Immunosuppressive drug therapy in small animals – optimising the old and understanding the new

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Although severe immune-mediated disease is relatively uncommon, a busy small animal practitioner may need to prescribe immunosuppressant drugs on a regular basis. Unfortunately the drugs available to us are not licensed for systemic immunosuppression in veterinary patients. Before reaching our clinics these drugs will all have shown efficacy in animal models of human transplantation (for preventing graft rejection). This is a very specific and somewhat artificial model and certainly does not imply that they will be effective when we prescribe them for the immune mediated diseases we confront, but does mean that we can get a basic idea of common drug toxicities and side effects before we start. In the case of veterinary licensed ciclosporin preparations we can start with a good understanding of how the drug is used to control atopic dermatitis.

Before prescribing an immunosuppressant, the following considerations are important:

- Is immunosuppression really indicated and likely to be effective for the condition?
- Is an appropriate and affordable formulation/tablet size available and is the owner aware of and able to afford necessary follow up monitoring?
- Will the owner be able to safely administer the product and take necessary precautions when handling the drug and animal waste?
- Are drug interactions likely?
- Are there any breed specific considerations?
- Is the owner aware of common drug side effects?
- How will treatment response be monitored?

This webinar will consider the well-established “traditional” drugs (corticosteroids, azathioprine, chlorambucil, cyclophosphamide and vincristine) and newer agents (ciclosporin, mycophenolate and leflunomide). Since these drugs are sometimes used in combination, it is vital that the clinician is aware of the class of drug and has at least a cursory idea of mode of action – efficacy may be increased and toxicity reduced by choosing drugs that act on different metabolic pathways and at different stages in the cell cycle.

Corticosteroids
Corticosteroids remain the mainstay of immunosuppressive therapy and have hugely diverse effects on different tissues. About 20% of all genes within leucocytes are regulated by steroids. Steroids cross the cell membrane then bind to a receptor in the cytoplasm. The steroid/receptor complex crosses into the nucleus and binds to regulatory gene sequences, altering gene transcription or interfering with action of the transcription factor NK-kappa B. This molecule has diverse effects on numerous other pathways. There are also poorly characterised membrane bound steroid receptors in many tissues and direct effects of cortisol on cellular processes. The effects are thus hugely more potent than simply inhibition of phospholipase (as shown in older pharmacology texts comparing the point of action of steroids versus non-steroidal anti-inflammatory agents on prostaglandin and leukotriene synthesis). There is a continuum rather than a clear distinction between anti-inflammatory and immunosuppressive effects. Inflammation can cause autoimmunity and tissue inflammation is a major manifestation and cause of symptoms for most immune mediated conditions.

One of the most important early glucocorticoid actions is reducing Fc receptor expression on the surface of macrophages/phagocytes – this will reduce phagocytosis of any antibody coated particle (such as erythrocytes in immune mediated haemolytic anaemia or platelets in immune mediated thrombocytopenia). Glucocorticoids can also reduce antigen presentation, MHC expression, lymphocyte proliferation and IgG production.

When prescribing corticosteroids consider:

1. Species differences: dogs are more steroid sensitive that cats, requiring about half the dose on a mg/kg basis. Cats may be more vulnerable to the diabetogenic effect of steroids. Prednisone is poorly absorbed in cats and variably in dogs – prednisolone is preferred. Occasionally a patient will not respond to prednisolone but will to dexamethasone.

2. Individual differences in steroid sensitivity – some individual dogs are more steroid sensitive than others. This is best documented in inflammatory bowel disease, where steroid resistant dogs may respond to ciclosporin. Large dogs may suffer fewer steroid side effects if dosed based on body surface area rather than body weight. Suggested starting immunosuppressive dose of prednisolone not to exceed 50mg/m²/day.

