D - Dermatology

NEW APPROACHES TO THE TREATMENT OF CANINE ATOPY

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Canine atopic dermatitis is a chronic often frustrating disease to treat. In the last few years there have been several new therapies that have been shown to be helpful or possible valuable in managing atopic dermatitis.

Cyclosporine (Atopica®) was initially shown to be effective for treating atopic dermatitis in 2002. (Olivry, Rivierre et al. 2002; Olivry, Steffan et al. 2002) Those along with many other studies have extensively evaluated the drug. It is the first alternative therapy to glucocorticoids that has shown similar efficacy to prednisolone and methylprednisolone. Cyclosporin has multiple effects on the skin immune and inflammatory response. Originally the mode of action was felt to be relatively specific for effects on T helper lymphocytes. Cyclosporin complexes bind calcineurin and inhibit the signal transduction to the nucleus resulting in blocked or impaired synthesis of multiple cytokines, most notably interleukin-2 (IL-2) and inhibits T-cell proliferation and the formation of cytotoxic lymphocytes. Cyclosporine is also thought to inhibit, via suppression of calcium-mediated signal transduction, mast cells and IgE-mediated immediate and LPR reactions. A recent study in dogs showed that suppression of mRNA for IL-2, IL-4 and gamma interferon but not TNF alpha as described in humans.(Kobayashi, Momoi et al. 2006) In additions dogs do not have an up regulation of TGF beta as in man. These results suggest species differences may occur. Multiple studies have demonstrated influences on mast cells, Langerhans cells, keratinocytes, eosinophils and lymphocytes. Cyclosporine has immunosuppressive and antiproliferative affects rather than cytotoxic or myelotoxic effects. It is likely that the numerous disease and types of disease that may respond to cyclosporine attest to the multitude of effects the drug may have.

The dose is 5mg/kg q24h. Once a response is seen then the dose may be tapered. In some cases it is better to continue the induction dose until clinical improvement is complete or reached a steady state of response. Tapering is done by maintaining the dose at 5mg/kg but changing to q48h and with continued response is further tapered to q72 or every q 4-7d dosing. In some cases long term remissions may be seen once the drug is discontinued, though the frequency of this needs to be determined in more controlled study. It make take several months for signs to return and this effect is another way to manage some cases, by going on and off the drug long term. This is another way to keep the costs of therapy within a clients comfort level. Some dogs may end up on relatively low levels of drug long term by doing the tapering or going on an off the drug. This makes the overall cost low enough to have even large dogs that initially may seem to expensive to treat actually respond well at an affordable cost.

Adverse reactions have been reported in a study of up to 268 atopic dogs(Steffan, Parks et al. 2005). The most commonly encountered side effects are vomiting and diarrhea. Vomiting is often short term or administration with food may alleviate it. In other cases temporary concurrent use of metoclopromide 0.2 to 1mg/kg q24h may allow continued use. For diarrhea temporarily stopping the drug then treating again with the addition of metronidazole or fiber to the diet may alleviate the diarrhea. However this has been the most common medical reason the drug has to be discontinued. Hirsutism and gingival hyperplasia have also been seen at the doses used for atopic disease. Hirsutism is often a generalized thickened more dense hair coat often associated with increased shedding. In other cases there are patterns where the hair growth is exceptionally long. This seems to most often affect the paws and head or face region. Papillomatous hyperplasia may also be seen and infrequently is viral and more often bacterial. Bacterial infections may appear as atypical lesions. Nephrotoxicity and hepatic toxicity has not been observed in dogs, as

a significant problem. This is more of a concern when ketoconazole is used for concurrently either for Malassezia or as dose sparing agent. Elevated blood pressure is concern in humans and though rare in dogs should be monitored for. In humans there is an increased risk for malignancy especially skin neoplasia with cyclosporine use.

