# ALTERNATIVES TO GLUCOCORTICOIDS: AN INTERNISTS' PERSPECTIVE

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Immunomodulatory agents are used in various disease conditions including immune mediated hemolytic anemia, immune mediated thrombocytopenia, inflammatory bowel disease, myasthenia gravis, autoimmune skin diseases, and some granulomatous diseases (granulomatous meningoencephalitis). In many circumstances glucocorticoids provide the main course of treatment. Unfortunately glucocorticoids have significant and often severe side effects that can in some circumstances overshadow the underlying disease being treated. Possible alternate immunomodulatory options require further exploration. Desirable properties would include a rapid onset of action, limited systemic side effects at therapeutic dosages, low risk of toxicity, and reasonable cost. The presumed mode of action, possible utility and adverse effects of mycophenolate, leflunomide, azathioprine, chlorambucil and hIVIG will be discussed.

## MYCOPHENOLATE MOFETIL (MMF)

Mycophenolic acid (MPA) is the active metabolite of mycophenolate mofetil.[1] While discovered in 1896 it was further developed as a human organ transplant drug with initial toxicity studies performed in dogs.[2] Mycophenolic acid (MPA) is a non competitive inhibitor of inosine monophosphate dehydrogenase which is the rate limiting enzyme in de novo synthesis of guanine and other purines. For most cell types this inhibition does not interfere with DNA synthesis because purines can be obtained from other sources. However, lymphocytes are poor purine salvagers, and at times of cell division upregulate an isoform of inosine monophosphate dehydrogenase that is more sensitive to the inhibitory effects of MPA, thus magnifying their susceptibility to this drug.[1] MPA inhibits proliferation of T and B lymphocytes and suppresses humoral responses of B lymphocytes.

Serum MPA concentrations after oral MMF administration in dogs are highly variable.[1] In humans a steady state serum concentrations is reached by day 7 but interpatient variability has been observed.[2] It binds to plasma albumin in a concentration dependent manner which is not affected by the presence of supratherapeutic concentrations of additional drugs including cyclosporine or prednisone.[2] It is primarily eliminated by the kidneys with 90% of the dose excreted as mycophenolic acid glucoronide (MPAG). Plasma MPA and MPAG alterations are observed in patients with renal insufficiency.[2]

In veterinary medicine utility has been found in IMHA, myasthenia gravis, inflammatory bowel disease, IMPA, and specific immune mediated skin diseases (including subepidermal blistering autoimmune disease).[3,4]

A broad range of dosages are found in the literature. A typical starting dose is generally 17-30 mg/kg divided daily. Adverse effects in dogs are related to the gastrointestinal tract and include nausea, vomiting and most commonly diarrhea. Gastrointestinal side effects may be ameliorated in affected patients by an overall reduction in total daily dose or tid therapy.[2] It has no significant renal or hepatotoxic properties.[2] Additional side effects include secondary infections (pyoderma, malassezia).[1] Monitoring should include periodic assessment of complete blood counts and evaluation of blood chemistries (specifically albumin levels and renal parameters as they affect plasma levels and excretion, respectively).[2]

## LEFLUNOMIDE

Leflunomide is an isoxazole immunomodulatory agent. It is an inactive prodrug that is hydrolyzed in the intestines and plasma to the active metabolite teriflunomide. Teriflunomide selectively and reversibly inhibits the mitochondrial enzyme required for de novo pyrimidine production. Lymphocytes require de

novo pyrimidine synthesis for proliferation. Additionally teriflunomide may inhibit tyrosine kinases associated with several cytokine and growth factor receptors.[5]

In people leflunomide has be utilized in immune mediated arthritides (rheumatoid arthritis and psoriatic arthritis), Crohns disease, systemic lupus erythrematosis, immune mediated vasculitides and some nephropathies. However its use is still limited because of the high prevalence of side effects, some of which are severe. These include gastrointestinal symptoms, skin rashes, severe life threatening idiosyncratic reactions (acute and chronic hepatotoxicosis, severe myelosuppression, interstitial lung disease and toxic epidermal necrosis).

