

## **BALD ISN'T ALWAYS BEAUTIFUL – THINKING OUTSIDE THE BOX PART ONE: CANINE DEMODICOSIS – WHAT'S NEW**

Anthony Yu DVM, MS, ACVD

Yu of Guelph Veterinary Dermatology, Guelph Ontario

Tel: 519-821-7546 email: [derm@yuofguelph.com](mailto:derm@yuofguelph.com)

### DEMODEX – THE MITES

In the dog, the most common species of *Demodex* is *Demodex canis*. More recently, *Demodex injai* and the short tailed demodex, *Demodex cornei* have been identified. ***Demodex canis*** is a “cigar-bodied” mite measuring 170-225 microns, and is transferred from the bitch to the suckling puppy within the first 3 days of life. It is considered a commensal organism of dogs and only becomes an issue in the immunocompromised pet. Clinical signs of demodicosis can range from focal or multifocal folliculitis along with hyperpigmented patches to a generalized scaling, alopecic and erythematous dermatosis also known as the "red mange". ***Demodex injai*** is a 330-370 microns long-bodied mite that causes seborrheic dermatitis on the dorsothoracolumbar region. This mite tends to affect adult dogs of 2 years or greater and the terrier breeds appear more predisposed. Iatrogenic Cushing's and hypothyroidism are commonly associated with the presence of ***Demodex injai***. ***Demodex cornei*** is an 80-115 micron, surface dwelling mite often found in conjunction with *D. canis* resulting in similar clinical findings. Diagnosis is made by hair plucks and/or pursuing multiple deep skin scrapings with mineral oil squeezing the skin midway to help increase the yield of mites. Key areas to scrape include those with hyperpigmented regions, areas with erythema and follicular casts. Be certain to lower the condenser on the microscope to increase the contrast of these translucent mites and improve your chances of identifying mites.

### ADDRESS UNDERLYING ETIOLOGIES

In juvenile generalized demodicosis or adult-onset localized and generalized demodicosis, appropriate diagnostic should be pursued to evaluate the patient for underlying etiologies such as: poor nutrition; stress; endoparasite burden; allergic disease (adverse food reaction or atopy especially if the patient is still pruritic after addressing the secondary bacterial infections); endocrinopathies (Cushing's, hypothyroidism, Diabetes) and neoplasia.

### ADDRESS SECONDARY INFECTIONS

Treatment of localized cases rarely encompasses miticidal therapy. The focus is to deworm for parasites, improve the pet's nutritional plane, minimize stress, and address accompanying/perpetuating secondary bacterial infections. Staphylococcus spp. feed the Demodex mites by releasing exfoliative toxins that result in desquamation of keratinocytes into the follicular lumen. As part of their symbiotic relationship, Demodex mites diffuse nutrients through their tails that encourage growth of the bacteria. Therefore, treatment for generalized demodicosis often involves the use of concurrent antibiotic therapy (Accelerated Hydrogen Peroxide (Pure Oxygen®; Ogena) or Benzoyl Peroxide (Pyoben®; Virbac) shampoo and/or systemic antibiotics) until 2 negative skin scrapings are achieved at monthly intervals--typically 3-7 months.

### MITCIDAL OPTIONS

#### **Fluralaner (Bravecto®, Merck)**

Fluralaner is a novel oral insecticide and acaricide that belongs to the isoxazoline compounds and has activity against  $\gamma$ -aminobutyric acid- (GABA-) and glutamate-gated chloride channels with significant selectivity for insect neurons over mammalian neurons. The effects of fluralaner were recently evaluated by Karas-Tecza J, et al (2015) when client owned dogs (n=163) of different breeds and both sexes with generalized demodicosis confirmed by deep skin scraping and/or hair plucking were divided into two age groups: Age of the presentation for the treatment 2-18 months (62,6%) and over 2 years of age (37,4%). Dogs were treated with fluralaner (25 mg/kg) orally, twice three months apart. No other treatment against demodicosis was used. Individuals with secondary pyoderma additionally received cephalexin (30mg/kg BID) until 7-14 days past clinical resolution. Skin scraping and/or hair plucking were performed 1, 2 and 3 months after the first fluralaner administration. The overall response to therapy was 100%. The majority of dogs (87,1%) had negative skin scrapings as soon as one month after first fluralaner administration.

