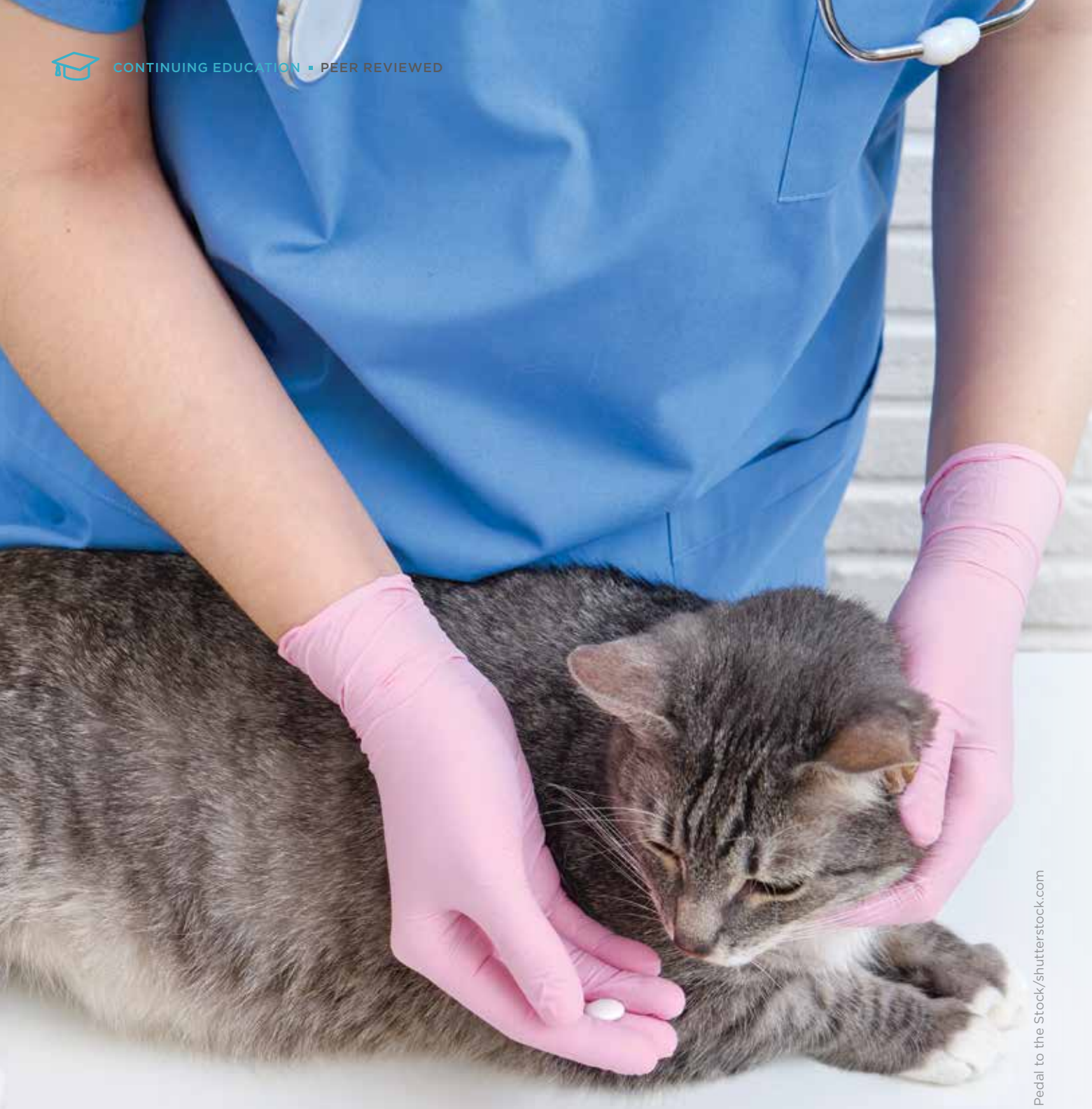

Pedal to the Stock/shutterstock.com

Abstract

Immune-mediated disease is a common diagnostic and therapeutic challenge in veterinary medicine. These diseases can be primary, with no identified trigger, or secondary, caused by the recent administration of medications or an underlying disease process. As immune-mediated diseases are increasingly recognized and diagnosed, veterinary practitioners need to understand and be comfortable with the use of immunosuppressive agents. This article reviews immunosuppressants currently used in veterinary medicine; their efficacy, recommended doses, and adverse effects; and how to choose an adjunctive immunosuppressant for immune-mediated disease.

CONTINUING EDUCATION

INTERNAL MEDICINE

Immunosuppressant Therapy: What, When, and Why

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An immunosuppressant is any agent that decreases the body's immune response. These drugs typically target a specific point of either the humoral or the cell-mediated immune response and can be used to treat primary or secondary immune-mediated disease. In primary disease, immunosuppressants are used to manipulate the body's own immune response. When a secondary cause of immune-mediated disease is identified, initial treatment should be aimed at discontinuing the inciting agent or treating the underlying disease process.

Currently, a variety of immunosuppressants are used in veterinary medicine. The most commonly used drugs are considered "maintenance" drugs in human medicine (i.e., long-term medications intended to manage the immune response). Initially, these drugs are commenced at a known immunosuppressive dose, with the eventual goal being to taper them to the lowest effective dose.

