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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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Introduction to Human Intravenous Immunoglobulin

Intravenous immunoglobulin is a preparation of highly purified immunoglobulin (Ig) collected from a large pool of healthy human plasma. Human IVIG contains over 90% intact, biologically active IgG, and trace amounts of IgA, IgM, CD4, CD8, and human leukocyte antigen molecules.[1] It has been utilized in human medicine since the 1940s to confer passive immunity to deficient patients and also as an immunomodulator for a myriad of immune-mediated conditions.[2–4] Donors are screened against human immune-deficiency virus (HIV), hepatitis B and C, and human T-cell lymphotrophic retroviruses.[5] After collection, the product is purified by a variety of methods including pasteurization, nanofiltration, and multiple washes with solvents and detergents.[5] The final preparation is free of aggregates, kinins, plasmin, kalikrein activators, and infectious agents.[6] Additionally, many human intravenous immunoglobulin (hIVIG) formulations have low pH ranges to deter growth of infectious agents and prevent aggregation.[1] The finished hIVIG product has a half life of 21–33 days and 7–9 days in humans and dogs, respectively.[4,7]

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hIVIG and Immunomodulation

Although it is intuitive that IgG replacement therapy would be beneficial for antibody-depleted patients, the mechanism of hIVIG's immunomodulatory activity is

not well established. Because hIVIG preparations are heterogeneous, it is difficult to determine the exact mechanism of action in every disease process. However, it is widely postulated that the efficacy of hIVIG therapy is secondary to its ability to block Fc receptors, eliminate pathogenic autoantibodies, modulate cytokine synthesis, inhibit complement, and mediate Fas-Fas ligand (FasL) interactions.[6–10]

Ig acts as an immunomodulator via interaction with membrane receptors that are vital for autoreactivity and tolerance to self.[4] Fc proteins are examples of such receptors, and are found on cell membranes of macrophages, neutrophils, natural killer cells, B cells, eosinophils, platelets, and mast cells.[4] In people, these receptors function via binding to antibody-antigen complexes and stimulating antibody-mediated phagocytosis. Human Ig has also been shown to effectively bind canine lymphocytes and monocytes.[11] Once bound, hIVIG blocks macrophage Fc receptors, inhibits phagocytosis, and subsequently decreases tissue damage.[4,8,11] Additionally, hIVIG is thought to regulate the immune system through elimination of pathogenic autoantibodies. Donor antibody present in hIVIG is postulated to bind directly with abnormal host antibodies, stimulating their removal.[7,8]

Cytokines are an additional component of the immune system affected by hIVIG administration. Studies have shown that stimulated T cells produce significantly less interleukin (IL2), interferon (IFN-γ), and tumor necrosis factor (TNFα) in the presence of hIVIG.[4] Overall downregulation of cytokine activity results in decreased activation of inflammatory pathways and less cellular damage.

Intravenous Ig further regulates the immune response through inhibition of complement.[4] The complement system consists of a group of blood proteins that mediate specific antibody response to antigenic stimulation. In the classical pathway, an IgG-antigen complex binds to circulating complement and initiates a cascade, which ultimately results in cell death. Human Ig curtails this chain of events through blockage of active C3 and C4 complement fragments, which prevents binding to target cells and subsequently inhibits acute complement dependant tissue injury.[4]

Finally, hIVIG administration is believed to mediate Fas-FasL interaction. The FasL is responsible for initiation of cellular death through transduction of apoptotic signals to keratinocytes.[7–9] Blockade of Fas-FasL complex formation by hIVIG inhibits signaling and results in keratinocyte stability. Fas-FasL blockade is considered the major mechanism behind the success in hIVIG therapy in dermatologic conditions, as it breaks the cycle of ongoing keratinocyte apoptosis.[9,11–14]

Uses in Human Medicine

Currently, there are 6 FDA-approved uses for hIVIG including Kawasaki disease, bone marrow transplantation, idiopathic thrombocytopenic purpura, chronic B-cell lymphocytic leukemia (CLL), pediatric HIV, and primary Ig deficiency.[15] However, hIVIG therapy is employed for over 50 conditions beyond those described by the FDA including sepsis, autoimmune hemolytic anemia, and myasthenia gravis (MG).[14–16] Over 50% of all hIVIG prescribed is used for the off-label conditions of necrotizing fasciitis, toxic epidermal necrolysis (TEN), and Guilliain-Barre syndrome.[15,17] In 2000, Chen et al[18] reported a multicenter evaluation of hIVIG use comparing the efficacy and adverse effects associated with labeled and off-label administration.[18] In this retrospective analysis, 107 patients received hIVIG for approved indications, and 130 patients were treated off-label. No significant differences in positive outcome or adverse events were noted.[18] The use of hIVIG in human medicine is continuing to grow, and approved indications will likely multiply as more studies are completed.

IVIG and Veterinary Medicine

Reports of successful hIVIG use in veterinary patients have been surfacing for almost 2 decades. Success in human medicine and anecdotal accounts of rapid resolution to multiple immune-mediated processes have contributed to the allure of hIVIG use in animals, but no consensus has been reached on indications, appropriate dosages, or safety of this compound in veterinary medicine. At this juncture, documentation of hIVIG use in animals has been limited to the subjects of immune-mediated hemolytic anemia (IMHA),[2,3,19–22] immune-mediated thrombocytopenia (ITP),[19–25] Evan's syndrome (ES),[26] cutaneous drug reactions,[9,12–14,26–28] pemphigus foliaceus (PF),[29,30] sudden acquired retinal degeneration syndrome (SARDS),[31] and MG.[32] In order to maximize the potential of hIVIG use in animals and identify the areas deficient in research, a review of the current literature is required.

