shutterstock.com/Dasha Iunskaya

PHARMACOLOGY

The Therapeutic Power of Monoclonal Antibody Therapy

Darren Berger, *DVM, DACVD, Assistant Professor*
College of Veterinary Medicine, Iowa State University, Ames, Iowa

Although biotherapeutics have been used in human medicine for more than 30 years, they are still relatively new in veterinary medicine.[1] Recent advances in the veterinary arena include updated labeling and industry acquisition and collaboration to develop new biologic agents. This article reviews biologic therapy as it relates specifically to monoclonal antibodies (mAbs) and covers the only fully licensed and commercially available product, lokivetmab (CYTOPOINT™), which is made by Zoetis.

PRINCIPLES OF BIOTHERAPY

Biotherapy differs from traditional pharmacotherapy in that it mimics the body's normal immune response to treat disease or protect against adverse events.[2] Biologic agents are commonly categorized into 3 groups:

1. Peptides and small proteins (hormones and cytokines)
2. Nonimmune proteins (replacement enzymes and blood factors)
3. Therapeutic antibodies and Fc receptor–like proteins

The major advantages of biotherapeutic agents over traditional drugs are the agents' specificity, which facilitates precise action (ideally with minimal unintended effects), and their long half-lives, which allow infrequent dosing.[1]

In human medicine, mAbs represent the area of biotherapy that offers the greatest array of potential therapies. This is also the therapeutic arena most likely to see peak growth in products brought to the veterinary marketplace for clinical use in treating arthritis, autoimmune disease, allergic conditions, infectious disease, and oncologic disorders.[2]

MONOCLONAL ANTIBODIES

Production

mAbs are essentially identical to naturally occurring antibodies produced and secreted by plasma cells in the body. However, in a normal immune response to stimulation by an infectious agent or disease, numerous plasma cells produce thousands of antibodies that recognize multiple

A UNIQUE APPROACH
Lokivetmab targets and neutralizes interleukin-31, a key itch-inducing cytokine in canine atopic dermatitis, without the side effects that can be caused by steroids.

epitopes on a particular antigen. mAbs arise from a single plasma cell line and recognize the same target region on an antigen.

Production of mAbs was historically accomplished by immunizing mice, isolating the desired B cells, and fusing these cells with an immortal myeloma cell line (the *hybridoma technique*).[3] However, when these murine antibodies were injected into nonmouse subjects, they stimulated significant undesired immune reactions. To resolve this problem, genetic engineering and recombinant DNA techniques have been developed, and speciated (humanized, caninized, or felinized) mAbs that are greater than 90% similar to those of the target species' composition can now be created.[3,4] This level of speciation limits the use of the products to only the labeled species but also decreases the risk of adverse effects.

As of September 2018, the label indication is that lokivetmab has been shown to be effective for the treatment of allergic dermatitis and atopic dermatitis in dogs.

Mechanism of Action

Therapeutic mAbs exert their biologic effect predominantly via one of three mechanisms. The first is through the binding or "soaking up" of soluble extracellular targets (i.e., cytokines) before these targets arrive at a cellular receptor.[2] This action prevents the target molecules from activating cellular receptors and is the primary mechanism by which lokivetmab exerts its effect.

The second mechanism is to simply bind a target receptor on the cell surface and block activation of signal transduction; mAbs that act through this pathway are classified as *antagonistic*.[2] Many currently approved human products act through this mechanism.[2]

The third mechanism is to bind to an infectious agent or cancer cell and either activate cell lysis (via complement-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity) or enhance clearance of the foreign agent by antibody-dependent phagocytosis.[1,2] The backbone or immunoglobulin (Ig) isotype also affects the specific mechanism of action and half-life of an individual mAb.[5]

Like any protein, mAbs undergo denaturation and proteolytic enzymatic breakdown in the stomach if given orally. Thus, all therapeutic mAbs are administered by intravenous, subcutaneous, or intramuscular injection. Once injected, they have long half-lives similar to those of naturally produced antibodies (roughly 20 days).[2]

Unlike traditional drugs, mAbs do not need to undergo biotransformation so that they can be inactivated or excreted from the body; rather, as biologic agents that mimic normal physiologic products, they are inactivated through pathways similar to that of the natural product. mAbs undergo intracellular catabolism within the lysosome, where they are broken down to amino acids that can either be recycled for the synthesis of new proteins or be renally excreted. This inactivation pathway provides mAbs a tremendous advantage over traditional drugs in that they are unlikely to result in adverse drug–drug interactions when administered to patients concurrently receiving other medications.

