21st Century Therapy for Allergic Dermatitis

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Allergy: Quick Review
- Flea
- Food
- Environment
- Combination


Flea Allergy
### Flea Allergy
- Prevalence??
- My dog doesn't have fleas......
- Diagnosis
  - Pruritus
  - Lesion distribution
- Treatment
  - Flea control

### Lots of Treatment Options

<table>
<thead>
<tr>
<th>Topical</th>
<th>Oral</th>
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<tbody>
<tr>
<td>Vectra/Vectra 3D</td>
<td>Isoxazilones</td>
</tr>
<tr>
<td>Revolution</td>
<td>Simparica</td>
</tr>
<tr>
<td>Frontline Gold</td>
<td>Bravecto</td>
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<tr>
<td>Advantage II</td>
<td>Nexgard</td>
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<td>Comfortis/Trifexis</td>
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### Food Allergy
Adverse Reactions to Food

Immunologic
- Food allergy
  IgE-mediated
  Dermatologic
  Gastrointestinal
  Respiratory
  Combination

Non-immunologic
- Food intolerance
  Toxic
  Metabolic
  Pharmacologic

Food Allergy
- Signalment
  Age
  Bimodal
  Breed
  Not really....
  Genetic predisposition to atopic disease?
  Sex
  None

- History
  Non-seasonal clinical signs
  Not steroid-responsive
  Dermatologic
  Gastrointestinal

Diagnosis
- History
  Non-seasonal
  Correlation with diet or indiscretion
  Can be “flare factor” for atopic dermatitis

- Clinical Signs
  Pruritus!
  Otitis
  Erythema, edema, exudate
  Dermatitis
  Face, feet, axillae, groin, perianal/perineal
  Urticaria, erythema, atopia, scale, papules, pustules, macules, plaques, excoriations, lichenification
  Recurrent infections
Diagnosis

- Diet trial
  - Novel or hydrolyzed protein
  - Confirm diagnosis by challenge
- Serum tests do not work!
  - Presence of IgE does not equal disease
- “Prick” and intradermal tests do not work!

Management

- Feed only proteins and carbohydrates that do not induce HPS
  - Other medications
  - Dermatologic and gastrointestinal signs
- Manage all contributing factors
  - Secondary infections
  - Concurrent allergies

Canine Atopic Dermatitis: Environmental Allergens
Canine Atopic Dermatitis

- Some criteria
  - Pruritus w/o lesions at onset
  - Onset at <3 years
  - Mostly indoor
  - Corticosteroid-responsive pruritus
  - Malassezia history
  - Affected front feet
  - Affected ear pinna
  - Non-affected ear margins
  - Non-affected dorsolumbar

Favrot et al., 2010
Olivry et al., 2011

Canine Atopic Dermatitis

- Prevalence
- Diagnosis
  - EXCLUSION!
  - NOT IDST or serum tests
  - Dermatologic signs indistinguishable from food allergy

Pathophysiology
  - Barrier involvement!!!!!!
  - Genetic predisposition?
  - IgE-mediated
  - Th2 cytokines!
  - IL-31!
  - Route of antigen entry
    - Percutaneous, not inhalation

IDST is used to identify allergens for desensitization. AFTER clinical diagnosis has been made.

Serum IgE levels in nonatopic vs atopic West Highland white terriers
**21st Century Medicine: Targeted Therapy**

- Apoquel
  - Oclacitinib

- Cytopoint
  - Caninized anti-IL-31 monoclonal antibody

**Canine Pathophysiology**

Cytokines convey information by binding to specific receptors on the cell membrane that induce biological responses.

**JAK Pathway**

Cytokines convey information by binding to specific receptors on the cell membrane that induce biological responses.
JAK/STAT Signaling

STATs go to the nucleus and activate gene transcription

PRURITUS
INFLAMMATION

JAK/STAT Signaling

X
APOQUEL

Mechanism of Action

APOQUEL
- Inhibits Janus kinase (JAK) enzymes, particularly JAK1 and JAK3
  Inhibits the activity of pruritogenic, pro-inflammatory and pro-allergic cytokines that use JAK1
- Has minimal impact on cytokines that work through JAK2
  The cytokines responsible for hematopoiesis and innate immunity
Apoquel: Target JAK1-dependent Cytokines, Minimize Effects on JAK2-dependent Cytokines

Data on file, Study Reports 7960-02-11-004, 7960-00-00-717, 7960-00-00-806, 1462-00-00-001, Zoetis Inc.