IMHA

The first studies evaluating hIVIG therapy in animals involved its use in IMHA.[2,3] Although glucocorticoids are the cornerstone of treatment for IMHA, additional immunomodulating agents are often necessary for successful management of this disease. Commonly advocated drugs (alone or in combination) include cyclosporine, azathioprine, cyclophosphamide, and hIVIG.[20–22] The majority of these agents take days to weeks to become

effective, and patients may decline precipitously in the interim. As blockade of Fc receptors by Ig is immediate, it is postulated that administration of hIVIG may be useful for initial stabilization in patients with IMHA allowing time for long-term immunosuppressive therapy to reach efficacy.[2,3,8,19–22]

Multiple retrospective studies have been conducted over the past 15 years, but no clear indications for hIVIG in IMHA patients have been established.[19–22] One of the earliest prospective studies was conducted by Scott-Moncreiff et al[3] in 1997, in which hIVIG was administered to 10 dogs that failed to respond to conventional immunosuppressive therapies.[3] Although rapid improvement was noted after administration of hIVIG, all dogs quickly relapsed. Additionally, because multiple agents were utilized during the study period, it was impossible to discern what drug or drug combination resulted in remission. The authors thus concluded that hIVIG might be useful for short-term stabilization until other agents become effective but that additional studies were required before this treatment could be recommended.[3]

In 2009, Whelan et al[22] reported a prospective, blinded, randomized clinical trial in 28 dogs diagnosed with IMHA.[22] At enrollment, dogs were randomly assigned to receive repeated doses of hIVIG or placebo for 3 consecutive days. For the subsequent 14 days, all dogs received immunosuppressive therapy solely in the form of glucocorticoids. No significant difference was noted in length of hospitalization, survival time, or the number of blood transfusions required prior to stabilization of any patients. It was unclear if the lack of statistical significance was attributable to the small study size or a true lack of difference in response to protocol. Regardless, Whelan et al[22] concluded that if a true difference was present, it was not significant enough to justify the additional cost of hIVIG therapy in this patient population.[22] Larger clinical trials are required to fully elucidate the role of hIVIG in the management of canine IMHA.

ITP

ITP is another condition that holds significant interest regarding the benefit of hIVIG therapy. Patients with primary ITP generally show resolution of severe thrombocytopenia within a week of initiation of glucocorticoid therapy, and within 5 days if vincristine is included in the treatment protocol.[24] However, severe complications are often encountered secondary to hemorrhagic events before traditional agents become effective. In human medicine, hIVIG is employed to rapidly and reliably increase platelet counts during this acute phase. Administration of hIVIG has been shown to decrease the number of blood transfusions required for stabilization, ultimately decreasing hospitalization time and maximizing patient recovery.[4,5,33] In hopes that hIVIG would have similar effects in canine ITP patients, several studies have been conducted.

In a retrospective study, Bianco et al[23] evaluated the effect of a single hIVIG transfusion in addition to glucocorticoid therapy in 5 dogs with ITP and uncontrollable hemorrhage.[23] Most (4/5) dogs rapidly and significantly responded to hIVIG therapy, with mean platelet counts increasing from 2.5×10^9/L (2,500 platelets/μL) to 62.7×10^9/L (62,750 platelets/μL) within 24 hours of Ig administration. Responders did not require additional packed red blood cell (pRBC) transfusions after treatment with hIVIG, and no adverse effects of Ig therapy were encountered. Additionally, responders in this study left the hospital an average of 46 hours earlier than subjects in another recent report who were managed with vincristine and prednisone.[23,24] The authors concluded that hIVIG was well tolerated, resulted in a rapid increase in platelet count, and led to resolution of clinical signs in most dogs presenting with ITP.[23] Although preliminary results of this study were extremely promising, the retrospective nature, lack of controls, and small sample size prompted further research.

The same group of investigators recently conducted a prospective, randomized, double-blinded, placebo-controlled study of hIVIG for management of primary ITP.[25] Their objective was to evaluate hIVIG as a fast-acting treatment option for use in the acute stages of ITP. This study compared the effects of standard corticosteroid therapy in the form of prednisone (1.5 mg/kg q 12 hours) with and without the addition of a single 0.5 g/kg dose of hIVIG. Impact on platelet count recovery, hospitalization time, transfusion requirements, cost of patient care, and mortality were subsequently evaluated. No concurrent immunomodulators were allowed until day 7. At that time, any immunosuppressive therapy could be added at the attending clinicians discretion. Significant statistical differences in resolution of thrombocytopenia and hospitalization time were recorded. Patients that received hIVIG produced $>40 \times 10^9$/L ($>$40,000 platelets/μL) a median of 4 days before those in the placebo group. Additionally, the hIVIG population reached "complete resolution" as defined by platelet counts $>160 \times 10^9$/L (160,000 platelets/μL) a median of 5 days before the placebo group. Most significantly, animals receiving hIVIG were discharged an average of 4 days earlier than those receiving glucocorticoids alone. The median volume of pRBC transfusions administered was not statistically different between study groups, nor was a significant difference noted in the median cost of hospitalization. Further, no significant difference in mortality was observed between the placebo and hIVIG groups. No adverse effects of hIVIG administration

occurred in any patients, and although platelet function was not specifically evaluated, no evidence of bleeding occurred after platelet counts reached 40 × 10^9/L (40,000/μL). Overall, the authors concluded that a single infusion of hIVIG administered within 24 hours of institution of steroid therapy is associated with a significant reduction in time to resolution of thrombocytopenia and duration of hospitalization without increasing the expense of medical care in dogs with presumed ITP.[25]

