IMHA in a Labrador Retriever

Marcella Ridgway, VMD, MS, DACVIM (SAIM)
University of Illinois

Dahlia, a 9-year-old spayed Labrador retriever, was presented with acute lethargy and anorexia. She had been receiving oral carprofen at 2.23 mg/kg every 12 hours and oral tramadol at 2.6 mg/kg every 12 hours to control osteoarthritis (OA) pain, along with monthly flea and tick and heartworm preventives. Physical examination revealed pale, icteric mucous membranes, tachypnea, and tachycardia. Immune-mediated hemolytic anemia (IMHA) was diagnosed based on findings of regenerative anemia (PCV, 18%; normal, 35%-45%), RBC macroagglutination, spherocytosis, mature neutrophilia (25 870/μL; normal, 3000-11 500/μL), and moderate hyperbilirubinemia (2.9 mg/dL; normal, 0.1-0.4 mg/dL). No significant abnormalities were evident on thoracic radiography or abdominal ultrasonography. Tick-borne disease testing and urine culture results were pending. Hematuria, pyuria, and gram-negative bacteriuria were identified on urinalysis.

Which of the following drugs would be appropriate for this patient?

Based on the information provided, how would you grade the following drugs and why?

🔴 RED = do not use   🟡 YELLOW = proceed with caution   🟢 GREEN = safe

Drug	RED	YELLOW	GREEN
Prednisone or prednisolone	🔴	🟡	🟢
Cyclosporine	🔴	🟡	🟢
Azathioprine	🔴	🟡	🟢
Carprofen	🔴	🟡	🟢
Tramadol	🔴	🟡	🟢
Mirtazapine	🔴	🟡	🟢
Aspirin	🔴	🟡	🟢
Amoxicillin–clavulanic acid	🔴	🟡	🟢
Enrofloxacin	🔴	🟡	🟢
Doxycycline	🔴	🟡	🟢

IMHA = immune-mediated hemolytic anemia

OA = osteoarthritis

TURN THE PAGE TO COMPARE YOUR RESULTS

Did you answer?

The following represents the best responses based on drug metabolism, pharmacokinetics, species, diagnostic differentials, clinical and laboratory data, and other pertinent findings.

Prednisone or prednisolone

CORRECT RESPONSE

Glucocorticoids, particularly prednisone and prednisolone, are first-line agents that provide mainstay treatment for IMHA. These drugs induce rapid suppression of lymphocyte and macrophage functions, leading to reduced erythrocyte destruction in dogs with IMHA. Significant adverse events (eg, polyuria/polydipsia, polyphagia, muscle wasting, dermatologic changes, hypercoagulability and/or hypertension) should be anticipated at the high glucocorticoid doses necessary to manage IMHA. Large-breed dogs are particularly predisposed to severe side effects, especially muscle wasting, when receiving immunosuppressive doses of glucocorticoids. Addition of a second immunosuppressant may allow for more rapid reduction of the glucocorticoid dose needed to control this dog's IMHA and, consequently, reduction in adverse glucocorticoid events. Because of the presence of autoagglutination and hyperbilirubinemia, which are identified in multiple studies as negative prognostic indicators, some practitioners may initiate treatment with another immunosuppressant in addition to prednisone or prednisolone at the outset of therapy rather than wait to assess sufficiency of corticosteroid monotherapy to control IMHA.[1-7]

For dogs weighing ≥20 kg, the current dose recommendation for prednisone or prednisolone is 40 mg/m^2 rather than the traditional 2-4 mg/kg immunosuppressive dose,[1] which still applies to dogs weighing <20 kg. An abstract presented at the ACVIM Forum 2015 showed equivalent peak concentrations and areas under the curve for prednisolone at 40 mg/m^2 in larger dogs and 2 mg/kg in smaller dogs.[8]

Cyclosporine

CORRECT RESPONSE

Cyclosporine should be considered as a second agent for this dog, especially if prednisone does not control anemia or is associated with unacceptable adverse events. Glucocorticoids alone may be insufficient to induce remission or may not be tolerated at high doses; thus, adjunctive immunosuppressants may be needed to achieve greater immunosuppression or allow a reduced glucocorticoid dose. Little evidence in the literature supports one adjunctive immunosuppressant over another, and reports are conflicted about the effectiveness of any agent other than corticosteroids in improving outcomes in dogs with IMHA.[1-3,9-13] Potential adverse events associated with cyclosporine use in dogs include GI upset, cutaneous papillomatosis, and gingival hyperplasia; nephrotoxicity is a significant potential side effect in humans and in cats (at higher doses),[9] but the agent is generally well tolerated. Cost is a limiting factor, especially for larger dogs.