Immunosuppressant drugs are categorized into steroid medications (e.g., prednisone, prednisolone, dexamethasone, budesonide), calcineurin inhibitors (e.g., cyclosporine), antiproliferative medications (e.g., azathioprine, mycophenolate, leflunomide), and mechanistic target of rapamycin inhibitors (not currently used routinely in veterinary medicine). This article focuses on the first 3 categories and includes some novel adjunctive therapies that are currently used in veterinary medicine.

Take-Home Points

- Immune-mediated disease is a common diagnostic and therapeutic challenge in dogs and cats.
- Glucocorticoids are considered the mainstay of therapy for most immune-mediated diseases, but numerous other immunosuppressive drugs are available for severe or refractory cases.
- Drug selection should be based on anticipated side effects, owner finances, dosing schedule, and time to expected response.
- Immunosuppressive medications should be tapered slowly, 1 at a time. Tapering should only be attempted after clinical remission has been achieved.
- Vaccination should be carefully considered in dogs and cats treated with immunosuppressive medications. Vaccine titers may be a reasonable alternative to routine vaccination.

INDICATIONS FOR IMMUNOSUPPRESSANT THERAPY

Immunosuppressants are used to treat primary disease. Immune-mediated disease, considered to be a disease of exclusion, generally involves ruling out as many secondary underlying causes as diagnostic abilities allow. Common disease processes thought to be driven by an inappropriate immune response include immune-mediated thrombocytopenia (ITP); immune-mediated anemias (e.g., immune-mediated hemolytic anemia [IMHA], precursor-targeted immune-mediated anemia, pure red cell aplasia); steroid/immunosuppressant-responsive enteropathy; immune-mediated polyarthritis (IMPA); atopic dermatitis; and meningoencephalitis of unknown etiology (MUE), including granulomatous meningoencephalitis, necrotizing meningoencephalitis, necrotizing leukoencephalitis, and steroid-responsive meningitis–arteritis.

Other diseases encountered less frequently include perianal fistulas, myasthenia gravis (MG), immune-mediated chronic hepatitis, immune-mediated polymyositis, and immune-mediated glomerulonephritis. Immunosuppressive therapy often addresses neoplastic disease as well, the treatment of which can have significant overlap with many idiopathic immune-mediated diseases. However, treatment of neoplastic disease and in-depth use of chemotherapeutics are beyond the scope of this article.

FIRST-LINE IMMUNOSUPPRESSANT DRUGS

Glucocorticoids

Glucocorticoids are the mainstay of therapy due to their availability, cost, efficacy, and rapid onset of action. Steroids are initially started at an immunosuppressive dose until clinical remission is achieved, then slowly tapered to the lowest effective dose over weeks to months (**TABLE 1**). Clinical improvement is often noted within 48 hours, with a steady state typically achieved by day 4.[1] However, clinical improvement can take up to 2 weeks.[1]

Prednisone and prednisolone are the most used steroids in veterinary medicine. Prednisone, a prodrug, requires hepatic metabolism to its active form prednisolone.[2] Prednisolone is preferable in cats because they lack the ability to convert prednisone into prednisolone.[2]

Dexamethasone can be used in animals unable to take or adequately absorb oral steroids (e.g., hospitalized animals, animals with severe protein-losing enteropathies [PLEs]). When patients are reliably eating or their disease has stabilized, oral steroids are initiated and dexamethasone can be discontinued. Dexamethasone is formulated as either pure dexamethasone or dexamethasone sodium phosphate.

TABLE 1 Glucocorticoids for First-Line Immunosuppressive Therapy

DRUG	POTENCY RELATIVE TO PREDNISONE/ PREDNISOLONE POWER	EFFECT	USES	DURATION OF ACTION	IMMUNOSUPPRESSIVE DOSE
Prednisone/ prednisolone	1	Systemic	Maintenance of dogs with immune-mediated disease	12–36 hours	2 mg/kg PO q24h or 50 mg/m² PO q24h (dogs >25 kg), not to exceed 60 mg PO total per day
Dexamethasone	7–10	Systemic	In-hospital, severe protein-losing enteropathy	32–48 hours	0.25–0.3 mg/kg q24h IV, IM, or SC
Budesonide	15	Intestinal tract, liver	Diabetic cats, dogs/cats with cardiac disease	Variable across dose and with individual patients, 10.1–15.1 hours (based on human literature)	3 mg/m² PO q24h or **Cat:** 0.5–0.75 mg/cat PO **Dog: ≤7 kg:** 1 mg PO q24h **7.1–15 kg:** 2 mg PO q24h **15.1–30 kg:** 3 mg PO q24h **>30 kg:** 5 mg PO q24h
Methylprednisolone acetate	1.25	Systemic	Fractious cats that require a longer-acting injectable agent	~21 days	**Dog:** 1 mg/kg (or 20–40 mg/dog) IM every 1–3 weeks **Cat:** 10–20 mg/cat IM every 1–3 weeks

Dexamethasone sodium phosphate is highly water soluble and has a rapid onset of action when administered intravenously.[1] Clinicians should note that dexamethasone sodium phosphate is labeled at a concentration of 4 mg/mL but only contains 3 mg/mL of dexamethasone. Dexamethasone may also be preferred in patients with cardiovascular disease when fluid retention is undesirable, due to minimal mineralocorticoid activity.[3]