In contrast the drug is well tolerated in dogs and has been utilized in a variety of conditions including IMPA, IMHA, ITP and Evans syndrome.[6,7,8] Doses typically used are 2 to 4 mg/kg once daily. Dose reductions can be considered at around 6 weeks after initiation of therapy but should be based on clinical response. Rarely leflunomide can cause thrombocytopenia and leucopenia and elevations in alanine aminotransferase levels. Periodic assessment of CBC and chemistry are recommended.

**AZATHIOPRINE**

Azathioprine is a prodrug which lacks immunosuppressive effects until converted by the liver to 6-mercaptopurine.[9] This active metabolite is structurally similar to the purine bases adenine and guanine, which make up RNA and DNA. As a result 6-MP insertion occurs into DNA that is being synthesized immediately prior to cell division. Random insertion results in nonsense mutations and eventual cell death due to disruption of critical genes or due to apoptosis triggered by a high mutation load. Azathioprine has a greater activity on delayed cellular immunity than on humoral response. It is cytotoxic to T cells and has its greatest effect on T cell dependent antibody synthesis.[1]

Adverse reactions typically include myelosuppression, diarrhea, an increased susceptibility to opportunistic infections, vomiting, hepatotoxicity and possible pancreatitis.[1] More rare but severe effects include fulminant hepatic necrosis and bone marrow suppression. Toxicity in humans depends in large part on tissue concentrations of thiopurine methyltransferase which is an enzyme responsible for the degradation of 6-MP.[10] It has been found that 10% of dogs have decreased concentrations of TPMT, with some breeds possibly being predisposed to azathioprine toxicity (Giant Schnauzers).[11,12] Toxicity in cats may be related to their significantly lower TPMT concentrations as compared to dogs and people. Severe and fatal bone marrow suppression can occur in this species when prescribed doses similar to those used in dogs.

Azathioprine may take at least 1-2 weeks to reach therapeutic serum concentrations and its slow onset of action may result in a period of 1-8 weeks before clinical effects are evident.[1] The initial dose is 2 mg/kg once daily for a loading period of 1 week and then dosing is reduced to every other day. For larger dogs dosing should be considered on a meter squared basis (50 mg/m2) with a similar reduction to every other day after the loading period. A CBC and chemistry should be considered after the loading dose (day 7) and then every month for the first 3 months of therapy. After that time period monitoring may be reduced to every 3 months.

**CHLORAMBUCIL**

Chlorambucil is an alkylating agent of the nitrogen mustard group. Alkylating agents work by affecting cross linking of DNA preventing replication and cell division. Compared to other alkylating agents it is less toxic and has a slower onset of action.[1]

Side effects include vomiting, diarrhea, anorexia and myelosuppression.

While more commonly used in chemotherapy protocols (lymphocytic leukemia (CLL), lymphoma, multiple myeloma) it has been additionally utilized in dogs to treat inflammatory bowel disease (PLE), immune mediated hemolytic anemia and immune mediated thrombocytopenia. It may have particular utility in feline immune mediated disease and has been used in the treatment of inflammatory bowel disease, lymphocytic cholangiohepatitis, intestinal small cell lymphoma, and feline pemphigus.[1] Dosing is generally at 0.1- 0.2 mg/kg every 24-48 hours. A CBC should be performed within 7-10 days of starting therapy, at 30 days and then likely bimonthly to monitor for evidence myelosuppression.

**HUMAN INTRAVENOUS IMMUNOGLOBULIN (hIVIG)**

Human IVIG is a sterile highly purified IgG preparation collected from a large pool of healthy human plasma.[13] It typically is made up of more than 90-95% biologically active IgG and contains only trace amounts of IgA, IgM, CD4, CD8, CD40, interferon gamma, IL-4 receptor, IL-1 gamma, interferon alpha, tumor necrosis factor alpha, IL-5 and human leukocyte antigen molecules.[13,14] After collection it is purified by pasteurization, nanofiltration and multiple washes with solvent and detergents. It is free of aggregates, kinins, plasmin, kallikrein activators and infectious agents. Preparations have low pH ranges to prevent growth of infectious agents and prevent aggregation.[13] It has been used since 1940 in human medicine to confer passive immunity in immunodeficient states and also as an immunomodulator in immune mediated conditions.[13]