When adding an immunosuppressant to a protocol, it is advisable to select one with a different mechanism of action than other current medications. The most commonly used adjunctive immunosuppressants are cyclosporine and azathioprine; in controlled trials, however, neither drug has consistently shown clinical benefit in patients with IMHA.[1-3,9-13] Other options include mycophenolate and leflunomide, which also have unproven efficacy in managing IMHA.

Adjunctive agents are generally administered in combination with a glucocorticoid. When remission is achieved and tapering of immunosuppressive doses initiated, generally the glucocorticoid is tapered and discontinued first, followed by the adjunctive agent.[10] It is important to recognize that the greater immunosuppression achieved by combination therapy may be accompanied by greater susceptibility to infection and possibly neoplasia.[1,14,15]

Azathioprine

CORRECT RESPONSE

Azathioprine, a lower-cost alternative to cyclosporine as an adjunctive immunosuppressant, is usually well-tolerated; however, little evidence supports use of azathioprine as an adjunctive agent in treating IMHA.[11] In addition, following initiation of azathioprine therapy in dogs, there is a demonstrated delay in onset of suppression of immune responses,[16] making azathioprine an even less attractive choice as adjunctive treatment of a potentially rapidly fatal disease. Adverse events (eg, hepatotoxicity, pancreatitis, bone marrow suppression) are considered to be infrequent but can be severe and life-threatening. In the author's experience, significant bone marrow suppression has occurred commonly in patients receiving chronic therapy. Monitoring CBC and serum chemistry profile parameters is indicated in patients receiving azathioprine. Concurrent use of other drugs that could affect bone marrow function (eg, trimethoprim–sulfamethoxazole for UTI) may increase the risk for myelosuppression and resultant hematologic abnormalities.[1]

Carprofen

CORRECT RESPONSE

Discontinuation of NSAIDs is advised because of planned use of high-dose glucocorticoids to control IMHA and the potential additive GI ulcerogenic effects of the 2 drugs. The recommended washout period before starting glucocorticoid administration is not warranted because of the immediately life-threatening nature of the disease process dictating glucocorticoid therapy. NSAIDs are implicated in drug-associated hemolytic anemia in humans,[17-19] and the potential for a similar association should be considered as a possible trigger for IMHA in this dog, despite the lack of controlled studies showing an association between IMHA in dogs and NSAID use. The anti-inflammatory effects of immunosuppressant therapy will likely control this dog's OA-associated inflammation, especially early in the course of treatment when the highest corticosteroid doses are administered.

Tramadol

CORRECT RESPONSE

Tramadol may be safely continued in this dog. If mirtazapine is initiated because of ongoing inappetence, the potential interaction of mirtazapine and tramadol in precipitating serotonin syndrome should be considered, but the risk is low.[20]

Mirtazapine

CORRECT RESPONSE

Although this dog was anorectic at presentation, administration of prednisone to manage IMHA will likely stimulate the dog's appetite, in addition to improving her general well-being after management of anemia. Use of mirtazapine as an appetite stimulant may be considered if inappetence persists after initiation of prednisone. If mirtazapine is used, the potential interaction of mirtazapine and tramadol in precipitating serotonin syndrome should be considered; however, the risk is low.[20]

IMHA = immune-mediated hemolytic anemia
OA = osteoarthritis

Aspirin

CORRECT RESPONSE

Anticoagulant therapy is indicated because patients with IMHA are at increased risk for thromboembolism, a major complication of IMHA and potential cause of death in these patients. Low-dose aspirin is an inexpensive option to prevent thromboembolism by inhibiting platelet function. Concurrent administration of ultralow-dose aspirin (0.5 mg/kg once a day) with high-dose glucocorticoids has not been shown to increase risk for GI hemorrhage.[21] Previous investigation of the effect of ultralow-dose aspirin showed significant reduction of platelet aggregation,[2] but other investigators have found this ultralow-dose to be insufficient.[22] A dose of 10 mg/kg has been shown to consistently inhibit platelet function,[22] but the safety of this dose with concurrent use of high-dose corticosteroids is uncertain. Alternatives include the more expensive clopidogrel for platelet inhibition or heparin for inhibition of the coagulation factor function. No evidence, however, supports the greater effectiveness of any particular anticoagulant regimen on patient outcome.[23]