Although the aforementioned results are compelling, it is currently unclear if hIVIG administration is more effective for resolution of ITP than alternative therapeutic options. A recent study by Rozanski et al[24] compared platelet recovery and hospitalization time in ITP patients receiving prednisone and vincristine against ITP patients receiving prednisone therapy alone.[24] Patient outcome, duration of hospitalization, and time to resolution of thrombocytopenia were similar to those described in the prospective study by Bianco et al[25] when hIVIG was added to prednisone therapy.[24,25] Prospective studies comparing the use of hIVIG versus vincristine as adjunctive therapy to corticosteroids in cases of ITP are indicated. Regardless, there is convincing evidence that hIVIG is valuable for the initial stabilization of ITP, especially in cases exacerbated by active hemorrhage.

Evan's Syndrome

The merits of IVIG for management of immune-mediated cytopenias were further evaluated in a 2009 case report describing a case of canine ES.[26] In this particular case, glucocorticoid therapy was relatively contraindicated due to pre-existing diabetes mellitus, and the dog was successfully managed with a combination of leflunomide and hIVIG therapy.[26] On presentation, the dog was severely thrombocytopenic with <2.0 × 10^9/L (<2,000 platelets/μL) and had a hematocrit of 0.12 L/L (12%). The dog was initiated on lefluonomide therapy at 2 mg/kg q 12 hours and administered a single dose of hlVIG at 1.3 g/kg. Immediately after completion of the hIVIG transfusion, the platelet count increased to 51.1 × 10^9/L (51,100/μL). Within 24 hours, platelet numbers further increased to 116.0 × 10^9/L (116,000/μL). Although 3 pRBC transfusions were required to maintain an appropriate packed cell volume, the patient's platelet numbers remained within reference intervals during hospitalization. One week after discharge, the dog represented for lethargy and was again anemic with a hematocrit of 0.19 L/L (19%). Mild thrombocytopenia was also documented with a platelet count of 136.0 × 10^9/L (136,000/μL). One additional pRBC transfusion was administered and the dog was discharged. No further relapses occurred within the next 10 months. Results described in this report are consistent with previous observations that the benefit of hIVIG in managing IMHA is questionable and often short lived.[19–22] Additionally, these results parallel findings in other cases of ITP managed with hIVIG, which suggest that Ig may positively contribute to rapid resolution of thrombocytopenia in immune-mediated disease.[23,25]

Cutaneous Disease

Although evidence of immune dysfunction can appear in almost any organ system, few manifestations are more dramatic than those involving the skin. Adverse drug reactions commonly have dermatologic impact, with associated high mortality rates. Examples of cutaneous drug reactions include TEN, erythema multiforme (EM), and Stevens-Johnson syndrome (SJS).[9] These conditions are characterized by varying amounts of full thickness epidermal detachment in conjunction with systemic clinical signs.[34] Historically, standard immunosuppressive therapies have not been successful in controlling these syndromes in humans or companion animals.

While hIVIG is not approved for the management of dermatologic disease in humans, this therapy has been widely utilized in the management of skin conditions including TEN and other cutaneous drug reactions.[9,12–14,17,35] No controlled, randomized trials have been performed; however, a retrospective study of TEN by Trent and Kirsner described an 83% decrease in human mortality rates with inclusion of hIVIG to standard treatment protocol.[36] In addition, a 2003 consensus statement was published recommending hIVIG therapy in patients with autoimmune blistering cutaneous disease that fails to respond or responds negatively to standard therapeutics.[37] Success in human medicine has generated much veterinary interest regarding potential advantages of hIVIG in treatment of cutaneous dysfunction.

A 2004 case report published by Nuttall and Malham[27] documented resolution of SJS after hIVIG transfusion in 1 dog. Prior to referral, the dog had been diagnosed with SJS following treatment with trimethoprim-potentiated sulfadiazine (TMS). No improvement in the condition was noted after withdrawal of the TMS or combined treatment with antimicrobials and topical fusidic acid/betamethasone gel. Upon presentation, complaints included a 2-week duration of mucocutaneous ulceration, sloughing of the nasal planum and footpads, and erythematous macular eruption of the interdigital skin, ventral pinnae, and ventral abdomen. Systemic malaise was also reported.

Methylprednisolone therapy was instituted initially, but discontinued due to evidence of secondary *Pseudomonas aeruginosa* infection.[27] The dog continued to decline until a single 0.5 g/kg transfusion of hIVIG was

administered. Twelve hours after the hIVIG transfusion, the dermal lesions began to improve and were completely healed 7 days later. Systemic issues also resolved, and no adverse effects secondary to hIVIG administration were encountered. Although these authors concluded that hIVIG may be an effective treatment for canine SJS and other EM diseases, cautious interpretation of this recommendation is merited until controlled clinical trials are performed.[12,27]

