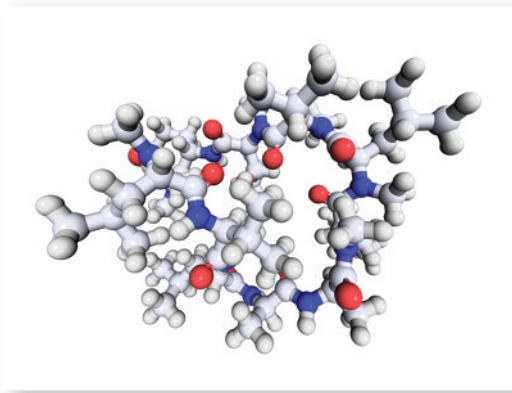


Cyclosporine: Case Studies for Alternative Uses

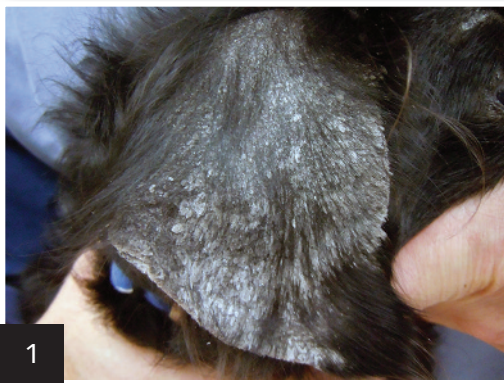
Alexander Werner, DVM, DACVD
 Animal Dermatology Center
 Studio City, California



This is the second installment of a two-part series outlining alternative uses of cyclosporine. The first installment discussed the pharmacology, dosing, and monitoring of cyclosporine (CsA); the following describes three dermatologic conditions with related studies supporting treatment with CsA.

Sebaceous Adenitis

Sebaceous adenitis (SA), an inflammatory disorder of undetermined cause, likely results from the immune-mediated destruction of sebaceous glands and anatomic or cornification defect of the sebaceous duct (causing inflammatory reaction). Autosomal recessive inheritance has been proposed for the standard poodle and Akita; however, the disease has been identified in most breeds. SA is rare in cats. Because of increased antigen-presenting cells in the inflammatory infiltrate associated with gland destruction, CsA may be effective in controlling disease progression.



1

Keratin collaring of hair shafts on patient with SA.

SA has several distinct presentations, but the hallmark clinical sign is adherent crusting of hair shafts with follicular casts, commonly referred to as *keratin collaring* (Figure 1). Over time, the hair coat becomes brittle and thin. SA may be classified into 2 types: long-coated breeds and short-coated breeds.

In long-coated breeds, lesions initially develop on the dorsal muzzle and temporal region, eventually progressing to include the body (dorsally and bilaterally symmetrical) and tail. The most commonly affected of the long-coated breeds are the standard poodle and the Akita; German shepherd dogs,

CsA may have a positive effect on controlling disease progression because of increased antigen-presenting cells in the inflammatory infiltrate associated with gland destruction.

MORE ►

CsA = cyclosporine, SA = sebaceous adenitis



2

SA in a standard poodle; the hair coat has become straight and thin, with accumulation of scale.



3

Scales and crusts on the head of a Vizsla with SA.



4

Perianal fistulae in a German shepherd dog.

Samoyeds, and Havanese are also reportedly predisposed. In standard poodles, initial crusts may be silvery and fine before progressing to tightly adherent and thickened fronds. The normally curly hair coat becomes thinned and straight, starting on the face/pinnae and moving dorsally to neck and trunk (Figure 2). Standard poodles may develop subclinical disease, diagnosed by histopathologic examination of skin biopsy samples. It is currently unknown whether some or all patients with abnormal biopsy findings will develop clinical disease or should be treated with CsA. In the Akita, signs develop in similar areas, compared with the standard poodle, but rapidly generalize with thick, adherent crusts and more severe, erythematous, greasy lesions, often leading to secondary, deep pyoderma. This can result in increased morbidity.

In short-coated breeds (eg, Vizsla, Dachshund), SA presents as discrete annular plaques with alopecia and adherent fine scale. Lesions develop primarily on the body, as well as on the face and pinnae (Figure 3). These patients develop significant scarring but infrequently have concurrent pyoderma.