Amoxicillin–clavulanic acid

CORRECT RESPONSE

Initiating empiric antimicrobial treatment for likely UTI pending results of culture and susceptibility testing is warranted in patients receiving immunosuppressant therapy. However, an association between use of penicillins and subsequent development of IMHA in humans has been identified[17-19]; a similar association with β-lactam antibiotics in dogs has been suggested,[1,10] making this agent a generally less desirable choice for use in patients with IMHA.

Enrofloxacin

CORRECT RESPONSE

Although fluoroquinolones are often effective in treating gram-negative infections, this class of agents is usually reserved for infections resistant to first-tier antibiotics (eg, amoxicillin, first-generation cephalosporins). Additionally, uropathogens are increasingly resistant to enrofloxacin.[24,25] However, because many first-tier antibiotics are anecdotally associated with onset of immune-mediated disease, enrofloxacin could be considered for empiric treatment of UTI in this dog. Of note, strong consideration regarding possible lack of efficacy and potential contribution to development of bacterial resistance should be weighed against risks associated with waiting for susceptibility test results to guide antibiotic choice. Because hyperbilirubinemia in this dog was attributable to hemolysis (prehepatic), hepatic function should be adequate for normal handling of drugs metabolized by the liver.

Doxycycline

CORRECT RESPONSE

Tick-borne agents sensitive to doxycycline may trigger IMHA, so empiric use of doxycycline would be warranted pending results of tick-borne disease screening. Because gram-negative uropathogens are often resistant to doxycycline, it would not, however, be an advisable choice for empiric treatment of bacterial UTI in this dog.[24,25]

IMHA = immune-mediated hemolytic anemia

MARCELLA RIDGWAY, VMD, MS, DACVIM (SAIM), is a clinical associate professor of small animal internal medicine at University of Illinois. Previously, she spent 10 years in private practice. Her primary clinical interests focus on hepatobiliary and GI disorders and infectious disease. After earning her veterinary degree from University of Pennsylvania, Dr. Ridgway completed an internship, small animal internal medicine residency, and master's program at University of Illinois.

References

1. Piek CJ. Canine idiopathic immune-mediated haemolytic anaemia: a review with recommendations for future research. *Vet Q*. 2011;31(3):129-141.
2. Weinkle TK, Center SA, Randolph JF, Warner KL, Barr SC, Erb HN. Evaluation of prognostic factors, survival rates, and treatment protocols for immune-mediated hemolytic anemia in dogs: 151 cases (1993-2002). *JAVMA*. 2005;226(11): 1869-1880.
3. Piek CJ, Junius G, Dekker A, Schrauwen E, Slappendel RJ, Teske E. Idiopathic immune-mediated hemolytic anemia: treatment outcome and prognostic factors in 149 dogs. *JVIM*. 2008;22(2):366-373.
4. McAlees TJ. Immune-mediated haemolytic anaemia in 110 dogs in Victoria, Australia. *Aust Vet J*. 2010;88(1-2):25-28.
5. Goggs R, Dennis SG, Di Bella A, et al. Predicting outcome in dogs with primary immune-mediated hemolytic anemia: ressults of a multicenter case registry. *JVIM*. 2015;29(6): 1603-1610.
6. Ke SS, Anderson GA, Connolly SL. Evaluation of prognostic indicators for canine primary immune-mediated haemolytic anaemia and application of a scoring system for the determination of prognosis. *Aust Vet J*. 2015;93(4):93-98.
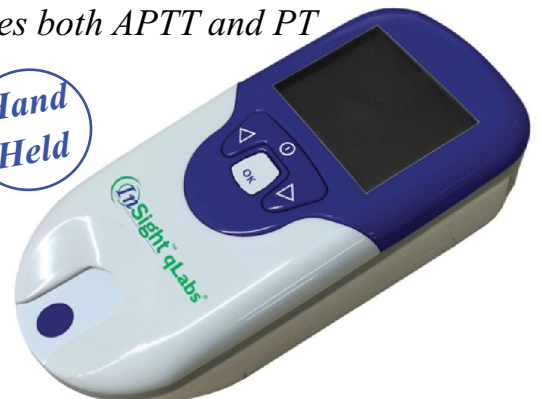
References

