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Dermatology

How I treat cutaneous lupus and other autoimmune diseases

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Introduction

Immune-mediated diseases represent less than 1.5% of all skin diseases seen in dogs and cats. Treatment of cutaneous autoimmune disease is often life long except in some cases of pemphigus, bullous pemphigoid or mucous membrane pemphigoid where spontaneous remission after a period of therapy may occur (1). Immunosuppressive drugs are given as a single medication or in combination to minimize side effects. The drugs used depend on the disease and the species of the patient. Maintenance therapy is based on the lowest dose and safest agents that will keep the patient in remission. Unfortunately, most autoimmune diseases are characterized by periodic exacerbations.

Since many of skin lesions described are complicated by bacterial infection (Malassezia overgrowth is less common), the initiation of immunosuppressive therapy should be accompanied by at least 4-8 weeks of antibiotics that are effective against staphylococci. These include cephalexin (20-30mg/kg BID), cephadroxil (20-30mg/kg SID) or amoxycillin-clavulanate (15-25mg/kg BID). If rod forms of bacteria are identified on cytology then therapy should be based on culture and sensitivity testing.

Principles of immune-suppressive therapy

1. Do not use immunosuppressive therapy without a definitive diagnosis. Infections, especially mucocutaneous pyoderma in dogs, can mimic immune-mediated disease. With the exception of pemphigus foliaceus and cutaneous lupus, other autoimmune diseases are rare. Consider and eliminate the other differential diagnoses. Ensure the cause is not a drug reaction.

2. Use the least potent drug or combination of drugs that will control the condition. Combination therapy is generally preferable to minimize the side effects of any one component.

3. Ulceration and erosion are usually accompanied by secondary infection that requires antibiotic therapy.

4. Do not use major drugs for minor disease. If the symptoms are mild, topical therapy, UV avoidance and less potent immunomodulators (tetracycline/niacinamide and/or vitamin E) should be used first.

5. Monitor the patient for side effects related to the drug(s).

6. An apparent deterioration in a patient’s condition may be an exacerbation of the original disease or a complication of the immunosuppressive therapy. In particular, demodecosis but also yeast/fungal infections and bacterial pyodermas are common complications in

Topical therapy

Topical glucocorticoids are useful for treating milder and more localized forms of autoimmune disease, especially in the case of cutaneous (discoid) lupus or pemphigus erythematosus. Topical treatment is also of value as an adjunct to systemic therapy. Treatment is usually begun using a more potent fluorinated corticosteroid such as 0.1% betamethasone valerate.
twice daily (apply with gloves!). The treatment interval can be progressively reduced, depending on response, to every 48 hours. Eventually, lower potency corticosteroids such as 1% hydrocortisone may be able to be used for maintenance. Topical corticosteroids, especially the more potent formulations, can create skin atrophy, alopecia and predispose to local pyoderma. Many cases remain in remission, especially during winter, using topical therapy combined with antibiotics (when required). Tacrolimus, like cyclosporine, is a calcineurin inhibitor (2). Tacrolimus has a different binding site to cyclosporine, is much more potent and too toxic for systemic use in domestic carnivores. There is a recent report of good results with topical 0.1% tacrolimus in cases of cutaneous (discoid) lupus erythematosus and pemphigus erythematosus. Of the 10 cases treated, 80% responded to topical tacrolimus and 75% of responding cases could be maintained on topical tacrolimus alone.

Systemic therapy
Systemic therapy is required when there are extensive and serious lesions or topical therapy fails to control localized disease.

Tetracycline and niacinamide
The combination of tetracycline and niacinamide is the first choice for the systemic treatment of cutaneous (discoid) lupus erythematosus. This form of therapy is effective in 25-65% of cases and can be combined with topical or systemic glucocorticoids or vitamin E. Tetracycline has anti-inflammatory properties affecting complement activation, antibody production, chemotaxis and prostaglandin synthesis while niacinamide inhibits mast cell degranulation. The dose for dogs over 10 kg body weight is 500mg of each medication TID. The dose is scaled down for smaller dogs. A lag period of 4-8 weeks occurs before any benefits are seen. If the patient responds then the dose interval can be progressively increased to twice and possibly once daily. The side effects are vomiting, diarrhea and anorexia (usually associated with the niacinamide). Tetracycline is effective as a sole agent only in rare cases. Doxycycline at double the normal dose rate (10-20mg/kg SID) can be substituted for the tetracycline component.

