NEW ADVANCES IN CANINE ALLERGIC DISEASE
THE NEXT HORIZON: TARGETED ANTIBODY THERAPY FOR CANINE ALLERGIC SKIN DISEASE

Zoetis is pleased to share with you the latest advances on Canine Atopic Dermatitis and how targeted antibody therapy may help manage itch and inflammation in allergic dogs.

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Dr. THIERRY OLIVRY

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Dr. DOUGLAS J. DeBOER

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Proceedings of a Symposium held at the 8th World Congress of Veterinary Dermatology, Bordeaux, France, June 1st 2016.

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ABOUT THE SPEAKERS

**DR. THIERRY OLIVRY**
DrVet, PhD, DECVD, DACVD
NORTH CAROLINA STATE UNIVERSITY

After graduating from veterinary school in Toulouse (France) in 1984, Dr. Olivry became a partner in a specialty practice in Paris. In 1991, he moved to the US for a residency in dermatology and a PhD in comparative pathology at the University of California Davis. He is board-certified by both European and American Colleges of Veterinary Dermatology. Dr. Olivry is Professor of Immunodermatology at the North Carolina State University College of Veterinary Medicine. He holds also an appointment as Adjunct Research Associate Professor of Dermatology at the University of North Carolina-Chapel Hill School of Medicine. From 2001 to 2004, he was the Chair of the International Task Force on Canine Atopic Dermatitis, and from 2008 to 2009, President of the European College of Veterinary Dermatology.

Dr. Olivry has been recognized with the “ACVD Award for Excellence for Outstanding Contributions to Science and Education” in 2004, the “NCSU Clinician of the Year award” in 2005, the “Pfizer Award for Research Excellence at NCSU” in 2010 and the “World Small Animal Veterinary Association (WSAVA) Hill’s Excellence in Veterinary Healthcare Award” in 2013. Dr. Olivry has authored more than 210 peer-reviewed original articles, and he has lectured extensively all over the world to veterinary and medical audiences. His current areas of research interest are canine atopic dermatitis and the mechanism and treatment of itch in dogs.

**ANDREA J. GONZALES**
PhD
GLOBAL THERAPEUTICS RESEARCH GROUP, ZOETIS

Dr. Gonzales is a Director in the Global Therapeutics Research group at Zoetis. She received her PhD from the University of North Carolina at Chapel Hill in 1997 and then trained as a postdoctoral fellow in the Cancer Research, Experimental Therapy group at Legacy Parke-Davis. She has over 15 years of experience in the pharmaceutical industry as a lead biologist in areas such as Allergy and Dermatology, Inflammation, Oncology, and Drug Safety Evaluation in Animal Health as well as Human Health divisions of Pfizer Inc. Current roles include understanding mechanisms involved in the pathobiology of canine atopic dermatitis (CAD) and identifying new targets for therapeutic intervention in allergic conditions in companion animals. She also manages a laboratory consisting of 12 colleagues with expertise in investigative pharmacology, in vitro assay design and biomarker identification for animal health indications. Her group employs state-of-the-art technologies and high-throughput screening approaches to aid in the identification and efficient progression of experimental therapeutics to registration.

**DR. DOUGLAS J. DEBOER,**
DVM, DACVD
UNIVERSITY OF WISCONSIN-MADISON

Dr. DeBoer joined the faculty of the School of Veterinary Medicine, University of Wisconsin-Madison, in 1986 and is presently a Professor of Dermatology there. His responsibilities include teaching foundation principles of clinical dermatology to veterinary students. Dr. DeBoer’s research and clinical interests center on the immunology of recurrent and chronic skin diseases, with a focus on canine allergic skin diseases and feline dermatophytosis. A diplomat of the American College of Veterinary Dermatology, he received the ACVD Award of Excellence for Contributions to Science and Education in 2003. Dr. DeBoer has served on the scientific editorial boards of the American Journal of Veterinary Research and Veterinary Dermatology and is chair of the International Committee on Allergic Diseases of Animals. He is a graduate of the School of Veterinary Medicine at University of California, Davis, and completed postgraduate training at Michigan State University and at UC Davis.
SUMMARY

Species-specific recombinant monoclonal antibodies (mAbs) belong to a new class of biotherapeutics. These biologics are capable of binding to a single antigenic epitope, and the specificity of the antigen-antibody bond gives them a unique target and mode of action.

