INTRAVENOUS IMMUNOGLOBULINS IN THE THERAPY OF IMMUNE-MEDIATED HEMATOLOGIC DISORDERS

Susan G. Hackner, BVSc.MRCVS.DACVIM. DACVECC.

Intravenous immunoglobulin (IVIG) is used for the treatment of numerous immunodeficiency, immune-mediated, and inflammatory disorders in humans. More recently, it has been described for the therapy of immune-mediated hematologic disease in dogs. While the potential benefits of IVIG are tantalizing, and initial reports in dogs are encouraging, there is a marked paucity of controlled studies in the veterinary literature. This talk will review the immunomodulating effects of IVIG, and our experience with this drug in veterinary medicine.

IVIG is a preparation fractionated from pooled human plasma, to contain primarily IgG. Plasma is pooled from 1,000 to 10,000 human donors, and contains a broad repertoire of antibodies. It contains at least 90% IgG, with a distribution of subclasses corresponding to that of normal human plasma, as well as smaller quantities of IgA, IgM, IgD, and IgE. Current US versions of IVIG contain IgM in trace quantities only, although a beneficial role for these antibodies is now supported. IVIG has also been shown to contain trace amounts of soluble CD4, CD8 and HLA molecules, as well as certain cytokines and intact Fc molecules.

Following infusion, approximately 55% of IVIG is distributed extravascularly. The half-life varies among human patients, averaging 21-25 days. The half-life in dogs is considerably shorter: 7-9 days.

Several commercial preparations are available (see Appendix). The drug is expensive, costing approximately $500-$800 to treat an average-sized dog.

Immunoregulatory Effects of IVIG

The mechanisms of action of IVIG are complex, involving: Fc receptor blockade, interference with complement activation and the cytokine network, provision of anti-idiotypic antibodies, and modulation of T- and B-cell activation and effector functions. Such a broad range of activities reflects the numerous functions of circulating immunoglobulins in the maintenance of tolerance to self and immune homeostasis in healthy individuals.

Fc receptor blockade. IVIG is able to transiently block the function of Fc□□receptors on phagocytes, by saturating, altering, or down-regulating the affinity of these receptors. Binding of IVIG to Fc□ receptors has been shown to decrease phagocytic activity of human and canine mononuclear cells in vitro. In canine blood samples, IVIG binds to CD4 and CD8 cells, B-cells, and monocytes. This results in a concentration-dependent inhibition of phagocytosis. Antibodies directed against the Fc receptor have been demonstrated to have similar effects to IVIG in human patients with thrombocytopenic purpura. The Fc receptor blockade is proposed to be the mechanism responsible for the rapid, early effect of IVIG. In humans, blockade occurs almost immediately, and immunomodulating effects are seen within 3 days. This rapidity of response has also been suggested in dogs treated with IVIG.

Attenuation of complement-mediated damage. IVIG scavenges active complement components, and diverts complement attack from cellular targets. This is due to binding of the complement components C3b and C4b, preventing deposition on target surfaces.

Induction of anti-inflammatory cytokines. Modulation of the production of cytokines and cytokine antagonists appears to be a major mechanism by which IVIG exerts its anti-inflammatory effects in vivo. Infusion of immunoglobulin results in rapid changes in the concentrations of both pro- and anti-inflammatory cytokines, and well as cytokine receptors, and receptor antagonists. IVIG has been shown to selectively trigger the production of interleukin-1 receptor antagonist, the natural antagonist of IL-1.

Neutralization of pathogenic autoantibodies. The manipulation of the idiotype network by IgG antiidiotype antibodies is believed to be an important mechanism in human patients. The body normally produces small amounts of autoantibodies to sequences of its own tissue proteins, and in turn, produces antiidiotype antibodies to these autoantibodies. The latter maneuver is designed to prevent any significant immunologic attack on the self. In normal serum, very small amounts of both autoantibodies to a specific protein can be detected. It follows that the concentrated IgG preparations will contain many thousands of autoantibodies, capable of reacting with many thousands of determinants, because of the diversity of the experience of the thousands of donors who contributed to the pool. Among such antibodies will be many with antiidiotype specificity. Antiidiotype antibodies manipulate the immune system by inhibiting binding of an autoantibody with its antigen, and by down regulating B cell receptors. The delayed, long-term effects of IVIG observed in human patients have been ascribed to this antiidiotype effect (since the half-life of IVIG in humans is only 18-32 days). It seems unlikely that the antiidiotype effect plays an important role in the response to treatment in dogs, due to species specificity of these antibodies. If a delayed response indeed occurs in dogs, alternate mechanisms are implicated.

