

Requirement for additional treatment for dogs with atopic dermatitis undergoing allergen-specific immunotherapy

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Allergen-specific immunotherapy (ASIT) is one of the main treatments for atopic dermatitis in dogs, but it often requires additional treatments such as antibacterial and antifungal therapy for secondary bacterial and yeast infections, or antipruritic drugs to control the clinical signs or treat the adverse effects of the immunotherapy. Twenty-seven dogs enrolled in a study of ASIT were clinically assessed four times over a period of nine months; their requirement for treatment for secondary bacterial and yeast infections, for the administration of glucocorticoids as additional antipruritic therapy, and for the treatment of any adverse effects of the ASIT were evaluated. Twenty (74 per cent) of the dogs were treated for superficial bacterial pyoderma, 18 (66.6 per cent) required treatment for *Malassezia* species dermatitis on one or more occasions, eight (29.6 per cent) required treatment for otitis externa due to *Malassezia* species or bacteria, and eight required glucocorticoids to control their clinical signs. Five (18.5 per cent) of the dogs experienced adverse effects due to the ASIT and two required treatment with antihistamines (H1 receptor antagonists) in order to continue with the ASIT.

ATOPIC dermatitis in dogs has recently been defined as a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical signs, most commonly associated with immunoglobulins (Ig) of the E class (IgE) to environmental allergens (Olivry and others 2001). The disease is very common (Griffin 1993, Scott and others 2001) and allergen-specific immunotherapy (ASIT) is one of its main treatments (Griffin and Hillier 2001).

ASIT is defined as the practice of administering gradually increasing quantities of an allergen extract to an allergic subject to ameliorate the signs induced by the subsequent exposure to the allergen (Olivry and others 2001), and it is considered to be safe and easy to administer. However, adverse effects such as pruritus, urticaria or angioedema occasionally occur (Griffin and Hillier 2001, Scott and others 2001); these signs can be managed with antihistamines given before each ASIT injection (Griffin 1993).

Many drugs have been claimed to be effective in the treatment of atopic dermatitis, including topical and systemic glucocorticoids, ciclosporin, topical tacrolimus, first- and second-generation antihistamines, essential fatty acids, phosphodiesterase inhibitors, leukotriene inhibitors, prostaglandin analogues and inhibitors, immunomodulating antibiotics, Chinese herbal preparations, homeopathic preparations and tricyclic antidepressants. However, a recent evidence-based review provided good evidence for recommending only oral glucocorticoids or ciclosporin and fair evidence for recommending pentoxifylline or misoprostol (Olivry and Mueller 2003). These drugs can be used in conjunction with ASIT or on their own.

Atopic dogs frequently develop secondary bacterial (usually *Staphylococcus intermedius*) or fungal (usually *Malassezia pachydermatis*) infections that may be a consequence of spontaneous or self-induced skin lesions, or may be part of the pathogenesis of the disease by stimulating the immune system and perpetuating the inflammation (DeBoer and Marsella 2001); antibacterial and antifungal agents are commonly used to treat these secondary infections (Olivry and Sousa 2001).

The management of atopic dogs often requires a combined approach, and ASIT, antipruritic drugs and antibacterial and/or antifungal drugs are frequently administered simultaneously to control the disease (Olivry and Sousa 2001). Although the requirement for such combined treat-

ments is common knowledge among veterinary dermatologists, there is little information in the literature about the prevalence of secondary infections in atopic dogs (Scott 1981, Saridomichelakis and others 1999). Moreover, there have been no studies of the frequency with which dogs undergoing ASIT require additional treatments. In the new climate of 'evidence-based' medicine, it is important that primary references are available to substantiate clinical opinion and reinforce anecdotal information.

Between 2001 and 2003, a randomised, prospective, double-blinded clinical study comparing the effectiveness of low dose and standard dose ASIT was undertaken by Colombo and others (2005). The present paper evaluates the requirements of the atopic dogs undergoing ASIT in that study, for additional treatments. The occurrence of secondary bacterial and yeast infections (superficial pyoderma, *Malassezia* dermatitis and otitis externa due to *Malassezia* species or bacteria) was assessed over a period of nine months, and the dogs' requirements for antibacterial and/or antifungal topical and systemic therapy were recorded. The requirements for antipruritic therapy (systemic glucocorticoids or antihistamines) of the dogs with severe clinical signs of atopic dermatitis or adverse effects of ASIT, respectively, were also evaluated.

