

Results of allergen-specific immunotherapy in 117 dogs with atopic dermatitis

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The success of the treatment of 117 dogs with atopic dermatitis with allergen-specific immunotherapy for up to 48 months was assessed. An excellent response (remission with exclusive immunotherapy) was recorded in 18 of the dogs, a good response (more than 50 per cent reduction in medication and improvement of clinical signs) was recorded in 57, a moderate response was recorded in 24 and a poor response in 18. The mould antigens in the allergen extract were stored in a separate vial before administration and the success rate of the immunotherapy including mould antigens was much higher than in an earlier study in which mould and pollen antigens had been stored in one vial. The success rate was not affected significantly by the age of the dogs when the disease developed, or by their age or the period for which they had shown clinical signs when the treatment began; it was also unaffected by whether pollens, moulds or dust mites were used as antigens, or by whether the offending allergens had been identified by intradermal testing or by serum testing for allergen-specific immunoglobulin E.

ATOPIC dermatitis is a common disease in dogs (Scott and Paradis 1990). It is most commonly treated with glucocorticoids, antihistamines and fatty acid supplementation (Olivry and Mueller 2003), but the only specific treatment is allergen-specific immunotherapy (Griffin and Hillier 2001). In recent years several studies have described the efficacy of this treatment (Gosselin and others 1983, Willemse and others 1984, Walton Angarano and Macdonald 1992, Scott and others 1993, Mueller and Bettenay 1996, Nuttall 1998, Zur and others 2002), which is not associated with the adverse effects commonly caused by the administration of glucocorticoids and is more effective than antihistamines, fatty acids or shampoo therapy (Paterson 1994, Scott and others 2001, Mueller and others 2004).

In human medicine the success rate of allergen-specific immunotherapy is influenced by factors such as the age of the patient and how long the patient has suffered the disease before the treatment was applied (Des Roches and others 1996, Durham and others 1999). In veterinary medicine, little is known about such factors and the available data are often controversial. Mould proteases have been reported to degrade pollen antigens in allergen extracts (Esch 1992, Rosenbaum and others 1996), and as a result human allergists advise against the use of mixed extracts of pollen and mould antigens (Joint Task Force on Practice Parameters 2003, Nelson 2004). Mueller and Bettenay (1996) reported that the success rate of immunotherapy with extracts containing mould antigens and pollen antigens was very low, but whether this was due to the degradation of the pollen antigens by mould proteases or to other factors is unknown. Because of this finding and the evidence of the degrading activity of mould proteases, mould antigens have been dispensed into a separate vial for the preparation of all allergen extracts including mould antigens in the authors' referral dermatology practice.

The main purpose of this retrospective study was to determine whether the efficacy of allergen-specific immunotherapy with extracts containing mould antigens was higher when the mould spores were stored in separate vials to protect other allergens. In addition, the study aimed to obtain information about the influence of the age of onset of the disease, the period for which the dogs had suffered the disease and their age when immunotherapy was started, the type of test used to identify the offending allergens (serum testing for allergen-specific immunoglobulin E [IgE] or intradermal testing) and the number of allergens included in the extract.

MATERIALS AND METHODS

The study included 117 dogs with atopic dermatitis. The condition was diagnosed on the basis of the dogs' clinical history, a physical examination and the exclusion of differential diagnoses such as adverse reactions to food, scabies or microbial infections (Mueller 2000, Scott and others 2001). The offending allergens were identified by intradermal testing, in vitro testing for allergen-specific IgE, or both.

The intradermal tests were performed by injecting 0.05 ml of aqueous allergen extracts into clipped skin on the lateral thorax as described by Mueller and Bettenay (1996). The reactions were graded from 0 to 4 in comparison with the reaction to a negative control solution consisting of 0.04 per cent potassium phosphate, 0.11 per cent sodium phosphate, 0.50 per cent sodium chloride and 0.40 per cent phenol (Sterile diluent for allergenic extracts; Greer Laboratories) and a positive control, consisting of 0.275 mg/ml histamine phosphate (Histatrol; Center Laboratories). Reactions graded 2 or stronger were considered positive. The concentration of allergen-specific IgE in samples of serum was determined by an enzyme-linked immunoassay in a commercial laboratory (Dermcare-Vet, Brisbane, Australia).

Allergens were included in the extract used for immunotherapy if the results of the intradermal tests correlated well with the dog's clinical history, and 2000 protein nitrogen units (PNU) of each offending allergen were included in the extract used for each dog. When moulds were to be included in the formulation, they were stored in a separate vial from the pollen and house dust mite antigens. When a dog reacted to more than 20 allergens, its owner was given the choice of including only the most relevant allergens (based on the dog's history of exposure and clinical signs) and using one vial (Mueller and Bettenay 1996), or including all the offending allergens and using two vials; in the latter case, two injections were administered to the dog each time.