- Compared to small molecules, mAbs have several advantages:
  - They are generally safe
  - They typically require infrequent dosing (weekly to monthly) as a result of a long serum half-life

They can often be administered by subcutaneous injections

Therapeutic mAbs can target soluble molecules, such as cytokines, before they bind and activate their receptor, or they can block the cytokine receptor itself. These biologics can also bind to membrane molecules on tumor cells to enhance their destruction by immune cells or activated complement. Monoclonal antibodies are also being developed as anti-infectious agents.

Monoclonal antibodies are exquisitely targeted therapies; the benefit and safety profile of a given mAb for treatment of prevention of a disease will depend mainly from the specificity of the targeted antigen.

In some diseases, identifying the molecule to be targeted by mAbs is straightforward due to relatively simple pathogenesis. Examples of such mAbs are rituximab that binds to CD20 expressed by neoplastic B cells in some subsets of non-Hodgkins lymphoma or omalizumab that was designed to inhibit IgE in cases of refractory asthma and chronic idiopathic urticaria.

KEY POINTS

- In heterogeneous syndromes such as atopic dermatitis and psoriasis, the pathogenesis of skin lesions varies depending upon their stage. Finding the right target is difficult because of the myriad of cells and mediators involved in the inflammation cascade. Recent research in the pathogenesis of these two complex inflammatory skin diseases has helped identify early pro-inflammatory cytokines that are now the target of therapeutic mAbs. For atopic dermatitis, dupilumab targeting the IL-4/IL-13 receptor alpha appears to have a remarkable beneficial effect. For psoriasis, brodalumab targeting the IL-17 receptor and tildrakizumab blocking the IL-23 p19 hold the highest potential for induction of lesion remission.

- Because of the unique specificity of the mAbs, knowledge of disease pathogenesis is key to identifying potential targets. Unfortunately, the more complex the disease pathomechanism, the less likely theory or experimental models may be fully predictive of the clinical impact of targeting a single antigen. Ultimately, clinical trials will have to prove whether laboratory predictions can translate into clinical benefit for either human or animal patients.
Human Atopic Dermatitis
Therapies: mAbs targeting cytokines and their receptors
- Reductions of AD skin lesions in a dosedependent manner
(Rep: Lezon 2019)

Targeted Skin Diseases with mAbs
- Targeted therapy: specific mechanistic therapy
- Targeted therapy: increased safety margin
- Targeted therapy: vulnerability to pathway redundancy

- Least target are theoretically the best?
- Theoretically benefit cannot predict clinical benefit
- Clinical data will remain limited for years
SUMMARY

This presentation reviews the role of cytokines in the pathophysiology of canine atopic dermatitis (CAD), how that provided the rationale to develop a Janus kinase inhibitor (APOQUEL), and the importance of continued investment into the mechanistic understanding of APOQUEL. The session will also outline how these efforts have led to new scientific insights into the pathways involved in the canine disease and how they have provided guidance on additional targets attractive for therapeutic intervention. Finally, work that allowed Zoetis scientists to develop a monoclonal antibody capable of neutralizing a key cytokine involved in itch (IL-31) will be discussed. Monoclonal antibody technology provides a way to evaluate the potential therapeutic benefit of inhibiting a single cytokine in dogs with atopic dermatitis.