Topical Immunomodulators (TIMs) are a new class of drugs that have been approved in humans for the treatment of atopic dermatitis. The initial approved formulation, Tacrolimus, has also been shown effective in dogs with atopic dermatitis, especially localized disease.(Marsella, Nicklin et al. 2004; Bensignor and Olivry 2005) Tacrolimus is a 23-member macrolide produced by Streptomyces tsukabaensis and the topical formulation is called Protopic® an ointment available as a 0.1% or 0.03%. The other approved drug in this category is Pimecrolimus (Elidel®) which is an ascomycin macrolactam derivative that acts similar to Tacrolimus. It is used similar to Protopic though studies documenting it efficacy have not been done. No comparisons have been done in dogs but anecdotal reports suggest that in some dogs it is less irritating and the cream base is preferred by some clients.

The TIMs have topical anti inflammatory effects without the atrophogenic effects and metabolic effects of topical glucocorticoids. The mechanism of action is similar to cyclosporine by inhibition of calcineurin, but 10 to 100 times more potent. Large multicenter human studies indicate it is a very safe drug with minimal systemic absorption. However animal studies have shown an increase risk for skin cancers and there is a concern that humans with long term use may also be predisposed to skin cancers including melanoma and possible lymphoma. This led the Food and Drug Administration to include this warning on the label and now recommend these drugs in more limited settings when other forms of therapy have been ineffective.

These drugs are used for localized atopic dermatitis that is not effective to topical glucocorticoids. Initial treatment is a light application of the ointment or cream until it is completely rubbed in twice daily for two weeks. If a response is seen the frequency may be lowered to once daily or less. To date problems other than irritancy have not been noted in dogs.

Interferons (INF) are a group of glycoprotein cytokines produced by a variety of inflammatory cells and fibroblasts that have numerous immunologic effects. There are several recognized interferons and they do vary in their immunologic effects. The initial commercial form of interferon is the recombinant human INF alpha-2b (Roferon-A®) and more recently a veterinary product became available. Carlotti used recombinant feline INF-omega (Virbagen®, Omega) has been shown helpful in an open trial of atopic dogs. A small open pilot trial with canine interferon gamma also suggests efficacy at high doses.(Iwasaki, Park et al. 2005) Interferon alpha (Roferon®) comes as a 3 million IU/ml solution and is diluted in 999ml lactated ringers and then divided into 30 ml ampoules that anecdotally will remain stable if frozen. Once thawed it is kept refrigerated for thirty days. The refrigerated ampoule is then used at 0.33 ml, 1,000IU given orally daily. The oral administration is done by injecting the solution in the buccal cavity as it is believed the absorption is from the upper oral mucosa. Anecdotally they are cases convinced that this low dose regimen if effective and also have used it concurrently with allergen specific immunotherapy. Controlled studies are needed to see if it improves the efficacy of ASIT.

Nutraceuticals and herbal remedies are also being evaluated in management of chronic pruritus and atopic disease. Controlled studies and studies on mechanism are needed. It has been suggested that some ingredients may be helpful but since many new diets have higher levels of omega 3 fatty acids this may also improve these patients.

References

Bensignor, E. and T. Olivry (2005). "Treatment of localized lesions of canine atopic dermatitis with tacrolimus ointment: a blinded randomized controlled trial." Vet Dermatol 16(1): 52-60.

Iwasaki, T., S. Park, et al. (2005). Effect of treatment with recombinant canine IFN-g on the clinical signs, histopathology and Th1/Th2-cytokine mRNA profiles in Shih Tzu dogs and a Basset hound with atopic dermatitis. Advances in Veterinary Dermatology. A. Hillier, A. Foster and K. Kwochka. Oxford, Blackwell Publishing. 5: 82-88.

Kobayashi, T., Y. Momoi, et al. (2006). Cyclosporine inhibits IL-2, IL-4 and IFN-gamma mRNA expression, but not TNF-alpha in canine peripheral blood mononuclear cells. Nt Am Vet Derm Forum, Palm Springs.

Marsella, R., C. F. Nicklin, et al. (2004). "Investigation on the clinical efficacy and safety of 0.1% tacrolimus ointment (Protopic) in canine atopic dermatitis: a randomized, double-blinded, placebo-controlled, cross-over study." Vet Dermatol 15(5): 294-303.

Olivry, T., C. Rivierre, et al. (2002). "Cyclosporine decreases skin lesions and pruritus in dogs with atopic dermatitis: a blinded randomized prednisolone-controlled trial." Veterinary Dermatology 13(2): 77-87.