Budesonide, a locally active glucocorticoid, has weak mineralocorticoid activity.[4] It is available as an enteric-coated tablet and can be used in patients with chronic enteropathies that cannot tolerate systemic glucocorticoid therapy, most commonly diabetic cats.[5] There is conflicting information on whether budesonide is efficacious in dogs with chronic enteropathies.[4,6,7] Although budesonide has less systemic action than prednisolone, it still suppresses the hypothalamic-pituitary-adrenal axis and should be used cautiously when steroids are relatively contraindicated.[8]

Methylprednisolone acetate (e.g., Depo-Medrol; Pfizer, pfizer.com), is a long-acting injectable steroid. Clinicians should use caution when prescribing this medication due to its diabetogenic and plasma volume–expanding effects.[9] While this drug may be beneficial when immunosuppressive therapy is warranted and daily medication administration is not possible, such as in fractious cats, its long-acting nature increases risk of significant side effects. A single intramuscular or subcutaneous dose can last for several weeks and may induce congestive heart failure in animals with underlying cardiovascular disease or clinical diabetes mellitus in predisposed animals.[9] Because of this, methylprednisolone acetate should not be considered routinely in animals requiring glucocorticoid therapy.

Alternative Drugs

Drugs generally considered as second-line therapy are, in certain disease processes, efficacious as a first-line agent (**TABLE 2**). Even in these cases, steroid therapy is initiated concurrently due to the delayed onset of action of other immunosuppressant drugs. However, patients commonly fail to respond to glucocorticoids or other first-line agents, leading to the need to use adjunctive, or second-line, agents. Few studies evaluating these drugs exist, with most clinicians choosing adjunctive immunosuppressants based on previous experience or anecdotal evidence. The addition of a secondary agent should be considered in severely affected patients or in patients that are refractory to a first-line agent.

Cyclosporine

Cyclosporine, a calcineurin inhibitor, is one of the most common secondary agents used in veterinary medicine.[11,13] Two commercial formulations (modified and nonmodified) exist. Nonmodified formulations (e.g., Sandimmune [Novartis, novartis.com]) have significant variability in absorption and pharmacokinetics among individuals.[13] Newer, modified forms (e.g., Neoral [Novartis], Atopica [Elanco, elanco.us]) are ultramicronized preparations that are more readily and predictably absorbed.[13] Only modified forms should be used in veterinary patients. Modified form bioavailability in dogs is approximately 35% compared with 20% to 25% for the nonmodified form.[13] Atopica, the only veterinary formulation approved by the U.S. Food and Drug Adminstration, is preferred based on extensive testing in veterinary patients. Generic modified forms of cyclosporine may have decreased efficacy but can be considered when Atopica is cost prohibitive.[11] Alternatively, cyclosporine can be combined with ketoconazole to reduce the immunosuppressive dose of cyclosporine.[14,15] It is important to note that clinical efficacy may not be seen for up to 3 to 4 weeks, and a steady state may not be achieved in some patients.[11]

In animals without immediately life-threatening disease and/or that cannot tolerate steroid therapy, modified cyclosporine has demonstrated efficacy as a sole agent for perianal fistulas.[14-16] Although improvement of lesions is expected after 4 weeks, tapering should only be attempted after lesions have completely resolved (12 to 16 weeks on average).[14-16] Cyclosporine has also been used with good success in cases of atopic dermatitis and inflammatory colorectal polyps, along with several other immune-mediated conditions.[11,13,17] Efficacy in these conditions is similar to that of glucocorticoids; however, cyclosporine is generally preferred due to fewer side effects.[13,18] Steroids are commonly initiated concurrently to achieve a rapid clinical response.

Mycophenolate

Mycophenolate, or mycophenolic acid, inhibits purine synthesis. It decreases proliferation of T and B cells.[2] Mycophenolic acid undergoes enterohepatic recirculation; therefore, 2 plasma peaks are observed, the first at 1 to 2 hours following oral administration

TABLE 2 Secondary Agents: Pharmacodynamics, Pharmacokinetics, Indications, and Dosing

DRUG	MECHANISM OF ACTION	PRIMARY METABOLISM/ EXCRETION	STARTING DOSE	FIRST-LINE THERAPY[a]
Prednisone/ prednisolone	▪ Nuclear factor-κB inhibitor ▪ Cytokine inhibition ▪ Lymphocyte apoptosis	Liver/urine	2 mg/kg PO q24h or 50 mg/m^2 PO (dogs >25 kg), not to exceed 60 mg total per day	▪ Atopic dermatitis ▪ IMHA ▪ IMPA ▪ Immune-mediated polymyositis ▪ ITP ▪ MUE ▪ SRE ▪ SRMA
Cyclosporine	▪ Calcineurin inhibitor	Liver (cytochrome P450)/bile	5 mg/kg PO q12h or 1–2 mg/kg PO q12h combined with ketoconazole 8–10 mg/kg PO q24h	▪ Atopic dermatitis (5 mg/kg PO q24h) ▪ Chronic hepatitis[10] ▪ IMPA ▪ Inflammatory colorectal polyps ▪ Perianal fistula (4–8 mg/kg PO q12h)
Mycophenolate	▪ Purine synthesis inhibitor	Liver/urine	10 mg/kg q12h (IV or PO)	▪ Immune-mediated glomerular disease
Azathioprine	▪ Purine antagonist	Liver/urine	2 mg/kg PO q24h for 2–4 weeks, then 1–2 mg/ kg PO q48h	▪ No evidence to support first-line therapy
Leflunomide	▪ Pyrimidine synthesis inhibitor	Gastrointestinal, liver/urine, bile	2 mg/kg PO q24h	▪ IMPA (3–4 mg/kg PO q24h)