Safety

As with anything new, biotherapy carries with it concern about the unknown. Many practitioners worry about a wide array of potential adverse events from mAb therapy, most of which are unlikely, as mAbs are very target specific and have unique metabolic aspects. Because mAbs do not have intracellular activity, it is easier to predict adverse events before clinical trials, based on the anticipated blockade of the target, and it is a generally accepted concept that mAbs tend to be a safer form of treatment than traditional drugs. This improved risk–benefit ratio is grounded by the fact that the likelihood of a mAb reaching the market is roughly 4 times greater than that of a newly developed pharmacologic agent.[1]

The overall safety of any particular mAb is largely determined by the mAb's target and level of speciation. Adverse events that have been encountered with therapeutic mAbs in human medicine are listed in **BOX 1**; these events are, for the most part, predictable based on the mechanism and target of the specific product.

LOKIVETMAB

To date, several mAbs have received conditional or full license approval. They include biologics for cancer therapy (blontuvetmab [Blontress®] and tamtuvetmab [Tactress®]) (aratana.com), osteoarthritis (ranevetmab and frunevetmab), and canine allergic dermatitis (lokivetmab). However, at this time, the only fully licensed commercially available product is lokivetmab.

Lokivetmab is a caninized anti–interleukin-31 (IL-31) mAb that works by neutralizing soluble IL-31 produced predominantly by lymphocytes. It was developed after IL-31 was shown to play a role in development of canine pruritus.[7] IL-31's potential role in the development of pruritus associated with atopic dermatitis has been further substantiated by more recent studies.[8,9]

Indication and Use

Lokivetmab is approved and licensed through the U.S. Department of Agriculture. The original label indication was to aid in the reduction of clinical signs associated with atopic dermatitis. As of September 2018, the label indication is that lokivetmab has been shown to be effective for the treatment of allergic dermatitis and atopic dermatitis in dogs.

Lokivetmab is provided in 1-mL sterile, ready-to-use vials (10, 20, 30, or 40 mg/mL). Individual vials are meant for single use and should be administered to a patient in their entirety via subcutaneous injection. The current labeled target dose is 2 mg/kg, which can be repeated every 4 to 8 weeks as needed.

Clinical Trials

Since lokivetmab's release, several published studies and research abstracts have assessed its clinical efficacy and safety in dogs. The first study was a dose-determination study using client-owned dogs to assess efficacy and safety of a single subcutaneous injection over a 56-day period.[10] In this study, dogs were randomly assigned to receive a dose of lokivetmab (0.125, 0.5, or 2 mg/kg) or placebo. Efficacy was evaluated by the clinician and the owner using objective scales. The study showed that clinical parameters were improved at the 2 higher doses compared with placebo and that the level and duration of response correlated with the dose given. In addition, pharmacokinetic data from this study revealed that the half-life for lokivetmab was 16 days, with peak serum concentration reached at 9.8 days after administration.

BOX 1 Adverse Events Observed in Human Medicine With mAb Therapy[1,6]

- Injection site discomfort
- Lethargy
- Fever
- Gastrointestinal upset
- Production of anti-drug antibodies
- Anaphylaxis
- Reactivation of infectious diseases
- Thrombocytopenia
- Leukopenia
- Hypothyroidism
- Pulmonary events
- Autoimmune disease
- Neoplasia (tumor necrosis factor-α specific products)
- Pruritus
- Erythema and rash
- Cardiotoxicity
- Tumor lysis syndrome
- Cytokine release syndrome

Safety data generated in this clinical trial revealed no hypersensitivity-related reactions to the single injection immediately after dosing, no evidence of treatment-induced immunogenicity, and no specific safety concerns associated with treatment.[10]

A second study provided additional safety data from canine patients with atopic dermatitis receiving 2 doses of lokivetmab (1.0 to 3.3 mg/kg) compared with placebo.[11] This study enrolled 245 dogs, and 2 injections were given 28 days apart. Adverse events observed in greater than 2% of participants included secondary skin or ear infections, pruritus, gastrointestinal (GI) upset (anorexia, vomiting, and diarrhea), and lethargy. Both treatment groups experienced GI upset and lethargy at a similar rate, which resolved spontaneously or with supportive care; no immediate hypersensitivity or injection site reactions were reported. However, 2.5% of lokivetmab-treated dogs developed treatment-induced immunogenicity. No adverse interactions with concomitant medications were observed in this study.[11]

A third investigation evaluated the safety and efficacy of lokivetmab compared with cyclosporine over a

3-month period, then followed 81 dogs for an additional 6 months as part of a continuation study.[12] Overall, lokivetmab-treated patients compared favorably with those treated with cyclosporine. No significant differences between groups were appreciated in measured clinical outcome parameters. The continuation phase demonstrated continued efficacy, with 76.3% of animals assessed to have a normal level of pruritus after the ninth month of treatment. This study had safety results similar to those of the first 2 clinical trials, with GI upset occurring significantly less frequently in dogs treated with lokivetmab than in those treated with cyclosporine. No hypersensitivity reactions or immediate post-dosing injection site reactions were appreciated during the 9-month study. Treatment-induced immunogenicity was seen in 2% of dogs during the initial 3 months but in no new dogs during the continuation phase.[12]