Multiple SA treatment options have been reported with recent focus on the use of CsA. A partly blinded, placebo-controlled study compared the use of CsA (5 mg/kg PO q24h) and topical therapy (concurrently and separately) for treating this disease and established that both treatment modalities were effective, but a synergistic effect was noted with concurrent administration.¹ In particular, CsA-treated groups (alone or with topical therapy) produced a significant increase in the number of sebaceous glands found in tissue samples after 4 months of therapy.¹ Significant improvements in alopecia and scaling were also reported, especially in the combined topical therapy and CsA treatment group.¹

Perianal Fistulae

Also known as *anal furunculosis*, canine perianal fistula (PAF) is a progressive inflammatory disease producing cutaneous as well as rectal fistulae with ulceration findings somewhat similar to those of Crohn's disease in humans. German shepherd dogs are predisposed. The cause is unknown, but immunohistochemical analysis of tissues from dogs with PAF supports an immune-mediated cause, likely from T-helper cell dysregulation.

Clinical signs of PAF can include perianal licking, tail tenderness, changes in tail carriage, constipation, tenesmus, dyschezia, and mucopurulent discharge from the anal area (Figure 4). Previous management of PAF (eg, immunosuppression and surgical debridement of affected tissues) has resulted in inadequate or temporary relief.

Successful treatment of PAF with CsA has been reported in several studies^{2,3} in which the effective dosage of CsA ranged from 2 mg/kg PO q24h to 10 mg/kg PO q12h. Concomitant administration of ketoconazole to reduce CsA dosage can minimize cost with similar efficacy. Current guidelines recommend treating PAF with CsA (5–7.5 mg/kg PO q24h) and ketoconazole (5–10 mg/kg PO q24h).^{2,3} Once lesions resolve, PAF can be controlled via continued q24h to q48h administration: few cases resolve completely, and daily or alternate daily administration at lower-than-induction dosages of both medications may be

required to prevent relapse. Tacrolimus, a topical macrolide that can be used in conjunction with CsA, has also demonstrated efficacy in the treatment and management of PAF.⁴

Unlike treatment of atopy and SA, when treating PAF serum trough level measurement of CsA can help determine dosage requirements; the measurement should remain between 100 and 300 ng/mL for maintenance (depending on the reference range for the laboratory).⁵

Feline Eosinophilic Skin Disease

Commonly referred to as *feline eosinophilic granuloma complex*, feline eosinophilic skin disease (FESD) is a term for 4 distinct syndromes: eosinophilic plaque, eosinophilic granuloma, indolent ulcer, and allergic miliary dermatitis. FESD lesions are grouped primarily because of clinical similarities, frequent concurrent (and recurrent) development, and positive response to corticosteroids. A genetic predisposition to develop lesions has been documented, but multiple studies have confirmed that the majority of lesions have allergic causes. Each syndrome remains distinct in presentation.

Eosinophilic Plaques

Eosinophilic plaques are alopecic and eroded, well-demarcated annular patches and steep-walled plaques with a glistening or exudative surface and usually occur in the inguinal, perineal, lateral thigh, and axillary regions (Figure 5).

Eosinophilic Granulomas

Eosinophilic granulomas have 5 occasionally overlapping presentations: linear granulomas (ie, individual to coalescing plaques arranged in a linear pattern on the caudal thigh), nonlinear granulomas (ie, individual to coalescing plaques anywhere on the body with an ulcerated and white or yellow cobblestone appearance), asymptomatic lip margin and chin swelling (eg, pouting), footpad swelling (including metacarpal and metatarsal) with pain and lameness, and oral granulomas (ie, ulcerated single to coalescing plaques on the tongue, palate, and palatine arches with a white/yellow cobblestone appearance) (Figure 6).

Indolent Ulcers

Indolent ulcers are large, concave, well-demarcated and indurated, often asymptomatic lesions confined to the upper lips adjacent to the philtrum (Figure 7).

Allergic Miliary Dermatitis

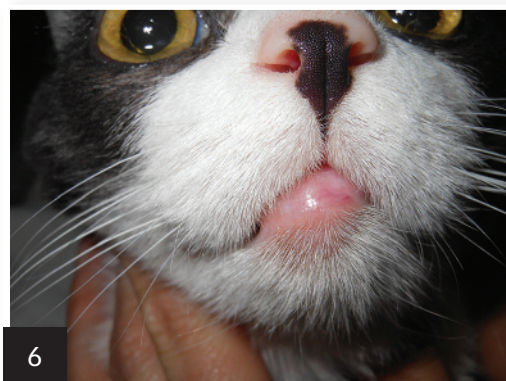
Allergic miliary dermatitis is commonly seen as multiple black/brown crusted and erythematous papules. Lesions are more often palpated than visualized and associated with moderate to severe pruritus.

Several case reports and retrospective and prospective studies have evaluated CsA for treating FESD lesions.^{6,7} Excellent response has been reported with dosages between 5 and 12.5 mg/kg q24h.^{6,7} Although administration of CsA to FESD patients can be successfully reduced to q48h, a higher dosage (7.5 mg/kg) than administered for uncomplicated atopy is often necessary to maintain adequate control of lesions.

