



Atopic dermatitis
Diagnostic and
therapeutic
updates

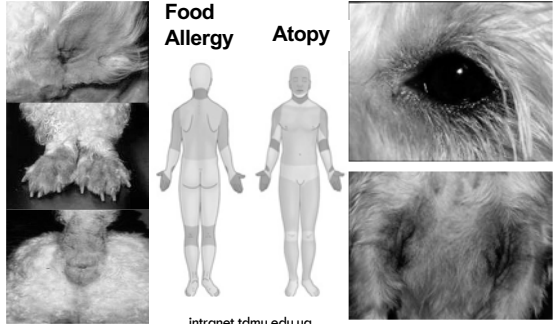


Anthony Yu, DVM, MS, Dipl. ACVD
Veterinary Allergy Dermatology Ear & Referral
(VADER) Clinic
www.vaderclinic.ca



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Distribution patterns
Food Allergy vs Atopy



Food Allergy Atopy

intranet.tdmu.edu.ua

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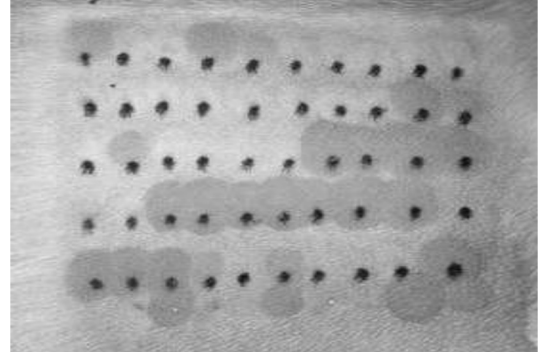
Eliminate other pruritic differentials



Food Allergy & Flea Allergy
Malassezia/bacterial dermatitis/hypersensitivity
Sarcoptes scabiei & Demodex injai
Trichophyton mentagrophytes
Metabolic disorders (Cushing's & Calcinosis cutis)
Cutaneous T-cell Lymphoma

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**Intradermal Allergy Testing -
ID allergens to avoid or ASIT**





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+ Serum test
Five serum tests are currently available in Canada
Radioallergosorbent test (RAST), enzyme-linked immunosorbent assay (ELISA)

Laboratory	Nextmune Labs	VARL	Heska	Greer IDEXX	Boa Labs
Location	Tempe AZ	Pasadena CA	Port Collins CO	Lenoir NC	Calgary AB
Test name	SPOT test	Liquid Gold	Intercept	Aller-g-complete	?
Method	Combined RAST/ELISA	ELISA	High affinity E receptor-based ELISA	Monoclonal antibody cocktail-based ELISA	ELISA ?
	Solid phase	Liquid phase	Solid phase	Solid phase	

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Extracts + components  



Summary on detectable sensitizations

Group	Item	Value
GRASS POLLEN	Bromegrass	0.000
	Timothy	0.000
	Orchard grass	0.000
	Kentucky bluegrass	0.000
	Redtop	0.000
	Timothy	0.000
	Orchard grass	0.000
	Kentucky bluegrass	0.000
	Redtop	0.000
	Timothy	0.000
TREE POLLEN	Alnus	0.000
	Betula	0.000
	Corylus	0.000
	Fraxinus	0.000
	Quercus	0.000
	Ulmus	0.000
	Alnus	0.000
	Betula	0.000
	Corylus	0.000
	Fraxinus	0.000
MITE & COCKROACHES	Dermatophagoides	0.000
	Blattella germanica	0.000
	Dermatophagoides	0.000
	Blattella germanica	0.000
	Dermatophagoides	0.000
	Blattella germanica	0.000
	Dermatophagoides	0.000
	Blattella germanica	0.000
	Dermatophagoides	0.000
	Blattella germanica	0.000

- First quantitative multiplex macroarray
- Over 200 allergens = lower testing cost
- Fully automated process = U standardization
- Double CCD blocking/detectors
- Only 0.5 ml of serum needed per test
- ID "primary" component of allergens
- ID allergen cross-reactivities
- Component immunotherapy (future)

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FAQ: How were IgE level classes determined?