MATERIALS AND METHODS

Twenty-seven dogs were enrolled in a randomised, prospective, double-blinded clinical study comparing low dose with standard dose ASIT (Colombo and others 2005). The breed, age and sex of the dogs are summarised in Table 1. The product used was an alum-precipitated vaccine (Artuvetrin Therapy, or Artuvetrin Therapy Forte; Artu) containing a mixture of allergens specific for each dog and formulated on the basis of the results of intradermal testing or allergen-specific IgE serology (ASIGES). The dogs receiving the standard dose of ASIT followed the standard protocol recommended by the manufacturer, and the dogs receiving the low dose ASIT received only 0.1 ml at the same standard intervals (Colombo and others 2005).

Clinical assessment

The dogs were examined and scored for cutaneous lesions and pruritus on the day ASIT was begun (day 0), and three

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TABLE 1: Breed, age and sex of the 27 dogs used in the study

Dog	Breed	Age (years)	Sex
1	English setter	2	ME
2	Labrador retriever	3.5	FN
3	German shepherd dog	4	ME
4	German shepherd dog	6	FN
5	West Highland white terrier	2.5	MN
6	Boxer	1	ME
7	West Highland white terrier	2.5	FE
8	Dalmatian	6	FN
9	Staffordshire bull terrier	1	MN
10	Labrador retriever	2.5	ME
11	Labrador retriever	1.5	MN
12	Cavalier King Charles spaniel	5	FN
13	Labrador retriever	6	ME
14	Labrador retriever	5	ME
15	Weimaraner	2	FE
16	Labrador retriever cross	3.5	ME
17	Border terrier	2	ME
18	Flat-coated retriever	1.5	ME
19	Labrador retriever cross	3	ME
20	Shetland sheepdog	8	ME
21	Labrador retriever	1.5	FN
22	West Highland white terrier	3	FN
23	Staffordshire bull terrier	2	MN
24	West Highland white terrier	3.5	ME
25	German shepherd dog	4	FE
26	Newfoundland	2	ME
27	Labrador retriever	2.5	FN

ME Male entire, FN Female neutered, MN Male neutered, FE Female entire

months (day 90), six months (day 180) and nine months (day 270) later. The lesions were scored by using a modification of the 'canine atopic dermatitis extent and severity index' (CADESI) (Olivry and others 1997), developed specifically for these studies (m CADESI) (Colombo and others 2005). Scores were given for erythema, hyperpigmentation and lichenification as clinical signs of atopic dermatitis, and for papular/pustular eruptions and greasy seborrhoea as clinical signs of secondary bacterial and yeast infections, respectively, on 36 different body sites. The lesions were graded on a scale of 0 to 3, 0 indicating none, 1 mild, 2 moderate and 3 severe lesions. Concurrent superficial pyoderma, *Malassezia* dermatitis and otitis externa due to *Malassezia* or bacteria were diagnosed on the basis of clinical signs and cytological examination, as described by Scott and others (2001). Pruritus was assessed by using a scoring system developed specifically for the study, on a 0 to 5 scale (Colombo and others 2005), the Edinburgh pruritus scale.

Additional treatments

Ectoparasite prevention was instituted by treating the dogs once a month with selamectin (Stronghold Spot-on; Pfizer Animal Health) to reduce the possibility of ectoparasites complicating the management of the atopic dermatitis. Secondary bacterial and yeast infections were managed as required; superficial bacterial pyoderma was treated with cefalexin (Rilexine; Virbac Animal Health) at 30 mg/kg twice daily, for four weeks; *Malassezia* dermatitis was treated with a 2 per cent miconazole/2 per cent chlorhexidine shampoo (Malaseb shampoo; Leo Animal Health) initially once or twice weekly, and in dogs suffering from frequent recurrences this treatment was continued throughout the study at weekly or bi-weekly intervals. Refractory cases of *Malassezia* dermatitis were treated with ketoconazole (Nizoral; Janssen-Cilag) at 5 to 10 mg/kg once daily for four weeks.

The dogs' ears were cleaned whenever otitis externa was diagnosed, using a product containing lactic acid, salicylic acid, docusate, propylene glycol, malic acid and benzoic acid (Epi-Otic ear cleaner; Virbac Animal Health) once daily. In dogs that had had frequent recurrences of otitis externa due

to *Malassezia* species or bacteria, ear cleaning was continued throughout the study as required. Otitis externa due to *Malassezia* species was treated with ear drops containing 23 mg/ml miconazole, 5500 iu/ml polymyxin B and 5 mg/ml prednisolone acetate (Surotan; Janssen Animal Health) twice daily for three weeks during the first six months of the study and with a 1 per cent clotrimazole solution (Canesten; Bayer) twice daily for three weeks during the last three months in order to obtain objective final clinical scores, which might have been influenced by the systemic effects of topical preparations containing glucocorticoids. For the same reason, bacterial otitis externa was treated with ear drops containing 5 mg/ml diethanolamine fusidate, 5 mg/ml framycetin, 100,000 U/ml nystatin and 2.5 mg/ml prednisolone (Canaural; Leo Animal Health) twice daily for three weeks during the first six months of the study and with 2.5 per cent injectable enrofloxacin (Baytril injectable 2.5 per cent; Bayer Animal Health) administered topically twice daily for three weeks during the last three months.

