
| * Kawasaki disease | 1-2 gm/kg |
| * Pediatric HIV | 0.4 gm/kg every 28 days |
| Sepsis | 0.3-0.6 g/kg/day x 2 days |
| Neurological disorders | |
| Guillain-Barré syndrome | 0.25 to 0.4 gm/kg x 5 doses |
| Chronic inflammatory demyelinating polyneuropathy | 0.4 gm/kg for 5 doses |
| Multifocal motor neuropathy | 0.4 gm/kg for 5 doses |
| Lambert-Eaton syndrome | 0.4 gm/kg for 5 doses |
| Dermatomyositis | 0.4 gm/kg for 5 doses |
| Acute humoral rejection | 1 g/kg/day for 2 doses |
| *Primary immunodeficiency disorders | 0.4-0.6 gm/kg every 28 days |
| Antiphospholipid syndrome | 1 gm/kg every 4 weeks from 5 weeks' to 33 weeks' gestation |

*Labeled Indications

Adapted from: Sacher RA. Intravenous Immunoglobulin. Consensus Statement. J Allergy Clin Immunol 2001;108(4 Suppl):S139-46

macrophage activity.⁵ IVIG also can regulate the expression of IL-6, a critical modulator of IgG expression and production for plasma cells.

Other biological activities attributed to IVIG include the alteration of cytokine profiles attributed to the presence of antibodies directed against inflammatory mediators like IL-1, TNF, IL-6 and IFNs (e.g., - α , - β , and - γ).

These findings may, either alone or in combination, explain why IVIGs have anti-infective activities as well as immunomodulatory activities and prevent cellular damage caused by inflammatory cytokines.

Some of the immunomodulatory activity of IVIG may be dose-dependent. At high levels of IGs, the F_c portion of the infused antibodies can compete for F_c receptor binding on phagocytic cells, thus reducing damage inflicted by these inflammatory effector cells. High concentrations of IGs also accelerate the catabolism and elimination of IgG autoantibodies, thus reducing the risk of autoimmune disorders.

Anti-idiotypic antibodies recognize and attach to the antigen binding region (Fab) of other immunoglobulin molecules. A network of these anti-idiotypic antibodies may regulate or prevent the onset of autoimmunity. This may explain why IVIG is able to produce a similar response in disorders such as Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP).⁶

(continued on reverse)

CLINICAL INDICATIONS and DOSAGE RECOMMENDATIONS (see Table 1): Idiopathic thrombocytopenic purpura (ITP) is a disorder involving autoantibodies directed against platelets, resulting in varying degrees of thrombocytopenia with markedly shortened platelet survival. It was the first syndrome where immunomodulating doses of IVIG demonstrated therapeutic effectiveness.⁷ ITP may be acute or chronic (lasting longer than six months).

The acute ITP syndrome, found mostly in children, usually resolves spontaneously without therapy. However, a small number of these patients will require therapy and IVIG has been shown to be effective in treating or preventing bleeding events. IVIG also can be used to defer splenectomy in chronic ITP in childhood.

In adults, who more commonly have chronic disease, IVIG can be effective therapy for patients with severe thrombocytopenia (< 20,000/ μ L) who are at risk of life threatening bleeding, or to prepare patients for surgery when platelet counts are < 50,000/ μ L. It is also effective in preventing peripartum hemorrhage or in preparation for cesarean section in pregnant patients with severe ITP. In this condition, IVIG plays the role of an immune modulator by blocking the attack of autoantibodies on the platelets. In a majority of patients treated with 400 mg/kg for 5 days or 1g/kg for 2 days, platelet counts usually reach 50,000 cells/ μ L within 2-5 days.^{8,9}

Chronic lymphocytic leukemia (CLL) is a malignancy of lymphocytes, usually B cells. Patients may develop recurrent bacterial infections due to hypogammaglobulinemia. These patients are particularly susceptible to recurrent infections due to encapsulated organisms. The ability of IVIG to prevent recurrent bacterial infections in CLL complicated with hypogammaglobulinemia is well established.¹⁰ IVIG may also be useful in the treatment of the autoimmune thrombocytopenia that can occur in CLL.