● class 0: < 28 ng/mL
 ● class 1: 28.00-99.99 ng/mL
 ● class 2: 100.00-399.99 ng/mL
 ● class 3: 400.00-799.99 ng/mL
 ● class 4: ≥ 800.00 ng/mL

WEED POLLEN

- Ragweed
- Mugwort
- Lomb's quarter
- Wall pellitory
- Ribwort / Plantain
- Dock/Sorrel
- Russian thistle
- Nettle

Highest measured IgE concentration per allergen group

< 30 ng/mL 30.00-99.99 ng/mL 100.00-399.99 ng/mL 400.00-799.99 ng/mL ≥ 800 ng/mL
 Negative or uncertain Low IgE level Moderate IgE level High IgE level Very high IgE level

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+ Intradermal Allergy Testing Versus PAX Testing

<p>IDT Pros & Cons</p> <ul style="list-style-type: none"> ■ Evaluates the local immune response in affected organ ■ Individual variation of reaction interpretation ■ 48 allergen panel ■ Drug withdrawal required ■ Need to shave hair + sedation ■ Immediate results 	<p>PAX Pros & Cons</p> <ul style="list-style-type: none"> ■ Evaluates CIRCULATING IgE ■ Fully automated evaluation of reaction scores ■ 300 antigens/components ■ Less drug withdrawal ■ 1.5mL of blood ■ Results available within 2 weeks
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+ Intradermal Allergy Testing Versus PAX Testing

<p>IDT Pros & Cons</p> <ul style="list-style-type: none"> ■ Currently crude extracts only ■ Subjective evaluation ■ Requires expertise to both read and manage the cases ■ +/- pan pollen reaction ■ Fewer false positive/negative ■ Requires case load to make testing cost effective ■ ASIT based on crude extracts 	<p>PAX Pros & Cons</p> <ul style="list-style-type: none"> ■ Evaluates crude and allergen components ■ Objective evaluation ■ Requires expertise to both read and manage the cases ■ CCD blocked X 2 ■ Fewer false positives ■ Tests ordered individually ■ ASIT based on crude extracts <ul style="list-style-type: none"> ■ Cross-reactivities to limit Ag ■ Derf2 ASIT being evaluated
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How would I treat this moderate to severely allergic dog?



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Atopic dermatitis in dogs and cats

How do I treat atopic dermatitis in dogs and cats? It depends....

Three types of clients

- Compliant and able
- Compliant and overwhelmed
- Non-compliant and useless




Three types of itch

- Inflammatory itch
- Neurogenic itch
- Psychogenic itch

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Immunotherapy still our best long term approach


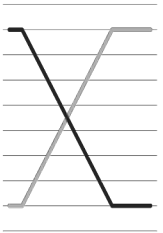
- **ONLY** treatment that **MODULATES** the pathomechanism of atopy
 - Increase IL-10 and IFN → Th1 + IgG blocking antibodies
 - All other treatments = symptomatic
- Potential to eventuate a cure/remission
- Fewest side effects
- Weight independent dosing - cost efficacious
- My personal response rates: 70-90%
- Subcutaneous (SCIT); Oral immunotherapy (trypanophobia; OIT)

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+ Immunotherapy

- NOT "light switch"
- SLIT - SID-BID PO
- SCIT - q48hrs 30d, then 0.5cc every 7 days
- Ancillary meds during induction
 - Glucocorticoids
 - Apoquel
 - Cytopoint
 - Atopica® - complimentary
 - ASIT - ↓ Th2 activation → ↓ IL-5
 - Atopica - ↓ Th2 proliferation
 - ASIT - ↑ release IL-10
 - Atopica® ↑ population of Treg → IL-10