Twenty-one individuals (12,9 %) (all belonging to group two) needed two months after the initial fluralaner administration to achieve negative scrapings. No side effects were observed.

This study is supported by another recent publication by Fourie et al. (2015) whereby a single oral administration of Bravecto® chewable tablet resulted in a reduction of mite numbers in skin scrapings by 99.8% on Day 28 and by 100% on Days 56 and 84. These findings were statistically superior to monthly dosing of Advantage-Multi (98.0% on Day 28; 96.5% on Day 56; 94.7% on Day 84).

As Fluralaner has been shown to be safe by Walther et al. (2015) when administered orally at overdoses of up to 5 times the maximum clinical dose at 8-week intervals in healthy Beagle dogs, and, at overdoses of 3 times the maximum clinical dose in Collies bearing a homozygous defect of the multi-drug-resistance 1 gene (MDR1  $-/-$ ), the recommended dose of 25mg/kg q 3 months appears ideal for treatment of most cases of demodicosis. As well, currently there appear to be no other drug known interactions of fluralaner with other veterinary medicinal drugs including ivermectin, milbemycin oxime and moxidectin.

At this time, my approach to demodicosis therefore includes the use of fluralaner at 3-month intervals with recheck exam and repeat skin scrapings monthly until 2 negative skin scrapings have been achieved. There appears to be encouraging unpublished findings with other isoxazoline compounds such as afoxolaner (Nexgard®, Merial).

My one concern about the fervent use of isoxazoline compounds is the possibility that we may perpetuate juvenile generalized demodicosis, attributable to a genetically pre-programmed immunologic T-cell defect, by “unintentionally” treating all breeding stock dogs, thereby masking any clinical signs/markers indicative of demodicosis, which are later revealed in client-owned dogs not treated with fluralaner or similar products.

**Amitraz** is still the only product that is licensed for the treatment of demodicosis, although dermatologists tend to double the concentration from 250ppm to 500ppm and dip on a weekly basis. This off-labeled use, along with the need to apply the dip in a well-ventilated area by veterinary personnel wearing protective clothing, the need for the solution to drip-dry on dogs, the drug interaction with other monoamine oxidase inhibitors, the  $\alpha$ 2-adrenergic agonist side effects such as sedation (treated pre- or post application with yohimbine or atipamezole), the adverse effects in humans such as migraine headaches and respiratory problems, have limited its use in current veterinary practices. The use of Preventic® collars (Virbac) with 9% amitraz may be of some benefit in dogs with chronic recurring demodicosis where the underlying etiology cannot be identified.

**Avermectins** (e.g. *ivermectin*) are macrocyclic lactones, which have gain increasing approval in veterinary literature. Ivermectin (e.g. Ivomec®, Eqvalan®) selectively binds to high affinity glutamate-gated chloride channels resulting in increased cell permeability and neuromuscular blocking ultimately causing paralysis and death of the *Demodex* mite. Most mammals are protected from the neurologic effects by active p-glycoprotein pumps located at the brain capillary endothelial cells (blood-brain barrier) that prevent ivermectin from entering the CNS. To monitor for any potential adverse reactions to the ivermectin, it is given in incremental doses orally at 0.1mg/kg for 3 days, increased to 0.2mg/kg for 3 days and finally 0.3mg/kg/day until the patient’s first recheck in 4 weeks or until an adverse reaction is noted (mydriasis, blindness, lethargy, ataxia, lateral recumbency, breathing problems; although reactions have been noted 2-4 months after initiation of treatment). Alternatively, MDR1 (multi-drug resistant) gene testing, is available at Washington State University ([www.vetmed.wsu.edu/depts-VCPL](http://www.vetmed.wsu.edu/depts-VCPL)) and the University of Montreal (David.w.silversides@umontreal.ca) to detect homozygous/heterozygous mutations (*mdr1-1Δ mdr1-1Δ*, *mdr1-1Δ* MDR1) causing a defective p-glycoprotein transport pump rendering the patient sensitive to the CNS effects of ivermectin. This has been detected in up to 35% of herding dogs such as Collies, shelties, Old English Sheepdogs, and other breeds. Note, that several drugs are also known to interfere with the p-glycoprotein pump and hence should not be used in conjunction with ivermectin (e.g. ketoconazole). Lastly, ivermectin needs to be protected from light throughout the treatment period to prevent premature breakdown and decreased efficacy of the active ingredient.

