PRACTICAL PHARMACOLOGY

Anti–Nerve Growth Factor Monoclonal Antibody Injection for Feline Osteoarthritis

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Osteoarthritis (OA) is a common, lifelong disease that is challenging for veterinarians and owners to recognize.[1,2] Radiographic evidence of feline OA is present in approximately 90% of cats over 12 years of age and 40% of cats generally.[1,3] Due to the frequent lack of overt lameness or joint pain in cats, owners often do not recognize decreased activity and jumping as signs of OA. During physical examination, cats with OA rarely display consistent signs of joint pain, crepitus, joint effusion/thickening, or abnormal range of motion.[1,2,4] Currently, the optimal mechanism for diagnosing OA in cats is a combination of the Feline Musculoskeletal Pain Index (FMPI), an owner questionnaire regarding mobility and behavioral changes at home, radiographs, and response to treatment.[1,2,5,6]

Chronic, maladaptive OA pain often requires a multimodal approach including nonpharmacologic treatments, such as weight loss, exercise/rehabilitation, nutritional supplements, and acupuncture, as well as pharmacologics.[2,4,7] Pharmacologics include anti-inflammatory analgesics (nonsteroidal anti-inflammatory drugs [NSAIDs] or potentially anti–nerve growth factor monoclonal antibodies [anti-NGF mAbs]) as a first line of treatment and other analgesics (e.g., gabapentin, tramadol, amantadine) used adjunctively, as summarized in **TABLE 1**.[2,7] Grapiprant, while shown to be safe in healthy cats, requires further research and is not included here.[6,11] In addition to potential side effects, NSAID and adjunctive analgesic use in cats has historically required daily oral medication, which contributes to medication compliance concerns.[8]

Abstract

Osteoarthritic pain often requires a multimodal approach, with anti-inflammatory analgesics as a first-line treatment. The anti–nerve growth factor (NGF) monoclonal antibody (mAb) class offers a new anti-inflammatory analgesic for feline osteoarthritis (OA) in a monthly subcutaneous injection. Frunevetmab is a felinized immunoglobulin G mAb that binds to NGF, which is elevated in joints with OA. Analgesia is achieved by blocking the receptor-mediated inflammatory and peripheral sensitization signaling cascades induced by NGF. This article describes the pharmacology and clinical considerations of frunevetmab for the management of feline OA pain.

Take-Home Points

- Frunevetmab is labeled for once-monthly subcutaneous injection (dose, 1 to 2.8 mg/kg). Clinical response may be delayed up to 6 to 8 weeks, until steady-state concentrations are reached.
- Frunevetmab appears safe and well tolerated by cats in the short term (up to 3 months), including cats with early chronic kidney disease. Adverse effects include mild dermatologic signs at and away from the injection site. Longer-duration studies are indicated to demonstrate long-term safety and efficacy.
- Due to the neuroprotective effects and contributions of nerve growth factor (NGF) to central nervous system development, frunevetmab should not be given to pregnant, breeding, or lactating cats or cats under 1 year of age and should be used with caution in cats with neurologic disease. Caution is also recommended in cats with a history of injection-site sarcoma and those receiving nonsteroidal anti-inflammatory drugs.
- Cats may form anti-frunevetmab antibodies, resulting in loss of analgesic effectiveness in the long term; further research is needed in this area.
- The humanized anti-NGF monoclonal antibody drug did not achieve regulatory approval due to a high prevalence of human patients with mild abnormal peripheral sensation and a smaller subset with rapidly progressive osteoarthritis (a condition not reported in small animals).

With the advent of the anti-NGF mAb class, we appear to have an alternative anti-inflammatory analgesic for feline OA in a monthly subcutaneous injection. This article focuses on the pharmacology and clinical considerations of a felinized anti-NGF mAb, frunevetmab (Solensia; Zoetis, solensiavetteam.com).