3. Common side effects to prepare the owner for: polyuria, polydipsia, polyphagia, panting, muscle wastage/muscle weakness, hair-coat and skin changes, urinary tract infections, blood test changes (leucocytes, ALKP, cholesterol)

4. Less common side effects that sometimes cause big problems
   a. Mineralocorticoid effects – cause sodium and hence water retention. This can precipitate congestive heart failure in predisposed individuals (for example a Cavalier King Charles Spaniel with advanced mitral valve disease).
   b. Gastrointestinal disturbance and ulceration - especially with concurrent NSAID use. Note that there is little evidence supporting prophylactic use of gastrointestinal protectants with steroids – there is more rationale
when GI ulceration is present. In this situation, the most physiologically appropriate agent would be the synthetic prostaglandin, misoprostol (Cytotec, Pfizer) although this drug may itself have GI side effects

c. Hypercoagulability. Some patients are already hypercoagulable because of their illness or breed. This includes
   i. patients with IMHA (pulmonary and portal vein thrombosis common)
   ii. Patients with anticoagulant proteins loss (protein losing nephropathy and enteropathy)
   iii. Cushings patients
   iv. Site hounds (one contributor may be high PCV causes higher blood viscosity)

Measuring prothrombin and activated partial thromboplastin times is insensitive for documenting hypercoagulability and other more promising technologies (such as thromboelastography and platelet aggregometry) are still not widely available/affordable. Hence empirical anticoagulant therapy is often prescribed for patients perceived as being at high risk and when such a patient is identified, the clinician should consider using both platelet inhibitors (aspirin or clopidogrel) and an inhibitor of secondary haemostasis (heparin is preferred to warfarin). Very recent studies on healthy dogs show that the dose of aspirin required to consistently achieve platelet inhibition is 2mg/kg/24 hr. The “ulcerogenicity” of this dose when prescribed concurrently with glucocorticoids is unknown.

d. Diabetogenic effects, especially in cats (studies on cats that have undergone renal transplantation show that around 1 in 5 will become diabetic as a result of very long term glucocorticoid use). Whilst it is perfectly possible to use steroids in diabetic patients, the higher doses of insulin required, and need for concurrent insulin dose adjustments when steroid dose is altered often make it undesirable.

e. Elevations in bile acids that can be profound, leading the unwary clinician to suspect hepatic insufficiency.

**Azathioprine (cytotoxic – do not confuse with azithromycin)**

Azathioprine (Immuran) – A purine agonist interfering with DNA synthesis. Azathioprine is cheap and has been a widely prescribed second line immunosuppressive agent in dogs, used alongside glucocorticoids. May have a greater effect on cell mediated immunity than humoral immunity (opinions vary). Inhibits macrophage production, but little effect on cytokine production by lymphocytes. Azathioprine can cause hepatotoxicity and pancreatitis. A recent retrospective study showed hepatotoxicity (defined as >2 fold increase in ALT) in 5/34 dogs (15%) with a median onset of 14 days. Thrombocytopenia and neutropenia were
less common and occurred later. German Shepherd dogs were suggested as being predisposed (Wallisch K and Trepanier L (2015) JVIM 29: 513-518). Both hepatotoxicity and myelotoxicity are considered idiosyncratic reactions and are typically reversible (if promptly recognised) on discontinuation of therapy.

a. Historically azathioprine was considered a slow acting drug (in the context of human Crohn’s disease it takes several months for full benefits to be seen). Recent work shows in vitro inhibition of canine lymphocyte proliferation within a few days (similar to most other immunosuppressants)

b. Obtain haematology and biochemistry profiles at 0 and 2 weeks and periodically thereafter. Myelosuppression occurs occasionally (less common than with cyclophosphamide). It may be very difficult to assess hepatotoxicity when azathioprine is added to an existing steroid regime if a fresh baseline biochemistry is not obtained, to ensure that pre-existing steroid effects on the liver enzymes are documented.

c. 2mg/kg q24 hours. 25 and 50mg tablets. Dividing tablets is not recommended. Compounding pharmacists (such as Nova Laboratories Ltd. (www.novalabs.co.uk)) can prepare 10mg capsules to order

d. Not recommended for use in cats

For interest only: metabolism of azathioprine into active and potentially toxic metabolites is somewhat complex. Important metabolites of azathioprine are 6-methyl mercaptopurine, 6-MMP (which is potentially hepatotoxic and is generated by the enzyme thiopurine methyltransferase, TMTP) and 6-thioguanine, 6-TG (levels of 6-TG correlate with clinical response, with high levels risking leucopenia). Polymorphisms in TMTP alleles in humans cause significant variations in TMTP levels between individuals. TMTP activity has also been shown to vary between different dog breeds but on average, levels are significantly higher in dogs than in people. Theoretically this might help explain the apparent vulnerability of dogs to azathioprine hepatotoxicity, However, low TMTP levels have not correlated with azathioprine hepatotoxicity in dogs and the risk may be best assessed by measuring 6MMP:6TGN ratios. Indeed one author speculates that high 6MMP:6TGN ratios could make azathioprine a relatively ineffective therapy in dogs (personal communication from Thierry Olivry). Very low TMTP levels in cats mean that the therapeutic margin is lower and great care with dosing and monitoring would be advised for anyone attempting azathioprine therapy in cats.

