A CLINICIAN'S BRIEF SUPPLEMENT

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ClinicalApplications

The Impacts of a Health-Related Quality-of-Life Questionnaire for Osteoarthritis Patients

Cathy Barnette, DVM

Key Takeaways

- Osteoarthritis (OA) is a widespread condition in both dogs and cats, often having a significant impact on patient quality of life.
- Pet owners are uniquely positioned to notice subtle changes in their pet's behavior and attitude, making pet owner assessments an important tool in OA management.
- Measuring both physical and emotional well-being, the VetMetrica™ behavior-based questionnaire aims to accurately measure health-related quality of life in dogs and cats and can be used as a method of gauging response to treatment.
- A recent Zoetis publication used the VetMetrica questionnaire to measure HRQL in a dog receiving Librela™ (bedinvetmab injection) to control canine osteoarthritis pain, during which both physical and emotional well-being scores increased after initiation of therapy.

THE PUBLICATION

Davies V, Reid J, Wiseman-Orr ML, Scott EM. Optimising outputs from a validated online instrument to measure health-related quality of life (HRQL) in dogs. *PLoS One*. 2019;14(9):e0221869

Osteoarthritis (OA) is a common condition in pets that is often diagnosed and managed by small animal general practitioners. OA is estimated to affect 20% of dogs >1 year of age,[1] and in studies of client-owned cats, >60% of cats ≥6 years of age and 90% of cats >12 years of age showed radiographic signs of OA.[2,3] These statistics underscore the widespread nature of osteoarthritis in companion animals.

OA-associated pain can have significant impacts on quality of life (QOL), emphasizing the need to manage this condition effectively. Although treatment cannot reverse or "cure" OA, the primary aim of OA treatment, along with optimizing diet, weight, and exercise, is focused on effective pain management, which can play a key role in helping restore mobility and improving QOL in affected patients.

To monitor a patient's response to OA therapy and determine the most effective treatment for an individual patient, QOL monitoring is essential. In addition, studies have shown that pet owners are becoming increasingly interested in addressing not just their pet's physical health but also their pet's overall QOL.[4] However, accurately evaluating QOL can be challenging in veterinary patients. In humans, QOL is typically self-reported via questionnaires, but with self-reporting not being feasible in veterinary patients, alternative methods for monitoring and measuring QOL are needed.

Pet owners are uniquely positioned to notice subtle changes in their pet's behavior and attitude, considering how much time they spend with their pet; thus, veterinary QOL measurement tools typically focus on owner observations of behavioral changes. However, owner QOL assessments have limitations. Behavioral changes and their significance may vary among species, breeds, and even individual patients; for example, appetite fluctuations are often used as a QOL indicator, but appetite may differ in nature between a Labrador retriever and a toy breed.

Given the limitations of existing QOL assessments, there is a recognized need for accurate QOL assessments in pets. This is especially true for pets with chronic diseases such as OA, as QOL assessment tools can provide insight into the efficacy of various therapies for chronic diseases, helping veterinarians and pet owners alike make rational choices for improving QOL in pets.

Health-Related, Quality-of-Life Assessments in Veterinary Medicine

Although the term health-related QOL assessment (HRQL) is often used interchangeably with QOL, the actual definitions of these terms differ. QOL encompasses all aspects of a patient's life, whereas HRQL specifically focuses on the effects of the illness and its treatment.

The VetMetrica™ behavior-based structured questionnaire aims to accurately measure HRQL in canine and feline patients.[5] This assessment is taken online and can be completed by an owner in ≈5 minutes. The canine version of the VetMetrica questionnaire includes 22 unique assessment items. Each item consists of a simple descriptive term that is positive or negative in nature. Owners rate the extent to which each term applies to their pet on a scale of 0 to 6, with 0 indicating that the term does not apply to the pet at all and 6 indicating that the term is extremely descriptive of the pet. A high score on a positive term suggests a very good HRQL, whereas a high score on a negative term suggests a very poor HRQL.