Enhanced clearance of IgG. IgG is usually endocytosed by reticuloendothelial cells, but some is bound to a protective receptor (FcRn), preventing its catabolism. So protected, the IgG can be released back into the circulation. IVIG competes for binding of this protective receptor, so increasing the destruction of pathogenic autoantibodies. This mechanism may contribute to the long-term effect of IVIG in some human patients.

Modulation of B- and T-cell function. IVIG contains antibodies to cell surface molecules important to immune recognition, including CD4, CD5, and T-cell receptor determinants. These may be important in modulating autoimmune responses, for example, by inhibiting cytotoxic T cells or autoantibody-producing B-cells. This mechanism is though to be key in T-cell mediated diseases such as dermatomyositis. IVIG also contains soluble CD4, CD8, and HLA antigens, which interfere with antigen recognition by T-cells, and may contribute to general immunosuppression.

Clinical Experience in Human Patients

IVIG therapy has been reported to be beneficial in more than 35 human immunopathologic diseases, including: immune thrombocytopenic purpura, autoimmune hemolytic anemia, red cell aplasia, autoimmune neutropenia, myasthenia gravis, rheumatoid arthritis, Kawasaki's syndrome, asthma, lupus, Crohn's disease, multiple sclerosis, dermatomyositis, multifocal neuropathies, polymyositis, immunodeficiencies, insulin-dependent diabetes mellitus, sepsis, and HIV infection in children.

IVIG is currently considered the treatment of choice for the management of immune thrombocytopenic purpura in children. Response rates are as high as 83%, with the majority of patients demonstrating a response within 48 hours. Response rates are higher in acute disease compared with chronic disease. Overall, human patients with immune-mediated hemolytic anemia (IMHA) respond less well to IVIG than do patients with thrombocytopenic purpura. Of these, it appears that the benefits are greatest in those with recent-onset IMHA.

Clinical Experience in Small Animal Patients

IVIG has been reported for the treatment of idiopathic IMHA in dogs. Scott-Montcrief, et al.(1997), evaluated the safety and efficacy of IVIG (1 g/kg) in a prospective clinical trial in 10 dogs with IMHA. In 8 dogs in which the response to treatment could be evaluated, 5 dogs had a clinically meaningful response, as determined by a significant increase in the hematocrit and hemoglobin concentration from day 0 to day 28. Since there were no controls, and since all animals in this study were receiving concurrent immunosuppressive therapy, the effect of IVIG on survival cannot be ascertained.

Kellerman, et al. (1997), evaluated the effects of IVIG (0.25 to 0.73 g/kg) administered to 13 of 37 dogs with IMHA. Response rate in the IVIG group was 85%, compared to 75% in the control group. This difference may be

biased since dogs were selected to receive IVIG based on an anticipated need for multiple transfusions, progressive clinical course, or perceived lack of response to glucocorticoids. Dogs without a PCV response after 7 days of prednisone therapy were more likely to respond during hospitalization if they received IVIG than if they did not. Long-term survival, however, was not significantly different between the 2 groups. The time to response after IVIG therapy ranged from 0.6 to 6 days.

Scott-Montcrief, et al. (1995), reported the beneficial use of IVIG in 5 dogs with nonregenerative anemia and myelofibrosis, believed to be immune-mediated. All dogs responded with an increased reticulocyte count and hematocrit. In 2 dogs, the response was transient, with return of pretreatment values within approximately 40 days. In the remaining dogs, the response was sustained, but normal hematocrit values were never achieved.

To date, there is only 1 published report on the specific use of IVIG in canine idiopathic immune-mediated thrombocytopenia (ITP) (Scott-Montcrief et al, 1997). This dog had failed to respond after 11 days of prednisone therapy. Platelet count was 5,000/□l prior to IVIG infusion (1 g/kg). Counts increased to 70,000/□l within 6 hours, 145,000/□l by 24 hours, and were normal by day 4. In one of the IMHA studies, 4 of the dogs had some degree of thrombocytopenia. In all of these, platelet counts returned to the reference range following therapy. (In 3 of the 4, however, the response was not sustained.)

We have administered IVIG (0.5 - 1.0 g/kg) to approximately 40 dogs with ITP, and results have been very encouraging. It is my unsubstantiated belief that response rates are higher in dogs with ITP than in dogs with IMHA. Since the drug is always administered to patients on concomitant glucocorticoids, however, it is unclear whether these responses are directly attributable to the drug, or to a delayed response to glucocorticoids. In my experience, significant increases in platelet numbers generally occur 1 to 3 days post-treatment. If this is true, the rapidity of response offers tremendous benefits, including a decreased risk of fatal hemorrhage, decreased need for multiple transfusions, and shortened hospital stay. These serve to offset the high cost of the drug. It is unclear whether the response is temporary or sustained. Even if temporary, it offers the benefit of increasing platelet counts out of the “danger” range, until other treatment modalities can be effective.

