Leflunomide

Lisa Singer, VMD, DACVIM
Veterinary Specialist Services
Queensland, Australia

In dogs, leflunomide is infrequently used as an immunomodulatory and immunosuppressive drug and an alternative or adjunct to corticosteroid therapy for immune-mediated and histiocytic disease.

Mechanisms of Action

- Leflunomide works as an immunomodulatory drug by inhibiting the enzyme dihydroorotate dehydrogenase, which is involved in pyrimidine synthesis.
  - Decreases lymphocyte proliferation
    - Affects both T and B cells
    - Decreases antibody production
  - Also inhibits cytokine production and tyrosine kinase-mediated signal transduction for a stronger immunosuppressant effect

- Leflunomide is rapidly metabolized to teriflunomide, the active metabolite responsible for the drug’s clinical effects.
  - Metabolism occurs rapidly in the GI tract and liver after oral administration.
  - The half-life is ≈1 day after oral administration in dogs and ≈2.5 days in cats.\(^2\)\(^3\)
  - Because of the need for hepatic cytochrome p450 enzyme metabolism, leflunomide should be used with caution in animals with hepatic disease.\(^4\)

Clinical Applications

- Leflunomide was originally studied to prevent renal transplantation rejection in dogs.\(^5\)
  - By inhibiting B and T lymphocytes, this drug reduces T-cell–mediated graft destruction in transplantation patients and prevents alloantibody production.
  - Doses >4 mg/kg once a day in dogs can prevent transplant rejection, but adverse reactions (eg, profound anemia from bone marrow suppression, anorexia, vomiting, diarrheal)\(^9\) can be severe, and the drug is not well tolerated.
  - Leflunomide inhibits feline herpesvirus type 1 (FHV-1) replication in vitro.\(^6\)
    - This drug may be an alternative to calcineurin-based immunosuppression in feline renal transplantation patients.\(^6\)

FHV-1 = feline herpesvirus type 1,
GI = gastrointestinal
Leflunomide is rarely used as a primary or lone immunosuppressive agent in dogs.

- The first cases evaluating leflunomide described administration to dogs as part of immunosuppressive therapy during experimental renal transplantation.\(^5,7-9\)
- This drug has been used as a single agent to achieve clinical remission in multiple cases of immune-mediated polyarthritis in dogs.\(^10\)
- In individual cases, leflunomide has reportedly had success as adjunctive treatment of immune-mediated disease (eg, IMHA, ITP, polymyositis, Evans syndrome, pemphigus foliaceus) and been used to treat inflammatory brain disease and systemic histiocytosis.\(^1,11,12\)

Leflunomide can be used as an adjunctive immunosuppressant to induce remission when glucocorticoids are ineffective, side effects are unacceptable, or concurrent clinical disease necessitates alternative long-term drug choices.

- It has been safely combined with prednisolone, cyclosporine, and IV immunoglobulin in dogs.\(^1,8,11\)
- Caution is advised when using this drug with azathioprine or other medications that induce hepatic cytochrome p450 enzymes because of the risk for hepatotoxicity.
  — Conversion of leflunomide to teriflunomide in the human liver is mediated by p450 enzymes; the exact mechanism in dogs is still unknown.\(^4\)

**Protocol**

**In dogs, 3-4 mg/kg PO once a day is recommended.**\(^2\) A loading dose is not recommended.

- Because this drug can take 15 to 18 days to reach a steady state based on pharmacokinetic projections, a tapering course of glucocorticoids may be indicated if more rapid induction of remission is needed.\(^2\)
  — Administration should be continued at least 4 to 6 weeks, then slowly tapered. Abrupt discontinuation is not recommended.
  — No consensus on tapering this drug exists. In the author’s clinical experience, tapering by dose reduction (eg, 20%-25% every 3-4 weeks) or by skipping treatment on some days (eg, 3 days on, 1 day off) can be effective.
- Little information on the use of this drug in dogs is available.

CBC = complete blood count,
IMHA = immune-mediated hemolytic anemia,
ITP = immune-mediated thrombocytopenia
In cats, 10 mg/cat PO once a day is tolerated clinically.\textsuperscript{13}

- Although uncommonly used, leflunomide treatment of feline erosive polyarthritis in combination with methotrexate has reportedly been successful.\textsuperscript{13}
- Dose reductions to 10 mg/cat every 2 to 3 days are suggested once disease has been controlled clinically.

Further investigation is needed to determine ideal therapeutic drug levels in dogs and cats.

- A high-performance liquid chromatography assay for drug monitoring has been described.
  - Drug monitoring for the active metabolite teriflunomide at 12- or 24-hour trough levels in dogs and cats is available from the clinical pharmacology laboratory at Auburn University.\textsuperscript{14,15}
  - Trough levels of 20 µg/mL have been shown to suppress lymphocytes in vitro.\textsuperscript{5}

### Adverse Effects & Cautions

In dogs, laboratory changes have included anemia, leukopenia, thrombocytopenia, and hypercholesterolemia.

- Reported clinical side effects include hematemesis, hematochezia, lethargy, and myelosuppression.
  - Long-term effects are not well-known.
- Anecdotal reports of severe bone marrow necrosis have been associated with leflunomide therapy in dogs.
- Rarely, cutaneous drug reactions have been noted on the face, foot pads, neck, and trunk.
  - These rapidly resolve when the drug is discontinued (anecdotal).
- Hepatotoxicity and liver enzyme elevations have been reported in humans.\textsuperscript{16,17}

In cats, known side effects include sedation and vomiting.

Routine CBC and serum chemistry profile monitoring is recommended after 2 weeks, then every 4 to 6 weeks.

LISA SINGER, VMD, DACVIM, is an associate in small animal internal medicine at Veterinary Specialist Services in Queensland, Australia. She completed an internship at Veterinary Medical and Surgical Group in California, an internal medicine specialty internship at University of Missouri, and an emergency and critical care internship at University of California, Davis. She also completed a small animal internal medicine residency at Michigan State University. Dr. Singer’s clinical interests are infectious and immune-mediated disease, topics on which she has authored several book chapters and research publications.

### REFERENCES