Chlorambucil (cytotoxic)

Chlorambucil (Leukeran) – is an alkylating agent (crosslinks DNA) – well tolerated and a good second choice agent in cats (normally used with steroids initially). Despite occasional GI side effects, chlorambucil is a useful drug for steroid refractory IBD in
cats (as well as for lymphocytic lymphoma) and a recent retrospective study on canine IBD suggests it may be superior to azathioprine as an adjunctive agent with glucocorticoids (Dandriuek et al 2013). Rarely, neurotoxicity occurs in cats. Suggested starting dose is 2mg/cat q 48 hours. Tablet size makes adherence to other suggested dosing regimes difficult without dividing the tablets. More practical to give whole tablets less frequently, especially when disease is apparently in remission and lower maintenance doses are desired. Myelosuppression is uncommon although periodic haematology profiles are advisable. Historically quite cheap, now more expensive.

**Cyclophosphamide (cytotoxic - do not to confuse with ciclosporin!)**

Cyclophosphamide, like chlorambucil, is an alkylating agent that cross-links DNA, preventing its separation. Despite widespread historical usage, especially for IMHA, it is my view that the side effect profile, and some study evidence suggesting increased mortality make it difficult to justify use of this drug as an immunosuppressant. However, it is suggested (not by myself) that it may still have a role in management of immune mediated arthritides. Of the cytotoxic agents described above, cyclophosphamide has the strongest myelosuppressive effects, and also causes haemorrhagic cystitis in some patients, that can be eventually fatal. This is not a rare side effect – I have seen it a number of times. In my opinion, it should only be used for cancer chemotherapy in companion animals. Interestingly, when used in metronomic chemotherapy it reduces regulatory T-cell numbers – a desirable attribute in a chemotherapy drug, but undesirable in an immunosuppressant.

**Vincristine (cytotoxic)**

Vincristine, widely used for treating lymphoma, has a niche role as an immunosuppressant, specifically in early management of immune mediated thrombocytopenia (ITP). Vincristine binds to tubulin, disrupting mitotic spindle assembly. When used in dogs at 0.02mg/kg IV vincristine can increase platelet count markedly within 3-5 days. The tubulin binding may stimulate megakaryocytes to release more platelets, but the main effect in dogs appears to be impaired phagocytosis of opsonised platelets by macrophages - because of the tubulin content of platelets, vincristine bound to platelets is delivered in high concentrations to any macrophage engulfing a platelet, immediately preventing any further phagocytosis of platelets by that cell. This has been referred to as the “Trojan platelet theory”. There is lack of consensus regarding whether platelets released in response to vincristine are functional. Recent good quality controlled studies shows that it reduces time to return of “safe” platelet counts and hence hospitalisation time in dogs with severe ITP and that it is as effective as intravenous human immunoglobulin in this regard. I now use vincristine routinely in ITP patients with severe thrombocytopenia. Myelosuppression is rare at this dose, but additional care is required in dogs with the ABCB1-1 (MDR-1) gene mutation.

**Ciclosporin**
Ciclosporin (Atopica, Cyclavance, Sporimmune, Modulis) is not strictly speaking cytotoxic in that it does not kill cells or cause myelosuppression. Ciclosporin acts primarily on T-cells by binding the intracellular receptor ciclophilin that binds calcineurin – an enzyme/transmitted involved in inhibiting IL-2 production. IL-2 is the most important T-cell growth factor. As well as reduced T-cell proliferation, other effects include reduced B-cell proliferation, reduced MHC class I expression on grafts and reduction in some granulocyte functions. The most common side effect is vomiting during the first few days of therapy. Provided this is not profuse it does normally subside. Some authorities have found that metoclopramide useful in short term management of this scenario. Administration of the (capsule) medication frozen is also suggested to reduce these effects (clearly this is not possible with the liquid formulations). Less common side effects include hirsutism (cat) and papillomas/gingival hyperplasia. Renal toxicity usually only when other nephrotoxic drugs used concurrently. Idiosyncratic liver toxicity is reported but rare. The original oil based formulation was Sandimmune, subsequently replaced by a veterinary formulation (ultramicronised), Atopica. Atopica is licenced for treatment of canine and feline atopic dermatitis, although is extensively used off licence for immunosuppression in other disorders. Several other veterinary formulations (all liquid) are now available for dogs. Extensive potential interactions, so worth close attention to the data sheet.