If you have identified an ivermectin-sensitive patient, then **milbemycins** (e.g. *milbemycin oxime*, *moxidectin*) may be a treatment option. Although similar neurotoxicoses have been demonstrated with milbemycins, this appears to be a dose-related effect. With 60-80% efficacy at addressing clinical demodicosis, a dose between 0.5-2 mg/kg/day of milbemycin oxime (Interceptor®) appears to be tolerated by most ivermectin-sensitive patients, although doses of 5-10 mg/kg can still result in neurotoxicity. Successful treatment of demodicosis using once weekly applications (89%) to twice monthly applications (64%) of topical 2.5% moxidectin with 10% imidacloprid (Advantage Multi®) fared well in comparison to 0.5mg/kg PO daily ivermectin (98%) over 4 months. Determining heartworm and MDR1 status prior to treatment, client education, removal of affected dogs from breeding stock, and informed consent by owners regarding knowledge of extra-label use of drugs is imperative in these cases.

### **Additional reading**

- Fourie** et al. Efficacy of orally administered fluralaner (Bravecto™) or topically applied imidacloprid/ moxidectin (Advocate®) against generalized demodicosis in dogs. *Parasites & Vectors* (2015) 8:187
- Gortel** K. Update on canine demodicosis. In: *Vet Clin North Am Small Anim Pract.* 2006;36(1):229-241
- Heine** J, Krieger K, Dumont P, et al. Evaluation of the efficacy and safety of imidacloprid 10% plus moxidectin 2.5% spot-on in the treatment of generalized demodicosis in dogs: results of a European field study. *Parasitol Res.* 2005;97(Suppl 1):S89-96
- Hillier** A, Desch CE. Large-bodied *Demodex* mite infestation in 4 dogs. *J Am Vet Med Assoc* 2002;220: 623-627
- Karas-Tecza** J, et al. Efficacy of fluralaner for the treatment of canine demodicosis. ESVD-ECVD Congress (Krakow, Poland) 2015:126 Abstract in Short Communications
- Kwochka** KW, Kunkle GA, et al. The efficacy of amitraz for generalized demodicosis in dogs: a study of two concentrations and frequencies of application. *Compendium on Continuing Education for the Practicing Veterinarian* 1985;7:8-17
- Mueller** RS, et al. Treatment of demodicosis in dogs: 2011 clinical practice guidelines. *Vet Dermatol.* 2012;23(2):86-96,
- Mueller** RS, Meyer D, Bensignor E, Sauter-Louis C. Treatment of canine generalized demodicosis with a 'spot-on' formulation containing 10% moxidectin and 2.5% imidacloprid (Advocate®, Bayer Healthcare). *Veterinary Dermatology* 2009;20(5-6):441-446.
- Mueller** RS. Treatment protocols for demodicosis: an evidence-based review. *Veterinary Dermatology.* 2004;15(2):75-89
- Paterson** TE, Halliwell RE, Fields PJ, et al. Treatment of canine-generalized demodicosis: a blind, randomized clinical trial comparing the efficacy of Advocate® (Bayer Animal Health) with ivermectin. *Veterinary Dermatology* 2009;20(5-6):447-455
- Scott** DW, Miller WH, Griffin CE. Canine Demodicosis in *Small Animal Dermatology.* 6th ed. Toronto: WB Saunders, 2001;457-476
- Walther** et al. Plasma pharmacokinetic profile of fluralaner (Bravecto™) and ivermectin following concurrent administration to dogs. *Parasites & Vectors* (2015) 8:508