Brandt et al, Allergy 2009; Nahm DH, Yonsei Med J 2012

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Three types of itch		
Psychogenic	Inflammatory	Neurogenic
DAP®/Feliway® Stress Reducing Pheromone	Atopica Calcineurin Inhibitor Inhibits T-cell activation → Decreased IL-2, IL-10, IL-15, IL-18, IFN-gamma and TNF-alpha	Apoquel® JAK 1/3 inhibitor BLOCKS IL-31
Fluoxetine Selective Serotonin Re-Uptake inhibitor (SSRI)		Binds capsaicin receptor TrpV1 (Vanilloid)
Clomipramine Amitriptyline Inhibit serotonin (5-HT) and norepinephrine reuptake	Antihistamine Blocks H1	Neuropathic pain
	Steroids GC/GCR binds to NF-κB, GResponseElements, and Activator Protein-1 → altering inflammation	Cytopoint® Monoclonal antibody directed against IL-31

Anthony Yu®


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Atopica™ - SAFE & reliable treatment option
Nuttall T, et al. Life-long diseases need life-long treatment: longterm safety of ciclosporin in canine atopic dermatitis. Vet Record 2014;174(suppl 2):3-12


- **Atopica ORAL cyclosporine CAPSULES**
 - 10mg, 25mg, 50mg, 100mg
 - 5mg/kg daily for 4-8 weeks then taper
 - FREEZE capsules
- **Atopica ORAL cyclosporine LIQUID**
 - 100mg/ml
 - Extra-label use in dogs - calibrate/change syringe
 - 7mg/kg daily for 4-8 weeks then taper (cats)
 - 5mg/kg daily for 4-8 weeks then taper (dogs)
 - REFRIGERATE liquid
- **Sandimmune INJECTABLE cyclosporine**
 - 50mg/ml ampules X box of 10 ampules
 - Extra-label use in dogs and cats
 - 2.5-5mg/kg SQ q48-72h (cats, dogs)
 - Koch, SN, et al. Vet Derm 2018;29:107



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Stability and pharmacokinetics of ciclosporin capsules stored at -20C
J. Bachtel et al. Vet Derm, 2015;26:133-159.

- -20° C storage at five time points (1 h and 1, 7, 15, 30 days)
- blinded, randomized crossover study
- 8 healthy beagle -20° C vs 15-25° C - 7 day washout
- Blood at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 10 and 24 h.
- Capsule and blood ciclosporin via HPLC
- No sig diff in capsule concentration
- No sig diff in pharmacokinetic parameters
 - area under the curve (P = 0.9273),
 - half-life (P = 0.71),
 - Cmax (P = 0.66)
 - Tmax (P = 0.41)

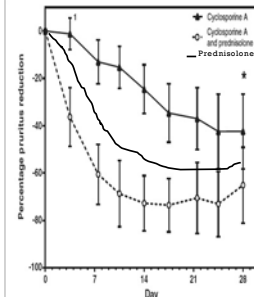


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Short-Term Strategies
Speeding up the response of Atopica


- **QUICK anti-inflammatory effect** with short-term steroids
- **How to institute**
 - 5mg/kg/day for 30-60 days
 - With steroids to start 14d ± 28d
- *Concurrent short-term use of prednisolone with cyclosporine A accelerates pruritus reduction and improvement in clinical scoring in dogs with atopic dermatitis*

Dip et al. BMC Vet Res 2013, 9:173



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Westies and Frenchies
BEST Atopica® responders



Scruffie Hoch
8 weeks Atopica®

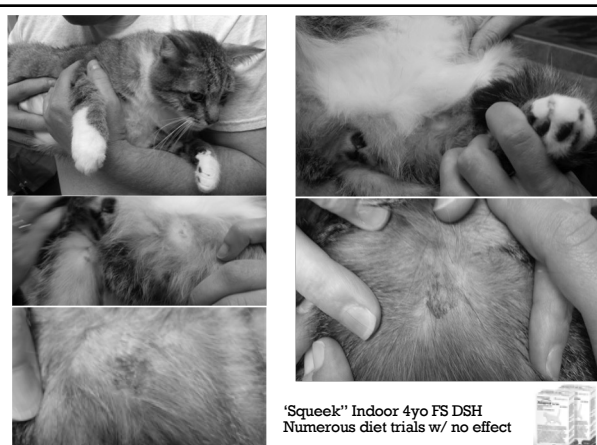
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Ulcer = viral
Do not use Atopica

www.bircchannel.com

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'Squeek' Indoor 4yo FS DSH
Numerous diet trials w/ no effect