IMHA = immune-mediated hemolytic anemia; IMPA = immune-mediated polyarthritis; ITP = immune-mediated thrombocytopenia; MG = myasthenia gravis; MUE = meningoencephalitis of unknown etiology; SA = sebaceous adenitis; SRE = steroid/immunosuppressant-responsive enteropathy; SRMA = steroid-responsive meningitis-arteritis.
[a]Doses only specified when recommendation differs from standard starting dose
[b]Most evidence to support use and authors' recommendations for adjunctive therapy

and the second 6 to 12 hours later.[19] The half-life in dogs is approximately 8 hours.[19] Although dosing every 8 hours would be ideal in order to optimize immunosuppression, this is not recommended due to unacceptable gastrointestinal toxicity.[19,20]

One benefit of mycophenolate over other secondary agents is the availability of an intravenous form. At the authors' institution, intravenous mycophenolate has been used adjunctively with injectable dexamethasone in unstable IMHA patients when therapeutic plasma exchange is cost prohibitive.

Based on anecdotal evidence, mycophenolate is considered a first-line therapy for immune-mediated glomerulonephritis, the diagnosis of which should ideally be supported by renal biopsy.[21] Mycophenolate also has demonstrated efficacy in immune-mediated skin disease (e.g., pemphigus foliaceus, vesicular cutaneous lupus erythematosus, epidermolysis bullosa) when combined with glucocorticoid therapy.[22]

Azathioprine

Azathioprine, a prodrug of mercaptopurine, antagonizes purine metabolism. This results in inhibition of lymphocyte proliferation and DNA and RNA production.[2] There is evidence that lymphocyte response is decreased within 7 days of therapy.[23] However, a steady state is not achieved for 2 to 3 weeks, and clinical response may not be observed for up to 5 weeks due to greater effect on delayed hypersensitivity and cellular immunity than on humoral antibody responses.[23]

SECOND-LINE THERAPY[a]	TIME TO STEADY STATE
	4–5 days
▪ Chronic hepatitis[b] ▪ IMHA[b] ▪ IMPA[b] ▪ ITP[b] ▪ MG ▪ MUE (5–10 mg/kg PO q12h)[b] ▪ SA (5 mg/kg PO q24h) ▪ SRE[b]	2–4 weeks (may not be achieved in some patients)[11]
▪ Chronic hepatitis ▪ IMHA[b] ▪ IMPA ▪ Immune-mediated skin disease[b] ▪ ITP[b] ▪ MG ▪ MUE (10–20 mg/kg PO q12h)[b] ▪ SRE	1–3 weeks
▪ IMHA ▪ IMPA ▪ Immune-mediated polymyositis[12] ▪ ITP ▪ MG ▪ MUE	2 weeks
▪ IMHA ▪ IMPA[b] ▪ Inflammatory colorectal polyps ▪ ITP	1–3 weeks

There is less evidence for use of azathioprine as a secondary agent than for cyclosporine or mycophenolate. It has been used successfully with IMHA, ITP, MG, immune-mediated polymyositis, and MUE.[21,24-26] A potential benefit of azathioprine is that after 2 to 3 weeks, the dosing interval may be decreased to every other day until treatment is discontinued, which may confer a significant financial advantage compared with other secondary agents.[27]

Leflunomide

Leflunomide, a pyrimidine synthesis inhibitor, inhibits autoimmune T-cell proliferation and autoantibody production by B cells. It acts almost exclusively via its primary active metabolite, teriflunomide.[28,29]

A loading dose is recommended in humans, but this recommendation does not translate to dogs and cats.[18,28,29] Studies on the use of leflunomide in animals are relatively limited. However, there is some evidence for leflunomide as a first-line agent for IMPA, and as a second- or third-line agent in refractory cases of inflammatory colorectal polyps.[18,30,31] Patients should be treated at an initial immunosuppressive dose for at least 6 weeks before tapering is attempted.[18,30]

SECOND-LINE AGENTS IN IMMUNE-MEDIATED DISEASE

In cases of immune-mediated anemia and ITP, the addition of a second-line agent should be considered if glucocorticoids alone are insufficient or if significant adverse effects are expected (**TABLE 3**). It is especially recommended in patients that have life-threatening illness at presentation and in patients that are transfusion dependent after 7 days of treatment.[27] Insufficient evidence exists as to the superiority of any single secondary agent over another for these diseases.

The authors preferentially use either cyclosporine or mycophenolate for both immune-mediated anemia and ITP. The choice between the 2 agents is generally based on the size of the patient, as cyclosporine can be cost prohibitive in larger dogs, along with the ability of the patient to take oral medications.

Second-line use of cyclosporine, mycophenolate, azathioprine, or leflunomide can also be considered in severe or refractory cases of MUE, MG, steroid-responsive enteropathy, and chronic hepatitis. Again, evidence is lacking for superiority of any second-line agent over another.

At the authors' institution, cyclosporine and mycophenolate are generally used as tertiary agents (after steroids and cytarabine) in severe or refractory cases of MUE.

The authors preferentially use cyclosporine as adjunctive therapy to glucocorticoids in cases of chronic hepatitis and inflammatory bowel disease.