Trotman et al[9] also evaluated hIVIG therapy in 2 dogs presenting with severe cutaneous drug reactions in 2006.[9] Both animals were referred with life-threatening necrotic dermatitis and systemic clinical signs after being treated for several days. Dog 1 had not received any therapeutic interventions prior to presentation. Dog 2 had been previously treated with antimicrobials and oral steroids. After presentation, both dogs continued to decline in the face of conventional treatment. Each subsequently received two 1 g/kg hIVIG transfusions 24 hours apart. Additionally, broad-spectrum antimicrobials, analgesics, and fluid therapies were employed. Initially, no additional steroids were administered to either dog due to significant concerns for secondary infection.[9] Resolution of systemic illness and healing of skin lesions was noted within 72 hours in both dogs. No adverse effects occurred secondary to hIVIG therapy, even though multiple transfusions were administered. Dog 2 was discharged with prednisone and azathioprine. Each animal was followed for 3 years after discharge and had no evidence of relapse or delayed transfusion effects.[9]

One case documenting the use of hIVIG in a cat with dermatologic disease was published by Byrne and Giger in 2002.[28] Presenting complaints included extensive crusting, ulcerated, purulent fissures, and systemic malaise developing shortly after a routine health examination in which the kitten received a rabies vaccine, oral antihelminthic therapy, and topical otic medications. The kitten returned to the referring veterinarian 2 days later, and was treated conservatively for crusting dermatitis with prednisone acetate. Although otherwise healthy during her recheck, the kitten developed systemic malaise shortly after discharge and presented on day 10 to the referral hospital. She was diagnosed with EM via cutaneous biopsy, and discharged with topical moisturizer, lime sulfur, and systemic antimicrobials. Fourteen days later (day 25), she represented with severe dermal compromise. Due to the severity of the lesions, the lack of improvement with supportive treatment, the progressive nature of EM, and the known resistance to conventional therapy, hIVIG was employed for more aggressive treatment. Two 1 g/kg hIVIG transfusions were administered 24 hours apart. Improvement was noted in skin health and overall condition within 4 days, and in 8 days, the lesions had largely resolved. No adverse reactions were noted after hIVIG administration, and no signs of relapse were recorded when the kitten returned for routine ovariohysterectomy 8 weeks later.[28] Although widespread use of hIVIG for management of cutaneous drug reactions cannot be recommended without more research, hIVIG therapy shows great potential in this arena.

Human Ig has also shown promise in the management of other severe cutaneous disorders including PF. Pemphigus is the most common canine immune-mediated cutaneous disease, and is associated with high morbidity and mortality.[29,30] Pathogenesis involves the destruction of adhesions between keratinocytes (desmosomes) and leads to severe blistering and pustule formation.[29,37,38] Standard immunosuppressant therapy for management PF includes prednisone alone or in combination with cyclosporine or azathioprine, but control of this condition is often frustrating and difficult.[30]

A case report by Rahilly et al[29] published in 2006 describes the successful use of hIVIG to treat a dog presenting with PF.[29] A significant concern for sepsis precluded the use of standard immunosuppressant therapy in this case; therefore, a multiple hIVIG transfusion protocol based on human methodology was instituted in response to the dog's declining condition.[29] The dog received 4 transfusions of hIVIG over 5 days, each at a dose of 0.5 g/kg. One additional hIVIG treatment was administered 3 weeks later. Although mild signs of relapse (fever, new skin lesion, weakness) were present on week 9, these rapidly resolved with 2 additional transfusions, 24 hours apart. Maintenance therapy was then scheduled for transfusions on weeks 12, 22, 26, and 31. The same hIVIG dose was employed for initial and follow-up treatment. Skin lesions rapidly improved during and after the course of hIVIG. Antimicrobial therapy was also included in the initial treatment protocol, but was discontinued on day 5. Also on day 5, more traditional therapeutics consisting of azathioprine and prednisone were implemented as significant improvement had occurred and concern for sepsis greatly decreased. The dog in question remained asymptomatic 1 year after initial presentation and 4.5 months after the final hIVIG transfusion before he was lost to follow-up. No adverse effects associated with hIVIG administration were observed at any time.[29] Although this is the first report of long-term hIVIG treatment for maintenance of clinical remission in canine immune-mediated disease, it is not entirely clear which therapy or combination of therapies resulted in successful resolution of PF. These results suggest that hIVIG may have a place in the treatment of PF, and also bring into question the long-standing belief that multiple hIVIG transfusions cannot be tolerated in dogs. Although large scale, prospective, clinical trials are indicted

for validation, these results imply that hIVIG may be useful for maintenance of remission in immune-mediated disease states.

Miscellaneous Disease

While most research concerning veterinary use of human hIVIG has focused on immune-mediated cytopenias and dermatologic conditions, recent studies have branched out to explore potential application to disease in other organ systems. Two notable studies have evaluated hIVIG therapy to combat the effects of SARDS and MG.[31,32]

Sudden Acute Retinal Degeneration Syndrome

Sudden acute retinal degeneration syndrome is a poorly understood condition resulting in acute and painless canine blindness. Etiology of SARDS is debatable, but extensive tissue analysis has revealed the presence of retinal Ig-producing plasma cells in SARDS patients.[39–41] These cells may be responsible for intraretinal production of autoantibodies and ultimately immune-mediated blindness. Ophthalmologists postulate that these immune complexes contribute to the development of antibody-mediated retinopathy and result in irreversible retinal damage.[39,42] Blindness may also be linked to antibody-mediated neuronal damage secondary to strong complement activity present in the retinas of SARDS patients.[31,41] Canine SARDS has long been considered untreatable due to a lack of response to anti-inflammatory, antimicrobial, and immunosuppressive medications. Similarly, antibody-mediated retinopathy in people is poorly responsive to conventional therapy, but blindness has been shown to be at least partially responsive to therapies involving hIVIG.[43]