FELINIZED ANTI–NERVE GROWTH FACTOR MONOCLONAL ANTIBODY (FRUNEVETMAB)

Mechanism of Action and Efficacy

Frunevetmab is a felinized immunoglobulin G mAb that binds to NGF.[5] NGF is among many chemical mediators that contribute to peripheral sensitization, neurogenic inflammation, and noxious signal generation interpreted as pain.[3] NGF becomes elevated in osteoarthritic joints, and frunevetmab provides pain relief by blocking the receptor-mediated signaling cascade induced by NGF.[3,5]

Two randomized controlled trials (RCTs) support analgesic efficacy in up to 75% of treated arthritic cats following the second monthly injection, although owner questionnaires did show evidence of placebo effect.[5,8] Objective outcome measures used included veterinary scores and activity collars, which also supported analgesic efficacy.[5,8]

Pharmacokinetics

Bioavailability of frunevetmab following intravenous then subcutaneous injection was 60.3% ± 15.8% in cats with OA.[12] The bioavailability following subcutaneous injection alone was 73.2% ± 14.8% in cats with OA.[13] Peak concentration was reached after 3 to 7 days, with steady-state concentrations reached after 2 subcutaneous doses given 1 month apart.[12,13] The half-life of frunevetmab is 10 to 12 days.[12,13]

Dosing and Administration

Frunevetmab is labeled for once-monthly subcutaneous injection with a dose from 1 to 2.8 mg/kg.[13] **TABLE 2** shows current dosing recommendations.

Safety

Frunevetmab appears safe and well tolerated by cats in the short term. The most common adverse effects in RCTs included gastrointestinal (GI) signs (vomiting and diarrhea) and dermatologic signs.[5,8] GI signs occurred at a similar frequency between cats receiving placebo and frunevetmab injections.[5,8] Dermatologic signs observed include alopecia, dermatitis/eczema, pruritus, nonspecific lesions, and bacterial infections.[8] These side effects were mild, required no treatment or responded to standard treatment, and resolved even after repeated administration of frunevetmab.[8] A recent case series reported dermatologic lesions and pruritus of varying severity (mild to severe), mainly of the head and neck, in 5 cats.[14] Lesions appeared away from the

TABLE 1 Standard Drugs for the Management of Feline Osteoarthritis

DRUG	DRUG CLASS	MECHANISM OF ACTION	INDICATION	DOSE
Meloxicam	NSAID	COX inhibitor	Analgesic and anti-inflammatory	▪ **Initial:** 0.3 mg/kg SC once OR 0.1–0.2 mg/kg PO once ▪ **Then:** 0.01–0.05 mg/kg PO q24–48h
Robenacoxib	NSAID	COX inhibitor	Analgesic and anti-inflammatory	▪ 2 mg/kg SC q24h for up to 3 days OR ▪ 1–2.4 mg/kg PO q24h
Frunevetmab	Felinized anti-NGF mAb	Blocks receptor-mediated signaling induced by NGF	Analgesic and anti-inflammatory	▪ 1–2.8 mg/kg SC monthly
Gabapentin	Anticonvulsant	Calcium channel blocker	Chronic analgesic	▪ 5–10 mg/kg PO q8–12h
Tramadol	Opioid	μ-Opioid receptor	Analgesic	▪ 1–4 mg/kg PO q8–12h
Amantadine	Adamantane	NMDA antagonist	Analgesic	▪ 3–5 mg/kg PO q12h

CKD = chronic kidney disease; COX = cyclooxygenase ; FDA = Food and Drug Administration; IRIS = International Renal Interest Society; mAb = monoclonal antibody; NGF = nerve growth factor; NMDA = N-methyl-D-aspartate; NSAID = nonsteroidal anti-inflammatory drug

injection site within 3 to 18 days of injection and resolved after varying treatments.[14] Further large-scale studies are warranted to better understand the pathogenesis and clinical outcomes of these dermatologic adverse effects to frunevetmab.

No clinically significant differences have been observed on complete blood count, serum biochemistry, or urinalysis following frunevetmab injection.[5,8] Both RCTs included cats with chronic kidney disease (CKD) up to International Renal Interest Society (IRIS) stage 2, but further research is needed to evaluate the long-term effects of frunevetmab on cats with renal insufficiency.