1. Davidson MG, Nasisse MP, English RV, Wilcock BP, Jamieson VE. Feline anterior uveitis: a study of 53 cases. *JAAHA*. 1991;27(1):77-83.

2. Peiffer RL Jr, Wilcock BP. Histopathologic study of uveitis in cats: 139 cases (1978-1988). *JAVMA*. 1991;198(1):135-138.

3. Jinks MR, English RV, Gilger BC. Causes of endogenous uveitis in cats presented to referral clinics in North Carolina. *Vet Ophthalmol*. 2016;19(Suppl 1):30-37.

4. Wilcock BP, Peiffer RL Jr, Davidson MG. The causes of glaucoma in cats. *Vet Pathol*. 1990;27(1):35-40.

5. Gettes BC, Belmont O. Tropicamide: comparative cycloplegic effects. *Arch Ophthalmol*. 1961;66(3):336-340.

6. Gelatt KN, Boggess TS III, Cure TH. Evaluation of mydriatics in the cat. *JAAHA*. 1973;9(3):283-287.

7. Margadant DL, Kirkby K, Andrew SE, Gelatt KN. Effect of topical tropicamide on tear production as measured by Schirmer's tear test in normal dogs and cats. *Vet Ophthalmol*. 2003;6(4):315-320.

8. Gomes FE, Bentley E, Lin TL, McLellan GJ. Effects of unilateral topical administration of 0.5% tropicamide on anterior segment morphology and intraocular pressure in normal cats and cats with primary congenital glaucoma. *Vet Ophthalmol*. 2011;14(Suppl 1):75-83.

9. Stadtbäumer K, Frommlet F, Nell B. Effects of mydriatics on intraocular pressure and pupil size in the normal feline eye. *Vet Ophthalmol*. 2006;9(4):233-237.

10. Rankin AJ, Khrone SG, Stiles J. Evaluation of four drugs for inhibition of paracentesis-induced blood-aqueous humor barrier breakdown in cats. *Am J Vet Res*. 2011;72(6):826-832.

11. Gabelt BT, Kaufman PL. Aqueous Humor Hydrodynamics. In: Kaufman PL, Alm A, eds. *Adler's Physiology of the Eye*. 10th ed. St. Louis, MO: Mosby; 2003:237-289.

12. Studer ME, Martin CL, Stiles J. Effects of 0.005% latanoprost solution on intraocular pressure in healthy dogs and cats. *Am J Vet Res*. 2000;61(10):1220-1224.

13. Manrai AK, Bhatia G, Strymish J, Kohane IS, Jain SH. Medicine's uncomfortable relationship with math: calculating positive predictive value. *JAMA Intern Med*. 2014;174(6):991-993.

14. Dubielzig RR, Everitt J, Shadduck JA, Albert DM. Clinical and morphologic features of post-traumatic ocular sarcomas in cats. *Vet Pathol*. 1990;27(1):62-65.

15. Grahn BH, Peiffer RL, Cullen CL, Haines DM. Classification of feline intraocular neoplasms based on morphology, histochemical staining, and immunohistochemical labeling. *Vet Ophthalmol*. 2006;9(6):395-403.

16. La Croix NC. Ocular manifestations of systemic disease in cats. *Clin Tech Small Anim Pract*. 2005;20(2):121-128.

17. Nerschbach V, Eule JC, Eberle N, Höinghaus R, Betz D. Ocular manifestation of lymphoma in newly diagnosed cats. *Vet Comp Oncol*. 2016;14(1):58-66.

18. Taylor SS, Goodfellow MR, Browne WJ, et al. Feline extranodal lymphoma: response to chemotherapy and survival in 110 cats. *J Small Anim Pract*. 2009;50(11):584-592.