After a pet owner enters their responses, the VetMetrica system creates a complete HRQL profile for the pet. This profile is made immediately available for the veterinarian to access online, and the veterinarian can then choose to make these results accessible to the client. Results are also available to VetMetrica for use in research and development.

Each dog receiving a VetMetrica HRQL assessment is assigned a score in 4 separate domains:

- **Energy**: Is the pet energetic/enthusiastic?
- **Happiness**: Is the pet happy/content?
- **Activity**: Is the pet active/comfortable?
- **Calmness**: Is the pet calm/relaxed?

In addition to these 4 scores, 2 summary scores are calculated for each patient: physical well-being and emotional well-being. The physical well-being score reflects energy and activity, whereas the emotional well-being score reflects happiness and calmness.

Each of these 6 scores is presented on a scale of 0 to 70. The scores are normalized such that the average healthy pet receives a score of 50; 70% of healthy animals tend to receive a score >44.8.[6] It should be noted that patient scores on the VetMetrica HRQL assessment will fluctuate over time, depending on weather, stress, and other external factors; thus, veterinarians and clients should focus on overall trends, not individual measurements.

Finally, the minimal important difference on the VetMetrica HRQL assessment is 7 for dogs. In other words, an increase or decrease of ≥7 points in a dog is clinically significant.[5]

The Publication

The validated VetMetrica questionnaire to measure HRQL[6] was used in a recent publication. A young, neutered male Staffordshire bull terrier diagnosed with OA pain was administered Librela (bedinvetmab injection) for control of that pain.

Librela was administered according to the label dosing chart on days 0, 28, and 56. VetMetrica assessments were performed by the client on days 0, 15, 24, 51, 59, and 61.

On day 0 (treatment day), the patient received low scores in all categories: energy (23.9), happiness (24.7), activity (21.1), and calmness (33.6) The patient's overall score for physical well-being was 22.5, and the score for emotional well-being was 29.2. These scores were well below the threshold of 44.8 at which 70% of healthy dogs score.[6]

Fifteen days after the dog's first treatment with Librela, increases were seen in all categories. Energy increased from 23.9 to 41.1, happiness increased from 24.7 to 36.7, activity increased from 21.1 to 29.8, and calmness increased from 33.6 to 42.8. The patient's overall score for physical well-being increased from 22.5 to 35.4, and the overall score for emotional well-being increased from 29.2 to 39.8. Each of these scores exceeded the minimal important difference for this test, indicating that the patient experienced clinically significant improvements in all 6 scores just 15 days after treatment with Librela.

On day 34 (after 2 treatments with Librela), further improvements were noted. The patient's physical well-being (46.9) and overall emotional well-being (46.1) scores then exceeded 44.8, the threshold above which 70% of healthy dogs score.

Scores on days 51, 59, and 61 continued to show gradual improvement. By day 61, physical well-being (50.8) and emotional well-being (55.3) scores exceeded those expected in an average healthy dog, with the patient showing significant improvement as compared with day 0 scores.

Implications for Practice

This case study elucidates the impacts of OA in pets. Prior to treatment, the patient's owner reported that the dog not only

experienced poor physical well-being but also poor emotional well-being. During treatment with Librela, the patient made rapid, significant gains in both physical and emotional well-being, reflecting significant improvement in overall HRQL.

Veterinarians often tend to focus on physical function when evaluating the success of arthritis treatments (eg, is the dog still limping after treatment?). Although this is valuable information, it provides an incomplete assessment of the pet's HRQL. This tendency toward incomplete assessment may be because an accurate, accessible way to assess a pet's emotional state is not available; physical function is often easier to assess in a relatively objective manner.