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< 1 week Update on Squeek

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Squeek Loy at 4 weeks recheck

- 1) DECREASE ATOPICA TO EVERY OTHER DAY
- 2) START DIET CHALLENGE IN 2WKS
- 3) DECREASE ATOPICA TO EVERY 3RD DAY IN 4WKS

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+ GINGIVAL HYPERPLASIA

- Cyclosporin increases intracellular Ca²⁺
- Collagenase is regulated by Ca²⁺ influx
 - Fibroblasts produce an inactive form of collagenase
 - increased extracellular matrix
 - Lin et al., 2007
- More often when CSA + KCZ
- ☉Gingival resection
 - REVERSIBLE with decrease dose
 - Azithromycin toothpaste – early and BID
 - Rosenberg A, et al Vet Derm 2013;24:337-345
 - Azithromycin orally

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+ Hirsutism

- Cyclosporin prolongs the anagen phase of the hair cycle

Cyclosporin
inhibits the expression
of Protein kinase C

↓

stimulating hair follicle growth
and
hair fibre production

HARMON et al., 1995; TAKAHASHI AND KAMIMURA, 2001

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+ Rocky 8 weeks post-Atopica®

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Malassezia can MASK the benefits of a diet trial and antipruritic therapy

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+ Gray L, et al The effect of ketoconazole on whole blood and skin concentrations of cyclosporine
Vet Derm 2012;23 suppl:13


- T1 = 5mg/kg Atopica
- T2 = 2.5mg/kg CSA
- T3 = 2.5mg/kg CSA + 5mg/kg KCZ
- T4 = 2.5 mg/kg CSA + 2.5 mg/kg KCZ

■ Blood: **T3 (644ng/ml)**>>T4 (417ng/ml), T1 (307ng/ml) > T2 (169 ng/ml)

■ Skin: **T3 (1.2 ng/mg)**>>T4 (0.7ng/mg), T1 (0.6ng/mg)>T2 (0.26ng/mg)

■ e.g. 30kg dog with yeast

- normal Atopica dose @5mg/kg = 150mg
- 2.5mg/kg KCZ (75mg) + 2.5mg/kg Atopica (75mg)
- Consider instead **5mg/kg KCZ (150mg → 200mg)** + 1.67mg/kg Atopica (50mg; 67% less Atopica)
- Cost savings and fewer side effects



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Honey Bear 8-weeks of Atopica/Keto

BEFORE **AFTER**




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Interleukin-31 blockers

Apoquel (oclacitinib) now available as chewable tablet with pork liver powder

Cytopoint (lokivetmab)

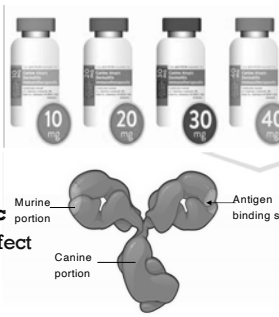


This combination does not address allergic inflammation
It helps itch and stop traumatically-induced skin irritation only

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+ Cytopoint® to Control Neurogenic Itch

- Lokivetmab
- "Caninized" moAb IL-31
- Weight dependent dosing
 - 2 mg/kg SQ q4-8weeks
 - 50-70% respond in 1-3 days
 - Test dose of 0.25-0.5mg/kg especially in larger dogs \$\$\$
- Antipruritic/Anti-neurogenic
 - Indirect anti-inflammatory effect
 - OK to use in cancer patients
 - NO age restrictions listed
- 3-4% may develop autoAb



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Veterinary Dermatology

Scientific Paper 2019;30(2):98-e26

Proactive maintenance therapy of canine atopic dermatitis with the anti-IL-31 lokivetmab. Can a monoclonal antibody blocking a single cytokine prevent allergy flares?