To investigate potential benefits for canine SARDS patients, hIVIG therapy was initiated in 8 dogs at Iowa State University in 2007.[31] The ISU protocol involved administering 0.5 g/kg over 6 hours on days 1 and 3. All 8 dogs showed significant improvement in visual maze behavior and recovery of photoreceptor-mediated pupil response, which the authors felt were the most reliable markers of clinical improvement.[31] It is noteworthy that even when subjects recovered visual navigation skills, vision was evaluated as very crude and likely absent in conditions of dim light. There was no improvement in menace response post-treatment in any patients; however, investigators did not find any correlation between a negative menace and ability to successfully navigate the visual maze. Grozdanic et al[31] also included data obtained from 11 dogs treated with hIVIG for SARDS outside of this study but utilizing the ISU protocol. Slightly less than half of those subjects (5/11) regained navigational skills when evaluated in the visual maze.[31] As in the ISU study, none of these subjects regained a menace response. Although the majority of canines treated with hIVIG outside of the original ISU study failed to recover vision, Grozdanic et al[31] concluded that significant improvement in visual behavior occurred in canine SARDS patients treated with hIVIG. The authors cautioned against treatment in patients with glaucoma, retinal degeneration, cataracts, or duration of blindness of over 2 months as concurrent ocular disease is thought to negate potential positive effects of therapy.[31] No adverse effects of hIVIG transfusion were encountered. Given the high cost and potential risks associated with hIVIG therapy in dogs, its utility in management of SARDS needs further evaluation before broad treatment recommendations can be made.

Myasthenia Gravis

MG has also recently been experimentally treated with hIVIG. Acquired MG is an immune-mediated neuromuscular disorder resulting from autoantibody-mediated destruction of acetylcholine receptors on the postsynaptic neuromuscular junction.[44] The condition results in focal or generalized weakness and may incorporate megaesophagus. Prognosis is guarded to poor, with severe potential complications including aspiration pneumonia and respiratory arrest. Anticholinesterase inhibition is a mainstay of therapy; however, efficacy is dependent on the number of acetylcholine receptors available for salvaged acetylcholine. This is problematic for patients suffering from MG as circulating autoantibodies competitively bind those same acetylcholine receptors.[32,44,45] The natural course of MG is often spontaneous remission; however, immunosuppression is utilized in cases of severe or refractory MG to decrease cost and improve prognosis.[32,45]

No prospective, randomized trials have been performed which evaluate the efficacy of immunosuppressive therapy in veterinary MG patients. Standard protocols often include prednisone, cyclosporine, azathioprine, and mycophenolate mofetil.[32] Many of these agents take weeks to months to become effective, and are associated with significant side effects and expense. Although off-label in humans suffering from MG, hIVIG is reported to be an effective treatment with a rapid onset of action.[45]

Abelson et al[32] reported a case series of 2 myasthenic dogs treated with hIVIG Ig.[32] The first dog received 1 0.5 g/kg hIVIG transfusion without any observed adverse effects. The other dog received a series of four 0.5 g/kg hIVIG transfusions over several weeks and experienced an anaphylactic reaction during the fourth transfusion. The reaction resolved after discontinuation of

the transfusion in addition to administration of corticosteroids and antihistamines. Both dogs improved initially with all weakness resolving within 48 hours; however, both dogs had recurrence of clinical signs within the subsequent days to weeks. Upon relapse, alternative therapies were employed in both patients.[32] Investigators concluded that benefits of hIVIG therapy in this limited population were questionable and did not justify treatment in the face of potential adverse effects and expense. As no additional veterinary studies exist evaluating hIVIG in the management of MG, no definitive conclusions can be made at this time.

Adverse Effects of IVIG Administration

Intravenous Ig is well tolerated in people, with less than 5% of patients suffering from adverse effects after transfusion.[3] The most common side effect of hIVIG use is acute hypersensitivity; other reported complications include thromboembolism, renal failure, hypotension, aseptic meningitis, and fluid overload.[15,17,46–55] Veterinary patients exposed to hIVIG are at risk for these same complications, but carry a higher risk of reaction as hIVIG administration involves xenoprotein introduction to the body.

Hypersensitivity and Anaphylaxis

Transfusion reactions are thought to occur secondary to IgG aggregation and complement activation, and result in a constellation of symptoms including fever, diarrhea, chills, dyspnea, circulatory shock, convulsions, back pain, arthralgias, and urticaria.[17,47–49] Type I hypersensitivity reactions are typically mild and transient, but can progress to anaphylaxis. Removal of aggregates from hIVIG preparations have markedly decreased the incidence of anaphylactic reaction in transfused humans, and use of slow transfusion rates further decreases risk.[48] It is well established that human patients with IgA deficiencies have a higher risk of developing anaphylaxis secondary to hIVIG transfusion; however, screening prior to transfusion is controversial.[47–49] Additionally, preparations containing very low levels of IgA are now available to decrease the danger and are frequently available in human hospitals (Table 1).[17,48] Screening is not typically employed in veterinary medicine; however, use of an alternative hIVIG product may eliminate undesired hypersensitivity and avoid life-threatening transfusion reactions in veterinary patients (Table 1).

Hypercoagulation

Thromboembolic events including deep vein thrombosis, myocardial infarction, pulmonary embolism, central retinal vein occlusion, cerebro-vascular accidents, and hepatic veno-occlusive disease have been reported in people following hIVIG transfusion.[15,46,52] A 2009 study by Tsuchiya et al[52] revealed increased concentrations of circulating thrombin-antithrombin complexes and fibrinogen degradation products in healthy beagles receiving human Ig, and concluded that hIVIG administration promotes hypercoagulability in dogs.[52] Human Ig is known to increase platelet numbers and platelet activation, and preparations also often contain prothrombotic factor Xa.[46,52] Further, many products are hyperosmolar secondary to a high sugar or salt content, which has been implicated in thrombotic complication.[52] Lyophilized products may also be hyperosmolar depending on the type and quantity of dilutant used for reconstitution (Table 1).