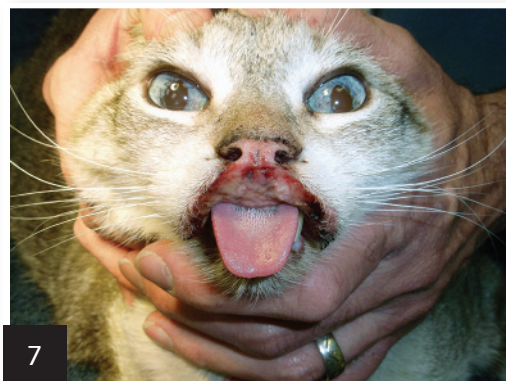
MORE ►



Eosinophilic plaques on the ventrum of a DSH cat.



Pouty chin of eosinophilic granuloma.



Indolent ulcer affecting the entire upper lip.

CsA is a potent medication; like glucocorticoids, it has dosage-dependent immunomodulatory and immunosuppressive activities.

For More



See **Cyclosporine: An Overview of Alternative Use** by Dr. Alexander Werner at cliniciansbrief.com/cyclosporine-overview

Because of increased wandering and hunting behaviors, cats have more potential for pathogen exposure than dogs, making immunosuppressive effects of CsA at higher dosages concerning, especially with concurrent glucocorticoid administration.^{8,9} In one study, 25% of renal transplantation cats receiving CsA developed an infectious disease complication.⁸ Appropriate guidelines for the use of CsA in cats include housing cats indoors, reducing parasite exposure (flea/tick control), feeding cooked or commercial food, monitoring blood trough CsA to maintain levels below 400 ng/mL, and obtaining pretreatment blood work with negative FeLV and FIV and *Toxoplasma* spp titers (if patient has outdoor exposure).

Conclusion

The list of diseases currently treated with CsA is rapidly expanding. CsA is a potent medication; like glucocorticoids, it has dosage-dependent immunomodulatory and immunosuppressive activities. CsA has a specific effect on the activation of T-cells and dendritic cells, as well as more general effects on inflammatory cells and keratinocytes. This makes it ideal for many dermatologic conditions. However, it is not a substitute for proper diagnosis and should not be prescribed without diligence.

CsA is often prescribed with other medications and topical therapy to minimize dosage and (therefore) potential for adverse events. The bioavailability and patient tolerance of CsA can vary widely. Appropriate monitoring (ie, routine blood counts, serum chemistries, urinalysis with culture) with CsA, as with all medications, is necessary. Over time, the dose of CsA may be reduced or even discontinued while still maintaining control. ■ **cb**

See **Aids & Resources**, back page, for references & suggested reading.

CsA = cyclosporine

Surolan®

otic suspension
(miconazole nitrate, polymyxin B sulfate, prednisolone acetate)
Antifungal, antibacterial and anti-inflammatory
For otic use in dogs only

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: SUROLAN contains 23 mg/mL miconazole nitrate, 0.5293 mg/mL polymyxin B sulfate and 5 mg/mL prednisolone acetate. Inactive ingredients are colloidal silicon dioxide and liquid paraffin.

INDICATIONS: SUROLAN is indicated for the treatment of canine otitis externa associated with susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria (*Staphylococcus pseudintermedius*).

DOSE AND ADMINISTRATION: Shake well before use. The external ear should be thoroughly cleaned and dried before the initiation of treatment. Verify that the eardrum is intact. Instill 5 drops of SUROLAN in the ear canal twice daily and massage the ear. Therapy should continue for 7 consecutive days.

CONTRAINDICATIONS: SUROLAN is contraindicated in dogs with suspected or known hypersensitivity to miconazole nitrate, polymyxin B sulfate, or prednisolone acetate. Do not use in dogs with known perforated tympanum. Do not use with drugs known to induce ototoxicity.

WARNINGS: Not for use in humans. Keep this and all drugs out of reach of children.

ANIMAL WARNINGS: Do not administer orally. For otic use only.

PRECAUTIONS: Before instilling any medication into the ear, examine the external ear canal thoroughly to be certain the tympanic membranes are not ruptured. If overgrowth of non-susceptible bacteria or fungi occurs, treatment should be discontinued and appropriate therapy instituted. Long-term use of topical otic corticosteroids has been associated with adrenocortical suppression and iatrogenic hypoadrenalism in dogs. The safe use of SUROLAN in dogs used for breeding purposes, during pregnancy, or in lactating bitches, has not been evaluated.