1. Suggested starting dose for systemic immunosuppression in dogs is 5mg/kg q12 hours. Drug concentration in the skin and the gut epithelium allows for lower and less frequent dosing (q 24 hrs rather than q 12 hrs) for some immune-mediated gut and skin conditions and means there is poor correlation between blood levels and clinical effect in atopy, hence the Atopica data sheet does not suggest routine monitoring of serum ciclosporin levels.

2. P450 dependent metabolism hence P450 inducers (ketoconazole and all other related antifungals, diltiazem, macrolides, metoclopramide and grapefruit juice may increase levels and TMS and phenobarbitone may decrease levels)

3. Substrate and inhibitor of MDR-1 P glycoprotein transporter – potential for inducing ivermectin or milbemycin toxicity

4. Avoid modified live vaccines

5. May antagonise insulin

6. Reduced immune surveillance may allow eruption of neoplasia (lymphoma) and unusual infections (toxoplasmosis, fungal, other)

Researchers at Mississippi Vet School have made great progress in the quest to find more reliable ways of determining whether ciclosporin is having an immunosuppressive effect in an individual dog, opening the door to truly individualised immunosuppressant dosing. RT-PCR is used to measure T-cell expression of selected
cytokines (IL-2 and IFN-gamma) whose levels change in response to ciclosporin therapy, enabling them to state whether they consider T-cell cytokines maximally, partially or minimally suppressed by ciclosporin in an individual dog. For greatest accuracy, baseline samples (pre-treatment) are also useful. A sodium heparin (not lithium heparin) tube is required and the sample must be couriered to USA in the first half of the week. It is hoped that this assay may be run by a UK laboratory in the near future.

For further information on the background to these studies consult the reference Archer, Fellman et al (2011). For information on submitting samples consult the following website:

http://www.cvm.msstate.edu/animal-health-center/pharmacodynamic-laboratory

The same group has recently shown that ciclosporin at immunosuppressive doses causes platelet activation in dogs and that low dose aspirin (1mg/kg/24 hrs) abrogates this effect, so may help prevent thrombosis.

Ciclosporin and prednisolone are the mainstay of lifelong immunosuppressant regimes in feline renal transplantation programmes, hence long term ciclosporin complications in cats are better documented than for other immunosuppressants. Two infectious complications of ciclosporin therapy merit specific discussion:

a. Toxoplasmosis in cats- a study commissioned by the manufacturers of ciclosporin for license application suggests that the main risk is when seronegative cats encounter Toxoplasma for the first time whilst receiving ciclosporin and that there is less risk to a cat that is already seropositive when treatment is started. However, convincing arguments for recrudescence of latent infection during treatment are proposed by the authors of older case reports. It is notable that in one of the major American feline renal transplant programs, recipients that are seropositive for toxoplasma receive clindamycin prophylaxis for life.

b. Systemic fungal infection in dogs – a recent publication describes opportunistic systemic fungal infections in 8 dogs receiving prednisolone and ciclosporin therapy. Whilst such cases are of concern, it is notable that the species of fungus was only identified in 4 dogs, yet in 5 cases fluconazole was used (this drug has a relatively narrow spectrum, since it has activity against yeast forms but not against filamentous fungus).

**Mycophenolate mofetil (cytotoxic)**

Mycophenolate mofetil (CellCept, Roche, generics), was originally developed as an alternative to azathioprine with reduced hepatotoxicity, and it should not be used with azathioprine. Like azathioprine, inhibits de-novo purine synthesis in B and T cells but it has cytostatic effects (other cell types have salvage pathways) with much reduced myelotoxicity compared with other agents, with some selectivity for activated T-cells (undergo apoptosis). Decreases antibody formation. May be synergistic with
ciclosporin. The rapid onset of immunosuppression (theoretically can act within hours) and availability of both an oral suspension and a parenteral preparation add appeal.