Olivry, T., J. Steffan, et al. (2002). "Randomized controlled trial of the efficacy of cyclosporine in the treatment of atopic dermatitis in dogs." J Am Vet Med Assoc 221(No 3): 370-377.

Steffan, J., C. Parks, et al. (2005). "Clinical trial evaluating the efficacy and safety of cyclosporine in dogs with atopic dermatitis." J Am Vet Med Assoc 226(11): 1855-1863.

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DEALING WITH MRSA IN SMALL ANIMAL PRACTICE

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Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) infection is now recognised as a worldwide problem in human medicine. Epidemic hospital strains (EMRSA) are a common in human medical institutions and strains that are distributed amongst people in the community (community-acquired MRSA) are being recognised increasingly. The very broad antimicrobial resistance profile of MRSA makes it a major hazard in human hospitals and to vulnerable individuals in the community; it is significant cause of human mortality.[1]

In 1988 colonisation of a cat with MRSA was first recognised when in-contact patients in a geriatric ward developed recurrent MRSA infection[2] and this case demonstrated that transfer from animals to man could occur. There are now many reports documenting transfer of MRSA, most commonly hospital EMRSA, from humans to animals,[3] and colonisation and infection of dogs and cats with MRSA is increasingly recognised in veterinary practice[4], particularly in the USA and UK.

The consequence of the occurrence of MRSA in domestic pets is that practitioners are now obliged to consider more carefully 1) the possibility that animals they are treating may be carriers or infected with MRSA, 2) the consequences this may have for treatment of affected animals and 3) the risks of transfer to other animals and to veterinary staff.

Recognising MRSA Infection and Colonisation in Dogs and Cats

Staphylococcal infection is well-recognised in small animal veterinary practice. Normally *S. intermedius* is the cause and isolates seldom have very broad antimicrobial resistance. The risks to associated humans are very low. *S. aureus* causes similar clinical presentations but infection in pets is much less common. In the past, *S. aureus* strains associated with pet animal infections have often shown a broader range of antimicrobial resistance than *S. intermedius* but with the advent of highly resistant MRSA, *S. aureus* presents a much greater challenge.[4]

In the British Isles, two reports in 2004, provided warning that MRSA infection was becoming a problem in small animal practice. Rich and Roberts[5] reported in 2004 isolation of 95 MRSA from specimens submitted to a veterinary diagnostic laboratory during 2003. In March 2004, Boag *et al.*[6] reported an increase in cases of MRSA infection seen at a small animal referral hospital; 12 cases had been confirmed in dogs and cats over the previous 5-months.

There is now increasing evidence that veterinary staff can become colonised by MRSA at relatively high frequencies and that transfer amongst staff and animals in veterinary practice can readily occur.[3] Furthermore, owners of MRSA-infected animals may be the original source of infection, particularly if they have had contact with human healthcare facilities, or may become colonised by MRSA from their infected or colonised pets. Thus animals that are susceptible to bacterial infection, especially those being treated with antimicrobials, are at risk of acquiring MRSA from owners or veterinary staff and from other MRSA-infected or colonised animals, and may

then be much more difficult or impossible to treat effectively.

Recognition of MRSA infection in pet animals should occur when diagnostic microbiology is carried out on appropriate samples but this is not always the case. Laboratories that are expecting to isolate *S. intermedius* may misidentify *S. aureus* particularly those strains which have very low levels of golden pigmentation. Suspicion should be raised if an isolate reported as *S. intermedius* has a very broad resistance profile, especially if it is resistant to cefalexin. Any case of bacterial infection that does not respond to properly administered antimicrobial drugs or suffers from recurrent infections should also be suspected. If there is doubt, the laboratory should be asked to recheck the identity of isolates or new specimens should be submitted with a request that checks be made for the presence of *S. aureus*.

