

Leflunomide

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Leflunomide is an isoxazol derivative immunosuppressive drug that was developed within the past two decades, initially for treatment of rheumatoid arthritis and prevention of transplant rejection. Leflunomide is a prodrug for its primary active malononitriloamide metabolite, A77 1726 (also known as teriflunomide). Malononitriloamides reversibly inhibit the mitochondrial enzyme dihydroorotate dehydrogenase, a key enzyme in pyrimidine synthesis, with resultant inhibition of the pyrimidine ribonucleotide uridine monophosphate (rUMP), and decreased DNA and RNA synthesis and G1 cell cycle arrest. Leflunomide inhibits B and T cell function, suppresses antibody production and has anti-inflammatory effects, possibly via inhibition of *de novo* pyrimidine biosynthesis and cytokine-associated and IL-2-stimulated tyrosine kinase activity.

Prior to commercial development, leflunomide was made available for small animal transplant research to Dr. Clare Gregory's group at the University of California, Davis. Because of the drug's availability to this group, a small number of canine patients with refractory naturally-occurring inflammatory and immune-mediated diseases such as immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, non-infectious inflammatory meningoencephalitis, systemic histiocytosis, immune-mediated polymyositis, immune-mediated polyarthritis, and pemphigus foliaceus were also treated, typically with promising success rates (Gregory). Unfortunately, when these initial promising results were reported at the ACVIM Forum and in the veterinary literature in the late 1990s, the drug was not commercially available. When leflunomide did become available, as the proprietary product Arava®, the drug was so prohibitively expensive that its use was very limited in small animal clinical studies. Even after the generic equivalent was approved in 2005, leflunomide remained expensive for several more years. Only recently did the generic drug become more affordable and, as a result, anecdotal and preliminary reports of leflunomide's use in small animal patients are beginning to surface. There are therefore currently very few published reports discussing the use of leflunomide in dogs and cats (Bianco, Ohno). Recently, a case series describing the use of leflunomide in 14 dogs with immune-mediated polyarthritis reported a high response rate with minimal side effects (Colopy)

One of the most promising features of leflunomide in dogs is that it appears to be very well tolerated although if, as anticipated, the drug attains more common usage, it is likely that less frequent but more serious side effects will be recognized. The most common side effect observed with leflunomide use in dogs is occasional inappetence, lethargy and vomiting (Gregory). Serious side effects occasionally reported in people, and thus with the potential to appear in our veterinary population with more common usage, include myelosuppression, cutaneous drug reactions and hepatotoxicity. In humans, traces of the active metabolite teriflunomide can persist for months or even years after drug discontinuation, and in the instance of severe drug reactions, cholestyramine or activated charcoal is needed to rapidly reduce drug levels. In dogs, the

terminal half-life of teriflunomide is much shorter than in humans, so the potential for persistent side effects is probably significantly less (Singer). Complete blood counts and serum biochemistry (especially ALT) should be regularly monitored in small animal patients on leflunomide.

The initial recommended starting oral dose for leflunomide in dogs is 2-4 mg/kg daily, with doses adjusted to attain a plasma trough A77 1726 (teriflunomide) level of 20 µg/ml within a few weeks of commencing therapy. For cats with immune-mediated polyarthritis, a leflunomide dose 10 mg (total dose) orally, once daily, in combination with methotrexate, has been suggested, with dose reductions to effect (Hanna). Measurement of teriflunomide levels is available through the Auburn University Veterinary Clinical Pharmacology Laboratory. One advantage of leflunomide is that it comes in tablet sizes (10 mg and 20 mg) that are convenient for dosing our smaller patients. Leflunomide as the proprietary product Arava® currently costs around \$40 for a 10 mg tablet and, interestingly, \$40 for a 20 mg tablet, although it is rumored to soon be discontinued. The generic leflunomide equivalent is currently priced at around \$1 for a 10 mg tablet and \$1.50 for a 20 mg tablet. Leflunomide generics, as with many commercially available generic problems, have an 'AB' rating by the FDA, meaning that the generic is 'equivalent' to Arava®. However, since 'equivalence' is often determined by pharmacokinetic data in healthy individuals, an AB rating does not guarantee identical performance in clinical patients.

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