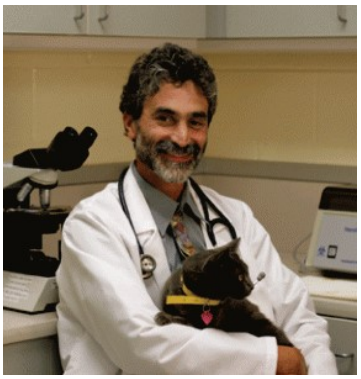
The Benefits of Leflunomide



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Leflunomide is a newer immunosuppressant drug that is rapidly becoming a commonly used drug in veterinary medicine. It has been used in human medicine for years, mainly for rheumatoid and psoriatic arthritis. It also has been used in transplantation medicine and other immune mediated diseases. Leflunomide, is a synthetic isoxazole prodrug that is not active until it is metabolized in the intestinal mucosa and liver to its active metabolite (A77 1726 or teriflunomide). The drug inhibits pyrimidine synthesis in the S phase of the cell cycle of lymphocytes that results in reduced production of both T and B cells, suppressed production of immunoglobulins and interference with leukocyte adhesion. At higher dosages, Leflunomide also inhibits tyrosine kinase activity. In addition to immunosuppressive effects, it also actively

decreases smooth muscle and fibroblast proliferation and has a direct anti-inflammatory effect. Non lymphoid cells are able to synthesize pyrimidine through alternate pathways, thus decreasing the drug's toxicity.

In dogs, Leflunomide has been used as a treatment (often combined with other immunosuppressants) for AIHA or ITP, as either a first line drug or for refractory cases. Additionally, we are commonly using Leflunomide combined with prednisone as initial therapy for immune mediated polyarthritis, rheumatoid arthritis and GME. Using Leflunomide as part of the initial treatment in immune mediated diseases allows for prednisone to be decreased more quickly in dogs that are sensitive to its side effects. Leflunomide used in combination with other drugs as an initial treatment in GME has also shown great promise in increasing longevity and preventing relapses.

Leflunomide was initially dosed similarly to human patients, but dogs are far more sensitive to the drug. Since the gastrointestinal tract metabolizes Leflunomide to its active metabolite, severe gastrointestinal side effects can be seen at higher doses such as those used in people. Fortunately, the canine lymphocyte is much more sensitive than the human lymphocyte to the effects of the active metabolite so significantly lower doses can be used that will still achieve therapeutic concentrations and avoid the GI side effects. Current recommended starting dosages in dogs are 2-4 mg/kg once a day. In cats we use 2mg/kg once a day (10mg/cat on average) for several days and then usually decrease to every other day. The drug reaches steady state fairly rapidly in about 4 days. Ideally a trough blood serum level (22-24 hours post pilling) should be measured about 10-14 days after starting and dosage adjustments may be made based on these values and the patient's clinical response. Because dosing is once a day and trough levels are required, we advise owners to give the medication each day in the late afternoon to early evening so blood levels are obtainable during working hours. Trough levels are generally obtained about 21-23 hours post pill.

Currently, we are sending blood samples to the Auburn University Clinical Pharmacology Laboratory for measurement of Leflunomide levels. The reported value represents the amount of detected active metabolite (A77 1726). Auburn lists the therapeutic range of the active metabolite, as 20-25 mcg/ml; however the University of California Davis, that originally studied this drug's clinical use in dogs, feels that the therapeutic range is actually 20 – 40 mcg/ml. Our clinical use of the drug over the past several years also supports the higher therapeutic range.

The drug is generally very well tolerated, but side effects include deceased appetite, vomiting, and diarrhea. Decreases in leukocytes, red cells and platelets can be seen. Possibly the most common side effect seen in dogs is a rapidly developing cutaneous, ulcerative drug eruption. This drug eruption is frequently seen on the nasal plane, face or food pads, but on occasion will occur on the neck or truncal skin. This drug eruption rapidly resolves if Leflunomide therapy is discontinued. In people, acute hepatic necrosis has been reported, and although this has not been reported in dogs, there have been suspected cases that can present similar to that of imuran toxicity. For these reasons, a CBC should be monitored monthly, as well as intermittent liver panels.

A generic form of Leflunomide, available in 10mg and 20mg sized tablets, has recently become available, making it much more affordable. Leflunomide may be used with prednisone and cyclosporine, but Azathioprine should be avoided.

For more information about Leflunomide or Angell's Internal Medicine service, please call 617 522-7282 or e-mail internalmedicine@angell.org. You can also reach Dr. Brum at dbrum@angell.org.

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