7. Carr AP, Panciera DL, Kidd L. Prognostic factors for mortality and thromboembolism in canine immune-mediated hemolytic anemia: a retrospective study of 72 dogs. *JVIM*. 2002;16(5):504-509.

8. Wang HB, Kim SM, Kim TH, et al. Pharmacokinetic comparison of body surface area and body weight based prednisolone dose on small and large breed dogs. Proceedings 2015 ACVIM Forum; Indianapolis, IN; June 3-6, 2015.

9. Gregory CR. Immunosuppressive agents. In: Bonagura JD, Twedt DC, eds. *Kirk's Current Veterinary Therapy XV*. St. Louis, MO: Elsevier Saunders; 2014:268-274.

10. Johnson V, Dow S. Management of immune-mediated hemolytic anemia in dogs. In: Bonagura JD, Twedt DC, eds. *Kirk's Current Veterinary Therapy XV*. St. Louis, MO: Elsevier Saunders; 2014:275-279.

11. Piek CJ, van Spil WE, Junius G, Dekker A. Lack of evidence of a beneficial effect of azathioprine in dogs treated with prednisolone for idiopathic immune-mediated hemolytic anemia: a retrospective cohort study. *BMC Vet Res*. 2011;7:15-24.

12. Swann JW, Skelly BJ. Evaluation of immunosuppressive regimens for immune-mediated haemolytic anaemia: a retrospective study of 42 dogs. *J Small Anim Pract*. 2011;52(7):353-358.

13. Grundy SA, Barton C. Influence of drug treatment on survival of dogs with immune-mediated hemolytic anemia: 88 cases (1989-1999). *JAVMA*. 2001;218(4):543-546.

14. Blackwood L, German AJ, Stell AJ, O'Neill T. Multicentric lymphoma in a dog after cyclosporine therapy. *J Small Anim Pract*. 2004;45(5):259-262.

15. Callan MB, Preziosi D, Mauldin E. Multiple papillomavirus-associated epidermal hamartomas and squamous cell carcinomas in situ in a dog following chronic treatment with prednisone and cyclosporine. *Vet Dermatol*. 2005;16(5):338-345.

16. Rinkardt NE, Kruth SA, Kaushik A. The effects of prednisone and azathioprine on circulating immunoglobulin levels and lymphocyte sub-populations in normal dogs. *Can J Vet Res*. 1999;63(1):18-24.

17. White JM, Brown DL, Hepner GW, Worlledg SM. Penicillin-induced haemolytic anemia. *Br Med J*. 1968;3:26-29.

18. Mayer B, Bartolmäs T, Yürek S, Salama A. Variability of findings in drug-induced immune haemolytic anemia: experience over 20 years in a single centre. *Transfus Med Hemother*. 2015;42(5):333-339.

19. Tandon VR, Khajuria V, Mahajan V, Sharma A, Gillani Z, Mahajan A. Drug-induced diseases (DIDs): an experience of a tertiary care teaching hospital from India. *Indian J Med Res*. 2015;142(1):33-9.

20. Park SH, Wackernah RC, Stimmel GL. Serotonin syndrome: is it a reason to avoid the use of tramadol wih antidepressants? *J Pharm Pract*. 2014;27(1):71-78.

21. Graham HA, Leib MS. Effects of prednisone alone or prednisone with ultralow-dose aspirin on the gastroduodenal mucosa of healthy dogs. *JVIM*. 2009;23(3):482-487.

22. Dudley A, Thomason J, Fritz S, et al. Cyclooxygenase expression and platelet function in healthy dogs receiving low-dose aspirin. *JVIM*. 2013;27(1):141-149.

23. Kidd L, Mackman N. Prothrombotic mechanisms and anticoagulant therapy in dogs with immune-mediated hemolytic anemia. *J Vet Emerg Crit Care (San Antonio)*. 2013;23(1):3-13.

24. Wong C, Epstein SE, Westropp JL. Antimicrobial susceptibility patterns in urinary tract infections in dogs (2010-2013). *JVIM*. 2015;29(4):1045-1052.

25. Thungrat K, Price SB, Carpenter DM, Boothe DM. Antimicrobial susceptibility patterns of clinical *Escherichia coli* isolates from dogs and cats in the United States: January 2008 through January 2013. *Vet Microbiol*. 2015;179(3-4):287-295.