State of the Art Review

Therapeutic options for immune-mediated thrombocytopenia

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Abstract

Objective – To review the therapeutic options for immune-mediated thrombocytopenia (IMT).
Data Sources – Original research publications and review articles using the PubMed search engine for the phrases "immune-mediated thrombocytopenia" or "immune thrombocytopenic purpura" or "immune thrombocytopenia."
Veterinary and Human Data Synthesis – There are a number of therapeutic options for adult-onset immune thrombocytopenia in human medicine with demonstrated efficacy in clinical studies although corticosteroids and immunoglobulin therapy remain the first-line medical treatments. Thrombopoietin receptor agonist therapy and, to a lesser extent, rituximab have shown great promise in initial clinical trials and may become standard of care in human medicine for the management of IMT. Therapeutic options in veterinary medicine are less diverse and only vincristine and human intravenous immunoglobulin therapies have been evaluated in controlled clinical studies.
Conclusions – There are a number of therapeutic options in the management of IMT veterinary medicine, most of which have not been investigated in clinical studies. Further research is warranted to best identify the optimal treatment strategy for IMT in veterinary patients.

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Introduction

Immune-mediated thrombocytopenia (IMT) is a common hematologic disorder in which antibody-sensitized platelets are removed by the monocyte-macrophage phagocytic system (MMPS).[1–4] In veterinary patients, it may be a primary condition or secondary to known antigenic stimuli such as neoplasia, infectious diseases, or drugs.[2,5–9] Immunosuppressive therapy of IMT decreases platelet-bound antibodies.[3,10,11] The ultimate goal is to minimize risk of bleeding by increasing platelet count to $>40 \times 10^9$/L ($>40 \times 10^3$/μL).[10] The purpose of this review is to discuss the management of immune thrombocytopenia (ITP) in human medicine compared

Abbreviations

6MP	6-mercaptopurine
BUN	blood urea nitrogen
EIgG	equine immunoglobulin G
hIVIg	human intravenous immunoglobulin
IL-2	interleukin-2
IMHA	immune-mediated hemolytic anemia
IMPDH	inosine monophosphate dehydrogenase
IMT	immune-mediated thrombocytopenia
ITP	immune thrombocytopenia
MMF	Mycophenolate mofetil
MMPS	monocyte-macrophage phagocytic system
SLE	systemic lupus erythematous
TPMT	Thyopurine methyltransferase
TPO	Thrombopoietin

with current therapeutic regimens for the treatment of IMT in veterinary patients.

ITP in people is an acquired immune-mediated disorder characterized by thrombocytopenia, defined as a peripheral blood platelet count $<100 \times 10^9$/L (100×10^3/μL), in the absence of any obvious initiating or underlying cause of the thrombocytopenia.[12] The incidence

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in adults is approximately equal between the sexes, except in the middle-aged years when the disease is more prevalent among women.[13,14] ITP is also classified by duration as newly diagnosed (eg, diagnosis to 3 mo), persistent (eg, 3- to 12-mo duration), or chronic (eg, 12-mo duration).[12] ITP in adults is typically insidious and chronic with no preceding illness.[15] Spontaneous major bleeding in adults with ITP occurs in less than 5% of patients with platelets counts $>10 \times 10^9$/L (10×10^3/μL) and in about 40% of individuals with a platelet count $<10 \times 10^9$/L (10×10^3/μL).[16] In children, it is typically short lived with at least two-thirds recovering spontaneously within 6 months and only 0.17–0.2% of children experiencing intracranial hemorrhage.[17,18] This article will focus on the management strategies for adult-onset ITP, and the division between first- and second-line therapies is in accordance with the most current human recommendations for management of adult-onset ITP.[16,18]

First-line therapy

Corticosteroid therapy

Corticosteroids are the standard initial treatment for people with adult-onset ITP.[16,18] The American Society of Hematology suggests to administer treatment for newly diagnosed adult ITP when patients have a platelet count $<30 \times 10^9$/L (30×10^3/μL).[18] The beneficial effect of glucocorticoids in ITP is primarily due to impaired macrophage destruction of antibody-sensitized platelets.[19,20] Other mechanisms include inhibition of antibody production and increased platelet output possibly by inhibition of phagocytosis of platelets by bone marrow macrophages.[21,22] Glucocorticoids have additional benefits in ITP therapy by increasing capillary resistance to hemorrhage (Table 1).[23–25]

The optimal dose for prednisone therapy in people has been investigated in the management of adult ITP. Two randomized studies compared standard immunosuppressive doses of prednisone (1 mg/kg/d) with low doses of prednisone (0.25 mg/kg/d) as initial therapy for patients with adult ITP. There was no difference in the likelihood of remission at 6-month follow-up in either study.[26,27] However, there was a trend toward an increased frequency of complete remission (46% versus 35%) in the group given the larger doses of prednisone in 1 study. In addition, a faster increase in platelet count was observed in the group receiving the larger doses of prednisone (77% versus 51% have a platelet count $>50 \times 10^9$/L [50×10^3/μL] after 14 d of therapy).[26]