Chie Tamamoto-Mochizuki, Judy S. Paps, Thierry Olivry

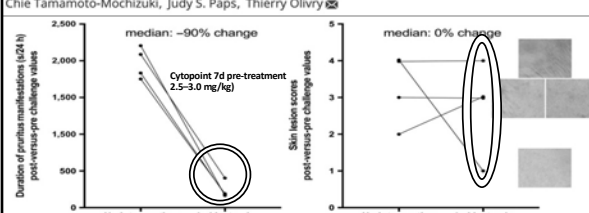


Figure 1. Comparison of duration of pruritus manifestations and skin lesion scores with or without lokivetmab proactive therapy. Although the lokivetmab abolished most of the pruritus manifestations, erythematous lesions still developed within 24 h of an episodic allergen challenge.

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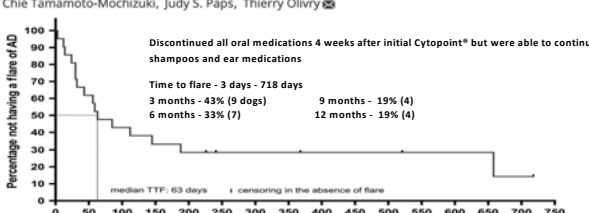


Figure 3. Probability of flares of atopic dermatitis (AD) in client-owned dogs receiving lokivetmab proactive therapy. TTF: time-to-flare.

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Janus Kinase Inhibitor **apoque!**
(oclacitinib tablet)

- QUICKLY BLOCKS JAK-Signal Transducer and Activator of Transcription (STAT) signaling pathway preventing IL-31 effect on neurons stopping NEUROGENIC itch
- 0.4-0.6mg/kg BID 14d, then once daily**

Veterinary Dermatology
Vet Dermatol 2015; 26: 171–e35

Long-term compassionate use of oclacitinib in dogs with atopic and allergic skin disease: safety, efficacy and quality of life

- SIGNIFICANT** improvement in Quality of Life
- SAFE** for longterm use
- q24h dose, mainly anti-ITCH, minimal anti-INFLAMMATORY
- Does decrease traumatically-induced inflammation

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Apoquel® in Cats [Extra label]

- Frank RK et al. Use of Oclacitinib (Apoquel®), Zoetis for treatment of cutaneous mastocytosis in a cat. Vet Derm 2014;25:153. **1 mg/kg BID 31 days**
- Whitehouse W et al. Clinical use of 10 emerging therapies. Update In Feline Therapeutics 2015;17:220–234 **0.5-1 mg/kg BID 28d**
 - eosinophilic airway inflammation and pruritus
- Loft KE. Feline idiopathic ulcerative dermatosis treated successfully with oclacitinib. Vet Dermatol (2015) 26:134–5 **1 to 1.5 mg/kg SID 6 weeks**

Veterinary Dermatology
Scientific Paper 2015;26(4):235–e52

Oclacitinib in feline nonflea-, nonfood-induced hypersensitivity dermatitis: results of a small prospective pilot study of client-owned cats

- 12 cats **0.47 mg/kg BID 5/12** good improvement

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Veterinary Dermatology

Scientific Paper 2019;30(2):110-e30

A double-blinded, randomized, methylprednisolone-controlled study on the efficacy of oclacitinib in the management of pruritus in cats with nonflea nonfood-induced hypersensitivity dermatitis

N=20 - Apoquel - 1mg/kg BID 28d
N=20 - Medrol - 0.5-1mg/kg BID 28d
Both equally efficacious
4/14 renal enzyme elevations w/Apoquel
Possible anemia

Chiara Noli, Irina Matricoti, Carlo Schievano

Macedonian Veterinary Review
sciendo
Apoquel 1mg/kg BID until resolved (3 months) then discontinued
Lesion free 5 months at time of writing the paper