Hyperviscosity is an additional contributory factor for generation of thromboembolic disease via impediment of capillary flow. Development of a hyperviscous state is believed to directly correlate with hyperosmolality, hIVIG product concentration, and rapid infusion of hIVIG.[47–49,51,52] To prevent an abrupt increase in viscosity, slow infusion of hIVIG is recommended in humans at a rate of less than 400 g/kg over 8 hours.[52]

Underlying disease and concurrent therapies may also contribute to the danger of hypercoagulability, but the overall effect of all factors is unclear. As many conditions treated with hIVIG are intrinsically hypercoagulable, it is important to recognize that hIVIG therapy may exacerbate coagulation issues exponentially. A study by Whelan et al[22] compared D-dimer concentrations in IMHA dogs receiving hIVIG to patients receiving placebo and found no statistical difference between the 2 groups.[22] Although the true risk of thrombosis associated with hIVIG administration in veterinary patients is unknown, many clinicians advocate anticoagulant therapy in conjunction with hIVIG administration in patients with preexisting prothrombotic conditions.[52]

Renal Failure

Renal failure is another reported adverse effect of hIVIG administration seen not only in people with chronic renal insufficiency, but increasingly in geriatric and diabetic patients.[6,47–49,53] Azotemia is usually transient and occurs within 2–5 days of therapy.[4,47–49,53] Acute renal failure (ARF) is a potential sequela, and is secondary to osmotic damage to the proximal tubules. Renal lesions are characterized by marked cytoplasmic vacuolization, cellular swelling, and tubular occlusion.[47–49,53,54] Renal toxicity is induced by sucrose used as a stabilizing agent in many hIVIG preparations. Over 90% of patients that develop ARF have received Ig preparations containing sucrose.[15] Alternative products are widely

Table 1: Human intravenous immunoglobulin products used in veterinary studies

	Flebogamma 5% DIF[a,f]	Gammaguard SD[b,f]	Gammaguard liquid[c,f]	Sandoglobulin[d,62]	Carimune NF[e,f]	Polygam SD[f]
Manufacturer	Grifols	Baxter	Baxter	Sandoz	CSL Behring	Baxter
Concentration (%)	5	5 and 10	10	3, 6, 9, or 12	3, 6, 9, or 12	10
pH	5–6	6.8	4.6–5.1	3%–6.5 6%–6.61 9%–6.64 12%–6.8	6.6	6.4–7.2
IgA content (μg/mL)	<50	2.2	37	Trace (μg/mL)	720	<2.2
Percentage IgG (%)	>97	>90	>98	>96	>96	>90
Sodium content at 5% concentration	<3.2 mmol/L	0.85%	Nondetectable	<20 mg nail/g protein	<20 mg NaCl/g protein	0.085%
Diluent	NA	Sterile H_2O	NA	5% dextrose Sterile H_2O 0.9% NaCl	5% dextrose Sterile H_2O 0.9% NaCl	Sterile H_2O
Osmolality (mOsm/L)	240–370	5%–636 10%–1,250	240–300	5% dextrose–444–1,020 Sterile H_2O –192–768 0.9% NaCl–498–1,074	5% dextrose–444–1,020 Sterile H_2O –192–768 0.9% NaCl–498–1,074	5%–636 10%–1,250
Sugar content	5% D-sorbitol	2% glucose	No sugar added	1.67 g sucrose/g protein	1.67 g sucrose/g protein	2% glucose
Form	Liquid	Lyophilized. Administration required <2 hours if reconstituted outside of a hood; may be refrigerated for 24 hours if reconstituted under a hood	Liquid	Liquid	Lyophilized. Administration required <2 hours if reconstituted outside of a hood; may be refrigerated for 24 hours if reconstituted under a hood	Lyophilized. Administration required <2 hours if reconstituted outside of a hood; may be refrigerated for 24 hours if reconstituted under a hood
Storage requirements	24 months (36–77°F)	24 months <77°F	36 months 36–46°F; 9 months at 77° if within 24 months of manufacture	24 months <80°F	24 months (36–77°F)	24 months <77°F
Filter size (μm)	15–20	15	15	Not required	15	15
Flushing compatibility	NA	0.9% NaCl or 5% dextrose	5% dextrose incompatible with 0.9% NaCl	5% dextrose or 0.9% NaCl	5% dextrose or 0.9% NaCl	Sterile H_2O
Donor pool size	>1,000	>10,000	Unlisted	>16,000	>16,000	>1,500

Table reviews products used in current veterinary literature that are available in the United States. Superscript letters indicate footnotes.

available without sucrose, and may contain albumin, glucose, maltose, glycine, or D-sorbitol for stabilization purposes.[15,49,a–f] Studies have shown that patients receiving preparations containing maltose have a much lower incidence of renal dysfunction.[15,47–49] Despite the risk of renal damage, hIVIG containing sucrose is sometimes used in diabetic patients, as it will not interfere with glycemic control.[15] Current recommendations dictate that sucrose should not be administered at a rate higher than 3 mg/kg/min in patients at risk.[4] Multiple hIVIG products with differing stabilizers are available for transfusion (Table 1). Although less frequent, proximal tubular damage can also occur with nonsucrose stabilizers, secondary to the high solute load encountered with hIVIG administration.[47–49,53,54]

