RESEARCH COMMENT

Anti-nerve growth factor monoclonal antibody: a prospective new therapy for canine and feline osteoarthritis

Mark E. Epstein

IT can be argued that chronic pain is the most ubiquitous disease process in all of medicine. All animals, should they live long enough, will probably experience it. And of all chronic pain syndromes, osteoarthritis (OA) remains the most predictable cause in both dogs and cats. Indeed, in dogs the pathophysiology of OA is commonly heritable and conformational, meaning that the disease process begins at a very young age and is lifelong, with at least 30 to 40 per cent of dogs affected clinically.[1] In cats, the aetiopathophysiology is less certain but equally prevalent clinically, and more than 90 per cent of cats over the age of 12 years have radiographic changes consistent with degenerative joint disease.[2,3] It follows that the hunt for novel therapy targets to address chronic pain in general and OA in particular needs to remain robust.

One of those targets, nerve growth factor (NGF) and its binding to tropomyosin receptor kinase A (TrkA) receptor, is at the forefront of this hunt. NGF, produced and utilised by many cell types (including epithelium, endothelium, immunoreactive cells and CNS glia), is found in abundance during neonatal and infant development, and gradually downregulates over time.[4] However, it upregulates once again with chronic inflammation, among other circumstances, and becomes an integral component of central sensitisation (wind up), spinal cord plasticity and maladaptive pain signalling. This inevitably results in hyperalgesia: lowered thresholds and exaggerated scope, character, duration and field of pain. Therefore, several anti-NGF/TrkA signalling strategies have been investigated for their pain-modifying capabilities and safety. Chief among these are anti-NGF monoclonal antibodies (mAbs). In a study summarised on page 23 of this issue of *Vet Record*, Enomoto and colleagues[5] provide a thorough review of NGF/TrkA mechanisms, their specific relationship to OA, the development of anti-NGF mAbs, their caninisation and felinisation from an original rat-derived molecule, the development of clinical therapys and their safety, pilot and pivotal clinical trials in people, dogs and cats. With this review, the authors provide important information to help clinicians to understand the potential role of anti-NGF mAbs in the management of canine and feline OA.

Once successful caninisation of anti-NGF mAbs was achieved (ranevetmab), favourable pharmacokinetics were established in dogs (mean tissue distribution phase half-life of 12 hours and mean plasma half-life of nine days, with no evidence of acute neutralising antibody).[6] To date, two pilot clinical trials have been performed to evaluate the efficacy of a single intravenous injection of ranevetmab for a study period of six weeks[7] and four weeks,[8] respectively. These trials utilised multiple validated clinical measurement instruments (CMI), with success/failure rates found to be similar to, or better than, those

WHAT YOU NEED TO KNOW

- Chronic inflammation, including osteoarthritis, can lead to peripheral (the affected site or sites) and central (dorsal horn of the spinal cord) hypersensitisation, resulting in lowered neuron firing thresholds and exaggerated scope, character, duration and field of pain.
- Upregulation of nerve growth factor (NGF) from endothelial, epithelial, immunoreactive and spinal glial cells is a critical component of hypersensitisation.
- Various anti-NGF strategies are under investigation as a therapy for chronic pain. At the forefront, in both human and veterinary medicine, are anti-NGF monoclonal antibodies (mAbs).
- Anti-NGF mAbs have been caninised and felinised through a proprietary technology.
- Pilot, safety and pivotal studies appear to demonstrate efficacy and safety, in both dogs and cats, following monthly subcutaneous injections for three months. These data are under review by the US Food and Drug Administration and may result in a commercial product in the near future.

Osteoarthritis (OA) is a common condition in both cats and dogs, but treatment options for the control of OA-associated pain are very limited. Thus, there is an urgent need to develop effective treatments

observed with carprofen and grapiprant and with no adverse events reported. An as-yet-unpublished pivotal study involving subcutaneous (SC) injection of ranevetmab once monthly for three months, for canine OA, established safety and efficacy using validated CMIs during the study period.

Similarly, upon felinisation, favourable pharmacokinetics of anti-NGF mAbs (frunevetmab) were established in cats (peak plasma concentration of three days and plasma half-life of nine days, with plasma concentrations still detected at 42 days), and mAb safety was also established at 14 times the therapy dose.[9] In a subsequent pilot study, the efficacy of frunevetmab was demonstrated in cats from two to six weeks following a single SC injection, utilising outcome measures of accelerometry and a validated CMI. During the first three weeks, a greater improvement was observed than in a previous study using meloxicam.[10] Data from an unpublished randomised placebo-controlled blinded pilot field study support the efficacy and safety of frunevetmab for six weeks following intravenous and SC administration, and a pivotal trial utilising three monthly SC injections is currently underway. Notably, for the first time ever in published literature, cat owners were able to differentiate treatment from placebo in a parallel group design.[11]

Of equal note, Enomoto and colleagues discuss the phenomenon of rapidly progressing osteoarthritis (RPOA) in people, described as a naturally occurring condition of uncertain aetiopathophysiology but which occurred in some patients during the initial phase 2 and 3 clinical trials of a human anti-NGF mAb (tanezumab),[12] resulting in temporary cessation of the trials. A disproportionate number of these patients were also receiving customary non-steroidal anti-inflammatory drugs (NSAIDs). Although the role of NSAID coadministration with anti-NGF mAbs in RPOA remains uncertain, the trials were re-started in 2015 with the exclusion of NSAID coadministration. RPOA is not described in the veterinary literature (indeed, even the normal rate of OA progression in dogs and cats has not been described), and it remains unknown whether it exists as a clinical phenomenon in dogs and cats, much less whether there would be an interaction with caninised or felinised anti-NGF mAbs. Thus, whether anti-NGF mAbs might become an adjuvant therapy to NSAIDs, or an alternative to NSAIDs, in canine and feline OA remains uncertain, but given the current widespread use of NSAIDs by veterinarians in the management of OA – indeed they are the primary therapy deployed – this becomes an important clinical consideration.