a. Starting dose for dogs: 10-20 mg/kg PO q24 hr or divided q 12 hr. Available as 250mg and 500mg tablets. Powder for reconstitution (slow IV infusion) and an oral suspension are also available.

b. The main toxicity is GI (with dysuria also reported) and whilst this toxicity may be reduced or avoided by using lower starting doses (10mg/kg q 12 hr), the diarrhoea caused by mycophenolate is often severe, and it is a common reason for discontinuation of therapy. Mycophenolate is less myelosuppressive than other agents, but monitoring still advised, especially as part of a multidrug regime.

c. Veterinary use is increasing (IMHA, ITP, myasthenia gravis, Pemphigus, myositis). In a recently publication, mycophenolate mofetil was effective as a single agent for treating ITP in 5 dogs. Another recent retrospective suggests that mycophenolate has promise as a treatment for canine GME. However, there is a lot to learn regarding efficacy in dogs, with recent data from Mississippi able to show a convincing in vitro effect on dog lymphocytes, but less convincing in vivo suppression of cytokines (this work is ongoing).

d. Theoretically mycophenolate should be poorly tolerated in cats due to lack of hepatic glucuronyl transferase enzymes, but its use has been described in 2 cats with IMHA without adverse side effects (this suggests that cats may have alternative/additional pathways for metabolising the drug).

e. Historically expensive, but generic 250mg tablets are much cheaper than ciclosporin, making it a drug that has increased markedly in popularity recently.

Leflunomide (cytotoxic)

Leflunomide – (Arava7, Hoeschst + generics) inhibits pyrimidine synthesis, decreasing DNA and RNA synthesis and causing G1 cell cycle arrest. Inhibits B and T cell function and antibody formation, has significant anti-inflammatory effects and may induce regulatory cells. Used in a variety of canine immune disorders (small retrospective recently published on canine polyarthritis, showing high response rate and few side effects) refractory to conventional therapies or when steroid side effects are problematic and for canine reactive histiocytosis. Has a long elimination half-life in humans (significantly shorter in dogs) and potential for myelotoxicity and severe hepatotoxicity, but incidence of adverse effects in dogs appears to be low (so far predominantly inappetance, lethargy and vomiting). Vets in USA advocate monitoring serum levels to avoid serious toxicity, (with a recommendation to maintain a plasma trough level of the metabolite teriflunomide 20ug/ml). I have not found a lab or hospital in UK offering this service. Auburn University (USA) were offering free measurement of serum levels for dogs and cats in order to try and better define a recommended therapeutic range. Further information available via this link:
Starting dose dogs: 2-4mg/kg/day, cats 10mg/cat once daily (NB I have not used this drug in cats). In a recent retrospective study the median dose used in dogs for a variety of diseases was approx. 2mg/kg q 24 hr. The availability of a generic formulation (20mg tablets) has made leflunomide a realistic choice as a second line agent, with costs for smaller dogs and cats unlikely to be dramatically different to the cost of ciclosporin or mycophenolate. 10mg, 20mg and 100mg tablets available, making dosing simpler in smaller patients. Complete blood counts and liver enzymes should be monitored regularly. A recent medicine list-serve discussion describes cases of Heinz body anemias in cats secondary to leflunomide therapy.

**Combination therapy**

A clinician may wish to use immunosuppressants in combination in the following circumstances:

- Where a single agent has been ineffective in gaining control of the disease
- In very aggressive disease presentations where rapid and profound immunosuppression is deemed essential to save life
- Where the side effects of a given agent are detrimental to patient welfare
- Where two immunosuppressants may have a synergistic effect
- Where there is published evidence for efficacy of the combination

Many clinical studies on immunosuppressants evaluate combination therapy, since they typically describe use of a given agent in combination with glucocorticoids. Historically glucocorticoids and azathioprine was the most commonly used combination, with the azathioprine regarded as a “steroid sparing” agent. It is only possible to give general guidelines for combination therapy, as follows:

1. Aim to combine different classes of drug, avoiding those with similar toxicity profiles. For example, prednisolone and azathioprine, prednisolone and ciclosporin, or azathioprine and ciclosporin may be reasonable choices, but azathioprine with mycophenolate would not.
2. If two potentially cytotoxic drugs are combined, they should target different pathways (i.e. have different mechanisms of action) and the dose of each agent should be reduced to avoid excessive myelosuppression. There is no formula stating how much the dose should be reduced. An example would be concurrent use of mycophenolate and chlorambucil.
3. Work on an experimental canine kidney transplantation model showed that when three immunosuppressants are employed concurrently, there is about a 25% incidence of sepsis. Hence, when the number of immunosuppressants increases, so should vigilance and active surveillance for infection. Keep in mind that the classic clinical signs of infection may be attenuated or absent because of the immunosuppressants.
**Monotherapies not involving glucocorticoids**

For many immune-mediated diseases, glucocorticoid treatment has long been considered “standard of care”, even though this has rarely been critically evaluated. However, there are situations where use of a different drug may be desirable, or even a better option than steroids. Small studies describe specific situations where this could be considered, namely:

- Use of either ciclosporin or leflunomide as monotherapies for control of immune mediated polyarthritis in dogs
- Use of mycophenolate mofetil for control of immune mediated thrombocytopenia in dogs.

**Weaning the patient off immunosuppressants**

Opinions vary on the optimal time to start reducing immunosuppressant drugs and the magnitude and frequency of dose reductions. The more gradual the reduction, the less the chance of disease relapse. Although there are occasions when severe drug side effects or infections will necessitate more rapid reductions, the following guidelines are suggested

1. The disease being treated should have been well controlled (in remission) for at least 2 weeks before any dose reduction is made
2. Total immunosuppressant dose should not be reduced by more than 25-33% in one go during the first few weeks. When a low once daily dose has been reached, a period of dosing every second day may be considered
3. Dose reductions should not be made more frequently than once every 2 weeks
4. Where more than one immunosuppressant is used, try to alter the dose of only one drug at a time
5. Monitoring for disease relapse is suggested for 2-3 months after therapy has stopped

By way of example, a 10kg dog that has responded well to prednisolone treatment for IMHA could be managed with the following schedule (note that PCV and blood smear would be checked before each reduction):

1. 10mg prednisolone q12 hr for 2 weeks ("induction" dose, continued for 2 weeks after disease remission documented), then
2. 7.5mg q 12 hr for 2 weeks
3. 5mg q 12 hr for 2 weeks
4. 2.5 mg q 12 hr for 2 weeks
5. 2.5mg q 24 hr for 2 weeks
6. 2.5mg q 48 hr for 2 weeks, then discontinue

Hence once disease remission is documented, 12 weeks of prednisolone treatment are given.
Emerging therapies and trends

Some more targeted immunosuppressants are emerging (Oclacitinib “Apoquel” for canine atopy, being a notable example) and companies are working hard to “import” monoclonal antibody therapy from the human sphere to the veterinary clinic. Meanwhile further work on existing agents continues (such as strategies for systemic use of tacrolimus in dogs). It is hoped that prospective (pre-treatment) evaluation of a patient’s lymphocytes for immunosuppressant sensitivity will become more accessible to clinicians, and in-vivo measurements of drug effects on the immune system (pharmacodynamic testing) will become available for drugs other than ciclosporin – such measures would allow more “bespoke” (i.e. individualised) therapy.

References


Online resource:

The website of the pharmacodynamics laboratory at Mississippi State University College of Veterinary Medicine is highly recommended, not only for information related to dosing and monitoring of ciclosporin, but also for the section on drug overviews for commonly used immunosuppressants:

http://www.cvm.msstate.edu/animal-health-center/pharmacodynamic-laboratory
<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Main actions</th>
<th>Indications</th>
<th>Speed of onset</th>
<th>Route</th>
<th>Preparations</th>
<th>Starting Dose</th>
<th>Main Toxicities</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>Synthetic adrenal hormones</td>
<td>Multiple, mainly via altered gene transcription</td>
<td>Systemic or local immunosuppression and anti-inflammatory activity</td>
<td>Rapid</td>
<td>IV, IM, SC, PO, topical, inhaled</td>
<td>Prednisolone 1mg and 5mg tablets Dexamethasone 2mg/ml solution. Numerous others.</td>
<td>Prednisolone (immunosuppressive dose) Dogs: 1mg/kg PO q 12 h. Cats 2mg/kg PO q 12 h.</td>
<td>Iatrogenic hyperadrenocorticism</td>
<td>Cheap</td>
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<td>Azathioprine</td>
<td>Antimetabolite</td>
<td>Purine synthesis inhibition</td>
<td>Systemic immunosuppression</td>
<td>Medium-slow</td>
<td>PO</td>
<td>25mg and 50mg tablets*</td>
<td>Dogs: 2mg/kg or 50mg/m2 q 24 h* Cats: DO NOT USE</td>
<td>Gl, marrow, liver, pancreas</td>
<td>Cheap</td>
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<tr>
<td>Chlorambucil</td>
<td>Alkylating agent</td>
<td>DNA breakage and cross-linking</td>
<td>Systemic immunosuppression</td>
<td>Slow</td>
<td>PO</td>
<td>2mg tablets</td>
<td>Dogs, cats: 1-2mg/m2 q24h*</td>
<td>GI, marrow</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>Calcineurin inhibitor</td>
<td>Inhibition of T-cell activation</td>
<td>Atopic dermatitis, systemic immunosuppression, KCS</td>
<td>Rapid-medium</td>
<td>PO, IV, ophthalmic</td>
<td>10, 25, 50 and 100 mg tablets, 100mg/ml oral solution, 50mg/ml injectable solution, 0.2% ophthalmic ointment</td>
<td>Atopic dermatitis Dogs, cats 5mg/kg PO q 24 h Systemic immunosuppression: Dogs, cats: 5mg/kg PO q 12h – q24 h Dogs: dose reduced by 50% when given concurrently with ketoconazole.</td>
<td>Transient GI signs (dogs), renal (rare), cytochrome P450 related drug interaction, deranged glycemic control, hirsutism, Papillomatosis, emergence of neoplasia</td>
<td>Expensive</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Calcineurin inhibitor</td>
<td>Inhibition of T-cell activation</td>
<td>Canine atopic dermatitis, perianal fistulae. KCS refractory to ciclosporin</td>
<td>Rapid-medium</td>
<td>Topical, ophthalmic</td>
<td>0.1% cream, Ocular: use small amount 0.03% cream</td>
<td></td>
<td>Toxic if ingested (vasculitis, GI, hepatic)</td>
<td>Expensive</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Novel antimetabolite</td>
<td>Purine synthesis inhibitor</td>
<td>Systemic immunosuppression</td>
<td>Rapid</td>
<td>PO, IV</td>
<td>250 and 500mg tablets, 500mg powder vials for reconstitution</td>
<td>Dog 20mg/kg q 12 h reducing to 10mg/kg Cat: no dose established</td>
<td>GI, marrow (rare)</td>
<td>Cheap (250mg)</td>
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<tr>
<td>Leflunomide</td>
<td>Novel antimetabolite</td>
<td>Pyrimidine synthesis inhibition, possible COX-2 and tyrosine kinase inhibition</td>
<td>Systemic immunosuppression</td>
<td>Slow</td>
<td>PO</td>
<td>10, 20 and 100mg tablets</td>
<td>Dogs: 2mg/kg PO q 24h Cats: 10mg PO q24</td>
<td>Hepatic (rare), marrow (rare)</td>
<td>20mg moderate</td>
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<td>Vincristine</td>
<td>Vinca alkaloid</td>
<td>Interfere with tubulin – cause microtubule breakdown</td>
<td>Immune mediated thrombocytopenia</td>
<td>Rapid</td>
<td>IV</td>
<td>1 mg vial</td>
<td>Dogs, cats: 0.01-0.025 mg/kg IV q 7d</td>
<td>Perivascular irritation/slough</td>
<td>Cheap</td>
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<td>Human intravenous</td>
<td>Derivative of pooled human</td>
<td>Derivative of pooled human plasma</td>
<td>Fc receptor blockade on macrophages/monocytes</td>
<td>Rapid</td>
<td>IV</td>
<td>Various</td>
<td>0.5-1.5g/kg IV infusion over 6-12 hr</td>
<td>Hypersensitivity reactions, hypercoagulability</td>
<td>Very expensive</td>
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<td>Cytosine arabinoside</td>
<td>Antimetabolite</td>
<td>Inhibits DNA polymerase</td>
<td>GME, breed specific meningoencephalitis</td>
<td>Medium</td>
<td>SC</td>
<td>100 mg vial</td>
<td>Dogs: 50mg/m2 SC q 12 h for 4 doses. Repeat in 3 weeks.</td>
<td>GI, marrow</td>
<td>Moderate</td>
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