Frunevetmab has not been evaluated in cats younger than 7 months of age or less than 2.5 kg (5.5 lb). Frunevetmab is contraindicated in patients that are hypersensitive to it, breeding cats, and pregnant or lactating queens.[13] It is unknown whether frunevetmab is effective or safe in cats with immune-mediated arthropathies or other causes of pain such as visceral, acute or postoperative, or neoplastic. The safety and immunogenicity of long-term administration (>3 months) are unknown. Cats may form antifrunevetmab antibodies, resulting in loss of effectiveness in the long term; continued research is needed in this area.[13]

COMPARATIVE ANTI-NGF mAb RESEARCH

Human Literature

Anti-NGF mAbs for the treatment of human OA have been evaluated in many large-scale RCTs.[15,16] Recent meta-analysis and systematic review of these RCTs support that anti-NGF mAb treatment can be an effective analgesic for human OA, across evaluated doses, frequencies (every 4 to 8 weeks), and

NOTES
▪ Approved by the FDA for single-dose injection only in cats ▪ Safe with stable CKD IRIS stages 1, 2, and 3 while monitoring for new/worsening azotemia and proteinuria[2] ▪ Improved mobility and jumping after 4–6 weeks[2]
▪ Approved by the FDA for postoperative pain use (up to 3 days) ▪ Safe with stable CKD IRIS stages 1 and 2 when used for 28 days[4,6] ▪ Efficacy for acute and chronic pain
▪ Approved by the FDA for use in cats ▪ Demonstrated improved mobility and jumping[2,5,8] ▪ Safe with stable CKD IRIS stages 1 and 2 while monitoring for new/worsening azotemia and proteinuria[9] ▪ Most common side effect is local skin irritation/excoriation[5,8,9] ▪ Use with caution in neurologic patients due to potential neuroprotective features of NGF[9]
▪ Not FDA approved for cats ▪ Improved activity and quality of life[2,5,6] ▪ Mitigates neuropathic pain[6] ▪ May cause sedation, ataxia, and muscle tremors[2,5,6,10] ▪ May need to dose reduce with CKD[10]
▪ Not FDA approved for cats ▪ Bitter taste may contribute to poor compliance[6] ▪ 2 mg/kg improved mobility, weight bearing, and quality of life.[2,6] ▪ Dose-dependent side effects include mydriasis, dysphoria, sedation, hyporexia, and diarrhea.[2]
▪ Not FDA approved for use in animals ▪ Used as adjuvant pain management for cats[6] ▪ Improved activity and quality of life after 2–3 weeks[2] ▪ Side effect: vomiting (self-limiting)[2]

administration routes (IV or SC).[15,16] About half of RCTs also support a decreased risk of GI and cardiovascular side effects with anti-NGF mAbs compared to NSAIDs.[16] Despite this, anti-NGF mAbs have not been approved for human OA in the United States or Europe due to safety concerns.[16]

The majority of human RCTs reported increased adverse effects in the anti-NGF mAb groups, including abnormal peripheral sensation (75% of RCTs) and rapidly progressive OA (RPOA, 17% of RCTs).[16] Abnormal peripheral sensation (hypoesthesia or paresthesia) was mild to moderate, consistent with peripheral neuropathy, often transient, and occurred in < 12% of patients.[15,16] RPOA is a previously documented process in humans and may have been related to higher doses of anti-NGF mAbs and/or chronic concurrent NSAID use.[13,15,16] NGF has been reported to promote tissue repair, and thus inhibition may adversely affect bone and/or cartilage remodeling.[16] It is also speculated that the analgesic effect of anti-NGF mAbs may result in increased or abnormal joint load, contributing to RPOA.[16]

Canine Literature (Bedinvetmab)