Another safety issue the authors address is the prospect of extended-term use, far beyond the three months for which there is current veterinary safety data (even in people the mean study duration is only 199 days). Since OA is a lifetime disease, one can imagine utilising any intervention, including, but of course not limited to, an anti-NGF mAb therapy, for potentially not just months but years (notwithstanding that upon CNS plasticity and general musculoskeletal health improvement, dose or frequency could theoretically be reduced). Although anti-NGF mAbs are not known to cross the blood-brain barrier, Enomoto and colleagues point out that NGF itself may have a neuroprotective effect,[4,13] and also may possess potential therapeutic

properties beyond the CNS (eg, tissue and corneal healing, protection against myocardial injury).[4,14] Since practical considerations generally limit, if not prohibit, extended-term clinical trials, the matter of safety over many months or years will be speculative at this time.

Anti-NGF mAbs may provide a valuable and much-needed new tool in the OA toolbox for dogs and cats. The question of whether they might be best deployed for dogs and cats as an adjunctive therapy to NSAIDs, or instead utilised as an alternative to NSAIDs, remains to be answered. Further, their role in the triage of other OA interventions for which we have evidence in veterinary medicine, ranging from the non-pharmacological (eg, weight optimisation, diets rich in omega-3, therapy exercise), pharmacological (eg, amantadine, gabapentin), and biological (eg, intra-articular mesenchymal stem cells, platelet-rich plasma) remains to be determined. However, the current data and ease of administration suggest that an anti-NGF mAb therapy is poised to become a valuable and much-needed advance in the management of canine and feline OA. Its off-label utility in other pain syndromes remains speculative, but Enomoto and colleagues cite rodent models that suggest possible benefits when central sensitisation and maladaptive pain processing is a component.

Mark E. Epstein, DVM, Dipl ABVP (C/F), CVPP,
TotalBond Veterinary Hospitals, c/o Forestbrook, 3200 Union Road, Gastonia, NC 28056, USA
email: mark.epstein@totalbondvets.com
doi: 10.1136/vr.k5292

References

1 Johnson JA, Austin C, Bruer GJ. Incidence of canine appendicular musculoskeletal disorders in 16 veterinary teaching hospitals from 1980 through 1989. *Vet Comp Orthop Traumatol* 1994;7:56–69
2 Lascelles BD, Henry JB 3rd, Brown J, *et al.* Cross-sectional study of the prevalence of radiographic degenerative joint disease in domesticated cats. *Vet Surg* 2010;39:535–44
3 Lascelles BD, Dong YH, Marcellin-Little DJ, *et al.* Relationship of orthopedic examination, goniometric measurements, and radiographic signs of degenerative joint disease in cats. *BMC Vet Res* 2012;8:10
4 Aloe L, Rocco ML, Balzamino BO, *et al.* Nerve growth factor: a focus on neuroscience and therapy. *Cur Neuropharmacol* 2015;13:294–303
5 Enomoto M, Mantyh PW, Murrell J, *et al.* Anti-nerve growth factor monoclonal antibodies for the control of pain in dogs and cats. *Vet Rec* 2018; doi: 10.1136/vr.104590
6 Gearing DP, Virtue ER, Gearing RP, *et al.* A fully caninised anti-NGF monoclonal antibody for pain relief in dogs. *BMC Vet Res* 2013;9:226
7 Webster RP, Anderson GI, Gearing DP. Canine brief pain inventory scores for dogs with osteoarthritis before and after administration of a monoclonal antibody against nerve growth factor. *Am J Vet Res* 2014;75:532–535 growth factor antibody alleviates pain and improves mobility and function in dogs with degenerative joint disease-associated pain. *BMC Vet Res* 2015;11:101
9 Gearing DP, Huebner M, Virtue ER, *et al.* In vitro and in vivo characterization of a fully felinized therapy anti-nerve growth factor monoclonal antibody for the treatment of pain in cats. *J Vet Intern Med* 2016;30:1129–1137
10 Gruen ME, Thomson AE, Griffith EH, *et al.* A feline-specific anti-nerve growth factor antibody improves mobility in cats with degenerative joint disease-associated pain: a pilot proof of concept study. *J Vet Intern Med* 2016;30:1138–1148
11 Gruen ME, Dorman DC, Lascelles BDX. Caregiver placebo effect in analgesic clinical trials for cats with naturally occurring degenerative joint disease-associated pain. *Vet Rec* 2017;180: 473, doi: 10.1136/vr.104168
12 Hochberg MC. Serious joint-related adverse events in randomized controlled trials of anti-nerve growth factor monoclonal antibodies. *Osteoarthritis Cartilage* 2015;23 Suppl 1:S18–21
13 Mantyh PW, Koltzenburg M, Mendell LM, *et al.* Antagonism of nerve growth factor-TrkA signaling and the relief of pain. *Anesthesiology* 2011;115:189-204
14 Bracci-Laudiero L, De Stefano ME. GF in early embryogenesis, differentiation, and pathology in the nervous and immune systems. *Cur Top Behav Neurosci* 2016;29:125-52