Sirolimus

Rapamune®

Mechanism of Action

According to the FDA NDA 021083, "sirolimus inhibits T lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (IL-2, IL-4, IL-5) stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12) to generate an immunosuppressive complex. This sirolimus:FKBP-12 complex has no effect on calcineurin activity. The sirolimus:FKBP-12 complex binds to and inhibits the activation of the mammalian Target Of Rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G1 to the S phase of the cell cycle."

Toxicology

According to the FDA NDA 021083: "Rapamycin was given orally to one male and one female beagle dog, 200 mg/kg, for 5 days, followed by a 10 day observation period. During the study, the male had emesis, and diarrhea, anorexia, and body weight loss, red lesions on gums and elevated monocyte and leukocyte counts. EKG changes were seen on day 10 of recovery. At necropsy, lesions were seen on the heart, liver, gall bladder and gums. The female had diarrhea, emesis and weight loss. A small spot was found on the pituitary at necropsy. A heart lesion was found in the right ventricular myocardium and was necrotic. Hepatic midzonal degeneration and thymic atrophy were seen in both dogs."

FDA Labeled Use

Rapamune® is not labeled for dogs; therefore use of this drug in the dog is off-label.

According to the FDA's Highlights of Prescribing Information (Reference ID 4538534):
Rapamune® is an mTOR inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in patients aged ≥13 years receiving renal transplants:

- Patients at low-to moderate-immunologic risk: Use initially with cyclosporine (CsA) and corticosteroids. CsA withdrawal is recommended 2-4 months after transplantation.
- Patients at high-immunologic risk: Use in combination with CsA and corticosteroids for the first 12 months following transplantation. Safety and efficacy CsA withdrawal has not been established in high risk patients.

Rapamune® is an mTOR inhibitor for the treatment of patients with lymphangioleiomyomatosis.

Selected Canine Publications

:: Preclinical

- "Oral administration of low-dose (0.1 mg/kg) rapamycin to healthy dogs achieved blood concentrations measured in ng/mL. The optional dose and administration frequency of rapamycin required to achieve therapeutic effects in tumor-bearing dogs, as well as toxicity after chronic dosing, needs to be determined" (Larson et al.).

:: Safety/dosing

- Young dogs (n=5, as young as 2 months old) with glycogen storage disease type III were treated with higher doses of rapamycin (0.5 - 1 mg/kg/day) for 8-14 months. "In this study, serum triglycerides and cholesterol concentrations were within normal ranges throughout the study in both rapamycin-treated and rapamycin-untreated dogs. In addition, rapamycin had no obvious effect on growth or serum enzyme activities." No major clinical side effects were reported (Yi et al.).

- In a study of 24 middle-aged [at least 6 years old] healthy dogs that received either placebo or a non-immunosuppressive dose of rapamycin, "10 weeks of rapamycin treatment at either 0.05 or 0.1 mg/kg delivered orally three times per week did not cause significant clinical side effects or abnormal hematological changes, but did result in favorable changes in cardiac left ventricular function during both diastole and systole" (Urfer et al.).

- In a prospective dose escalation study of a *parenteral* formulation (daily intramuscular injections) of rapamycin in dogs with appendicular osteosarcoma, no maximally tolerated dose of rapamycin was attained through escalation to the maximal planned dose of 0.08 mg/kg. Pharmacokinetic analysis revealed a dose-dependent exposure. IN all cohorts, modulation of the mTOR pathway in tumor and PBMC (pS6RP/S6RP) was demonstrated. No change in pAKT/AKT was seen in tumor samples following rapamycin therapy (Paoloni et al.).

:: Efficacy

- In a prospective clinical trial, "a total of 324 pet dogs diagnosed with treatment-naive appendicular osteosarcoma were randomized into a two-arm, multicenter, parallel superiority trial whereby dogs received amputation of the affected limb, followed by adjuvant carboplatin chemotherapy +/- oral sirolimus therapy [0.1 mg/kg/day x 4 days, off 3 days]" (LeBlanc et al.).
    - Results: "There was no significant difference in the median DFI or overall survival between the two arms of this trial; the median DFI and survival for standard-of-care (SOC; defined as amputation and carboplatin therapy) dogs was 180 days and 282 days and for SOC + sirolimus dogs, it was 204 days and 280 days, respectively."
    - Discussion: "Whereas the lack of improved progression-free and overall survival time in dogs treated with sirolimus was disappointing, any limitations of mTOR inhibition for delaying osteosarcoma micrometastatic disease progression identified in this study should be viewed contextually through the lens of disease biology, pharmacokinetics, and clinical trial design."

    1) "In the absence of genomic/molecular subtyping, pan-mTOR inhibition strategies might only benefit a minority of human or canine patients treated, and any positive

treatment effects achieved in a small percentage of individuals could become indiscernible with aggregated data analysis."
2) "Based upon the relatively low trough concentrations of (sirolimus <10 ng/mL) achieved in the majority of dogs enrolled in this study, it remains a distinct possibility that insufficient drug exposure (concentration) or duration of exposure (maximum four cycles) might have contributed to the absence of antimetastatic activities in pet dogs receiving sirolimus."
3) "...the delayed introduction of sirolimus into the treatment protocol of dogs at week 15 might have resulted in a "too little too late" effect, and it is reasonable to speculate that exposure to sirolimus, and consequent mTOR inhibition, would be more successful when administered concurrently with exogenous biological stressors, such as chemotherapy."