Anti-NGF mAbs have been less thoroughly evaluated in canine OA, with only 1 safety study and 2 RCTs published.[17,18] The literature supports analgesic efficacy of bedinvetmab (Librela; Zoetis, librelavetteam.com) in > 50% of treated dogs, with a potential adverse effect of mild, transient injection-site reaction.[18,19] Studies reported the development of antidrug antibodies (ADAs) in 0% to 3% of dogs, with up to 1.4% of dogs developing reduced efficacy of the drug.[17-19] One study evaluated concurrent NSAID use with bedinvetmab for 2 weeks in healthy dogs and reported no adverse effects, including pathologic examination of joint tissue.[17]

Additional rare adverse effects were noted in the RCTs, with unclear relation to anti-NGF mAb administration. Within the bedinvetmab groups, several dogs were withdrawn due to worsening OA, 1 due to paraparesis of unknown cause, and 1 for a degenerative myelopathy diagnosis; 2 dogs were withdrawn due to bone fractures (1 coronoid process, 1 distal humeral condyle).[19] In both the placebo and bedinvetmab groups, a small number of dogs developed cranial cruciate ligament ruptures.[18,19] As a preventive measure to avoid new injuries and maximize analgesic efficacy, Zoetis now recommends a graded return to activity levels in dogs receiving bedinvetmab.[20]

CLINICAL APPLICATIONS OF FRUNEVETMAB

Frunevetmab is an additional medication to consider for feline OA patients, particularly those for which daily medication is not possible.[7] Although some cats demonstrate clinical improvement within 2 weeks of the first injection, clinical response may be delayed 6 to 8 weeks, when steady-state concentrations are reached.[5,8]

TABLE 2 Frunevetmab Recommended Dosing[13]

BODY WEIGHT	MONTHLY DOSE (MG)	NUMBER OF 1-ML VIALS
2.5–7 kg (5.5–15.4 lb)	7	1
7.1–14 kg (15.5–30.8 lb)	14	2

Case Selection

Considering monthly subcutaneous dosing protocols, patients with travel and/or handling anxiety may not be ideal candidates for frunevetmab. Due to the novelty of this medication and the recurrence of injection, alternative therapies may be warranted in patients with historic injection-site sarcoma.

Due to the neuroprotective effects and known positive contributions of NGF to growth of the developing central nervous system, frunevetmab should not be given to pregnant, breeding, or lactating cats or cats under the age of 1 year and should be used with caution in cats with underlying neurologic disease.[8,9]

Monitoring

Frunevetmab has demonstrated safety for short-term use in cats with CKD IRIS stages 1 and 2.[8] However, monitoring for progressive azotemia, proteinuria, and clinical signs is recommended.[2,8] If dermatologic adverse effects are significant or noted to recur with repeated administration of frunevetmab, discontinuation of treatment should be considered.[8]

In canine and feline anti-NGF mAb studies, a single case of each species was noted to develop pancreatitis.[3,5,19] Pancreatitis was deemed unrelated to administration of the anti-NGF mAb, although analgesia due to NGF/tyrosine kinase receptor A blockade may have masked initial abdominal discomfort.[3,5,19] Thus, additional monitoring may be warranted for patients with historic pancreatitis.

Due to the newness of this medication and comparative research in other species, monitoring feline patients receiving frunevetmab for RPOA (especially those on concurrent NSAIDs), reduced analgesic effectiveness, and new or worsening neurologic symptoms is recommended.[13,15,16] As in dogs, it may be prudent to recommend gradual increases in exercise and/or a rehabilitation plan for cats starting anti-NGF mAb therapy. This approach can contribute to muscle strengthening and prevent sudden increases in joint and bone loading.

FUTURE DIRECTIONS

Current literature supports the analgesic efficacy and overall safety of anti-NGF mAbs for feline OA; however, additional longer-duration (> 3 months) studies are indicated.[5,8] These studies should ideally evaluate for the development of ADAs, monitor dermatologic adverse effects, and include objective outcome measures. Additionally, alternative dosing frequency could be evaluated. Based on comparative human literature, the authors have anecdotally reduced dosing frequency from monthly to up to every 8 weeks in some patients without detecting clinical worsening. TVP

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