ALTERNATIVE IMMUNOMODULATORY AGENTS

Options outside of traditional immunosuppressants that have been demonstrated to be efficacious in specific disease processes include:

1. **Vincristine for ITP.** Vincristine increases circulating platelet numbers by day 5 postadministration.[32] These platelets are thought to function similarly to mature platelets.[33] The drug is often administered as a single intravenous injection at 0.02 mg/kg. This dose should be used cautiously in dogs that exceed 25 kg and should be compared to a mg/m^2 dose. The total dose should never exceed 0.5 mg/m^2. Although vincristine shortens hospitalization time, it is not associated with increased survival or remission rates.[32,33]
2. **Human intravenous immunoglobulin (IVIG).** At a dose of 0.5 g/kg, administered as a constant-rate infusion over 6 to 12 hours, IVIG has shown results similar to those of vincristine in ITP patients, but it is not readily available for use in many veterinary hospitals and is much more expensive than vincristine.[34]
3. **Cytarabine.** Cytarabine is routinely used as an adjunctive initial treatment for MUE. Two protocols exist:
    A. Subcutaneous: 50 mg/m^2 q12h for 2 consecutive days or q2h for 4 doses.[35,36]
    B. Constant-rate infusion: 100 to 200 mg/m^2 over 8 to 24 hours.[35,36]

    If necessary based on clinical signs, both protocols can be followed with subcutaneous injections 3 weeks later at a dose of 50 mg/m^2 q12h for 2 consecutive days. This protocol can be repeated every 3 weeks for 3 to 4 cycles.[35,37]
3. **Chlorambucil.** Chlorambucil should be considered as an adjunctive therapy in refractory cases of PLEs. Initial doses of 4.4 mg/m^2 PO q24h have resulted in significant improvement in serum albumin concentration after 2 weeks.[38] Alternatively, dosing may be spread out and administered at 20 mg/m^2 every 2 weeks in cats and dogs.[2] Chlorambucil, in combination with prednisolone, has been associated with increased survival time compared to treatment with prednisolone and azathioprine.[38]

CHOOSING THE RIGHT IMMUNOSUPPRESSANT

Although glucocorticoids are often the first-line therapy for immune-mediated disease, potential profound side effects, especially in larger dogs, and conditions in which glucocorticoid therapy is considered suboptimal (e.g., diabetes mellitus, cardiovascular disease, renal disease) often warrant a second immunosuppressant in patients needing long-term therapy. Although numerous agents exist, there is little evidence to support their routine use for or superiority in specific diseases.

Clinician considerations when choosing a second immunosuppressant therefore include:

- Patient comorbidities
- Other medications the patient is receiving and potential interaction with the drugs being considered
- Existing evidence for the use of specific agents in the disease being treated
- Monitoring requirements
- Availability of appropriate formulation/tablet size for patient
- Onset of action
- Adverse effects
- Frequency of dosing and realistic owner commitment
- Financial commitment

Drug choice should ultimately be based on anticipated side effects, financial commitment, dosing schedule, and time to expected response. When choosing a secondary or tertiary agent, it is important to avoid drugs that have similar mechanisms of action. At initiation of immunosuppressive therapy, clinicians should have a plan in place for monitoring and dose adjustment, as well as a contingency plan if the animal does not respond appropriately.

MONITORING AND DOSAGE CHANGES

Prior to initiating immunosuppressant therapy, a comprehensive assessment (i.e., complete blood count, serum biochemical profile, urinalysis) of the patient should be performed. These values should be monitored periodically, with timing based on the specific drug (**TABLE 3**). Due to an increased risk of infection, urinalysis and urine culture should be performed if lower urinary tract signs (e.g., pollakiuria, stranguria, hematuria) develop. A complete blood count should be performed if patients become systemically unwell (e.g., fever, lethargy, decreased appetite). In patients that develop nonhealing wounds, fungal and bacterial culture and susceptibility testing is recommended due to the increased risk of opportunistic infection.[39] Additionally, if a systemically ill patient develops a new heart murmur, an echocardiogram should be performed to look for evidence of endocarditis.

Drug tapering can be attempted in patients that are clinically stable or in remission for at least 2 weeks.[27] Tapering should be no more than 25% every 2 to 4 weeks.[27] Clinicians and owners should monitor these patients for signs of relapse. If signs of relapse are

noted, the dose should be increased back to either the initial induction dose (if fulminant disease is present) or the last dose the patient was receiving before the most recent dose reduction (in cases of mild disease).[27] In patients receiving multiple immunosuppressants, the first agent should be tapered completely before attempting to taper the second agent. Glucocorticoids are initially tapered due to adverse effects associated with long-term use.

Therapeutic drug monitoring (TDM) may be considered in patients that are refractory to the drug or experience unexpected side effects. TDM is most effective in diseases for which a therapeutic level exists that correlates with clinical response.

Cyclosporine

Cyclosporine monitoring is performed to avoid toxicosis and establish an individual's therapeutic range. Trough therapeutic range concentrations (i.e., blood sampling just prior to the next dose) have been established for inflammatory bowel disease and perianal fistulas at 100 to 600 ng/mL (the higher for induction, the lower for maintenance). These ranges have been associated with positive clinical response.[11,17]

Currently, the only laboratory offering TDM for cyclosporine is Auburn University's Clinical Pharmacology Laboratory. Pharmacodynamic testing was previously offered at Mississippi State University but is no longer available.

