

Outline

- Importance and consequences of immune mediated disease
- Review of commonly used immunosuppressant drugs in canine and feline
- Review of recent literature evaluating use of these drugs in patients

Immune Mediated Disease

- Immunity essential for a healthy functioning body
- Balance between immune response and attenuating response
- Certain diseases result from a loss of balance favoring a state of hyperimmune response

Immune Mediated vs. Autoimmune

- Immune mediated encompasses true auto-immune
- Avoiding using the term “autoimmune” allows for other etiologies
 - Environmental factors, drug therapy, infectious disease, neoplasia act as triggers
- Autoimmune
 - Must be identification of an “auto-antigen”
- Examples of disease in veterinary patients
 - Immune mediated hemolytic anemia
 - Immune mediated thrombocytopenia
 - Inflammatory bowel disease
 - Immune mediated polyarthritis
 - Atopic dermatitis
 - Steroid responsive meningitis/arteritis
 - Autoimmune disease
 - Lupus, pemphigus

Why does it matter?

- Systemic inflammation
- Local inflammation
- End organ damage
- Increased morbidity and mortality

Glucocorticoids

- At immunosuppressive doses down regulates macrophage ability to present antigens, suppress TH1 cell function and induces T cell apoptosis and some patients B cell antibody disruption
- Advantages – quick onset (2-4 day), both anti-inflammatory effects, suppresses humoral and cell mediated pathways, very inexpensive
- Disadvantages – well known side effects

Azathioprine

- Purine analogue that renders DNA/RNA it is incorporated into non-functional
- Decreases T-cell function
- Disadvantages
- Myelosuppression, hepatic necrosis, pancreatitis, delayed onset of action (days to weeks)
- Dose – 2 mg/kg q 24 hr dogs only
- Use in cat discouraged due to risk of myelosuppression

Mycophenolate

- Inhibits purine synthesis pathway which is critical step specific to T-cell and B cell proliferation and antibody production
- Dose 10 mg/kg q 12 hrs
- Theoretically adverse side effects similar to azathioprine but...
- Clinically patients seem to tolerate better
- Newer drug, less use overall in patient population?

Cyclosporine

- Polypeptide originally derived from Norwegian soil fungus
- Wide variety of actions
- Inhibits T cell activation and proliferation
- Attenuates some inflammatory cytokines
- Decreases actions of natural killer cells, macrophages, eosinophils and mast cells
- It is a first line agent for transplant patients in human medicine
- Little risk of bone marrow suppression in human or animal models

Need to measure levels?

- Routinely done in human and veterinary patients being managed for organ transplant rejection
- Trough whole blood levels 400-600 ng/mL used as therapeutic target
- References also cite 200-400 ng/mL
- Lack of access to this test
- Lack of correlation between clinical efficacy and blood levels across multiple diseases processes

Chlorambucil

- Chemotherapeutic agent whose immunosuppressive properties have not been evaluated in veterinary patients
- Alkylating agent that interferes with DNA replication
 - CYTOTOXIC
- Used mostly for GI inflammatory disease that is poorly responsive to steroids
- Most predictable side effect is myelosuppression, q2 – 4 week CBC monitoring

Adjunct therapies

- Vincristine
 - Decreases phagocytosis of platelets
 - Induces thrombopoiesis
 - Microtubule assembly is altered in these platelets but does not appear to be clinically relevant
- IVIG
- These drugs are typically only used ONCE during course of treatment
- Little evidence to suggest they positively impact long term outcome

Drug Potpourri

- Leflunamide
 - Pyrimidine synthesis inhibitor
- Methotrexate
 - Inhibits folate production → decrease purine production
- Tacrolimus
 - Similar to cyclosporine
 - Limited to topical use
- Lomustine (CCNU)
 - Alkylating chemotherapeutic agent
- Not considered first line agents

One Drug or Two?

- Argument for single agent therapy (prednisone)
 - Cost
 - Efficacy
- Potential challenges when two agents started at the beginning of disease course
 - If patient has side effects early on...
 - If patient responds well early on...
 - If patient does not respond after a few weeks...

How Long Before Taper?

- IMHA, ITP
 - Spherocytosis, regeneration
 - Platelet counts normalize
- IBD with PLE
 - Albumin level
- Meningitis, IMPA
 - Ideally monitor for cytologic resolution of inflammation
 - Usually treatment guided by clinical signs

Taper Schedule

- 4 weeks therapy prior to beginning taper or 2 weeks beyond normalization
- Taper prednisone completely first
- Similar dose reduction/schedule for second agent
- No physiologic reason for most second agents to be tapered
 - Can be stopped cold turkey
 - Taper may better identify a lowest effective dose if long term therapy is needed

Examples of Use in Literature

- Limited search results to last 10 years
- Limited scope of disease to IMHA, ITP, IMPA, PLE
- Found mostly small retrospective studies
- ACVIM consensus statement on IMHA (2018)

Discussion and relevance of the following research studies:

- Treatment of canine idiopathic immune-mediated haemolytic anaemia with mycophenolate mofetil and glucocorticoids: 30 cases (2007 to 2011). Wang, Smith JR, Creevy KE *Journal of Small Animal Practice* (2013) 54, 399–404
- Treatment of presumptive primary immune-mediated thrombocytopenia with mycophenolate mofetil versus cyclosporine in dogs. Cummings FO, Rizzo SA. *Journal of Small Animal Practice* (2017) 58, 96–102
- Comparison of the efficacy of prednisone and cyclosporine for treatment of dogs with primary immune-mediated polyarthritis Rhodes AC, Vernau W, Kass PH, Herrera MA, Sykes JE. *J Am Vet Med Assoc.* 2016;248:395–404
- Comparison of a chlorambucil-prednisolone combination with an azathioprine-prednisolone combination for treatment of chronic enteropathy with concurrent protein-losing enteropathy in dogs: 27 cases (2007–2010). Dandrieux J.R.S., Noble PM, Scase TJ, Cripps PJ, Alexander, German AJ. *J Am Vet Med Assoc.* 2013;242(12):1705-1714

Conclusions

- Very limited number of immunosuppressant agents that are FDA approved for veterinary use
- Steroids are considered first line agent for majority of immune mediated conditions
- Choice of second agent is largely based on anecdotal evidence
- Opinion should be taken as dogma
- Have a taper and monitoring plan in place
- Understand which side effects to look for depending on which medication is being used
- Be ready to change treatment if no response to therapy
- Client education