Glucocorticoids
For severe forms of cutaneous lupus erythematosus, all forms of pemphigus foliaceus/vulgaris and bullous pemphigoid immunosuppressive doses of glucocorticoids are required. Glucocorticoids have wide ranging effects on the immune system including reducing the number of lymphocytes and monocytes and inhibiting inflammatory mediator and antibody production. It is important to note the following dose rates are immunosuppressive dose rates of corticosteroids and are much higher than those used to control allergy and inflammation. In the dog, prednisolone (2-4mg/kg SID) or methylprednisolone (1.5-3mg/kg SID) are commonly used. The same medications are used in cats but at double the canine dose rates. Methylprednisolone has less mineralocorticoid properties than prednisolone. In the case of failure to respond or intolerable behavioral or mineralocorticoid effects, the dose can be split and given twice daily or a longer acting glucocorticoid (with reduced mineralocorticoid action) can be substituted (dexamethasone 0.2-0.4mg/kg dogs, doubled dose for cats). In feline pemphigus, triamcinolone (0.6 to 2 mg/kg daily) may give better results than prednisolone alone or prednisolone/chlorambucil. Triamcinolone can be used in dogs as an immunosuppressant at 0.2-0.4mg/kg SID.

When the initial lesions have reached a level of satisfactory remission and no new lesions are seen to form (usually 10-20 days) the dose interval can be increased. Once-daily treatment
can be changed to an interval of every second day. If the patient is receiving twice-daily treatment, the medication should be reduced to once daily dosing with half the prior daily dose. The dose rate/frequency is adjusted every two weeks until the lowest dose required to control the symptoms is reached (see chapter 6). If longer acting corticosteroids such as triamcinolone or dexamethasone are used, it is preferable to give maintenance doses 72 hours apart to minimize suppressing the hypothalamus-pituitary-adrenal axis. In cats that resist ingesting tablets, injectable dexamethasone can be administered orally/in food or methylprednisolone acetate injection (20mg/cat) can be given as required.

Side effects in dogs include polyphagia, polydipsia, polyuria and behavioral changes. There may be progressive induction of liver enzymes (especially alkaline phosphatase) and muscle atrophy, eventually leading to the development of iatrogenic Cushing’s syndrome. Corticosteroids predispose the patient to the development of diabetes mellitus, pancreatitis, gastric ulceration and steroid hepatopathy. Glucocorticoid induced immunosuppression may lead to demodecosis, pyoderma, Malassezia dermatitis, dermatophytosis and other forms of systemic infection (e.g. cystitis). Cats are more tolerant of corticosteroids than dogs but this does not mean that these side effects will not occur. The induction of type-II diabetes mellitus is a particular risk in overweight cats. Patients receiving long term corticosteroid therapy should be monitored regularly for side effects and in the maintenance phase, semi-annual blood/biochemistry panels and urinalysis are advisable.

Combination therapy
Corticosteroid therapy alone often results in relapses or the doses required to maintain the patient result in undesirable side effects. It is common practice to combine corticosteroid therapy with another immunosuppressive agent to significantly lower the glucocorticoid dose rate.

In the dog, the most common agent used is azathioprine (1-2mg/kg SID or every 48 hours). Azathioprine interferes with purine metabolism inhibiting nucleic acid synthesis (DNA and RNA). This effect is most marked on rapidly dividing cells especially T lymphocytes, resulting in a depression of cell-mediated immunity and T cell dependent antibody production. Azathioprine can suppress synthesis of all blood cell elements resulting in side effects of neutropenia, lymphopenia, anemia or thrombocytopenia. For this reason, dogs treated with azathioprine should have a complete blood count (CBC) every 2-4 weeks until a maintenance dose is reached and then every two months during the maintenance phase. If the total leucocyte count falls below 5000/mm$^2$ or there is thrombocytopenia, the drug should be suspended for 1-2 weeks and then restarted at a lower dose rate with fortnightly CBC monitoring. Cases of potentially fatal pancreatitis and hepatitis are occasionally reported. Azathioprine has a delayed onset of action of about 2-3 weeks. Azathioprine should be given together with glucocorticoids in the initial phase of treatment. The dose of corticosteroids can be progressively reduced and some cases can be maintained on azathioprine without corticosteroids. If the patient is being maintained solely on azathioprine then the dose can be reduced or the treatment interval extended to every other day.

