THERAPEUTICS SNAPSHOT
PEER REVIEWED

Leflunomide

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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.[1]

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 supression, anorexia, vomiting, diarrhea)[5] 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

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Leflunomide has been used as a single agent to achieve clinical remission in multiple cases of immune-mediated polyarthritis in dogs.[10]

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.[13]

- Although uncommonly used, leflunomide treatment of feline erosive polyarthritis in combination with methotrexate has reportedly been successful.[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.[14,15]
  - —Trough levels of 20 µg/mL have been shown to suppress lymphocytes in vitro.[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.[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.

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