Type III allergic reactions may also lead to renal failure. Glomerulonephritis may develop secondary to allergen-IgG complex precipitation in tissues, resulting in inflammation via complement fixation.[49,53]

Finally, it has been postulated that hIVIG may induce renal artery vasoconstriction and subsequently lead to ischemic injury.[49,53] Although possible, this is a less

likely explanation for the development of ARF after hIVIG administration, as lesions secondary to derangements in blood flow are primarily found in the distal nephron.[53]

Hypotension

Hypotension is infrequently encountered secondary to hIVIG transfusion, and is thought to be associated with the presence of IgG dimers in some hIVIG preparations.[15,48,55] Dimer formation results in hypotension secondary to complement activation and is directly related to the number of donors contributing to the finished product.[15,48,55] Larger donor pools increase the risk of hypotensive events.[15,48,55] It is also postulated that a drop in blood pressure may occur secondary to effects of hIVIG leukocyte activation and release of a platelet-activating factor.[15,48,55] Anaphylactic reaction can also contribute to hypotensive crises. As previously mentioned, use of an alternate product with a decreased IgA concentration may eliminate some of these adverse effects (Table 1). Additionally, a study by Kroez et al[55] concluded that administration of hIVIG preparations with a low pH (ideally 4.7) substantially reduces IgG dimerization and decreases the risk of hypotension.

Miscellaneous Risks

Pseudohyponatremia is a common finding after hIVIG infusion. Derangements in measured sodium levels occur secondary to an increases in plasma protein levels and decreases in the plasma water volume.[54] The effect is mild, but recognition is important for avoidance of unnecessary treatment with fluid restriction or infusion of concentrated sodium chloride.[54]

Aseptic meningitis rarely develops after Ig transfusion, and is a dose-related complication.[50] In people, meningitis is more commonly noted in patients with a history of migraine headaches.[15,50] The pathophysiology is unknown, but symptoms generally occur 6–48 hours post-transfusion. Cerebrospinal fluid analysis often demonstrates pleocytosis and elevated protein levels.[50]

As with other transfusion products, fluid overload can occur in people and companion animals after Ig administration.[47–49,54] Overload is most commonly seen in patients with pre-existing cardiac disease or after large doses are administered.[50] It is important to consider the total volume and rate of infusion, especially in patients with compromised cardiac or renal function, elderly patients, and neonates.[50] Preparations of hIVIG are available in concentrations of 3–16%, and those administered at a higher concentration can reduce volume load.

Administration Recommendations for Veterinary Patients

Human Ig is available in lyophilized and freeze-dried forms. Liquid preparations are convenient but require refrigeration to prevent aggregate formation and to decrease the risk of bacterial contamination (Table 1).[56,57] Lyophilized products are reconstituted over 15–20 minutes. Prior to rehydration, these products can be stored at room temperature for up to 24 months.[57,a–f] A variety of diluents may be used depending on the product, which allows some flexibility in customizing the concentration and osmolality of the final solution.[49,a–f] During reconstitution, the preparation must be handled with care to prevent shaking, which may lead to foaming.[57,58] After rehydration, the product requires refrigeration and must be administered within 24 hours to reduce the danger of contamination.[a–f] Table 1 contains detailed information regarding available hIVIG preparations, and package inserts provide further information on reconstitution and handling.[a–f]

Ig can be administered through a peripheral catheter.[56,57] An existing catheter may be employed; however, a dedicated line is required for hIVIG transfusion. It is important to closely monitor the catheter site for swelling secondary to perivascular leakage.[56,57] Most hIVIG manufactures advocate using a filter during transfusion, and have differing recommendations regarding appropriate filter size (Table 1).[a–f] Before transfusing, refrigerated products must be allowed to come to room temperature to reduce side effects such as headache and shivering.[57,a–f] Some clinicians advocate discontinuation of other fluids, medications, and feeding during hIVIG transfusion to decrease the likelihood of adverse reaction, but no consensus exists on this practice.[4,9,56–58]

The optimal dose of hIVIG in veterinary patients is unknown. Historical doses of hIVIG in animals range from 0.5 to 1.5 g/kg, but current studies report doses ranging from 0.25 to 2.2 g/kg.[3,9,12–14,19,21–23,25–29,31] In 5 dogs with ITP, Bianco et al[23] concluded that low-dose therapy (0.28–0.34 g/kg) is effective and may reduce the cost associated with hIVIG therapy.[23] Although some human pediatric ITP studies have shown a more rapid increase in platelet counts and fewer nonresponders associated with higher doses of Ig (1 g/kg), the majority of children are reported to respond to lower dosing regimens (0.3–0.6 g/kg).[59] Some pediatricians advocate an initial low dose if hIVIG (0.8 g/kg) followed by an additional identical dose if patients are persistently thrombocytopenic 48–72 hours post hIVIG transfusion.[59]

Serial transfusions of hIVIG with gradual tapering is employed in human patients to effectively treat and maintain remission in patients with multiple immune diseases.[4–8,10] Protocols for multiple hIVIG transfusions

Table 2: Veterinary studies utilizing hIVIG

Condition	Dose	Pretreatment	Adverse effects observed	Study design	Human intravenous 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		

IMHA, immune-mediated hemolytic anemia; ITP, immune-mediated thrombocytopenia; SJ, Stevens-Johnson syndrome; PF, pemphigus foliaceus; SARDS, sudden acquired retinal degeneration; MG, myasthenia gravis.