The VetMetrica survey, as used in this case study, serves as a reminder of the importance of both physical and emotional well-being in pets. Measures of emotional well-being (eg, happiness, calmness) may be just as impactful to patients and clients as physical well-being, especially when managing OA and other chronic conditions. Even patients without significant activity gains can make dramatic HRQL gains in other areas.

Using Librela to Manage Canine Osteoarthritis

Nerve growth factor (NGF) is a key driver of OA pain and inflammation[7] and is elevated in the synovial fluid of dogs with OA.[8] Librela, the first and only monthly injectable anti-NGF monoclonal antibody, targets NGF in dogs, controlling the pain associated with OA. Librela is administered once monthly as a subcutaneous injection by a veterinary professional.

Librela has been approved as safe and effective for the control of pain associated with OA in dogs.[9-12] Librela is eliminated like naturally occurring antibodies, with minimal liver or kidney involvement.[13] The most common adverse events reported in a clinical study were UTIs, bacterial skin infections, and dermatitis.[10]

To accurately measure response to Librela therapy, veterinarians can implement HRQL screenings and other client-reported measures. These HRQL assessments can not only provide a tool to assess treatment response and guide therapy, but they can also allow clients to be involved in monitoring their pet, leveraging the veterinarian–client relationship to make the best treatment decisions for every pet. ●

EXPERT COMMENTARY

The validated VetMetrica HRQL assessment, which accounts for both physical and emotional patient well-being, was developed for patients with OA pain to monitor their response to treatment and demonstrate improvements in quality of life. This assessment highlights that quality of life is not tied exclusively to increased activity level but rather offers a more comprehensive view of the patient. In the publication discussed, the use of Librela over a 2-month period demonstrated the usefulness of this tool in assessing response to treatment and allowed for adjustment of therapy as necessary. The VetMetrica HRQL assessment can be a valuable tool for unifying clinicians' and pet owners' approach to OA management.—*Sharon Campbell, DVM, MS, DACVIM*

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Brief Summary of full Prescribing Information.

Librela™
(bedinvetmab injection)

Canine anti-nerve growth factor monoclonal antibody for subcutaneous use in dogs only.

Single-Use Vial

CAUTION
Federal law restricts this product to use by or on the order of a licensed veterinarian.

INDICATION
LIBRELA is indicated for the control of pain associated with osteoarthritis in dogs.

DOSAGE AND ADMINISTRATION
The minimum target dose of LIBRELA is 0.23 mg/lb (0.5 mg/kg) body weight, administered subcutaneously once a month. Dogs should be dosed by weight range according to the specific dosing information below.

The product does not contain a preservative. The full content of each vial is for single-use only. Once punctured, contents of the vial should be used immediately and any remaining solution should be discarded.

Dogs weighing ≥ 11 lb (≥ 5 kg):
Dogs should be dosed by weight range according to the Dosing Table below (Table 1). Dogs are given the full content of 1 or 2 vials of the appropriate concentration based on body weight. Aseptically withdraw the total dose into a single syringe and administer immediately.

Table 1. Dosing Table

Dog Body Weight in Pounds (lb)	Dog Body Weight in Kilograms (kg)	Number and Strength (mg/mL) of LIBRELA Vials to be Administered				
		5 mg/mL orange	10 mg/mL blue	15 mg/mL green	20 mg/mL gold	30 mg/mL purple
11-22.1	5-10	1 vial				
22.2-44.1	10.1-20		1 vial			
44.2-66.1	20.1-30			1 vial		
66.2-88.2	30.1-40				1 vial	
88.3-132.3	40.1-60					1 vial
132.4-176.4	60.1-80				2 vials	
176.5-220.5	80.1-100				1 vial	1 vial
220.6-264.6	100.1-120					2 vials

Dogs < 11 lb:
Aseptically withdraw 0.045 mL/lb (0.1 mL/kg) from a 5 mg/mL vial (orange vial) into a single syringe and administer immediately. Discard the vial after the dose has been withdrawn.

Effectiveness may not be achieved until after the second dose (see **EFFECTIVENESS**).