Kawasaki disease is an acute vasculitis of unknown etiology that occurs predominantly in infants and young children. Without treatment with high-dose IVIG, coronary artery ectasia or aneurysms develop in approximately 15% to 25% of afflicted patients. IVIG administration during the acute phase can reduce the incidence of coronary dilation to <5%. It is well established that Kawasaki's patients can be effectively treated with IVIG at 1-2 gm/kg together with aspirin.¹¹

The mechanism of action of IVIG is poorly characterized in pediatric HIV infection because of the complexity of the immunologic abnormalities observed in these patients.¹² IVIG also may provide anti-idiotypic antibodies, which can produce negative feedback to B cells, resulting in a decrease in immunoglobulin production. Reduction in bacterial infections possibly may slow progression of the HIV induced immunodeficiency itself.

IVIG has been shown to be effective in a number of immune-related neurological conditions. Its efficacy for patients with Guillain-Barré syndrome has been demonstrated in two large controlled trials.¹³ In these studies, IVIG was compared either to placebo or to plasmapheresis, where IVIG was found to be as effective, if not superior to the paired controls. Similar outcomes were demonstrated when patients with chronic inflammatory demyelinating polyneuropathy were treated with high dose IVIG in controlled trials.¹⁴ Additional uses of IVIG have been reported and are reviewed by Ratko *et al.*¹⁵

SAFETY: Recent advances in IVIG purification and refinement in its specificity have achieved an improved margin of safety. Strategies have been implemented to eliminate the

potential for transmission of infectious agents and to prevent systemic reactions. Rare reports of renal insufficiency, thrombotic events, and aseptic meningitis have been made. These seem to be related to sugar stabilizers and osmolality and have not been reported with all preparations.

References

1. Nydegger UE, Mohacsi PJ. Immunoglobulins in Clinical Medicine. Chapter 24 in: Rossi's Principles of Transfusion Medicine, 3rd ed. Simon TL et al, editors. Williams and Wilkins, Philadelphia. 2002; 316-32.
2. Eijkhout HW et al. The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia. A randomized, double-blind, multicenter crossover trial. *Ann Intern Med*. 2001;135:165-74.
3. Hartung HP *et al.* Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy. in: Clinical Neuroimmunology. Antel J, Birnbaum G, Hartung HP, eds. Blackwell Science, Malden, Mass., 1998;294-306.
4. Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Eng J Med* 2001;345:747-55.
5. Samuelsson A *et al.* Anti-inflammatory activity of IVIG mediated through the inhibitory Fc Receptor. *Science* 2001;291:484-6.
6. Yu Z, Lennon VA. Mechanism of intravenous immune globulin therapy in antibody-mediated autoimmune diseases. *N Engl J Med*. 1999;340:227-8.
7. Imbach P *et al.* Intravenous immunoglobulin versus oral corticosteroids in acute immune thrombocytopenic purpura in childhood. *Lancet* 1985;2:464-8.
8. Sacher RA. Evaluation and review: Symposium covers indications for the use of intravenous immune globulin. *J Allergy Clin Immunol* 2001;108:S1-2.
9. Sacher RA, IVIG Advisory Panel. Intravenous Immunoglobulin Consensus Statement. *J Allergy Clin Immunol* 2001;108:S139-46.
10. Boughton BJ *et al.* Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia. *Clin Lab Haematol* 1995;17: 75-80.
11. Dajani AS *et al.* Diagnosis and therapy of Kawasaki disease in children. *Circulation* 1993;87:1776-80.
12. Mofenson LM *et al.* Prophylactic intravenous immunoglobulin in HIV-infected children with CD4+ counts of 0.20 x 10⁹/L or more: effect on viral, opportunistic, and bacterial infections. *JAMA* 1992; 268:483-8.
13. Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome. *Lancet* 1997;349:225-30.
14. Hahn AF *et al.* Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy: a double-blind, placebo controlled, crossover study. *Brain* 1996;119:1067-77.
15. Ratko TA *et al.* Recommendation for off-label use of intravenously administered immunoglobulin preparations. *JAMA* 1995;273:1865-70.



This edition of *BloodNEWS* is a reprint of *Blood Bulletin*, which is issued periodically by America's Blood Centers. Editor: Jay E. Menitove, M.D. The opinions expressed herein are opinions only and should not be construed as recommendations or standards of ABC or its board of trustees. Publication Office: 725 15th St., NW, Suite 700, Washington, DC 20005. Tel: (202) 393-5725; Fax: (202) 393-5527; E-mail: abc@americasblood.org. Copyright America's Blood Centers, 2003. Reproduction is forbidden unless permission is granted by the publisher. (ABC members need not obtain prior permission if proper credit is given.)