In the induction period, the dogs received weekly injections with gradually increasing amounts and concentrations of allergens, starting with 0.2 ml of an extract containing between 40 and 580 PNU/ml (depending on the number of allergens included). The maintenance protocol typically involved the injection of 1.0 ml of allergen extract containing between 4000 and 58,000 PNU/ml every three weeks, although the frequency and total dose of the injections depended on the individual dog's response (Mueller and Jackson 2003).

The responses were graded as excellent, good, moderate or poor. An excellent response resulted in complete remis-

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TABLE 1: Numbers of the dogs that had excellent, good, moderate or poor responses to immunotherapy, according to whether they were diagnosed by intradermal testing (ID) or by serum testing for allergen-specific immunoglobulin E (IgE), and overall

Response	ID	IgE	Overall
Excellent	13	5	18
Good	39	14	57*
Moderate	18	6	24
Poor	16	2	18

* Four of the dogs were tested by both methods and are not included in the previous columns

sion with no other medications; a good response led to an improvement in clinical signs and a reduction in medication by more than 50 per cent; a moderate response led to a minor improvement, but the level of medication could not be decreased; a poor response resulted in no clinical change or a deterioration in the condition of the dog. After a follow-up period of at least 12 months, the dogs' owners completed a questionnaire giving details of the duration of the disease before the immunotherapy was instituted, its duration, and its duration before some clinical benefit was observed. The questionnaire was sent out in late spring/early summer to evaluate dogs with seasonal disease at the height of their disease cycle. The level of pruritus was assessed by using a visual analogue scale with one end of the scale indicating no pruritus and the other end severe and constant pruritus. These subjective evaluations by the owners were then quantified. The medications given were recorded before the immunotherapy began and when the questionnaire was completed. When possible, the data obtained from the owners were confirmed by evaluating the dogs' medical records. The age of the dog when the disease began and its current age were determined from the medical records. The number and type of allergens included in the immunotherapy extract and the average intake of prednisolone/prednisone in the month before the immunotherapy began and in the month before the questionnaire was completed were also recorded.

The success rate of the immunotherapy was determined for dogs of different age groups (less than three years of age, three to six years of age and more than six years of age), for the dogs in which the offending allergens were identified either by intradermal testing or by serum testing for allergen-specific IgE, and in dogs in which the disease had been present for different periods before the immunotherapy began (less than one year, one to three years, three to six years and more than six years). Similarly, the success rate of the immunotherapy with the different types of allergens (pollens, moulds and dust mites) was compared; for this comparison, all the dogs receiving an allergen extract containing either pollens, dust mites or moulds were included in the respective group. Furthermore, it was determined how long it took before any benefit of the immunotherapy became apparent and whether there were differences in the time of response in relation to variables such as the type of test and the types of antigen.

Fisher's exact test was used to determine whether there was a difference in success rates between the individual groups, and $P < 0.05$ was considered statistically significant. The test was applied to the dogs that had an excellent response and to the dogs that had either an excellent or a good response.

RESULTS

Of the 117 dogs, 86 underwent intradermal testing, in 27 the offending allergens were identified by serum testing for aller-

TABLE 2: Numbers of dogs that had excellent, good, moderate or poor responses to immunotherapy according to whether they were treated (a) with one vial* with two to 19 allergens, (b) with two vials containing 22 to 29 antigens, or (c) with one vial* and had more than 20 allergenic reactions in an intradermal test

Response	(a)	(b)	(c)
Excellent	18	0	13
Good	50	7	39
Moderate	21	3	18
Poor	18	0	16

* Or treated with two vials if mould antigens were in a separate vial

TABLE 3: Numbers of dogs that had excellent, good, moderate or poor responses to immunotherapy after receiving allergen extracts containing pollens, dust mites or moulds

Response	Pollens	Dust mites	Moulds
Excellent	14	17	2
Good	53	41	11
Moderate	24	18	0
Poor	14	16	2

gen-specific IgE, and in the other four dogs both diagnostic methods were used. The average age of the dogs when the disease began was 8.3 months (range one to 94 months), and their average age when the immunotherapy began was 28.9 months (range six to 149 months).

Details of the success rates and other variables are given in Tables 1 to 7. Eighteen of the dogs (15.4 per cent) had an excellent response and were in complete remission after being treated exclusively by immunotherapy, and 57 (48.7 per cent) had a good response with a more than 50 per cent reduction in medication and improvement of clinical signs; 24 of the dogs (20.5 per cent) had a moderate response and the other 18 (15.4 per cent) derived no benefit from the treatment.

For the dogs with excellent or good responses, there was no significant difference in response between those whose offending allergens had been identified by intradermal testing and those whose serum had been tested for allergen-specific IgE (Table 1).