CONTRAINDICATIONS
LIBRELA should not be administered to dogs with known hypersensitivity to bedinvetmab.

LIBRELA should not be used in breeding dogs or in pregnant or lactating dogs. Immunoglobulin G class antibodies such as LIBRELA can pass through the placental blood barrier and be excreted in milk. Fetal abnormalities, increased rates of stillbirths and increased postpartum fetal mortality were noted in rodents and primates receiving anti-NGF monoclonal antibodies.

WARNINGS
User Safety Warnings
Not for use in humans. Keep this and all drugs out of reach of children. For use in dogs only.

Hypersensitivity reactions, including anaphylaxis, could potentially occur in the case of accidental self-injection.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet, vial or carton to the physician.

Pregnant women, women trying to conceive, and breastfeeding women should take extreme care to avoid accidental self-injection.

The importance of Nerve Growth Factor in ensuring normal fetal nervous system development is well-established and laboratory studies conducted on nonhuman primates with human anti-NGF antibodies have shown evidence of reproductive and developmental toxicity.

PRECAUTIONS
Administration of monoclonal antibodies may be associated with hypersensitivity reactions and delayed hypersensitivity reactions. If anaphylaxis or other hypersensitivity reaction occurs, discontinue use and institute appropriate therapy.

The safe use of this product with other monoclonal antibodies has not been evaluated. Use with caution in dogs with known hypersensitivity to other immunoglobulin therapy.

Evaluations were not made to determine if interactions occurred between LIBRELA and veterinary vaccines.

Treatment with LIBRELA may result in the formation of anti-bedinvetmab antibodies and potentially the loss of product effectiveness (see **IMMUNOGENICITY**).

The safe use of anti-NGF monoclonal antibodies with concurrent non-steroidal anti-inflammatory drugs (NSAIDs) has not been established in dogs. In human clinical trials, rapidly progressing osteoarthritis (RPOA) has been reported in a small number of patients receiving humanized anti-NGF monoclonal antibody therapy. The incidence of these events increased in human patients receiving NSAID treatment long term in combination with an anti-NGF monoclonal antibody. RPOA has not been characterized or reported in dogs.

The safety and effectiveness of LIBRELA has not been evaluated in dogs less than 12 months of age.

LIBRELA has not been studied in dogs that have a history of cruciate ligament rupture within six months before initial product use as these cases were excluded from the field studies.

Long term effects which may occur more than 9 months after the use of LIBRELA have not been evaluated.

NGF is expressed within the heart and vasculature, and the long-term effects of reduced NGF in dogs with cardiac disease are unknown.

Primates receiving high doses of anti-NGF monoclonal antibodies had anatomical changes in postganglionic cell bodies (reduced size and number of neurons). The change in cell body size returned to normal after anti-NGF monoclonal antibody administration was discontinued. NGF is involved in the normal development of sensory and sympathetic nerve fibers in developing animals. This may be important with use of LIBRELA in young growing dogs.

ADVERSE REACTIONS
The safety of LIBRELA was assessed in a masked, controlled 84-day US field study evaluating the effectiveness of LIBRELA for the control of pain associated with osteoarthritis. Enrollment included 272 dogs, 135 dogs treated with LIBRELA and 137 dogs treated with a negative control (sterile saline). The enrolled dogs were at least 1 year of age (1 to 17 years old), weighed between 1.8 to 62.7 kg and were of various breeds or non-purebred. Dogs were dosed at 28-day intervals and received up to three injections. The most common adverse reactions reported during the study are summarized in Table 2 below.