Other glucocorticoids

Dexamethasone and methylprednisolone have also been investigated in the management of newly diagnosed adult ITP. The American Society of Hematology recommends longer courses of corticosteroids (eg, prednisone 1 mg/kg orally for 21 d then tapered off) over either shorter courses of corticosteroids (eg, dexamethasone 40 mg orally for 4 d) or human intravenous immunoglobulin (hIVIg) because longer courses of corticosteroids are associated with a longer time to the loss of response in the only study that has compared short-course therapy (hIVIg or IV corticosteroids on days 1–3 followed by placebo on days 4–21) with long-course therapy (hIVIg or IV corticosteroids on days 1–3 followed by oral corticosteroid therapy on days 4–21), based on a randomized, multicenter trial.[18,28] However, dexamethasone may be a valuable treatment option for adult ITP.[29–32] A recent study found that high-dose dexamethasone therapy produced an 86% response rate with 74% having responses lasting a median time of 8 months.[31] Another study found similarly high response rates (85%) with oral dexamethasone therapy in 125 patients with ITP.[32] High-dose methylprednisolone therapy was also investigated as a first-line therapy in 21 adults with severe thrombocytopenia and severe or persistent mucosal or vaginal bleeding. The results were compared with 36 patients with a less-severe presentation who were treated with conventional doses of prednisone. Patients treated with high doses of methylprednisolone responded more rapidly (4.7 versus 8.4 d) and had a higher overall response rate (80% versus 53%) despite presenting with more severe clinical disease. However, no difference was found between the 2 groups in the frequency of complete or persistent remission.[33]

IV immunoglobulin

Human IVIg is a sterile immunoglobulin (Ig) preparation that contains IgG and trace amounts of IgM, IgA, CD4, CD8, and human leukocyte antigen molecules from a healthy human donor population.[34] The mechanism of action of hIVIg in ITP patients is not fully understood, but appears to be due to blockade of Fc receptors on MMPS, modification of complement activation, and suppression of antibody production and binding.[34–38]

Studies have shown hIVIg therapy to result in response rates comparable to those of corticosteroids but with a shorter time to response.[16,18] Human IVIg is effective in increasing the platelet count in approximately 85% of ITP patients, with 65% achieving normal platelet counts.[39] Platelet counts may begin to increase after 1 day and usually reach peak numbers within 1 week after treatment.[40] However, responses are generally transient, lasting no longer than 3–4 weeks, after which the platelet count decreases to pretreatment levels.[39,40]

The optimal dose of hIVIg in ITP cases has been investigated in several studies. A randomized study

Table 1: Summary of therapeutic options for immune thrombocytopenia (ITP) in human patients

Therapy	Mechanism of action	Comments
First-line therapies		
Corticosteroids	• Impaired macrophage destruction of antibody-sensitized platelets[19,20] • Inhibition of antibody production[21,22] • Increased platelet production[21,22] • Direct effect on inhibition of bleeding at level of endothelium[23–25]	• Possible benefit at higher doses of corticosteroids[26] • High-dose methylprednisolone may accelerate response time and improve response rate[33]
Intravenous immunoglobulin	• Blockade of Fc receptors on monocyte-macrophage phagocytic system (MMPS)[34–38] • Suppression of antibody production and binding[34–38] • Modification of complement activation[34–38]	• Response rate comparable to corticosteroids with shorter response time[16,18] • Higher doses may be more beneficial[42,43]
Anti-D immunoglobulin	• Mediates clearance of opsonized red blood cells via receptors of MMPS, thereby minimizing removal of platelets[49]	• Only in Rh D-positive nonsplenectomized patients[51]
Platelet transfusions	• Direct replenishment of platelet numbers[52]	• Rapidly destroyed, typically several transfusions are required[53]
Vinca alkaloids	• Accelerated fragmentation of megakaryocytes and impaired platelet destruction[56,57] • May also decrease rate of phagocytosis by MMPS[56,57]	• No typically useful as a single agent[58]
Second-line therapies		
Azathioprine	• Inhibits purine synthesis, which suppresses lymphocyte proliferation and activation[59]	• Lack of recent research evaluating effectiveness of therapy[61,62]
Cyclosporine	• Inhibits phosphatase activity of calcineurin, which prevents transcription of many cytokines necessary for proliferation and maturation of T cells[63,64]	• As effective as prednisone as a single agent[65,66]
Danazol	• Reduces number of Fc receptors on monocytes[70,71] • Acts synergistically with glucocorticoids by displacing cortisol from human glucocorticoid binding globulin[70,71]	• Typically favorable outcomes in studies[73,74]
Mycophenolate mofetil	• Inhibitor of inosine monophosphate dehydrogenase, which is key enzyme in de novo purine biosynthesis (selective lymphocyte inhibitor)[75,76]	• Variable response rates[78,79]
Rituximab	• Monoclonal antibody directed against B-cell antigen CD-20[80,81] • Produces profound B-cell depletion[80,81] • Macrophage blockade by opsonized B cells also proposed[80,81]	• Higher response rates when combined with high-dose dexamethasone therapy[83]
Melatonin	• Stimulates platelet generation, probably by promoting megakaryocyte fragmentation[86]	• Data are limited to only a few case series[86–88]
Dapsone	• Causes hemolysis, which causes blockade of MMPS[91]	• Response rate is similar of azathioprine and danazol[89,91]
Eradication of *Helicobacter* infection	• Comorbidity in some immune-mediated thrombocytopenia (IMT) patients[92]	• Treat if identified as may improve response rates[93]
Romiplostin and eltrombopag	• Thrombopoietin receptor agonists[95–97]	• Found improved response rates compared to standard therapy[98]
Splenectomy	• Remove primary organ response for destruction of antibody-sensitized platelets[16,18]	• Performed when first-line therapy has failed[16–18]

demonstrated no difference in response rate between 2 dosing schedules of 0.4 g/kg/d versus 1 g/kg/d.[41] However, other studies have found that higher doses (1 g/kg) appeared to be more effective than the standard treatment regimens (0.5 g/kg/d).[42,43] As such, the current recommendation for hIVIg in the treatment of adult ITP is to use an initial dose of 1 g/kg as a onetime dose, and this dosage may repeated if necessary.[16,18]