In severely pruritic dogs, treatment with systemic glucocorticoids was instituted after secondary infections had been ruled out. Prednisolone was administered orally at the lowest possible anti-inflammatory dose (0.5 to 0.75 mg/kg once daily in the morning tapering to every other day) during the first six months of the study, but was not allowed during the last three months.

The dogs were also monitored for the adverse effects of ASIT (pruritus, urticaria or angioedema) at each ASIT administration, and the requirement for treatment was recorded. Dogs experiencing adverse effects of ASIT were treated, where necessary, with chlorphenamine (Piriton; GlaxoSmithKline) at 0.25 mg/kg twice daily for three days before and 10 days after subsequent ASIT injections. The administration of antihistamine after the ASIT injection was considered to be necessary owing to the slow absorption of the alum-precipitated vaccine. The antihistamine treatment was continued in the same manner until the end of the study, unless the dog had been withdrawn. The reasons for withdrawal were that the dog was experiencing unacceptable discomfort, that it required treatment with glucocorticoid over the last three months of the study, or that it was suffering severe adverse effects of ASIT, or that the owner was not complying with the conditions of the trial.

RESULTS

There were no statistically significant differences between the effectiveness of the standard and low doses of ASIT (Colombo and others 2005), and the data from the two groups were therefore combined.

Secondary infections

The occurrence of secondary infections is summarised in Table 2.

Twenty of the dogs (74 per cent) were diagnosed as having superficial pyoderma, nine of them on only one occasion and 11 on more than one. *Malassezia* dermatitis was diagnosed in 18 (66.6 per cent) of the dogs, as a recurrent secondary infection in seven of them but only once in the other 11. Otitis externa due to *Malassezia* species or bacteria was diagnosed in eight of the dogs (29.6 per cent), seven of them experiencing only one episode and the other having two recurrences. Combinations of these secondary infections were diagnosed in 12 of the dogs (44.4 per cent) at one or more of the examinations.

Six of the dogs (22.2 per cent) did not complete the study. Of the 21 that did 17 (80.9 per cent) were being bathed with the shampoo once or twice weekly at that time to prevent relapses of superficial pyoderma or *Malassezia* dermatitis,

TABLE 2: Occurrence of superficial pyoderma (P), *Malassezia* dermatitis (M) and otitis externa (O) due to *Malassezia* species or bacteria, the use of glucocorticoids (G) and the time and cause of dogs being withdrawn from the study

Dog	Day 0	Day 90	Day 180	Day 270	Withdrawn (day, cause)	Glucocorticoids
1	P, O	M, P	M, O, P		180 E	
2	M, O					G
3			P	P		G
4	P	P	M, O	M, P		
5						
6	M, P				180 E	G
7	P M					
8			O			
9	P	P				
10	P	O, P	M			
11	M, P					
12		M	P			
13	O		M, P			
14	M	M	M	M, P		
15	P	P		P		
16	P		M, P		180 C	G
17		P	P			
18	P		P		180 E	G
19	P	O	P			
20	M	M	P			
21		P				
22				M		G
23	M	M	M	M		
24			M			
25		O			90 C	
26	M	M, P	M, P	P		G
27		M	M, P		180 E	G

E Excessive pruritus, C Compliance poor

and eight (38 per cent) were being treated with the ear cleaner as required to prevent recurrences of otitis externa due to *Malassezia* species or bacteria.

Glucocorticoid requirement

Eight of the dogs (29.6 per cent) required glucocorticoids during the first six months of the study (Table 2); four of them were treated from day 0, and the other four were treated from day 90. Four of the eight completed the study, their glucocorticoid treatment being withdrawn at day 180 as required by the protocol; the other four were withdrawn at day 180, three because they were suffering unacceptable discomfort and required glucocorticoids after day 180, and the other because its owner failed to comply with the protocol.

Treatment of adverse effects of ASIT

Five of the dogs (18.5 per cent) experienced apparent adverse effects after ASIT. Two (7.4 per cent) of them developed urticaria or angioedema and required treatment with chlorphenamine to control these adverse reactions. One of these was withdrawn because it suffered unacceptable discomfort and required glucocorticoids after day 180, but the other successfully completed the study. The other three dogs experienced more severe pruritus after the ASIT injections but did not require treatment. Two of them completed the study but the other was withdrawn for the same reasons. All the dogs experiencing adverse effects were in the group receiving the low dose of ASIT.