Plasma concentration oclacitinib 0.6 mg/kg BID
Plasma concentration oclacitinib 0.6 mg/kg SID

JAK1 dependent cytokines IC50s
JAK2 dependent cytokines IC50s

IL-6
IL-13

EPO, GM-CSF
IL-12, IL-23

Time (Hours)
Concentration (ng/mL)

APOQUEL® Works Fast
Mean APOQUEL® Scores Were Significantly Better Than Placebo Scores on Each Assessment Day


Apoquel® for Short-Term and Long-Term Pruritus Control

Minimal Side Effects
Safe for Long-Term Use
Can Be Used Concomitantly with Many Other Medications
Allows You to Diagnose the Underlying Cause

Side effects of APOQUEL® were similar to placebo without many of the side effects associated with the use of steroids.

Owner-reported minimal side effects in dogs who were given APOQUEL® for more than 3 years in an unapproved, observational continuation study.

APOQUEL® can be used in combination with many common therapies including vaccines, antibiotics, and allergen immunotherapy.

APOQUEL® does not compromise diagnostic testing, allowing veterinarians to diagnose the underlying cause of the itch and improve the quality of life for dog and its owner.

Apoquel: Not just for atopy

- Flea Allergy
- Food Allergy
- Contact Allergy
- Atopic Dermatitis

APOQUEL works on all of them!

References:

Apoquel and Adverse Effects

- CBC
  - Lymphopenia?
  - Rare
- Chemistry
  - No effect on liver or kidneys
- Thyroid
  - No effect
- Urinalysis
  - Common with glucocorticoids, cyclosporine
  - Subclinical UTIs in trials?
- CSU Prospective Study
  - Dogs with no history or predisposition to UTIs
  - Quantitative urine culture negative at Day 0
  - 58 to 280 days Apoquel: no UTIs
  - Neoplasia?
    - No evidence of increased risk
    - No difference in type or prevalence of neoplasia compared with general population
Apoquel and Neoplasia?

- Oclacitinib does not damage DNA, not genotoxic
- Immunosuppression and cancer
  - Viral infections
- No increase in malignancy in humans treated with JAK inhibitors
- IL-6 drives tumor development and metastasis
  - Inhibited by JAK-1 inhibitors
- Clinical trial data
  - No evidence of increased risk
  - No difference in type or prevalence of neoplasia compared with general population

Cytopoint

- Anti-IL-31 monoclonal antibody
What Are Antibodies and Antigens?
Antibody (Immunoglobulin) structure modeled on structural protein data

- Constant regions
- Variable regions
- Heavy chains
- Light chains
- LOCK-AND-KEY (CDR-Complementarity Determining Region)
- Constant regions
How Do Antibodies Work?

The body naturally produces antibodies in response to ‘foreign’ protein (antigen) as part of its normal response to disease.

Using the same principles, antibodies can now be administered by injection and used therapeutically.

Caninization of Monoclonal Antibodies

A. Murine antibody

B. Canine-murine chimeric antibody

C. 90% Caninized antibody
Cytokines Involved in Canine Allergic Skin Disease

Interleukin-31

- Associated with AD
- Th2 lymphocytes and CLA+ skin homing T cells (mice, humans)
- Serum levels correlate with disease severity in atopic humans
- Pathways activated:
  - JAK-STAT
  - MAPK

Interleukin-31 Receptors

- Keratinocytes
- T lymphocytes
- Macrophages
- Eosinophils
- Dorsal root ganglia
Cytopoint

- IL-31
  - Th2 lymphocytes
  - Keratinocytes
  - Pruritus and inflammation

- Anti-IL-31 mAb
  - Binds to IL-31
  - PREVENTS RECEPTOR ACTIVATION!!!

2. Protocol C863R-US-12-018

Canine Pathophysiology

Cytopoint Results

- Decreases pruritus
- Duration of control 3 to 6 weeks
- Increased benefit after 2 to 3 injections
- To date, no injection site or other adverse reactions
- Other therapies?
Need for complementary treatments varied
- Cytopoint alone
- Cytopoint with Apoquel or Temeril P
  Decrease dose of complementary therapy
  Improved quality of life vs. either alone

Results
- Block itch
- Decrease inflammation
- Monthly biologic vs. daily pill
- Opportunity to re-evaluate patient
- Not every treatment works for every patient—we need everything we can get!

Role in Multimodal Therapy
- Block itch
- Decrease inflammation
- Monthly biologic vs. daily pill
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- Not every treatment works for every patient—we need everything we can get!

Summary: 21st Century Dermatology
- The more we understand about pathways, the more targets we can identify
  - Skin barrier
  - Pro-inflammatory cytokines
  - Microbiologic control/microbiomes
- The more specific the target, the more effective the therapy.
  - Pro-allergic cytokines
    - Inhibit
    - Block