Submission of whole blood is recommended as 50% of the drug in blood is located in red blood cells. Studies are lacking to support whether peak (2 hours after drug administration) or trough concentrations better represent clinical response (except for in cases of inflammatory bowel disease and perianal fistulas, as previously mentioned). The more aggressive approach is to target trough concentrations; however, peak concentrations may be sufficient.[11] Use of cyclosporine and TDM should be considered carefully in dogs with the *MDR1* (multidrug resistance 1) gene mutation due to possible increased sensitivity.[11,16]

Leflunomide

Trough concentrations can be measured 1 to 2 weeks after starting therapy or adjusting dose.[40] In some cases, the half-life may be short enough to necessitate measurement of peak and trough concentrations. The therapeutic range is 20 to 30 µg/mL.[29] TDM can be

TABLE 3 Secondary Agents: Monitoring, Adverse Effects, and Cost

DRUG	MONITORING PARAMETERS[a]	THERAPEUTIC DRUG MONITORING	ADVERSE EFFECTS	RELATIVE COST[b]
Prednisone/ prednisolone	CBC and serum biochemical profile 2 weeks after initiation of therapy, then every 2–3 months throughout therapy	None	Polyuria/polydipsia, polyphagia, thinning of skin, muscle loss, excessive panting	$
Cyclosporine	Serum biochemical profile every 2–3 months throughout therapy	Drug level performed at Auburn University	Vomiting, diarrhea, gingival hyperplasia, opportunistic fungal infections	$$$
Mycophenolate	CBC every 2 weeks for the first month of therapy, then every 2–3 months throughout therapy	Not performed in veterinary patients	Diarrhea, myelosuppression	**IV:** $$ (single 500 mg vial) **PO:** $
Azathioprine	CBC and serum biochemical profile every 2 weeks for the first 2 months of therapy, then every 1–2 months throughout therapy	Not performed in veterinary patients	Hepatotoxicity, myelosuppression, gastrointestinal effects	$
Leflunomide	CBC and serum biochemical profile every 2 weeks for the first 2 months of therapy, then every 1–2 months throughout therapy	Drug level performed at Auburn University	Dose dependent: gastrointestinal effects, idiopathic hemorrhage, myelosuppression, cough, hepatotoxicity	$

CBC = complete blood count
$ = <$50; $$ = $51–$100; $$$ = >$100
[a]Monitoring parameters vary depending on disease process. Listed recommendations represent minimum standards in patients receiving long-term therapy.
[b]Based on GoodRx (goodrx.com) cost for 1 month at standard starting dose for a 20-kg dog

performed at the Auburn University Clinical Pharmacology Laboratory. This level may not correlate to a positive clinical response but can be used as a guide. If no clinical response is noted after the expected treatment duration and trough concentrations are above the therapeutic range, clinicians should consider either increasing the drug dose or switching to a different immunosuppressive drug.

ADVERSE EFFECTS

Treatment with any immunosuppressive medication increases risk of infection, gastrointestinal upset (e.g., vomiting, diarrhea, anorexia), and myelosuppression. Common side effects associated with specific medications are discussed below and are listed in **TABLE 3**. Owners should be educated on signs to be aware of that may necessitate immunosuppressant dose adjustment or may require symptomatic supportive care. These include:

1. Decreased appetite, vomiting, or diarrhea. These are self-limiting and do not require medication discontinuation in most cases. Addition of supportive medications (e.g., maropitant, mirtazapine) or adjustment of how the medication is given (e.g., give with a small amount of food, split dose throughout the day) may be necessary.
2. Signs that may be suggestive of infection or sepsis, including fever, lethargy, or decreased appetite.
3. Evidence of relapse. These signs will be specific to the disease being treated.

It is recommended that dogs and cats receiving immunosuppressants be kept on monthly flea, tick, and heartworm preventives. Immunocompromised patients should not be fed a raw diet due to increased risk of bacterial translocation leading to systemic infection with food-borne pathogens.[41,42]

Steroids

Side effects commonly seen in animals receiving short-term steroid therapy are polyuria and compensatory polydipsia, polyphagia, and excessive panting.[1,2] Long-term effects include thinning of skin and haircoat, muscle atrophy, hypertension, and hypercoagulability. Side effects tend to be more pronounced in dogs than in cats.[2] They are also pronounced at higher doses; therefore, larger dogs that require higher doses may be more severely affected. For this reason, it is recommended to use mg/m^2 rather than mg/kg dosing in large-breed dogs (**TABLE 1**).

Cyclosporine

Vomiting and diarrhea are the most common side effects of cyclosporine. Side effects are self-limiting, last several days to several weeks, and are responsive to dose reduction.[2,11,13] Side effects can be mitigated by freezing capsules 30 to 60 minutes prior to administration and dividing the dose throughout the day. Cyclosporine is most effective when given on an empty stomach but can be given with a small amount of food to try to mitigate gastrointestinal effects.