There are currently no clinical studies of IVIG in cats. I have used IVIG in one cat with longstanding thrombocytopenia, unresponsive to other immunosuppressive therapies, with an excellent and sustained response, and without adverse effects.

Adverse Effects

Adverse effects of IVIG in human patients are relatively uncommon, with a reported incidence of 1-15%. Most of these are transient, and self-limiting. Some patients develop a symptom complex that includes headaches, fever and flushing. The etiology is uncertain, but is believed to result from IgG aggregates that form during the fractionation process, and subsequently activate complement. Symptoms are related to the infusion rate. They can be avoided or ameliorated by starting infusions at a slow rate. Sudden hypotension is a rare adverse effect, and is believed to be caused by IgG dimers. As with any large volume infusion, volume overload may occur, especially in circulatory-compromised patients.

Acute renal failure occurs rarely. The risk is increased in patients with pre-existing renal compromise, and with the use of sucrose-containing solutions (which result in osmotic injury to the proximal renal tubules).

Thromboembolism has been associated with IVIG therapy, including deep vein thrombosis, pulmonary thromboembolism, myocardial infarction, and stroke. Proposed mechanisms include increased blood viscosity, factor XIa containing solutions, platelet activation, and direct endothelial effects. Risk is increased with high doses, rapid infusions, and in patients with pre-existing thrombotic tendencies.

The canine studies showed no adverse effects that could be directly attributed to IVIG administration. In Scott-Montcrief's study in dogs with IMHA, thrombocytopenia was observed in 60% of dogs after therapy, and evidence of thromboembolism was detected at necropsy in 5 of 7 dogs that died. Because the incidence of both thrombocytopenia and thromboembolism in IMHA is high, it is unclear whether these were caused by the IVIG, or by the underlying disease. I have observed adverse reactions to IVIG administration in only 2 dogs. These included: facial swelling, urticaria, and pruritis. Signs abated with slowing of the infusion rate.

IVIG of canine origin is not commercially available. The antigenicity of human IVIG in dogs is unknown. The half-life of human IVIG in dogs is substantially shorter than in humans. This may be due to an antibody response. The safety of administering multiple doses to dogs has yet to be established. Administration of 2 doses of IVIG several weeks to months apart has not resulted in any apparent adverse effects.

Conclusions and Current Recommendations

IVIG appears to be a safe and efficacious therapy for immunohematologic disease in dogs. Evidence in humans, and largely anecdotal evidence in dogs, suggests we might expect the drug to be beneficial in the management of ITP, IMHA, and possibly other immune-mediated and inflammatory diseases. Potential benefits of IVIG, compared to other immunosuppressive drugs, are the rapidity of response, and the low incidence of adverse effects. These benefits would serve to offset the expense. Convincing evidence of its efficacy in veterinary patients, however, remains to be established, and it is possible that long-term benefits are less than in humans. Large, randomized, controlled studies are necessary to determine short-term efficacy, effects on overall survival, incidence of adverse effects, potential antigenicity with repeated administration, and to determine the populations of patients that would benefit from therapy.

In the meantime, IVIG is a treatment option in dogs with IMHA and with ITP that fail to respond to conventional therapy. It is also an option for the initial treatment of dogs with severe ITP, where the risk of fatal hemorrhage is considered substantial, and a rapid increase in platelet count is desirable. Doses from 0.5 to 1.5 g/kg may be effective, although most studies have used 1 g/kg. IVIG is administered as an intravenous infusion over 6-12 hours. It should be started at a slow rate (0.01 ml/kg/min) and gradually increased every 30-60 minutes to a maintenance fluid rate (maximum 0.08 ml/kg/min). Excessively high rates should be avoided in individuals that are fluid intolerant. Patients should be carefully monitored for adverse reactions during administration.

At this time, IVIG cannot be recommended as single agent therapy. It should be used together with glucocorticoids with/without other immunosuppressive agents. Benefits may be limited to only short-term improvement in some patients. The possibility of an increased risk of thromboembolism should be considered. The safety of multiple infusions remains to be determined.

Appendix. Commercial Preparations of Human Intravenous Immunoglobulins
Gamimune N: Bayer.
Gammar-IV: Centeon.
Sandoglobulin: Sandoz Pharmaceutical.
Gammagard: Hyland Division, Baxter Healthcare.
IVEEGAM: Immuno-US.
Venoglobulin-I: Alpha Therapeutics.
Venoglobulin-S: Alpha Therapeutics.
Polygam S/D: American Red Cross.

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