

A review of current indications, adverse effects, and administration recommendations for intravenous immunoglobulin

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Abstract

Objective – To review and summarize the body of literature regarding human intravenous immunoglobulin (hIVIG) therapy in veterinary medicine. Mechanism of action, usage in human medicine, adverse effects of therapy, implications for veterinary use, and administration recommendations are discussed.

Data Sources – Current human and veterinary peer-reviewed medical literature including original research articles and scientific reviews.

Human Data Synthesis – There are currently 6 labeled uses for hIVIG in human medicine, but preparations are used off-label to successfully treat multiple immune-mediated conditions. To maximize the potential of hIVIG use in animals and identify areas deficient in research, a review of the current literature is warranted.

Veterinary Data Synthesis – Investigation of hIVIG therapy in veterinary patients has been limited to the subjects of immune-mediated hemolytic anemia (IMHA), immune-mediated thrombocytopenia (ITP), Evan's syndrome, cutaneous disease, myasthenia gravis (MG), and sudden acquired retinal degeneration (SARDS). Proponents of veterinary hIVIG use believe administration may reduce transfusion requirements and decrease hospitalization time.

Conclusion – Immunoglobulin (Ig) has not been shown to decrease transfusion requirements in IMHA patients, but shows great promise for treatment of ITP and dermatological diseases. Although serial transfusion of hIVIG is employed in human medicine, repeated transfusion is not recommended in animals due to risk of severe allergic reaction. Other potential adverse effects of transfusion include delayed hypersensitivity reactions, thromboembolism, renal failure, hypotension, and aseptic meningitis.

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Keywords: hIVIG, immune-mediated disease, transfusion medicine

- > 90% IgG
- Efficacy is due to multiple mechanisms including blocking Fc receptors, elimination of pathogenic autoantibodies, modulation of cytokine synthesis, inhibition of complement and mediation of Fas- FasL interactions.
- Appears to have promise for ITP and various skin diseases, however questionable efficacy for IMHA.

1. Intro

- a. hIVIG is > 90% IgG
- b. free of aggregates, kinins, plasmin, kallikrein activators and infectious agents and usually with a low pH to deter growth of infectious agents and aggregation
- c. half life of 7-9 days in dogs

- d. efficacy likely due to ability to block Fc receptors, eliminate pathogenic autoantibodies, modulate cytokine synthesis (less IL2, IFN- γ , TNF α), inhibit complement (block active C3 and C4) and mediate Fas-Fas ligand (FasL) interactions (major mechanism of success in dermatologic conditions)
- e. documentation of hIVIG use in animals: IMHA, ITP, ES, cutaneous drug reactions, pemphigus foliaceus (PF), sudden acquired retinal degeneration syndrome (SARDS) and MG

2. Uses

- a. IMHA: no significant difference in prospective, blinded, randomized clinical trial (N=28) [2009 Whelan et al]
- b. ITP: single 0.5 g/kg dose hIVIG complete resolution 5 days earlier than placebo, discharge from hospital 4 days earlier, no difference in pRBC transfusion requirements, cost of hospitalization or mortality. [Bianco et al 2009]
- c. Evans Syndrome: 1 case report in a diabetic dog.
- d. Skin disease:
 - i. 1 case report in a dog with SJS (Stevens-Johnson Syndrome) after TMS administration. Lesions improved within 12 hours and resolved by 7 days.
 - ii. Another case series in 2 dogs with severe cutaneous drug reactions (life-threatening necrotic dermatitis and clinical signs) where two 1 g/kg hIVIG transfusions 24 hours apart lead to healing in 72 hours. (Trotman et al 2006).
 - iii. Case report in a cat with EM (erythema multiforme) receiving two 1 g/kg hIVIG transfusions administered 24 hours apart with improvement in 4 days and resolution in 8 days. (Byrne and Giger, 2000.)
 - iv. 1 case report in a dog with PF treated long term with multiple hIVIG transfusions whose case resolved and suffered no ill effects of hIVIG administration. (Rahilly et al, 2006.)
- e. SARDS and MG: more studies needed

3. Adverse Effects of IVIG

- a. humans (< 5%): acute hypersensitivity, thromboembolism (hypercoaguability, see Tsuchiya et al 2009), renal failure (sucrose mediated osmotic damage to renal tubules, Type III hypersensitivity), hypotension (IgG dimers), aseptic meningitis, fluid overload, pseudohyponatremia.
 - i. consider anticoagulant therapy with hIVIG in patients with pre-existing prothrombotic conditions.
- b. veterinary patients: increased risk due to introduction of xenoprotein

4. Transfusion Rates:

- a. give over 4-8 hours
- b. transfusion is initiated at a slow rate (0.1 mL/kg/min) and increased q30-60mins to a maintenance rate no to exceed 0.8 mL/kg/min.

Questions:

1. List 3 of the 5 mechanisms that make hIVIG effective:
2. Is hIVIG likely to be more beneficial in IMHA or ITP?

1. List 3 of the 5 mechanisms that make hIVIG effective:
 - a. blocking Fc receptors, elimination of pathogenic autoantibodies, modulation of cytokine synthesis, inhibition of complement and mediation of Fas- FasL interactions
2. Is hIVIG likely to be more beneficial in IMHA or ITP?
 - a. ITP

Condition	Dose	Pretreatment	Adverse effects observed	Study design	immunoglobulin product
IMHA ²²	0.5g/kg over 6 hours × 3 consecutive days	None	Swelling at the catheter site (2/28) Volume overload (1/28)	Blinded, randomized, clinical trial of 28 dogs	Gammaguard SD
ITP ^{23,25}	0.28–0.76 g/kg in a 5% solution over 6 hours; once	Diphenhydramine 0.5 mg/kg IM	None	Case series of 5 dogs	Polygam SD
	0.5 g/kg in a 6% solution over 6 hours; once	Diphenhydramine 0.5 mg/kg IM	None (followed over 6 months)	Prospective, randomized, double-blinded, placebo-controlled trial of 18 dogs	Carimune NF
Evan's syndrome ²⁶	1.3 g/kg in a 5% solution over 8 hours; once	Diphenhydramine 0.5 mg/kg SC	None	Case report of 1 dog	Polygam SD
Cutaneous drug reactions ^{9,28}	Dog 1: 1g/kg over 4 hours × 2 consecutive days	None	None	Case series of 2 dogs	Sandoglobulin
	Dog 2: 1 g/kg over 4 hours × 2 consecutive days	None	None	Case report of 1 kitten with EM	Sandoglobulin
	1 kitten: 1 g/kg over 4 hours in a 6% solution × 2 consecutive days	None	None		
SJS ²⁷	0.5 g/kg in a 5% solution over 7 hours; once	None	None	Case report of 1 dog	Flebogamma
PF ³⁰	0.5 g/kg over 5 hours × 4 followed by the same dose 3 weeks after discharge, 2 doses 9 weeks post discharge (consecutive days), and 1 transfusion q 7 days on weeks 12, 22, 26, and 31	None	None	Case report of 1 dog	Polygam SD
SARDS ³¹	0.5 g/kg in a 5% solution over 7 hours; once	None	None	Case series of 8 dogs	Not listed
MG ³²	Dog 1: 0.5 g/kg/ over 6 hours × 2 on consecutive days. Two additional doses administered 12 days after discharge and 17 days post discharge	None	Erythema and anxiety during transfusion 3, anaphylaxis during transfusion 4	Case series of 3 dogs	Gammaguard
	Dog 2: 0.5 g/kg over 6 hours; once	None	None		