A less common side effect, specifically in dogs, is gingival hyperplasia, which is more likely to necessitate drug discontinuation.[2,11,13] Rarely, hirsutism and hyperplastic dermatitis have been reported.[11] Caution should be used in patients with diabetes mellitus due to the possibility of the drug increasing serum glucose.[43] Additionally, cyclosporine therapy has been associated with the development of opportunistic fungal infections in dogs, reported to be 7 times more likely than with other immunosuppressive medications.[38]

Mycophenolate

Dose-dependent diarrhea is the most common side effect of mycophenolate use.[20] The incidence of diarrhea is higher with oral use than intravenous use and typically does not occur until after 1 to 2 weeks of therapy.[20] Clinicians should start at the lower end of the dosing range (10 mg/kg) and titrate up if the dose is well tolerated after 2 weeks.[20] Absorption is most effective when given on an empty stomach but can be given with a small amount of food to try to mitigate gastrointestinal effects.[19] Uncommonly, patients may develop anemia, neutropenia, or thrombocytopenia.[20]

There is a black box warning for increased risk of lymphoma, pregnancy loss, and congenital malformations in humans; therefore, owners should use caution when handling this drug.

Azathioprine

Azathioprine has the potential to cause hepatotoxicosis.[2,44] This generally occurs within the first several weeks of treatment and can be idiosyncratic or dose-dependent. Marked hepatotoxicity appears to be an idiosyncratic reaction.[27] However, subclinical hepatotoxicity is relatively common (15% of patients in 1 study) and can be dose-dependent, primarily manifesting as increases in alanine transaminase and alkaline phosphatase levels.[44]

Myelosuppression is uncommon in dogs.[2,45] Marked myelosuppression appears to be idiosyncratic and may be reversible if discovered early. As with many other immunosuppressants, caution is advised when handling azathioprine, as there is a black box warning for increased risk of lymphoma in humans.[46]

Azathioprine is not recommended in cats due to low activity of thiopurine methyltransferase, leading to a greater incidence of azathioprine toxicity.[45]

Leflunomide

Adverse effects of leflunomide reported in dogs appear to be dose related and can include gastrointestinal disturbances, dyspnea, cough, increased liver enzymes, unexplained hemorrhage, thrombocytopenia, leukopenia, anemia, and hypercholesterolemia.[30,47] Vomiting and lethargy have been reported in cats.[28]

DRUG INTERACTIONS

Before an additional medication is administered to a patient, consultation of a drug formulary is recommended to review any possible interactions. Combining immunosuppressive medications not only has additive effects on immune system suppression but also increases the risk for myelosuppression. Numerous medications have been reported to alter the metabolism or absorption of immunosuppressive agents and increase the risk of adverse effects. Select drug-specific interactions are listed in **TABLE 4**.

TABLE 4 Important Drug Interactions[a]

DRUG	DECREASES METABOLISM/SERUM CONCENTRATION	INCREASED RISK OF ADVERSE EFFECTS	INCREASED SERUM CONCENTRATION/RISK OF TOXICITY
Prednisone/ prednisolone	Azole antifungals (e.g., ketoconazole), cholestyramine, mitotane, phenobarbital	▪ **Gastrointestinal ulceration:** nonsteroidal anti-inflammatory drugs (e.g., carprofen), other steroids ▪ **Hypokalemia:** amphotericin B, digoxin, furosemide ▪ **Tendonitis/tendon rupture:** fluoroquinolones ▪ Steroid use in diabetic patients increases insulin requirements	Macrolide antibiotics (e.g., azithromycin), tylosin
Cyclosporine	Azathioprine, clindamycin, famotidine, phenobarbital, potentiated sulfonamides (e.g., sulfamethoxazole-trimethoprim), sulfadiazine, terbinafine	▪ **Hyperkalemia:** potassium supplementation, spironolactone	Allopurinol, amiodarone, amphotericin B, angiotensin-receptor blockers (e.g., telmisartan), azole antifungals, calcium channel blockers (e.g., amlodipine), cisapride, fluoroquinolones (e.g., enrofloxacin), macrolide antibiotics, metronidazole, proton pump inhibitors (e.g., omeprazole)
Mycophenolate	Amoxicillin, cephalosporins, cholestyramine, clindamycin, fluoroquinolones, furosemide, macrolide antibiotics, metronidazole, potentiated sulfonamides, proton pump inhibitors, telmisartan	▪ **Myelosuppression:** azathioprine	Salicylates (e.g., aspirin)
Azathioprine	No reported interactions[b]	▪ **Myelosuppression:** mycophenolate, ACE inhibitors (e.g., enalapril), potentiated sulfonamides	Allopurinol, cyclophosphamide, leflunomide, sulfasalazine
Leflunomide	Cholestyramine	▪ **Hepatotoxicity**: azithromycin, amiodarone, ACE inhibitors	No reported interactions[b]

ACE = angiotensin-converting enzyme
[a]Caution should be used when combining any pharmacologic agents. This is not an exhaustive list of interactions, and clinicians should consult a pharmacology text.
[b]Although no clinically significant interactions have been reported, this does not mean that none exist.

VACCINES FOR IMMUNOCOMPROMISED PATIENTS

At this time, the full effect of immunosuppressive therapy on vaccines is unknown. Vaccine efficacy may be diminished with immunosuppressant therapy. Evidence is lacking for appropriate vaccine strategies in dogs and cats receiving immunosuppressive therapy. The decision to vaccinate should ultimately be based on the assessed risk for patients contracting the disease they are vaccinated against. Owners should implement the following lifestyle modifications for dogs and cats:

1. Avoid dog parks or boarding facilities.
2. Limit exposure to heavily wooded areas (e.g., hiking, swimming in rivers or lakes).
3. Screen for feline leukemia/immunodeficiency virus before starting an immunosuppressant. Change to a lifelong indoor-only lifestyle.