While the mechanisms of hIVIG immunomodulatory activity is not well understood it is presumed to involve the blockade of Fc receptors, the elimination of pathogenic autoantibodies, modification of cytokine synthesis, inhibition of complement and alteration of Fas-Fas ligand interactions.[13,14] Fc receptors are found on multiple cell membranes (macrophages, neutrophils, natural killer cells, B cells, eosinophils, platelets and mast cells). They bind antibody antigen complexes and stimulate antibody mediated phagocytosis. Human IVIG binds lymphocytes and monocytes in dogs, blocking Fc receptors thereby inhibiting phagocytosis and decreasing tissue damage. Donor antibodies present in hIVIG bind with abnormal host antibodies stimulating their removal. In the presence of hIVIG T cells down regulate cytokine activity including IL-2, interferon, and tumor necrosis factor resulting in an overall dampening of inflammatory pathways and less cellular damage. Acute complement dependent tissue injury is lessened due to hIVIG blockage of C3 and C4 complement preventing their binding to target cells. Blockage of Fas-Fas ligand complex formation by hIVIG prevents transduction of apoptotic signals to keratinocytes thereby resulting in keratinocyte stability.[13,14]

In human medicine IVIG has 6 FDA approved usages (Kawasaki disease, bone marrow transplantation, ITP, CLL, pediatric HIV, primary Ig deficiency) but is employed in over 50 other off label conditions.[13] In veterinary medicine it has been used for over 2 decades without any clear consensus about indications for use, or guidelines on dosing or ideal infusion period. The veterinary literature contains reports on its use in IMHA, ITP, Evans syndrome, cutaneous drug reactions, pemphigus foliaceous, SARDS and myasthenia gravis(MG).[13,15,16,17,18,19] While its utility in IMHA, SARDS and MG seem as yet unproven there is strong evidence to suggest it has utility in cases of ITP and Evans syndrome. With regards to immune mediated skin disease, several case reports have documented the use of hIVIG. In general it was used in the face of critical deterioration in patient clinical condition, a failure to respond to more conventional treatments, and in some cases to avoid the use of standard immunosuppressive therapy in the face of concerns about sepsis or infection. In all cases hIVIG use prevented progressive decline and in some cases resulted in relatively rapid amelioration of symptoms (1-4 days after infusion).[15,16,17,18]

Adverse effects in dogs are likely similar to those seen in humans and include acute hypersensitivity, thromboembolism, renal failure, hypotension, fluid overload, aseptic meningitis and delayed hypersensitivity reactions.[13] Dosage ranges are broad (0.25 g – 2.2 g/kg) and transfusions are generally given over 4-8 hours using a very slow rate initially (0.1 ml/kg) with a gradual increase very 30-60 minutes to a maintenance rate not greater than 0.8 ml/kg/min. Use of a lyophilized product is

recommended. It should be reconstituted over 15-20 minutes without shaking. There is some flexibility on diluents allowing the clinician to alter concentration and osmolality which may help reduce the chance of fluid overload. After reconstitution it can be refrigerated for 24 hours. Prior to administration the product should be allowed to come to room temperature. It can be administered via a peripheral catheter but this catheter must be a dedicated line that is monitored closely. A filter is required; its size is dependent on the product being used.[13] Monitoring of temperature, heart rate, respiratory rate and blood pressure should occur at periodic set intervals throughout the transfusion. In the case of an acute hypersensitivity reaction the transfusion should be stopped and the patient should be administered an antihistamine. Most patients will tolerate reinitiation of the infusion at a slower rate. Close monitoring should continue 24 hours post the transfusion with follow up for 6 months to rule out delayed adverse effects. While serial transfusions with gradual tapering are employed in human patients to treat and maintain remission in multiple immune mediated diseases more studies are needed to evaluate the risk of serial transfusions in our patients.[13,19] Additionally while subcutaneous administration is used in human medicine this route has not been explored in dogs.

**References**


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