The most common side effects of hIVIg infusion in people are headaches, which usually occur during the first infusion and can affect up to one-half of patients. Occasionally, the headache is severe enough to precipitate nausea and vomiting.[44,45] Less-common side effects in people include renal failure, thrombosis, and possible transmission of infectious diseases such as human immunodeficiency virus and hepatitis C virus.[46–48]

Anti-D Immunoglobulin Therapy

The anti-D immunoglobulin is effective only in blood-type Rh D-positive nonsplenectomized patients whereby

the antibody binds to the erythrocyte D antigen. Consequently, antibody-bound erythrocytes are preferentially phagocytosed by the MMPS rather than antibody-coated platelets.[49] Anti-D immunoglobulin can be administered intravenously over a few minutes, and the response rate in 1 series was 70% and the increase in platelet count lasted more than 3 weeks in 50% of the responders.[50] The standard dosage requires 72 hours to produce a clinically significant platelet increase.[51] Anti-D immunoglobulin therapy is less expensive than hIVIg (although much more expensive than corticosteroids) and is easier to administer than hIVIg.[16] The dose-limiting toxicity is hemolytic anemia and it also appears to have minimal efficacy in splenectomized patients.[51]

Platelet Transfusions

Transfusion of multiple units of platelets is necessary because transfused platelets are destroyed extremely rapidly in ITP cases.[52] In people with ITP, as many as 10 units of platelet concentrate may be required every 4–6 hours to maintain platelet counts $>10 \times 10^9$/L (10×10^3/μL).[53] Platelet transfusion increases the posttransfusion platelet count by $>20 \times 10^9$/L (20×10^3/μL) in 42% of bleeding ITP patients.[52] In a retrospective study of 40 patients, concurrent administration of hIVIg and platelet transfusions was associated with resolution of bleeding, rapid restoration of adequate platelet counts, and minimal side effects.[53] Interestingly, recent randomized controlled clinical trials were conducted to evaluate the use of low doses of prophylactic platelet transfusions to decrease the incidence of hemorrhage in patients with severe thrombocytopenia and reported conflicting results.[54,55]

Vinca Alkaloids

In people with ITP, vincristine is occasionally administered with corticosteroids.[55,56] Vincristine is thought to increase platelet counts by several mechanisms including accelerated fragmentation of megakaryocytes and impaired platelet destruction.[56,57] Vincristine may also reduce the degree of phagocytosis by the MMPS, decrease synthesis of platelet antibodies, and interfere with antibody binding to platelets.[56,57] As a single agent, vincristine induces a platelet-count increase in only a small fraction of chronic ITP patients, but may be useful when combined in patients requiring emergency treatment.[58]

Second-Line Therapy: Medical Options

Azathioprine
Azathioprine is converted by the liver to 6-mercaptopurine (6MP), which is a purine analogue that

functions as a competitive purine antagonist, thereby inhibiting cellular proliferation.[59] It primarily suppresses lymphocyte activation and proliferation, thereby reducing antibody production. Azathioprine also suppresses macrophage function, which reduces inflammatory cytokine production and phagocytic efficiency.[60] Azathioprine is initially converted in the liver and other tissues in 6MP. Thyopurine methyltransferase (TPMT) is a key enzyme in the metabolism of 6MP. Variation in TPMT activity correlates with clinical outcome in human patients receiving azathioprine, with high TPMT activity associated with reduced activity and low TPMT activity associated with increased risk of bone marrow toxicity.[59] There is a paucity of recent research into azathioprine therapy in ITP management,[61,62] but the current consensus is that it is still useful[17] as investigators have reported complete responses in 45% of 53 patients (40 splenectomized) treated with azathioprine for a median of 18 months.[61] Leukemia has been reported as a rare complication of azathioprine use although not in ITP patients.[62]

Cyclosporine A
Cyclosporine inhibits phosphatase activity of calcineurin, thereby preventing transcription of many cytokines, particularly interleukin-2 (IL-2), which is necessary for proliferation and maturation of T-cells.[63,64] Cyclosporine is effective in ITP patients as a single agent or when given with prednisone, but its side effects may make it unsuitable for some patients.[65,66] Clinical improvement was observed in more than 80% of patients resistant to first-line therapy, with 42% achieving a complete response.[65] Side effects are moderate but transient and include fatigue, renal insufficiency, neoplasia, hypertension, and neuropathy.[65]