Case Report
DIFFUSE CUTANEOUS MASTOCYTOSIS (PIGMENTED MACULOPAPULAR CUTANEOUS MASTOCYTOSIS) IN A CAT

Marcin Szczepanik¹, Piotr Wilkolek¹, Anna Śmiech², Iwona Taszkun¹

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Veterinary Dermatology

Vet Dermatol 2019; 30: 17–e6
DOI: 10.1111/ivde.12696

Immunomodulatory in vitro effects of oclacitinib on canine T-cell proliferation and cytokine production

Frane Banovic¹, Jaime Tariqot¹, Hannah Gordon¹, James P. Barber¹ and Robert M. Gogal Jr²

- Oclacitinib (Apoquel®) at 337 ng/ml (prescribed dose) NO effect on T-cell proliferation/inflammation
- Cyclosporine (Atopica) at 200 ng/ml (prescribed) significantly inhibited T-cell proliferation; ↓ IL-2, IL-10, IL-15, IL-18, IFN; TNF-α

CONSIDER COMBINATION THERAPY
ANTI-INFLAMMATORY + ANTINEUROGENIC

French bulldog on Apoquel alone

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Can I use Apoquel with Atopica ?

Veterinary Dermatology

Vet Dermatol 2016; 27: 22–e7
DOI: 10.1111/ivde.12278

Repeated oral dose tolerance in dogs treated concomitantly with ciclosporin and oclacitinib for three weeks

Alessandro Panteri¹, Günther Strehlau¹, Rainer Helbig¹, Christine Probst¹ and Kelly Doucette²

- N=8 dogs (4F:4M/group) – Apoquel® or Apoquel®+Atopica
- Dosed daily at labelled doses for 3 weeks

Conclusions and clinical importance

- No increase number of adverse events or laboratory abnormalities beyond those associated with oclacitinib given alone.

- Consider combination therapy**
 - Start Apoquel® BID for 14d, then SID for 14d OR SID 28d then as needed
 - Start Atopica +/- ketoconazole every OTHER day for 6 weeks, then taper
 - Day 1 - Atopica/KCZ; Day 2 - Apoquel; repeat
 - Day 1 - Atopica/kCZ; Day 2 - Apoquel; Day 3 - Apoquel; repeat
 - Day 1 - Atopica/KCZ; Day 2 - Apoquel; Day 3 - dexamethasone; repeat

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Can I use **Apoquel** with **Steroids**?

Veterinary Dermatology

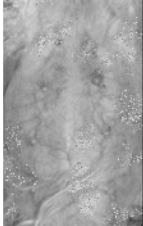
Scientific Paper **Vet Dermatol 2015;26:171-E35**

Long-term compassionate use of oclacitinib in dogs with atopic and allergic skin disease: safety, efficacy and quality of life

Drug Class	Prescription (n=247)	
	n	(%)
Antihistamines	85	(34.4)
Systemic Glucocorticoids	37	(15.0)
Topical Glucocorticoids	51	(20.6)
Psycholeptics	46	(18.6)
Omega 3 Fatty Acids	42	(17.0)
Analgesics	41	(16.6)
Non-steroidal anti-inflammatory products	38	(15.4)

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Steroids Are Good BUT...




- Infections
 - bladder infections, skin infections,
 - septicemia, respiratory infections
 - generalized demodicosis
- Alopecia, thin skin, skin fragility (cats)
- Calcinosis cutis, atrophic remodeling of scars,
- Milia-like comedones, follicular cysts,
- Musculoskeletal atrophy, ruptured cranial cruciate
- Hyperlipidemia, steroid hepatopathy, colitis,
- Adrenal suppression/atrophy,
- DM, ESS, increased PTH levels,
- Behavioral changes, PU/PD, polyphagia, panting


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Iatrogenic effects of steroids

ALTERNARIA




**MUSCLE ATROPHY/
CALCINOSIS CUTIS**



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Adult-onset demodicosis
rule-out iatrogenic steroids or Apoquel




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Address Concurrent Factors


Maximum allowable steroid dose per year

- Prednisone/olone dose: 0.5-1.0mg/kg/d 7d, taper EOD
 - Max Pred dose/yr = 30mg X BW in kg (doubled in cats)
- Dexamethasone dose: 0.05-0.1mg/kg/d 7d, q2d 14d, q3d
 - Max Dex dose/yr = 4.5mg X BW in kg (doubled in cats)

Sousa C. Glucocorticoids in veterinary dermatology. CVT XIV 2009; 400-405.