have also been followed for treatment of veterinary patients with cutaneous drug reactions, PF, EM, and SARDS.[9,12,13,27–29,31] Although no significant adverse effects were noted in those patient populations, other studies have reported anaphylactic reactions after multiple hIVIG transfusions.[32] More studies are needed to fully elucidate the risks of serial hIVIG transfusion. As hIVIG therapy involves introduction of foreign proteins to veterinary patients, repeated treatment is not currently recommended due to the risk of severe immediate or delayed allergic reaction.[32] Additionally, canine patients are sometimes treated prophylactically with diphenhydramine prior to hIVIG transfusion to decrease the risk of transfusion reactions (Table 2). Human patients do not typically receive prophylactic treatment against allergic reactions prior to hIVIG transfusion unless they have suffered a previous allergic episode.[56,57]

Table 3: Example transfusion log

Date:								
Transfusion product:								
Donor/unit ID:								
Product volume:								
Total volume of transfusion:								
Start time:						End time:		
If there is a significant change in vitals at any time please notify DVM								
Time	Time due (fill out when starting)	Actual time done	RR	HR	Temp	DVM notified (if changes)	Rate of infusion mL/h	Volume of transfusion infused
Pretransfusion								
If no change within 15 minute vitals, continue at 1/2 transfusion rate								
15 min post start								
If no change within 30 minute vitals, continue at 3/4 transfusion rate								
30 min post start								
If no change within 30 minute vitals, continue at 3/4 tranfusion rate								
45 min post start								
60 min post start								
90 min post start								
150 min post start								
210 min post start								
270 min post start								

DVM, veterinarian; HR, heart rate; RR, respiratory rate.

There is no current consensus on appropriate monitoring during hIVIG transfusion in veterinary patients, but it is apparent that it must be comprehensive. In people, the product is typically administered as an IV infusion over 6–12 hours to decrease the risk of anaphylaxis, fluid overload, and the development of hyperviscosity.[58] Veterinary studies reviewed here have employed administration rates ranging from 4 to 8 hours.[3,9,12–14,19,21–23,25–29,32] In all species, transfusion is initiated at a slow rate (0.1 mL/kg/min) and gradually increased every 30–60 minutes to a maintenance rate not to exceed 0.8 mL/kg/min. Temperature, pulse rate, respiratory character, and blood pressure should be measured before transfusion and frequently during administration (Table 3).[56,57] Signs of acute hypersensitivity warrant prompt cessation of the infusion and antihistamine administration. Most patients will tolerate reinstitution and completion of the transfusion at a slower infusion rate. The same parameters require assessment post-transfusion as well as every 4 hours for the next 24 hours.[43,56,57] Follow-up monitoring for 6 months has been employed by some clinicians to rule out the development of delayed adverse effects.[26]

Although most human patients receive Ig IV, the subcutaneous route is an alternative for patients with poor venous access.[60] This route is also used in patients that have difficulty maintaining a therapeutic trough level of Ig, or who experience severe side effects after IV therapy.[60,61] Subcutaneous administration has been used in people since the 1990s, with a significant body of literature demonstrating efficacy.[60,61] In January 2006, the first subcutaneous IgG product was approved for use in people with primary immune deficiency.[61] No studies have been performed in veterinary patients investigating subcutaneous administration of human Ig.

Human Ig therapy may be cost prohibitive for many veterinary patients. Currently, manufacturer guidelines recommend estimating $100 USD/g of hIVIG, which equates to $1,250–2,500 USD for a 25-kg dog.[a] Proponents of hIVIG use in veterinary patients believe administration may be practical for induction of remission and may significantly reduce transfusion requirements and decrease hospitalization time. At this juncture, hIVIG has not been definitively demonstrated to decrease transfusion requirements in patients with IMHA, but shows great promise for treatment of ITP and dermatologic disease. Adequate data are not currently available to fully discern the appropriate role of hIVIG in veterinary medicine, or to fully describe potential adverse effects. Large-scale, prospective, controlled clinical trials are needed to fully define the benefits of hIVIG use in animals.

Footnotes

[a] Flebogamma 5% DIF (package insert). Grifols Biologicals Inc, Los Angeles, CA; 2006. http://www.grifolsusa.com/pdfs/pi/PI_Febrero.pdf (accessed August 10, 2010).

[b] Gammaguard S/D [Immune Globulin Intravenous (Human) (package insert). Baxter Healthcare Corporation, Westlake Village, CA; October 2009. http://www.baxter.com/downloads/healthcare_professionals/products/GGLIQ_PI.pdf (accessed August 10, 2010).

[c] Gammaguard Liquid [Immune Globulin Intravenous (Human)] 10% (package insert). Baxter Healthcare Corporation, Westlake

Village, CA; October 2009. http://www.baxter.com/downloads/healthcare_professionals/products/GGLIQ_PI.pdf (accessed August 10, 2010).

[d] Sandoglobulin Immune Globulin Intravenous (package insert). http://www.pharma.us.novartis.com/product/pi/pdf/sandoglobulin.pdf (accessed January 20, 2011).

[e] Carimune NF Nanofiltered Immune Globulin Intravenous (Human) (package insert). CSL Behring LLC, Kankakee, IL; February 2009. http://www.cslbehring-us.com/docs/777/98/Carimune%20PI.pdf (accessed August 10, 2010).

[f] CSL Behring. Immune Globulin: Therapeutic, Pharmaceutical, Cost, and Administration Considerations (medical pamphlet). Pharmacy Practice News, New York, NY. 2010.

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