Cyclophosphamide
Cyclophosphamide is an alkylating agent that crosslinks DNA helixes to prevent separation, thus inhibiting cell replication. Cyclosphosphamide is toxic to both resting and dividing cells and suppresses both cell-mediated and humoral immunity, and may also suppress MMPS function.[59] Immunosuppression with cyclophosphamide has been used for ITP patients refractory to corticosteroids or splenectomy. Response rates varied from 24% to 85%.[33,67,68] However, there are also reports of ITP, systemic lupus erythematous (SLE), and acute myeloid leukemia developing subsequent to cyclophosphamide therapy.[69]

Danazol
Danazol is an attenuated androgen that reduces the number of Fc receptors on monocytes and acts

synergistically with glucocorticoids by displacing cortisol from human glucocorticoid binding globulin.[70,71] Antiplatelet autoantibody production has not been shown to decrease subsequent to danazol therapy.[72] Response rates of 60% have been reported in 57 ITP patients after splenectomy. Older females and splenectomized patients may have the highest response rate.[73] A review of 25 publications evaluating danazol therapy in chronic ITP management found favorable outcomes in 21 of the 25 studies.[74] Danazol is generally well tolerated, and the most frequent adverse effects include headache, nausea, rash, weight gain, hair loss, myalgia, and liver dysfunction.[74]

Mycophenolate mofetil
Mycophenolate mofetil (MMF) is an effective, reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), which is a key enzyme in de novo purine biosynthesis.[75,76] Most other cell lines can maintain their function through the salvage pathway of purine biosynthesis alone, but proliferating lymphocytes depend on both the salvage and de novo pathways. Due to the high specificity of MMF for IMPDH, MMF is a very selective lymphocyte inhibitor.[75,76] Blockade of IMPDH by MMF was shown to deplete the guanosine pool in lymphocytes and to inhibit T- and B-cell proliferation, differentiation of alloreactive cytotoxic T-cells, and antibody responses.[75,76] MMF may also induce apoptosis of activated T-cells and impairment of the maturation of dendritic cells.[77] MMF has been used in a variety of human immune mediated diseases including myasthenia gravis, Crohn's disease, SLE, immune-mediated hemolytic anemia (IMHA), and ITP.[75,76] Administration of MMF at progressively increasing doses produced platelet increase in 39% of patients with refractory ITP, but this increase was not sustained.[78] Another study evaluating MMF use in ITP patients reported an overall response rate of 78%.[79]

Rituximab
Rituximab is a monoclonal antibody directed against the B-cell antigen CD20, and the proposed mechanisms in ITP therapy are by macrophage blockade by the antibody-coated B-cells or the development of an autoreactive B-cell clone.[80,81] Publications suggest that about 60% of patients respond, with approximately 40% achieving complete response.[82] Higher response rates have been reported for a combination of rituximab with high-dose dexamethasone as initial therapy.[83] Adverse effects reported include a low incidence of infection.[82,84]

Melatonin
Melatonin, the main pineal gland hormone, stimulates platelet generation, probably by promoting the megakaryocyte fragmentation and modulating the cytokine network involved in platelet production.[85] In a randomized, prospective, placebo-controlled clinical trial including 200 patients with persistent thrombocytopenia due to different causes, melatonin at 20 mg/d orally in the evening rapidly and significantly increased the mean platelet count to normal platelet numbers in 72% of cases.[86] Few case series of patients with refractory ITP successfully treated with melatonin have been published.[86–88]

Dapsone
Dapsone is an antimicrobial that inhibits synthesis of dihydrofolic acid via competition with para-aminobenzoate for the active site of dihydropteroate synthetase. It is inexpensive and free of the long-term complications of steroids and other immunosuppressive agents.[89] The most common side effect is hemolysis that can occur in 80–90% of cases.[89–91] It has been suggested that the mechanism of action of dapsone in ITP depends on the occurrence of hemolysis, which blocks the MMPS in a similar mechanism to anti-D immunoglobulin.[91] The response rates of dapsone in the management of ITP is consistently higher than response rates of azathioprine and danazol.[89,91]

Eradication of *Helicobacter pylori* infection
The relationship between *Helicobacter pylori* infection and ITP was initially described in 1998 when investigators reported a significant increase in the platelet count in 8 of 11 ITP patients in whom the bacterium was eradicated.[92] Since then the association between *H. pylori* eradication and ITP has been studied extensively and a systematic review was recently completed on 25 studies investigating the effect of *H. pylori* eradication on IMT patients.[93] *Helicobacter pylori* eradication produced an overall response rate of between 35% and 42%, with higher response rates in countries with a higher prevalence of *H. pylori* infection and in patients with a milder degree of thrombocytopenia. Therefore, detection and eradication of *H. pylori* infection should be considered in patients with IMT.[93]

Thrombopoietin receptor agonists: romiplostin and eltrombopag
A new therapeutic approach in the management of ITP in people is to stimulate platelet production.[16,18] Thrombopoietin (TPO) is the primary factor regulating platelet production,[94] and several TPO-receptor agonists have been developed that activate the TPO receptor and

increase platelet production.[95–97] Romiplostin is administered as a weekly injection while eltrombopag is an oral TPO-receptor agonist that is administered daily.[97] Both drugs have been highly effective in increasing platelet counts in both healthy volunteers and ITP patients.[95–97]

Romiplostim was recently compared to standard of care in 234 adult patients with ITP. Patients receiving romiplostin had a significantly lower incidence of treatment failure than those receiving the standard of care. Splenectomy was also performed less frequently, and the romiplostim group had a lower rate of bleeding events, fewer blood transfusions, and greater improvements in the quality of life than the standard of care group.[98] TPO-receptor agonists may represent the gold standard for ITP management in people in the future.