Ideally, patients diagnosed with immune-mediated disease should not receive routine vaccinations in order to minimize the risk of relapse. At a minimum, patients receiving immunosuppressants should not receive live or modified-live vaccines. Only core vaccines should be considered. If vaccination is deemed necessary, clinicians should consider administering only 1 vaccine per visit, separated by several weeks.

Alternatively, annual antibody titers may be considered in lieu of routine vaccination. Many states do not accept titers as proof of vaccination for zoonotic diseases, specifically rabies, but waivers are available for animals with medical exceptions, such as immunosuppression.[48,49] Antibody titers in cats and dogs are available for rabies virus (e.g., Kansas State University, Auburn University) and for canine distemper and canine and feline parvovirus (e.g., University of Wisconsin, Kansas State University, Auburn University).

SUMMARY

Immune-mediated disease is commonly encountered in veterinary medicine and poses a diagnostic and therapeutic challenge for clinicians. Glucocorticoids are considered the mainstay of therapy. Clinicians should be aware of other immunosuppressive medications for severe cases or cases that are refractory to glucocorticoid therapy. Choice of a second agent is largely based on anecdotal evidence or small retrospective studies. Drug selection should be based on published evidence supporting the use of a certain medication as well as patient- and client-specific factors. Clinicians should be aware of the potential adverse effects, monitoring parameters, and dose adjustments of commonly used immunosuppressants to facilitate long-term management of immune-mediated disease. TVP

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CONTINUING EDUCATION

Immunosuppressant Therapy: What, When, and Why

TOPIC OVERVIEW

This article provides an overview of commonly used immunosuppressants in veterinary practice; outlines their efficacy, recommended doses, and how to monitor their effectiveness; and describes potential adverse effects. Readers will also be able to identify second-line and alternative immunomodulatory agents, as well as alternate vaccination recommendations for the immunocompromised patient.

LEARNING OBJECTIVES

After reading this article, practitioners should be able to explain why they choose and start a first-line immunosuppressant and be able to identify a second-line agent to use when there is refractory disease. Readers should be able to explain the dosing for each immunosuppressant, what monitoring is used to assess the efficacy and potential side effects of each immunosuppressant, what adverse side effects could occur when specific immunosuppressants are used, and finally answer questions regarding vaccination of the immunocompromised patient.

This article has been submitted for **RACE approval for 1 hour of continuing education credit** and will be opened for enrollment upon approval. To receive credit, take the test at **vetfolio.com** by searching the name of the article or scanning the QR code below. Free registration is required. Questions and answers online may differ from those below. Tests are valid for 2 years from the date of approval.

1. **Which immunosuppressive drug should not be used concurrently with azathioprine due to a similar mechanism of action?**
   a. Leflunomide
   b. Mycophenolate
   c. Cyclosporine
   d. Budesonide

2. **Which immunosuppressive drug has been associated with a higher risk of opportunistic fungal infections?**
   a. Cyclosporine
   b. Mycophenolate
   c. Prednisone
   d. Azathioprine

3. **True or false: Platelets evaluated after vincristine administration have been shown to function similarly to mature platelets.**
   a. True
   b. False

4. **Which would be the best option for a patient with perianal fistulas when the owner expresses financial constraint?**
   a. Use a generic formulation of modified cyclosporine
   b. Switch to the nonmodified formulation of cyclosporine
   c. Initiate concurrent use of ketoconazole with cyclosporine
   d. Switch from cyclosporine to mycophenolate

5. **Which would not be an appropriate choice for management of an overweight, middle-aged cat with inflammatory bowel disease?**
   a. Prednisolone
   b. Budesonide
   c. Methylprednisolone acetate
   d. Dexamethasone

6. **Which is an indication for starting a dog with immune-mediated hemolytic anemia on a second immunosuppressive drug?**
   a. Clinical features at presentation consistent with severe or immediately life-threatening disease
   b. Dependence on blood transfusions after 7 days of treatment
   c. Development (or expected development) of severe adverse effects related to the use of glucocorticoids
   d. All of the above

7. **At what point after initiation of therapy with mycophenolate would diarrhea be expected?**
   a. Within 5 days
   b. After 1 to 2 weeks
   c. After 3 to 4 weeks
   d. After 4 weeks

8. **Which would *not* be an appropriate preventive medicine recommendation for a dog receiving immunosuppressive therapy?**
   a. Consider performing an antibody titer for rabies virus instead of routine vaccination every 3 years

b. Use a modified-live distemper/parvovirus combination vaccine to ensure adequate protection
c. Administer only 1 vaccine per visit, ideally spread out by several weeks
d. Continue giving monthly flea, tick, and heartworm preventives

9. Which statement is *not* appropriate regarding tapering immunosuppressive drugs?

a. Decrease dose by no more than 25% every 2 to 4 weeks.
b. If signs of relapse are noted, increase dose either back to previous dose or induction dose (depending on disease severity).
c. For patients on multiple immunosuppressive drugs, taper drugs concurrently to minimize side effects.
d. Tapering should only be attempted once the patient has been in clinical remission for at least 2 to 4 weeks.

10. Risks of therapy with multiple immunosuppressive drugs include all of the following except:

a. Increased risk of myelosuppression
b. Increased risk of secondary infection
c. Increased risk of developing endocrine disease
d. All of the above are risks of using multiple immunosuppressive drugs

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