Pharmacokinetics

- In a pharmacokinetic study consisting of 2 experiments for orally administered low-dose rapamycin (Larson et al), pharmacokinetic parameters for rapamycin after administration of 5 daily doses differed significantly from those after administration of 1 dose:
  - Experiment 1: each dog received rapamycin 0.1 mg/kg PO once.
  - Experiment 2: with a 2-week washout after Experiment 1, each dog received rapamycin 0.1 mg/kg PO once daily for 5 days.
  - Results excerpted from Larson et al.:

In experiment 1, the mean ± SD $AUC_{0\text{-}48h}$ was 140 ± 23.9 ng•h/mL (range, 116 to 168 ng•h/mL), $t_{1/2}$ was 38.7 ± 12.7 hours (range, 27.2 to 59.6 hours), T_{max} was 3.3 ± 2.5 hours (range, 0.5 to 6 hours), C_{max} was 8.39 ± 1.73 ng/mL (range, 5.86 to 10.6 ng/mL), and concentration 48 hours after drug administration was 1.38 ± 0.45 ng/mL (range, 0.78 to 1.86 ng/mL). In experiment 2, the mean ± SD $AUC_{0\text{-}48h}$ was 126 ± 27.1 ng•h/mL (range, 95.9 to 160 ng•h/mL), $t_{1/2}$ was 99.5 ± 89.5 hours (range, 39.1 to 231 hours), T_{max} was 4.5 ± 1.0 hours (range, 4 to 6 hours), C_{max} was 5.49 ± 1.99 ng/mL (range, 3.70 to 8.18 ng/mL), and concentration 48 hours after drug administration was 1.70 ± 0.40 ng/mL (range,1.45 to 2.30 ng/mL).

Sources

- Best Pet Rx+ (https://bestpetrx.com/): (as of September 7, 2021) Available in many doses; prices
vary by dose ranges:

Dose range 0.1 mg - 1 mg capsules, quantity 30, $91.99
Dose range 1.1 mg - 2 mg capsules, quantity 30, $98.99
Dose range 2.1 mg - 3 mg capsules, quantity 30, $114.99.
Dose range 4.1 mg - 5 mg capsules, quantity 30, $127.50
Dose range 5.1 mg - 6 mg capsules, quantity 30, $141.99.
Dose range 6.1 mg - 7 mg capsules, quantity 30, $161.99.

+Please check their website to confirm that they can serve your state.

- Stokes Pharmacy (https://www.stokespharmacy.com/veterinary-rx/for-veterinarians/): (as of August 31, 2021) Available in dose range of 0.8 mg to 6.5 mg capsules:

Dose 0.8 mg capsules, quantity 30, $225.
Dose 6.5 mg capsules, quantity 30, $225.

- Wedgewood Pharmacy (https://www.wedgewoodpharmacy.com/items/sirolimus-capsule.html): (as of September 7, 2021) Available in dose range* of 0.2 mg to 7 mg capsules

Dose 0.2 mg capsules, quantity 30, ~ $70.
Dose 7 mg capsules, quantity 30, ~$232.

Oil oral suspension available in 3 concentrations*

Concentration 0.2 mg/mL, 30 mL bottle $121.50.
Concentration 0.34 mg/mL, 30 mL $124.50.
Concentration 5.6 mg/mL, 15 mL bottle $131.75.

**This dose range/concentrations may not appear on your online portal. If so, please call Wedgewood Pharmacy (call center 877.357.6613) to prescribe this drug.*

Anecdotal Information from Veterinary Oncologists

"Dosing has been 0.1 mg/kg/day. Have seen GI side effects (anorexia) and fever."

References

Larson JC et al. Pharmacokinetics of orally administered low-dose rapamycin in healthy dogs. *Am J Vet Res*. 2016 Jan;77(1):65-71. doi: 10.2460/ajvr.77.1.65.

LeBlanc AK et al. Adjuvant Sirolimus Does Not Improve Outcome in Pet Dogs Receiving Standard-of-Care Therapy for Appendicular Osteosarcoma: A Prospective, Randomized Trial of 324 Dogs. *Clin Cancer Res*. 2021 Jun 1;27(11):3005-3016. doi: 10.1158/1078-0432.CCR-21-0315.

Paoloni MC et al. Rapamycin pharmacokinetic and pharmacodynamic relationships in osteosarcoma: a comparative oncology study in dogs. *PLoS One*. 2010 Jun 8;5(6):e.11013. doi:10.1371/journal.pone.0011013.

Rapamune® (Sirolimus/Rapamycin); Pharmacology Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, NDA 021083, September 1999.

Urfer SR et al. A randomized controlled trial to establish effects of short-term rapamycin treatment in 24 middle-aged companion dogs. *Geroscience*. 2017 Apr;39(2):117-127. doi: 10.1007/s11357-017-9972-z.

Yi H et al. Correction of glycogen storage disease type III with rapamycin in a canine model. *J Mol Med (Berl)*. 2014 Jun;92(6):641-50. doi: 10.1007/s00109-014-1127-4.

Disclaimer: Any information regarding therapy does not promise or guarantee that a particular drug or treatment regimen will be safe, effective, or helpful in the treatment of disease in any patient. The selection of any drug or drugs for patient treatment is done at the discretion of the treating veterinarian. Use caution when combining multiple drugs and be aware of potential drug interactions. Drug costs were provided by the respective pharmacies on the dates indicated, and drug costs and availability are subject to change at the discretion of the providing pharmacy. The treating veterinarian is encouraged to refer to drug labeling, published literature, and safety data for warnings, precautions, and dosing guidelines. Referenced articles, if any, were manually selected and do not necessarily reflect the entirety of literature on the drug or drugs. Vidium Animal Health®'s services, including but not limited to the information contained herein, are governed by Vidium's Terms & Conditions, which are available via email by requesting them at vidiuminfo@tgen.org.

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