Second-Line Therapy: Surgical Options

Splenectomy
The spleen is the organ primarily responsible for destruction of antibody-sensitized platelets, and splenectomy is traditionally considered to be a second-line treatment in adults with ITP who have failed to achieve a safe platelet count with first-line medical therapy.[16,18] Eighty percent of patients respond to splenectomy, and response is sustained in 66% with no additional therapy for at least 5 years.[99,100] Many patients without a complete response have a partial or transient response.[101] Approximately 14% of patients do not respond, and approximately 20% of responders relapse.[99] Complications include bleeding, infection, thrombosis, prolonged hospitalization, readmission to the hospital, and therapeutic failure.[100]

Plasmapheresis
Plasmapheresis is a process whereby the components in plasma believed to cause or exacerbate disease are removed. The clinical effectiveness of plasmapheresis in the treatment of autoimmune disease may be due to partial removal of autoantibodies, immune complexes, complement components, proinflammatory agents, and soluble adhesion molecules.[17,101] Plasmapheresis is most useful for rapidly reducing plasma concentrations of autoantibodies while other immunosuppressive measures are applied to prolong the effect.[17,101] Plasmapheresis has been studied in ITP patients and no patients with chronic ITP showed a response.[102] As such, plasmapheresis no longer is a recommended therapy in the management of adult chronic ITP in humans.[16]

Management of IMT in Veterinary Patients

Although the veterinary literature regarding the treatment of IMT in dogs and cats is scarce when compared to the human field, many recent publications have revamped some interest over this hematologic disorder and its therapy.[3,103,108–111,115,116,167,168] This section will discuss the available information regarding the acute and chronic management of IMT in dogs and to a much lesser extent cats.

Transfusion Therapy and Supportive Care

Life-threatening hemorrhage is uncommon in dogs with IMT.[1,3,103–107] The gastrointestinal tract is the most common site of hemorrhage in dogs with presumed primary IMT.[3,103,108] Minimizing trauma and use of gastroprotectant agents is considered standard therapy in dogs with IMT,[1] although a recent study found no survival benefit to the use of gastroprotectants.[103] Hypovolemia or anemia should be treated by administration of crystalloid or colloid solutions, packed red blood cells, or fresh whole blood.[1] Results of platelet transfusions in dogs with IMT are not well documented.[1,3,103–106] However, recently there have been a number of studies on platelet transfusions suggesting they may become more readily available in the near future.[109–111]

Corticosteroids

Corticosteroids are the initial therapy of choice for dogs with IMT due to their consistent effect and relatively low cost. Prednisolone or prednisone is used most frequently,[3,103,104,107,112,113] although dexamethasone therapy has been reported as well.[3,103,105] The majority of dogs with IMT will attain a platelet count $>50–100 \times 10^9/L$ ($50–100 \times 10^3/\mu L$) within 7 days of commencing immunosuppressive corticosteroid therapy.[3,103–108] Comparison studies of different types or doses of corticosteroids in the management of IMT in veterinary patients have not been published. Adverse effects of corticosteroids include iatrogenic hyperadrenocorticism, gastrointestinal ulceration, hypercoagulability, iatrogenic suppression of the hypothalamic-pituitary-adrenal axis, and myotonia (Table 2).[114–119]

Human IVIg Therapy

The primary mechanism for the observed response to hIVIg in dogs with immune-mediated disease is blockade of Fc receptors on the MMPS.[120] A prospective, randomized, double-blind, placebo-controlled study of hIVIG for acute management of presumptive primary IMT in dogs found that a single hIVIG infusion at 0.5g/kg over 6–12 hours was safe and was associated with a significant decrease in platelet-count recovery time and duration of hospitalization without increasing the expense of medical care.[121] No difference in survival

time was noted between the 2 groups, and the transfusion requirements were lower in the hIVIg group although this did not reach statistical significance.[121]

The optimal dose for hIVIg for the treatment of dogs with IMT remains to be identified, and a wide variety of doses have been reported, ranging from 0.28 g/kg to 1.30 g/kg.[121–123] In the previously discussed trial, the investigators utilized a low dose of hIVIg (0.5 g/kg) because of cost.[121] In another study, an IV infusion of hIVIg at 1 g/kg in healthy dogs was shown to promote hypercoagulability and a proinflammatory state.[124]

To the authors' knowledge, the use of equine immunoglobulin G (EIgG) in dogs with IMT has not been reported and only an abstract regarding the retrospective evaluation of EIgG therapy in 20 dogs with IMHA has been reported. The study reported a higher rate of severe complications, including collapse, vomiting, cardiac arrest, facial swelling, vasculitis and acute respiratory distress syndrome, and a higher mortality rate (40% versus 23.8%) when compared with a control group of 21 dogs with IMHA and not treated with EIGg. The study conclusion was that EIgG is associated with an increase in morbidity and mortality in the treatment of canine IMHA.[125]

Vincristine

Besides the previously discussed mechanisms of vincristine in IMT therapy in people, vincristine appears to stimulate thrombopoiesis in healthy dogs.[126,127] Adverse effects associated with use of vincristine in dogs are uncommon but include vomiting, diarrhea, perivascular sloughing with extravasation, and rarely, peripheral neuropathy.[126]