Table 2. Number (%) of Dogs with Adverse Reactions Reported in the US Field Study

Adverse Reaction*	LIBRELA n (%) (Total N = 135)	Negative Control n (%) (Total N = 137)
Urinary tract infection	15 (11.1)	11 (8.0)
Bacterial skin infection	11 (8.1)	9 (6.6)
Dermatitis	10 (7.4)	8 (5.8)
Dermal mass	8 (5.9)	5 (3.6)
Erythema	6 (4.4)	5 (3.6)
Dermal cyst(s)	4 (3.0)	2 (1.5)
Pain on injection	4 (3.0)	2 (1.5)
Inappropriate urination**	4 (3.0)	1 (0.7)
Histiocytoma	3 (2.2)	0 (0.0)

*An adverse reaction may have occurred more than once in a dog; only the first occurrence was counted.
** Of these, two dogs treated with LIBRELA were among those reported with a urinary tract infection.

The safety of LIBRELA was also evaluated in a masked, controlled 84-day European field study evaluating the effectiveness of LIBRELA for the control of pain associated with osteoarthritis. Enrollment included 281 dogs, 138 dogs were treated with LIBRELA and 143 treated with a negative control (sterile saline). The enrolled dogs were at least 1 year of age (1 to 17.5 years old), weighed between 1.7 to 66 kg and were of various breeds or non-purebred. Dogs were dosed at 28-day intervals and received up to three injections. The most common adverse reactions reported during the study are summarized in Table 3 below.

Table 3. Number (%) of dogs with Adverse Reactions Reported in the European Field Study

Adverse Event Reported*	LIBRELA n (%) (Total N = 138)	Negative Control n (%) (Total N = 143)
Increased Blood Urea Nitrogen (BUN)**	19 (13.8)	7 (4.9)
Lethargy	5 (3.6)	0 (0.0)
Emesis	4 (2.9)	1 (0.7)
Anorexia	3 (2.2)	0 (0.0)
Lameness	3 (2.2)	1 (0.7)
Cough	3 (2.2)	1 (0.7)

*An adverse reaction may have occurred more than once in a dog; only the first occurrence was counted.
** Two dogs treated with LIBRELA suffered serious adverse events and were euthanized during or after study completion: A 13-year old Bichon Frise had pre-existing increased urine protein-creatinine ratio and heart failure that worsened during study; the dog also had an increase in creatinine during the study and was diagnosed with renal failure and was euthanized 3 days after completing the study. An 8-year-old mixed breed dog had pancreatitis and was euthanized on Day 74. The remainder of the dogs that had elevations in the BUN did not have any obvious adverse events associated with this finding.

One dog in the LIBRELA group was diagnosed with pyelonephritis on Day 15; this dog had pre-existing increased serum BUN and creatinine and a recent history of urinary tract infection that was not confirmed resolved prior to enrollment. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen were initiated on Day 7 for osteoarthritis-associated joint pain but NSAIDs were discontinued on Day 10 due to anorexia and gastroenteritis; azotemia worsened at Day 13 and the dog received no further LIBRELA treatment.

One dog in the LIBRELA group with a history of atopy, developed mild alopecia and mild erythema on the injection site on Days 5 and 23. Both episodes of alopecia and erythema resolved with treatment.

A total of 89 dogs were enrolled in a 6-month, single arm, open labeled, uncontrolled continuation of the EU field study and received monthly subcutaneous injections of LIBRELA. The study provided additional field safety information.

One dog experienced acute gastroenteritis and recovered following treatment for abdominal pain, fever, vomiting, and anorexia. One large breed dog enrolled for stifle osteoarthritis developed acute forelimb lameness that was diagnosed as elbow dysplasia. Two dogs presented with rear limb paresis of unknown etiology, one of whom responded to ongoing NSAID treatment and one who did not.

CONTACT INFORMATION
To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Zoetis Inc. at 1-888-963-8471.

For additional information about reporting adverse drug experience for animal drugs, contact FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.