The final published report at this time is a retrospective study that evaluated the experiences of dogs treated with lokivetmab over a 1-year period at a dermatology specialty hospital.[13] Treatment with lokivetmab improved pruritus scores in 87.8% of dogs, with 77% of dogs experiencing >50% reduction in pruritus. There was no association of improvement with the dosage and response, but a trend was observed that larger dogs were more likely to be classified as treatment successes, as defined by reduction in pruritus scores. The study evaluated speed of onset and found that almost 96% of dogs responded within the first 72 hours after administration, with more than half (55.9%) experiencing improvement by 24 hours. Additionally, dogs with pruritus considered "severe" or "very severe" before treatment were more likely to be classified as treatment successes. Of note, 71.4% of dogs that had an inadequate response to oclacitinib, an oral JAK inhibitor, were considered treatment successes with lokivetmab.[13] Adverse events were reported in 11 of 132 dogs (8.3%) treated with lokivetmab; the most common adverse effect reported was lethargy within 72 hours of receiving the injection (8 of 11 patients).[13]

CONCLUSION

Taken together, the clinical studies show that lokivetmab appears to be a safe and effective treatment option for dogs with allergic dermatitis. In addition, lokivetmab offers several advantages over traditional drugs (cyclosporine, oclacitinib, and glucocorticoids) used in the management of allergic dogs; namely, it can be given to dogs of all ages, with any concomitant medication, and with any concurrent medical condition. This therapy offers some exciting new opportunities in treating dogs with allergic dermatitis. TVP

Darren Berger

Darren Berger is assistant professor of dermatology at Iowa State University's College of Veterinary Medicine. Dr. Berger's research interests include clinical pharmacology and the clinical management of canine atopic dermatitis and equine hypersensitivity disorders. A graduate of Iowa State University, he worked as a small animal general practitioner before completing a dermatology residency with Dermatology for Animals in Gilbert, Arizona.

References

1. Hansel TT, Kropshofer, Singer T, et al. The safety and side effects of monoclonal antibodies. *Nat Rev Drug Discov* 2010;9:325-338.
2. Olivry T, Bainbridge G. Clinical notes: Advances in veterinary medicine: therapeutic monoclonal antibodies for companion animals. *Clinicians Brief* 2015;13:76-79.
3. 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* 2019;184(1):23.
4. Moyaert H, Van Brussel L, Borowski S, et al. A blinded, randomized clinical trial evaluating the efficacy and safety of lokivetmab compared to ciclosporin in client-owned dogs with atopic dermatitis. *Vet Dermatol* 2017;28:593-e145.
5. Bergeron LM, McCandless EE, Dunham S, et al. Comparative functional characterization of canine IgG subclasses. *Vet Immunol Immunopathol* 2014;157:31-41.
6. Baldo BA. Adverse events to monoclonal antibodies used for cancer therapy: Focus on hypersensitivity responses. *Oncoimmunology* 2013;2(10):1-15.
7. Gonzales AJ, Humphrey WR, Messamore JE, et al. Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. *Vet Dermatol* 2013;24:48-e12.
8. Marsella R, Ahrens K, Sanford R. Investigation of the correlation of serum IL-31 with severity of dermatitis in an experimental model of canine atopic dermatitis using beagle dogs. *Vet Dermatol* 2018;29:69-e28.
9. Messamore JE. An ultrasensitive single molecule array (Simoa) for the detection of IL-31 in canine serum shows differential levels in dogs affected with atopic dermatitis compared to healthy animals. *Vet Dermatol* 2017;28:546.
10. Michels GM, Ramsey DS, Walsh KF, et al. A blinded, randomized, placebo-controlled, dose determination trial of lokivetmab (ZTS-00103289), a caninized, anti-canine IL-31 monoclonal antibody in client owned dogs with atopic dermatitis. *Vet Dermatol* 2016;27:478-e129.
11. Michels GM, Walsh KF, Kryda KA, et al. A blinded, randomized, placebo-controlled trial of the safety of lokivetmab (ZTS-00103289), a caninized anti-canine IL-31 monoclonal antibody in client-owned dogs with atopic dermatitis. *Vet Dermatol* 2016;27:505-e136.
12. Moyaert H, Van Brussel L, Borowshi S, et al. A blinded, randomized clinical trial evaluating efficacy and safety of lokivetmab compared to ciclosporin in client-owned dogs with atopic dermatitis. *Vet Dermatol* 2017;28:593-e145.
13. Souza CP, Rosychuck RA, Contreras ET, et al. A retrospective analysis of the use of lokivetmab in the management of allergic pruritus in a referral population of 135 dogs in the western USA. *Vet Dermatol* 2018;29:489-e164.