A prospective study comparing the use of prednisone and vincristine to prednisone alone in the treatment of primary IMT cases in dogs found a significantly more rapid increase in platelet numbers and a shortened duration of hospitalization of dogs treated with both medications.[108] In addition, the dogs receiving vincristine did not develop side effects such as gastrointestinal upset, thrombophlebitis, or peripheral neuropathy. The dogs that received vincristine also had lower transfusion requirements than those that did not receive vincristine, although the difference was not statistically significant. The study concluded that the use of vincristine appears warranted in dogs with severe primary IMT.[108]

There are some concerns regarding the function of platelets produced in response to vincristine.[112,127,128] Results of 1 study suggest that in vivo platelet function is not altered by vincristine in clinically normal dogs, whereas another study revealed abnormal in vitro platelet function in dogs with lymphoma treated with vincristine.[127,128] Platelet function in dogs with IMT

receiving vincristine has not been studied. However, Rozanski et al speculated that platelet function was adequate as no dogs with platelet counts exceeding 40×10^9/L (40×10^3/μL) showed evidence of active hemorrhage.[108]

Azathioprine

In veterinary patients, azathioprine at 2 mg/kg is administered once daily and then tapered in tandem with glucocorticoids to every 48 hours. However, the onset of effectiveness can require more than 4 weeks so azathioprine is unlikely to be of benefit in the acute hospitalization period.[129,130] Azathioprine is initially converted in the liver and other tissues in 6MP, and TPMT, a key enzyme in its metabolism, is measurable in canine erythrocytes.[131] Variation in TPMT activity correlates with clinical outcome in human patients receiving azathioprine, and significant breed-related variation in TPMT activity has been documented in dogs, with TPMT activity being much lower in giant schnauzers and much higher in Alaskan malamutes than in other breeds.[131,132] Six single nucleotide polyphormisms have been found to account for much of the variation in TPMT activity in the canine population.[131,133] Studies evaluating effectiveness of azathioprine in dogs with IMT are lacking. The most common side effects of azathioprine therapy are gastrointestinal disturbances, myelosuppression, pancreatitis, and hepatopathy.[134–136]

Cyclosporine

Efficacy of cyclosporine has been demonstrated in cats and dogs undergoing renal transplantation and in dogs with immune-mediated disorders.[137] Cyclosporine (15–30 mg/kg once daily to maintain trough blood concentrations of 400–600 ng/mL), in addition to other immunosuppressive therapies, was administered to 4 dogs with IMT refractory to glucocorticoids. Three dogs achieved normal platelet counts in 3–5 weeks and the fourth dog died from systemic aspergillosis.[138] Adverse effects of cyclosporine in dogs include vomiting, diarrhea, anorexia, gingival hyperplasia, weight loss, alopecia, hirsutism, and papillomatosis.[139] As in people, chronic administration of cyclosporine have been reported to promote the development of malignancies in dogs, including lymphosarcoma and squamous cell carcinoma, and cats, particularly lymphosarcoma.[140–142]

Cyclophosphamide

The role of cyclophosphamide as a rapidly acting immunosuppressive agent has been questioned based on

failure of the drug to impair lymphocyte mitogenesis in normal dogs or to have any benefit in the acute management of dogs with IMHA at the dose of 50 mg/m^2, PO, once daily for 4 consecutive days a week.[143,144] The efficacy of cyclophosphamide in dogs with IMT has not been documented.[3,103,105–107] Cyclophosphamide also has serious adverse effects including gastroenteritis, myelosuppression, sterile hemorrhagic cystitis, and secondary neoplasia.[129,145,146]

Danazol

The veterinary literature evaluating anabolic steroids and IMT is limited to 2 case reports.[147,148] Two dogs with IMT refractory to prednisone therapy had platelet counts $>100 \times 10^9$/L (100×10^3/μL) within 1–2 weeks of starting danazol therapy (5 mg/kg, PO, twice a day) in conjunction with prednisone (1 mg/kg, PO, twice a day).[147,148] Danazol can cause dramatic weight gain and may be hepatotoxic in dogs.[149,150]

Leflunomide

Leflunomide is converted by hydrolysis in the plasma and intestinal mucosa to its primary metabolite, a malononitriloamide (A771726), which reversibly inhibits dihydro-orotate dehydrogenase, the rate-limiting enzyme in de novo pyrimidine synthesis. At high concentrations, A771726 also inhibits protein cytokine and growth factor.[151,152] A single dose of 4 mg/kg of oral leflunomide was well tolerated in healthy dogs and resulted in a half-life that can permit 24-hour dosing intervals.[153] Leflunomide at 4 mg/kg/d has been reported in conjunction with hIVIg in a diabetic dog with Evans' syndrome.[123] The drug was well tolerated by the dog, but substantially more expensive than glucocorticoid therapy.[123] Because larger studies are needed to evaluate efficacy and safety of leflunomide, the authors recommended to use it as either an adjunct to glucocorticoids or in cases when glucocorticoids are contraindicated.[123]

Mycophenolate Mofetil

MMF (10 mg/kg, PO or IV, twice a day) has been described in the management of various immune-mediated diseases in dogs and in 1 dog with IMT.[103,154–156] An experimental study in dogs showed that MMF can cause adverse gastrointestinal effects (eg, diarrhea, vomiting).[157] Furthermore, mild suspected allergic reactions have been reported with the parenteral preparation.[156] Because of the lack of larger studies evaluating safety and efficacy of MMF in dogs with IMT, the authors recommend to use it only for refractory cases or in those with glucocorticoid intolerance.

