

# 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 (IVIg) 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 IVIg in human medicine, but preparations are used off-label to successfully treat multiple immune-mediated conditions. To maximize the potential of IVIg use in animals and identify areas deficient in research, a review of the current literature is warranted.

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

**Conclusion:** Intravenous IgG has not been shown to decrease transfusion requirements in IMHA patients, but does improve the treatment of ITP and dermatological diseases. Although serial transfusion of IVIg 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:** IVIg, 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- $\gamma$ , TNF $\alpha$ ), 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 (hypercoagulability, 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.

| Condition                              | Dose                                                                                                                                                                                     | Pre-treatment                      | Adverse effects observed                                                    | Study design                                                                 | Immunoglobulin product |
|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------|
| MeV <sup>21</sup>                      | 0.1g/kg over 6 hours x 3 consecutive days                                                                                                                                                | None                               | Swelling at the catheter site (2/30) Volume overload (1/30)                 | Blinded, randomized, clinical trial of 30 days                               | Gammagard SD           |
| COPD <sup>22</sup>                     | 0.25-4.75 g/kg in a 5% solution over 6 hours once                                                                                                                                        | Oxycodone/hydrocodone 0.1 mg/kg SC | None                                                                        | Case series of 5 days                                                        | Polygyn SD             |
|                                        | 0.5 g/kg in a 5% solution over 4 hours once                                                                                                                                              | Oxycodone/hydrocodone 0.1 mg/kg SC | None (followed over 6 months)                                               | Prospective, randomized, double-blinded, placebo-controlled trial of 10 days | Carmuna NF             |
| Everts syndrome <sup>23</sup>          | 1.0 g/kg in a 5% solution over 4 hours once                                                                                                                                              | Oxycodone/hydrocodone 0.1 mg/kg SC | None                                                                        | Case report of 1 day                                                         | Polygyn SD             |
| Cutaneous drug reactions <sup>24</sup> | Day 1: 1g/kg over 4 hours x 2 consecutive days                                                                                                                                           | None                               | None                                                                        | Case series of 2 days                                                        | Sentogridulin          |
|                                        | Day 2: 1 g/kg over 4 hours x 2 consecutive days                                                                                                                                          | None                               | None                                                                        | Case report of 1 patient with 28                                             | Sentogridulin          |
|                                        | 1 mg/kg: 1 g/kg over 4 hours in a 5% solution x 2 consecutive days                                                                                                                       | None                               | None                                                                        |                                                                              |                        |
| SJS <sup>25</sup>                      | 0.5 g/kg in a 5% solution over 7 hours once                                                                                                                                              | None                               | None                                                                        | Case report of 1 day                                                         | Pellegemma             |
| PS <sup>26</sup>                       | 0.5 g/kg over 6 hours x 4 followed by the same dose 2 weeks after discharge, 3 doses 4 weeks post discharge (consecutive days), and 1 transfusion q 7 days (in weeks 10, 20, 30, and 35) | None                               | None                                                                        | Case report of 1 day                                                         | Polygyn SD             |
| SARS-CoV <sup>27</sup>                 | 0.5 g/kg in a 5% solution over 7 hours once                                                                                                                                              | None                               | None                                                                        | Case series of 6 days                                                        | Not listed             |
| MS <sup>28</sup>                       | Day 1: 0.5 g/kg over 6 hours x 2 on consecutive days<br>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 days                                                        | Gammagard              |
|                                        | Day 2: 0.5 g/kg over 6 hours once                                                                                                                                                        | None                               | None                                                                        |                                                                              |                        |