Azathioprine causes fatal bone marrow suppression in cats. In the cat, the combination agent of choice is chlorambucil, an alkylating agent inhibiting the cross-linking of DNA. The dose for cats is 0.1-0.2 mg/kg SID or every other day. Chlorambucil has the same myeloid suppression potential as azathioprine and the same monitoring protocol is recommended. Chlorambucil, as an alternative to azathioprine, can be used in dogs at the same dose rate.
Other pharmaceuticals used in the treatment of autoimmune disease

Cyclosporine
Cyclosporine is used for the management of recalcitrant atopic dermatitis and anal furunculosis in dogs. There are several published and anecdotal reports of its use in sebaceous adenitis, alopecia areata (3), metatarsal fistulae, histiocytosis and other immune-mediated diseases, whereas the results in classical autoimmune diseases such as pemphigus and lupus are not satisfactory. It has a variety of immunosuppressant actions; in particular it’s ability to suppress T cell proliferation and activation by inhibiting the production of interleukin-2. Oral cyclosporine has been used at 5-10mg/kg. Cost is a significant issue with cyclosporine therapy. Cyclosporine can be used as a sole agent or in combination with corticosteroids. Its side effects are mainly gastrointestinal, gingival hyperplasia and hirsutism.

Dapsone and sulfasalazine
Dapsone is an antibacterial agent used in the treatment of mycobacterial infections but with a wide range of anti-inflammatory actions. Dapsone inhibits lysosomal enzymes, neutrophil chemotaxis, mast cell degranulation, alternate pathway complement activation, T cell responses and the synthesis of immunoglobulins and prostaglandins.

About 50% efficiency has been reported in dogs with pemphigus foliaceus or pemphigus erythematosus. Dapsone can be used in maintenance therapy to reduce the amount of azathioprine or corticosteroid required. Dapsone is also used in combination with corticosteroids for the treatment of vasculitis. There is a lag phase of several weeks. The initial dose of dapsone is 1mg/kg TID for 2-4 weeks then gradually reduced to twice then once daily. Some patients can be maintained on 2-3 times weekly dosing. Side effects include leucopenia, thrombocytopenia, anemia and hepatotoxicity (manifest as increased liver enzymes or possible severe hepatitis). Dapsone should not be used in cats because of their sensitivity to the side effects. Fortnightly monitoring with CBC and a biochemistry panel is advisable during the first four months of therapy then the testing interval progressively extended.

Sulfasalazine is converted in the colon to sulfapyridine 5-aminosalicylate. Sulfasalazine is given at 10-40mg/kg TID and may be more effective in cases with extensive neutrophil infiltration. Sulfasalazine can lower tear production, resulting in keratoconjunctivitis sicca. Laboratory monitoring and tear measurement should be performed as described for dapsone.

Pentoxifylline
Pentoxifylline is a xanthine derivative that inhibits phosphodiesterase enzymes (PDE). It has a variety of actions including decreased cytokine production (TNF-α and various interleukins) by lymphocytes and macrophages. Pentoxifylline decreases lymphocyte and leukocyte responsiveness to cytokines and reduces endothelial expression of adhesion molecules (integrins). Neutrophil mobility and chemotaxis is increased. Pentoxifylline increases erythrocytes and leukocytes pliability, decreases platelet aggregation and reduces blood viscosity. The drug has been used in vasculitis and as adjunct therapy in cases of atopic dermatitis and immune-mediated diseases (4). A lag period of 4-12 weeks occurs before which any benefits are seen. The intial dose of pentoxifylline is 10mg/kg BID-TID. The drug has a very short half-life and there are anecdotal reports that higher doses are required in some cases. Pentoxifylline is a gastrointestinal irritant and must be taken with food. In dogs, major side effects are uncommon.
**Human intravenous immunoglobulin therapy**

Intravenous immunoglobulin therapy has been used in human autoimmune disease. The mode of action of high doses of immunoglobulins is not clear. Reports of the use of human immunoglobulin therapy in dogs and cats are very limited and often anecdotal. Studies have shown variable responses in dogs with refractory isoimmune hemolytic anemia. The dose rate cited by some authors is 1gm/kg IV over 4-6 hours on one or two consecutive days then repeated monthly on a tapering out basis. There are presently no clinical trials in animals to determine the safety or efficacy of this treatment method in veterinary dermatology.

**Sunscreens**

Since several autoimmune diseases are aggravated by UV radiation (e.g. cutaneous lupus erythematosus or pemphigus erythematosus), sunscreens can be useful adjunct therapy agents. Sun protection factor (SPF) 20+ formulations in gel penetrate well into the skin and leave little residue but are difficult to obtain.

**References**