ADVERSE REACTIONS: In the field study, 161 dogs treated with SUROLAN were included in the safety database. Two dogs experienced reduced hearing at the end of treatment; on follow-up one dog had normal hearing capacity while the other case was lost for follow-up. The owner of another dog reported that on day 4 of treatment, build-up of the medication decreased the dog's hearing. At the end of treatment, this dog had normal hearing as assessed by the investigator. Residue build-up was reported in 1 dog and pain upon drug application in another dog. A total of 161 dogs treated with the active control was included in the safety database and adverse reactions were reported in 8 dogs treated with the active control. One dog experienced reduced hearing at the end of treatment. Residue build-up was noted in 1 dog. Four dogs vomited during treatment. 1 dog showed red pustules on the pinna and head shaking was observed in another dog. Foreign market experience: the following adverse events were reported voluntarily during post-approval use of the product in foreign markets: deafness, reduced hearing, topical hypersensitivity reactions and red blisters on pinna. For a copy of the Material Safety Data Sheet (MSDS), for technical assistance or to report adverse reactions call Vetoquinol USA Inc. at 1-800-835-9496.

PHARMACOLOGY: By virtue of its 3 active ingredients, SUROLAN has antibacterial, antifungal, and anti-inflammatory activity. Polymyxin B sulfate is a broad-spectrum polypeptide antibiotic with activity against both Gram-positive and Gram-negative species. Miconazole nitrate is a synthetic imidazole derivative with antifungal activity and antibacterial activity against Gram-positive bacteria. Moreover, synergistic effects between miconazole nitrate and polymyxin B sulfate have been demonstrated in an *in vitro* study(1). Prednisolone acetate is a glucocorticoid with anti-inflammatory activity. A study performed using an experimentally-induced model of ear inflammation in mice demonstrated the effectiveness of prednisolone acetate in treating ear inflammation either alone or in combination with the other active ingredients of SUROLAN(2).

MICROBIOLOGY: The compatibility and additive effect of each of the components in SUROLAN was demonstrated in a component effectiveness and non-interference study. An *in vitro* study of organisms collected from clinical cases of otitis externa at a veterinary teaching hospital and from dogs enrolled in the clinical effectiveness study for SUROLAN determined that polymyxin B sulfate and miconazole nitrate inhibit the growth of bacteria and yeast commonly associated with canine otitis externa. Furthermore, a synergistic effect of the two antimicrobials was demonstrated. The addition of prednisolone acetate to the combination did not impair antimicrobial activity to any clinically-significant extent.

ANIMAL SAFETY: The following adverse reactions were reported in a study when SUROLAN was administered at 1X, 3X and 5X for 42 consecutive days (6 times the recommended treatment duration) in laboratory Beagles: hypersensitivity reactions which included mild erythema and hyperemia, painful and sensitive ear canals on examination, changes in hematology, clinical chemistry and urinalysis values consistent with the systemic absorption of topical corticosteroids, and veterinary observations of pale ear canals.

EFFECTIVENESS: Of 337 dogs enrolled in the field study, 176 dogs were included in the effectiveness database; 91 were treated with SUROLAN and 85 were treated with an FDA-approved active control. Clinical evaluations of otitis externa included pain/discomfort, swelling, redness, and exudate. A non-inferiority evaluation was used to compare SUROLAN with the active control with respect to each clinical sign of otitis externa and overall clinical improvement. SUROLAN was determined to be non-inferior to treatment with the active control for otitis externa. *Malassezia pachydermatis* and *Staphylococcus pseudintermedius* were identified pre-treatment in at least 10 cases that were clinically responsive to SUROLAN.

Table 1. Mean Percentage of Improvement in Clinical Signs of Otitis Externa

Clinical Sign	SUROLAN N=91	Active control N=85
Pain/discomfort	94.4%	91.7%
Swelling	89.1%	90.5%
Redness	91.2%	86.1%
Exudate	83.1%	82.1%
Overall	96.7%	95.2%

HOW SUPPLIED: SUROLAN is available in 15 mL and 30 mL plastic dispensing bottles with applicator tip for otic use.

STORAGE AND HANDLING: Store at or below 25°C (77°F).

NADA 141-298, Approved by FDA.

Manufactured for Vetoquinol USA Inc. by:
Janssen Pharmaceutica NV

Turnhoutseweg 30

B-2340 Beerse

Belgium

Copyright © 2009, Janssen Animal Health

Date of most recent labeling revision: 09/2009

REFERENCES

1. Pletschmann S, et al. (2009) Synergistic effects of miconazole and polymyxin B on microbial pathogens. *Veterinary Research Communications* 33(6):489-505
2. Bolinder A, et al. (2006) *In vivo* efficacy study of the anti-inflammatory properties of Surolan The Canadian Journal of Veterinary Research 70, 234-236