Splenectomy

Splenectomy in dogs with IMT has been reported to have an extremely variable response rate.[103–107,113] Of the 14 dogs with IMT who had splenectomy performed, 7 had an improved platelet count following the procedure, 5 had no response, and 3 had not enough follow-up information available.[103,105–107,113] Splenectomy was typically performed after initial medical therapy had failed. There are no prospective trials evaluating splenectomy as a treatment for dogs with IMT.

Plasmapheresis

Plasmapheresis has been reported for use in dogs with IMHA and SLE but not for use in dogs with IMT.[158–160]

Prognosis

The majority ($>70\%$) of dogs with IMT will have platelet counts $>50 \times 10^9$/L (50×10^3/μL) subsequent to initial therapy (glucocorticoids alone or in combination with vincristine, cyclphosphamide, azathioprine) within 1 week.[1,3,103–106] Initial studies reported that approximately 30% of dogs with IMT die or are euthanized during the initial episode of thrombocytopenia or because of disease recurrence.[104–106] However, more recent studies have reported lower mortality rates, between 10% and 15%.[3,103] One of these studies found significantly lower survival rates for dogs that presented with melena on presentation compared to those that did not (60% versus 90%), and a lower survival rate for dogs that presented with an increased BUN on presentation compared to those with a normal BUN concentration (57% versus 90%).[103] In addition, dogs that presented with melena at the time of admission were also more likely to receive blood transfusions during hospitalization.[103] The recurrence rate for dogs with IMT was initially reported as high as 40%.[104–106] However, 2 recent studies with long-term follow-up data reported a 26% recurrence rate in 19 dogs with primary IMT and a 9% recurrence rate in 54 dogs with presumed IMT, respectively.[3,103] The prognosis for dogs with both IMT and IMHA (Evans syndrome) is worse than for dogs with IMT alone.[161,162]

IMT in Cats

In cats, presumed primary IMT has been reported in only a few individual case reports and 2 case series.[163–168] Of the 13 reported cats with presumed primary IMT reported in the literature, 11 were alive at

Table 2: Review of therapeutic options of IMT in veterinary patients

Therapy	Dose	Side effects	Comments
Corticosteroids	Dog Prednisone, 1–2 mg/kg, PO, q 12 h[3, 103–108, 121, 122] Dexamethasone sodium phosphate, 0.35 mg/kg, IV, q 24 h[3, 103–105] Prednisolone acetate, 2.3 mg/kg, SC, q 24 h[103] Cat Prednisolone, 2–4 mg/kg/d PO or dexamethasone, 0.6 mg/kg/d PO[165–168]	Dog • Iatrogenic hyperadrenocorticism (including cutaneous lesions, polyuria, polydipsia, polyphagia, panting, lethargy, increased hepatic enzymes, recurrent infections)[114] • Gastrointestinal ulceration[115, 116] • Hypercoagulability[117] • Iatrogenic suppression of hypothalamic-pituitary-adrenal axis[118] • Myotonia[119] Cat • Iatrogenic hyperadrenocorticism (including transient diabetes mellitus)[167, 171]	Dog • Most will attain a platelet count > 50,000 within 1 week at immunosuppressive doses[3, 103–108] Cat • Most cats with IMT had a good initial response to corticosteroids, but relapses are frequent[165–168]
Human intravenous immunoglobulin	Dog 0.28–1.30 g/kg, IV, over 6–12 hours[121–123] Cat 1.21 g/kg, IV, over 6 hours[169]	Dog • Proinflammatory and prothrombotic effects[124]	Dog • Significant reduction in platelet recovery time and hospitalization when combined with prednisone compared to prednisone alone[121] Cat • Single case report.[170]
Platelet transfusions	Dog Lack of data in the clinical setting for the treatment of canine IMT	Dog • There are too few reports of platelet transfusions to estimate the frequency of potential adverse events[109, 111]	Dog • Platelet transfusions may become more readily available in the near future[109–111]
Vincristine	Dog 0.02 mg/kg, IV, once[108] Cat 0.4 mg/m^2 or 0.02–0.025 mg/kg, IV, once[165–167]	Dog • Uncommon[126] • Vomiting[126] • Diarrhea[126] • Perivascular sloughing[126] with extravasation[126] • Peripheral neuropathy[126] • Myelosuppression[172] Cat • Constipation[172] • Myelosuppression[173] • Voice change[174]	Dog • More rapid response rates and shortened duration of hospitalization when combined with prednisone compared to prednisone alone[108] Cat • The only 3 reported cats with IMT and treated with vincristine had minimal or no improvement in their platelet count[165–167]
Azathioprine	Dog 2 mg/kg, PO, q 24 h for 1 week then q 48 h thereafter[149] Cat 0.3 mg/kg, PO, q 24 h for 1 week then q 48 h thereafter[165]	Dog • Bone marrow suppression[134–136] • GI upset[134–136] • Hepatotoxicity[134] • Pancreatitis[135] Cat • Significant risk of severe myelosuppression[134]	Dog • Delayed onset of effectiveness (1–4 wk)[129, 130] Cat • Single case report[165]
Cyclosporine	Dog 5–10 mg/kg, PO, q 24 h or 6 mg/kg, IV, q 24 h[129, 149] or 15–30 mg/kg, PO, q 24 h[138] Cat 5 mg/kg, PO, q 12 h[159, 160]	Dog • Vomiting, diarrhea, anorexia, gingival hyperplasia, weight loss, alopecia, hirsutism, papillomatosis[139] • Opportunistic infections[138] • Neoplasia[140, 141] • Anaphylaxis[149] Cat • Neoplasia[142] • Infections[175, 176] • Diabetes mellitus[176, 177]	Dog • Only a small case series available in the literature[135] Cat • Only two single reported cases[165, 166]
Cyclophosphamide	50 mg/m^2, PO, q 24 h × 4 consecutive days a week[143, 144]	Dog • Gastroenteritis[131] • Myelosuppression[131] • Sterile hemorrhagic cystitis[145] • Secondary neoplasia[146]	Dog • Rapid beneficial effects have been questioned in dogs with hematologic disorders[131, 144, 149]