TARGET ANIMAL SAFETY
6 Month Margin of Safety Study:
LIBRELA (bedinvetmab injection) 15 mg/mL and 30 mg/mL concentrations were administered subcutaneously to 11 to 12-month old, healthy Beagles (8 dogs per group) at doses of 1 mg/kg (1X), 3 mg/kg (3X), and 10 mg/kg (10X) every 28 days for seven consecutive doses. The control group (8 dogs) received sterile saline injections. Dogs weighed 5.6-11.7 kg at study initiation.

There were no clinically significant changes noted in neurological examinations, body temperature, heart and respiratory rate, blood pressure, electrocardiography, and organ weights. Detailed pathology evaluation of the shoulder, elbow, hip, and knee joints were conducted.

Vomiting and soft stool were noted across all groups throughout the study. Scabbing on the face, neck and thorax was seen across all groups except the 1 mg/kg group. Injection site redness was noted sporadically for 1 control dog, 2 dogs in the 1 mg/kg treatment group, 5 dogs in the 3 mg/kg treatment group, and 5 dogs in the 10 mg/kg treatment group. One dog in the 3 mg/kg treatment group had a temporary, mild swollen facial area 26 days after the first dose that resolved spontaneously. Two dogs in the 3 mg/kg treatment group had lymphadenopathy on the last study day with no related histopathology findings. One dog in the 10 mg/kg treatment group had an approximately 2.5 cm X 3.5 cm circular raised firm erythematous lesion with slight serosanguinous discharge and mild scabs of the shaved cervical area that resolved over 14 days.

One dog in the 1 mg/kg treatment group had an increasing ALP value over the course of the study that increased threefold above the high end of the reference range at study completion. There was no gross or histopathology correlate.

One dog in the 1 mg/kg treatment group had mild cartilage necrosis in the left ulna and an erosion in the cartilage of the right ulna. One dog in the 3 mg/kg treatment group had mild bilateral, femoral neck enthesophytes observed on radiographs pre-treatment. On end of study radiography and pathology evaluation, this dog had an osteophyte of the left acetabulum, mild left acetabulum remodeling and severe left femoral neck enthesophytes. Microscopically, mild to moderate cartilage degeneration with erosion and proteoglycan depletion was also noted in the left proximal femur and acetabulum. The mild right femoral neck enthesophytes were the same grade as pre-treatment. The findings may be progression of an underlying musculoskeletal condition; however, a potential relation to treatment cannot be ruled out.

None of the LIBRELA-treated dogs developed anti-drug antibodies due to bedinvetmab administration.

Additional Safety Studies:
In a two-week laboratory safety study, eight dogs concurrently received one subcutaneous injection of LIBRELA at the high end of the inherent dose band (1 mg/kg) and fourteen days of an injectable NSAID. This limited laboratory study did not provide sufficient data to support a conclusion on the safety of concurrent use of LIBRELA and NSAIDs.

In a 3-month exploratory laboratory safety study using a non-final formulation of bedinvetmab administered by subcutaneous injection monthly for four doses, a dog administered a 4 mg/kg dose had a reddened and/or swollen muzzle abrasion, with an elevated white blood cell count, and elevated globulin level and fibrinogen level. At one of the injection administrations, one dog administered a 4 mg/kg dose had a 4 cm X 2 cm injection site erythema with an eschar that resolved; and one dog administered a 1 mg/kg dose had 3 cm X 1 cm injection site erythema that resolved. Another dog administered a 1 mg/kg dose had injection site erythema, scabbing, and mucopurulent discharge for 18 days.

STORAGE CONDITIONS
LIBRELA (bedinvetmab injection) should be stored in a refrigerator, 2° – 8°C (36° – 46° F). Do not freeze. Store vials in their boxes to protect from prolonged exposure to light. Once punctured, contents of the vial should be used immediately and any remaining solution should be discarded.

HOW SUPPLIED
LIBRELA is available in 5 strengths packaged in 4 mL glass vials containing an extractable volume of 1 mL of clear solution. Each strength is available in cartons containing 2 or 6 vials.

Approved by FDA under NADA # 141-562

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