Calcinosis Cutis due to Steroids
Courtesy of Dr. John MacDonald




Iatrogenically steroid-induced feline skin fragility syndrome
(Also watch HCM and DM)

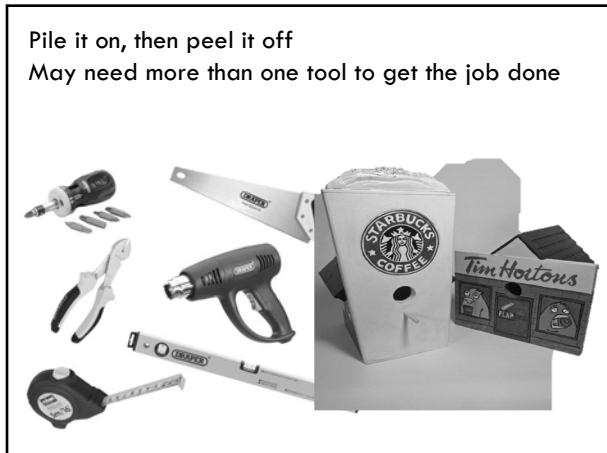
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Vanectyl-P® (CDN)/Temaril-P® (USA)

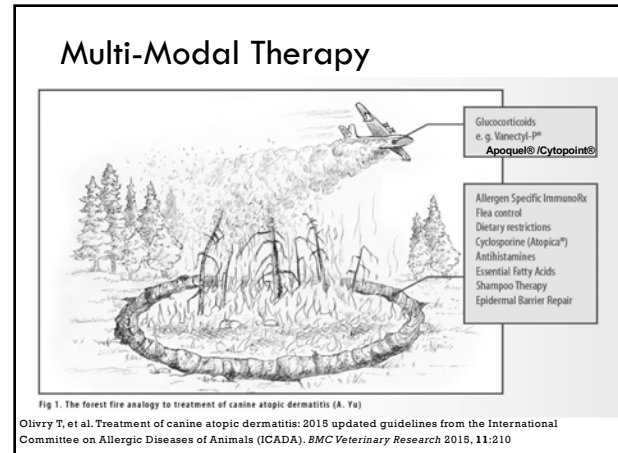
- **ANTI-INFLAMMATORY**
 - PrednisOLONE 2mg
 - Trimeprazine 5mg
 - DOGS: 1 tab/10kg q24h 7d, then q48h
 - CATS: 1 tab/5kg q24h, then q48h
 - Extra-Label Use
- **SYNERGISTIC EFFECT**
 - Effect of 10mg tablet
 - 1/5 the dose of prednisolone
 - Can use 5 times longer
- 5kg X 30mg/kg = 150 mg/yr
 - 5kg dog = ½ tab = 1mg pred
 - Therefore can use 150 days at q24h and 300 days at q48h



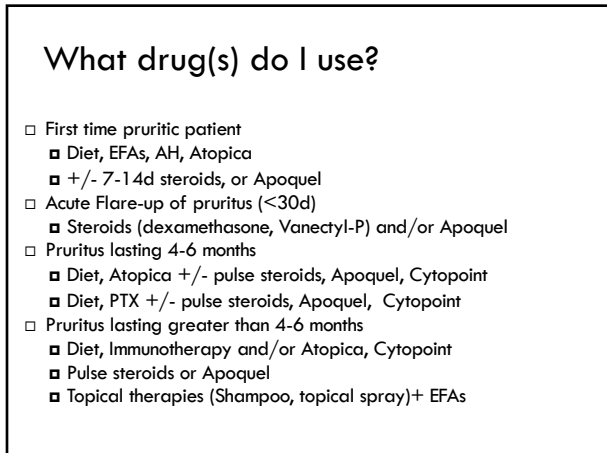
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