DISCUSSION

Twenty of the 27 dogs (74 per cent) were diagnosed with secondary superficial pyoderma, 18 (66.6 per cent) developed *Malassezia* dermatitis and eight (29.6 per cent) developed otitis externa due to *Malassezia* species or bacteria; these conditions required specific treatment on one or more occasions during the nine months. A recent study of the clinical findings in 91 dogs with atopic dermatitis described superficial

pyoderma in 33 per cent of cases, *Malassezia* dermatitis in 2.2 per cent, and otitis externa, consisting of non-exudative, ceruminous and purulent otitis externa, in 47.3 per cent of cases (Saridomichelakis and others 1999). In an older study, which did not comment on *Malassezia* dermatitis, pyoderma was diagnosed in 33 per cent, and otitis externa was diagnosed in 55 per cent of the cases (Scott 1981). Both of these studies were retrospective and secondary infections were reported only when atopic dermatitis was diagnosed. In the present study, the dogs were followed for nine months, making comparisons with previous studies difficult. However, the prevalence of infections secondary to atopic dermatitis is continually changing and it would be expected that the prevalence observed in this study would be higher than the prevalence observed at a single time.

Secondary fungal and/or bacterial infections are common in dogs with atopic dermatitis, and many studies have been conducted to explain the finding. Dogs with the disease have more staphylococcal bacteria per unit area on their skin than healthy dogs, and the absorption of bacterial antigens through the epidermis is increased as a result of mast cell degranulation (Mason and Lloyd 1989, 1995); the adherence of staphylococci to keratinocytes is also enhanced (McEwan 2000, Simou and others 2005). Atopic dogs have also recently been shown to have larger numbers of *M. pachydermatis* yeasts on their skin than normal dogs (White and others 1998), and both humoral and cell-mediated immunological responses to *M. pachydermatis* antigens have been observed (Morris and others 1998, 2002, Nuttall and Halliwell 2001, Chen and others 2002).

In this study, superficial pyoderma was a recurrent problem in 11 of the dogs and episodes of *Malassezia* dermatitis recurred in seven of them, in most cases requiring continuous topical treatment with a 2 per cent miconazole/2 per cent chlorhexidine shampoo throughout the study to try to prevent relapses. Otitis externa due to *Malassezia* species or bacteria recurred after treatment in only one dog. However, the owners of all the dogs that experienced at least one episode continued to use the recommended ear cleaner on a variable but regular basis until the end of the study, treatment which may have contributed to the small number of recurrences.

Eight of the dogs (29.6 per cent) required glucocorticoids to control the signs of pruritus during the initial six months of ASIT; in four of them the treatment could then be discontinued, but three had to be withdrawn because they suffered unacceptable discomfort, and the last dog was withdrawn owing to its owner's poor compliance.

The administration of systemic glucocorticoids might have reduced the effectiveness of the ASIT, because both treatments act on the immune system, particularly on T lymphocytes (Shida and others 2004). This hypothesis has not been tested in dogs, and some authors suggest that glucocorticoids should be avoided in the initial stage of ASIT (Griffin 1993), whereas others consider that they have no influence (Scott 1981). However, some dogs develop severe pruritus and need glucocorticoid treatment, at least initially. It is also possible that by breaking the itch/scratch cycle and reducing cutaneous inflammation in the early stages of ASIT, glucocorticoids might have long-term beneficial effects by preventing the development of chronic cutaneous changes.

Adverse reactions to ASIT have been reported in 11 to 38 per cent of dogs treated with either aqueous or alum-precipitated ASIT, and are most commonly characterised by increased pruritus, urticaria, angioedema and, more rarely, anaphylaxis (Willemse and others 1984, Rosser 1997, Griffin and Hillier 2001). In this study, five of the dogs (18.5 per cent) experienced adverse reactions, two of them developing urticaria and/or angioedema that required treatment with a H1 receptor antagonist in order to continue the ASIT. The other three dogs suffered more severe pruritus, which is dif-

difficult to assess objectively unless it occurs at the time or at the site of the injection, but they continued the ASIT without requiring treatment with an antihistamine. The fact that all five dogs were in the low-dose group was probably due to chance.

In this study the vaccine used for the ASIT contained alum-precipitated allergens, but aqueous allergens are preferred in the USA and are also used in Europe and the UK. The results of this study cannot be extrapolated to treatments with aqueous allergens, which may require different supplementary treatments. Similar prospective studies would be needed to determine whether aqueous allergens might give better control of secondary infections and induce fewer adverse effects.

The results of this study provide the first 'evidence-based' information about the prevalence of secondary infections, poorly controllable signs of atopic dermatitis and adverse effects of the treatment in atopic dogs undergoing ASIT. Such infections and effects require additional treatments to control them, emphasising the importance of managing and controlling secondary infections as part of the long-term management strategy for atopic dogs treated with alum-precipitated allergens. Owing to the small number of dogs, further work is required to confirm prevalences of the complications reported.

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