Treatment of MRSA Infection in Pets

MRSA can be very highly resistant. In some cases there may be no antimicrobials that are effective against them. Fortunately, isolates from animals have generally proved to be susceptible to potentiated sulphonamides and oxytetracycline, and also topical products including fusidic acid and mupirocin.[3] Clindamycin sensitivity is quite common but inducible resistance to this antibiotic has been reported in 71% of 285 MRSA animal isolates and screening for such inducible resistance is recommended if clindamycin is to be used.[7]

There is evidence indicating that when small animals become infected with MRSA, the nasal mucosae commonly become colonised. This colonisation may persist for a substantial time. Thus when animals are found to be infected or colonised with MRSA, the need for decolonisation must be considered. Otherwise the animals may continue to pose a risk to themselves, to other animals and to people who are in contact. No well-established methods for decolonisation have been described but combination of systemic therapy with treatment of mucosal sites with topical antimicrobials to which the MRSA is sensitive may be effective. Fusidic acid has been shown to be effective, at least in the short-term, with *S. intermedius*.[8] Treatment for about three weeks with topical mucosal application twice or three times daily may be effective.

Controlling Transfer of MRSA Infection in Practice

Preliminary data indicate that owners and veterinary staff in contact with MRSA-infected dogs and cats may often be colonised by MRSA. Although in healthy individuals the risk posed by MRSA appears to be no greater than that of methicillin-sensitive strains, the risk of transfer to susceptible animals or people must be considered. There is now abundant evidence that this occurs and infection of animals under veterinary treatment, particularly those with wounds or subjected to surgery, has been documented. In addition, transfer of MRSA to the environment can readily occur and survival of such organisms in the environment for many months is possible.[9]

Thus veterinary surgeons need to monitor possible MRSA colonisation amongst their staff, and MRSA infection and colonisation amongst the animals they treat. Hospital hygiene methods need to be rigorously maintained at a high level of efficiency and when MRSA infection is recognised or suspected, comprehensive disinfection must be carried out. Members of staff need to be given appropriate training so as to understand the risks posed by MRSA and enable them to adopt appropriate disinfection and aseptic techniques. Isolation facilities should be reserved for infected animals or if these cannot be supplied, strict barrier nursing must be maintained.

In the UK, the British Small Animal Veterinary Association has published very useful guidelines for dealing with MRSA in small animal practice at its website (http://www.bsava.com/resources/mrsa/mrsaguidelines/).

References

1. APPELBAUM PC. MRSA - the tip of the iceberg. *Clinical Microbiology and Infection* 2006; **12** Suppl 2: 3-10.

2. SCOTT GM, THOMSON R, MALONEY-LEE J, RIDGWAY GL. Cross-infection between animals and man: possible feline transmission of Staphylococcus aureus infection in humans? *Journal of Hospital Infection* 1988; **12**: 29-34.

3. LOEFFLER A, BOAG AK, SUNG J, et al. Prevalence of methicillin-resistant Staphylococcus aureus among staff and pets in a small animal referral hospital in the UK. *Journal of Antimicrobial Chemotherapy* 2005; **56**: 692-7.

4. DUQUETTE RA, NUTTALL TJ. Methicillin-resistant Staphylococcus aureus in dogs and cats: an emerging problem? *Journal of Small Animal Practice* 2004; **45**: 591-7.

5. RICH M, ROBERTS L. Methicillin-resistant Staphylococcus aureus isolates from companion animals. *Veterinary Record* 2004; **154**: 310.

6. BOAG AK, LOEFFLER A, LLOYD DH. Methicillin-resistant Staphylococcus aureus in small animal practice. Veterinary Record 2004; 154: 411.

7. RICH M, DEIGHTON L, ROBERTS L.

Clindamycin-resistance in methicillin-resistant Staphylococcus aureus isolated from animals. *Veterinary Microbiology* 2005; **111**(3-4): 237-40.

8. SAIJONMAA-KOULUMIES L., PARSONS E., LLOYD, DH. Elimination of Staphylococcus intermedius in healthy dogs by topical treatment with fusidic acid. *Journal of Small Animal Practice* 1998; **39**: 341-7.

9. WAGENVOORT JH, SLUIJSMANS W, PENDERS RJ. Better environmental survival of outbreak vs. sporadic MRSA isolates. *Journal of Hospital Infection* 2000; **45**: 231-4.