Table 2: (Continued)

Therapy	Dose	Side effects	Comments
Danazol	Dog 5 mg/kg, PO, q 12 h[147,148]	Dog • Weight gain[149] • Hepatotoxicity[150]	Dog • Only two single-case reports[147,148]
Leflunomide	Dog 4 mg/kg, PO, q 24 h[151–153]	Dog • Anorexia[123,152] • Diarrhea[152] • Vomiting[152] • Hair thinning[123]	Dog • Only a case series and a single case report available in the literature[123,152]
Mycophenolate mofetil	Dog 10 mg/kg, PO or IV, q 12 h[103,154–156]	Dog • Vomiting[157] • Diarrhea[157] • Loss of appetite[157] • Mild allergic reaction for parenteral use[156]	Dog and Cat • Lack of data for the treatment of canine and feline IMT
Splenectomy	Dog Typically performed after initial treatment failed[103,105–107,113]	Dog and Cat • A thorough search for any underlying infectious diseases is mandatory before proceeding with splenectomy.[149]	Dog • There are only retrospective studies describing splenectomy in dogs with IMT[103,105–107,113]

discharge.[163–168] The 2 nonsurvivors suffered from suspected pulmonary hemorrhage and pulmonary thromboembolism, respectively.[167,169] Detailed information regarding treatment was available in only 11 of these 13 cats and all of them were treated with immunosuppressive doses of corticosteroids (10 received prednisone or prednisolone at a dosage of 2–4 mg/kg/d, 1 of them was switched to oral dexamethasone at a dosage of 0.63 mg/kg once daily initially and then every other day, and the remaining cat was treated with IV dexamethasone at a dosage of 0.3 mg/kg twice daily).[165–168] Adjunctive therapy included a onetime IV administration of vincristine in 3 cats (0.4 mg/m^2 in 1 cat, 0.025 mg/kg in another cat, and 0.02 mg/kg in the remaining cat), oral cyclosporine in 2 cats (5 mg/kg twice daily), oral chlorambucil in 1 cat (0.2 mg/kg once daily for 7 d then 0.1/kg), and oral azathioprine in 1 cat (0.3 mg/kg once daily for 1 wk, then every other day).[165–168] Because of its significant risk of causing severe myelosuppressive adverse effects in cats, azathioprine should not be used at the oral dose of 2.2 mg/kg every other day, commonly adopted in dogs.[169] Furthermore, even when azathioprine is used in cats at reduced dosages (0.3 mg/kg every other day), frequent monitoring of complete blood count is mandatory.[165] Human hIVIg has been successfully used in a cat with immune-mediated megakaryocytic aplasia at the dose of 1.21 g/kg, IV, over 6 hours.[170] In a case series of cats with presumed primary IMT with long-term follow-up data, 3 of the 4 cats with presumed primary IMT appeared to experience side effects from chronic use of glucocorticoids characterized by diabetes mellitus in 2 cats and recurrent bacterial urinary tract infections in another cat.[167] Consequently, the authors stated that alternative immunosuppressive protocols should be considered for chronic management of cats with presumed primary IMT.[167] Signs of iatrogenic hyperadrenocorticism, including skin lesions, anorexia, lethargy, polyuria, polydipsia, atrophy of the thigh muscles, leukocytosis, increased alanine aminotransferase concentrations, hyperglycemia, transient diabetes mellitus, and transient hypothyroidism, have been reported in cats treated with corticosteroids.[171]

Recommendations for Future Studies

As mentioned throughout the review of veterinary literature, there is a paucity of controlled clinical studies evaluating therapeutic options in veterinary medicine in the management of IMT cases. There are no studies comparing different types or doses of glucocorticoids in the treatment of IMT. While vincristine and hIVIg have shown promise in clinical studies, these results have not been verified in multi-institutional studies with greater population numbers nor have the 2 drugs been compared. Studies evaluating second-line therapeutic options including azathioprine, MMF, cyclosporine, and leflunomide are also lacking. To the authors' knowledge, TPO-receptor agonists have not yet been developed for veterinary patients, but they may become the standard of care in human patients and thus should be evaluated if and when they become available in veterinary medicine.

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