KEY POINTS

- Increasing evidence suggests cytokines can orchestrate many of the clinical signs associated with allergic skin disease in dogs.
- Cytokine production/dysregulation can be detected after allergen exposure under experimental conditions and in dogs with atopic dermatitis.
- Apoquel (oclacitinib) is a Janus kinase inhibitor that was developed for the treatment of pruritus associated with allergic skin disease and treatment of atopic dermatitis.
- Oclacitinib can inhibit the function of many Th2 cytokines involved in allergic skin disease (e.g., IL-2, IL-4, IL-6, IL-13, IL-31).
- Oclacitinib rapidly inhibits pruritus in a variety of acute and chronic models as well as in client-owned animals with allergic skin disease including atopic dermatitis.
- Rapid inhibition of pruritus by oclacitinib in flea allergic dogs was the impetus for further research that revealed:
  - Canine IL-31 can activate JAK pathways in cells, and oclacitinib can inhibit IL-31 function.
  - Canine IL-31 can induce pruritus in purpose-bred beagle dogs, and oclacitinib inhibits its pruritic activity.
  - IL-31 can be detected in the serum of dogs with atopic dermatitis.
- Zoetis has built a platform for designing canine monoclonal antibody therapies and has produced a caninized anti-IL-31 mAb that neutralizes the effects of IL-31 in dogs.
  - Anti-IL-31 mAb inhibits the ability of IL-31 to activate cells.
  - Anti-IL-31 mAb inhibits the ability of IL-31 to induce itch in laboratory beagle dogs.
- Monoclonal antibody technology allows us to evaluate the therapeutic potential of inhibiting a single cytokine in allergic skin disease.
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August 2015 in the United States:

Canine Atopic Dermatitis Immunotherapeutic (caninized anti-IL-31 mAb) was conditionally licensed by the US FDA for helping to reduce clinical signs associated with atopic dermatitis.
Monoclonal antibody (mAb) therapy is a type of "passive immunotherapy" that holds great promise in treatment of several diseases of veterinary importance, including skin diseases. We are fortunate that one of the first veterinary mAb products for companion animals was developed for dogs with atopic dermatitis (AD), specifically to interfere with interleukin-31 (IL-31) - mediated pruritus in dogs. Lokivetmab is the active contained in Canine Atopic Dermatitis Immunotherapeutic (CADI)*, an anti-c-IL31 mAb developed by Zoetis which is currently conditionally licensed in the United States. The mechanism of action of lokivetmab is different than that of oclacitinib (Apovet), but the two treatments work on similar biological pathways. Lokivetmab has the advantage of being extremely targeted and having a very long half-life, remaining in circulation for several weeks. The label allows for repeated administration, monthly, as needed. Initial experience suggests lokivetmab CADI may be successful in some individual patients that had an insufficient response to oclacitinib, but there is no way to predict which patients will respond to which product. This certainly speaks to the complex pathogenesis of canine AD, and reinforces the concept of using multimodal therapy to achieve the best result for each patient.
Canine Atopic Dermatitis Immunotherapeutic

Active Ingredient: Iluvzel®
- Caninized mAb targeted at IL-31

CADI vs. Apoquel®

- Apoquel®
  - Several different cell types have receptor
  - Other pathways - via JAK/STAT signaling free
  - Not stimulating signaling by 700%
  - Short half-life, short duration
  - Less targeted, shorter duration

CADI vs. Apoquel®

- CADI mAb
  - Single target
  - CADI and complete removal over a long period of time

CADI vs. Apoquel®

Conclusion
- Some crossover in how they work
- But they are different treatments
- We can expect some differences in clinical experience and subset patients benefit

Practical Experience with CADI

- Which patients benefit?
  - Urticaria and exfoliation
  - Speaks to complex pathogenesis of CAD
  - When Apoquel® has limited efficacy or duration of effect
  - Looked for: IgE only

Practical Experience with CADI

- How fast, how long?
  - Fixed markers, but improvement within 2 weeks after injection
  - 40% treatment success at Day 3
  - Administer monthly, as needed

Practical Experience with CADI

- What about infection?
  - Infection associated pruritus, milo-dlog
  - Optimum/experience varies
  - CAD may not resolve pruritus
  - CAD may resolve pruritus, potential of non-pruritic infection may or may not occur

Practical Experience with CADI

- What about infection?
In Summary

- mAb therapy is a cutting-edge, unique, exciting, potentially exceptionally useful treatment in veterinary medicine, with many potential targets and constantly advancing technology.

- No single treatment is perfect.
  - We’ll still have to patch as needed.
  - Avoidance, inflammation control, barrier enhancement, ADIT, etc.