In the 107 dogs that received either only one vial of allergen extract, or two vials, owing to the separation of the moulds from the pollens and dust mites, the number of allergens included ranged from two to 19 (Table 2); in the other 10 dogs, which received more than one vial owing to the large number of allergens included, the range was 22 to 29. Sixty-eight (63.6 per cent) of the dogs that received fewer than 20 allergens had an excellent or good response, and seven of the 10 dogs that received more than 20 also had an excellent or good response. The difference was not statistically significant. When the 10 dogs that received more than 20 allergens were compared with the 27 that received fewer than 20 but had more than 20 positive reactions on skin or

TABLE 4: Periods for which the dogs received immunotherapy before they showed signs of improvement, depending on whether they received pollens, dust mites or moulds and whether their treatment was based on an intradermal (ID) test or an immunoglobulin E (IgE) test

Period before improvement	Pollens	Dust mites	Moulds	ID	IgE	Total
<2 months	24	18	2	18	7	25
2-5 months	48	44	8	42	14	53
>5 months	18	14	3	14	7	20
No response	14	15	2	15	3	18

TABLE 5: Numbers of dogs that had excellent, good, moderate or poor responses to immunotherapy depending on their age when atopic dermatitis developed

Response	<3	Age (years) 3 to 6	>6
Excellent	11	1	0
Good	37	8	1
Moderate	15	4	1
Poor	13	1	1

TABLE 6: Numbers of dogs that had excellent, good, moderate or poor responses to immunotherapy depending on their age when the treatment began

Response	<3	Age (years) 3 to 6	>6
Excellent	5	7	6
Good	23	21	13
Moderate	8	8	8
Poor	6	8	4

serum testing, the numbers with excellent or good responses were, respectively, seven (70 per cent) and 14 (51.9 per cent), and this difference was also not statistically significant (Table 2).

In terms of the numbers of dogs that had excellent, or good or excellent responses, the success rates with immunotherapy containing pollens, dust mites or moulds were not significantly different (Table 3). In most of the dogs beneficial responses became apparent after two to five months, although some dogs improved more quickly. In 116 of the dogs it was possible to determine how long it took for the immunotherapy to produce an improvement; there were no significant differences between the times taken by the dogs that were treated with pollens, moulds or dust mites, or whose treatment was based on intradermal testing or serum testing for allergen-specific IgE (Table 4).

In the 22 dogs that were still being treated with prednisone/prednisolone at the end of the study, their mean dose rate had decreased from 1.2 mg/kg per week to 0.4 mg/kg per week. It was possible to discontinue the treatment of 18 of the dogs with glucocorticoids during their immunotherapy as a result of their clinical improvement.

DISCUSSION

Seventy-five (64.1 per cent) of the dogs had an excellent or good response to the allergen-specific immunotherapy, a result that is comparable with the results of previous studies with similar evaluation criteria and periods of follow-up. Nesbitt (1978) recorded that 102 (77.3 per cent) of 132 dogs responded favourably, and in a prospective, double-blinded, placebo-controlled study, Willemse and others (1984) reported that 16 (59 per cent) of 27 dogs showed significant improvement. In a retrospective American study, 60 per cent of dogs improved by 50 per cent or more (Scott and others 1993). In a previous study by two of the authors at the same practice, using the same grading system and aqueous allergens, the success rate was slightly lower (Mueller and Bettenay 1996). In a recent retrospective study, 88 (52 per cent) of 169 dogs showed more than 50 per cent improvement and a reduction in the medical treatment required (Zur and others 2002). In other studies, the evaluation criteria were either very different or unclear (Gosselin and others 1983, Scott 1981, Walton Angarano and Macdonald 1992), so that no comparison is possible.

TABLE 7: Numbers of dogs that had excellent, good, moderate or poor responses to immunotherapy depending on the period for which they had suffered atopic dermatitis before the treatment began

Response	<1	Duration of disease (years)		>6
		1 to 3	3 to 6	
Excellent	2	6	2	1
Good	12	18	14	1
Moderate	6	5	6	2
Poor	6	4	2	2

No significant difference was observed between the efficacy of the immunotherapy that was based on allergen-specific IgE testing or based on intradermal testing. In the past, IgE tests have frequently resulted in large numbers of positive reactions, which have been interpreted as due to either increased sensitivity (Sousa and Norton 1990) or false-positive reactions (Griffin and others 1990). The fact that serum tests of dogs with non-atopic skin diseases gave positive reactions to numerous allergens (Griffin 1989) supports the latter possibility. However, allergen-specific immunotherapy has been reported to have the same success rate, regardless of whether the extracts were formulated on the basis of serum IgE tests or intradermal tests (Scott and others 1993, Zur and others 2002). Advances in technology and monoclonal antibodies have improved the correlation between the results of serum IgE tests and intradermal tests (Mueller and others 1999). Nevertheless, it is generally agreed that a diagnosis of atopic dermatitis must be made before any intradermal or serum tests are performed (Mueller and Jackson 2003, Scott and others 2001). However, the allergens to be included in the extract for immunotherapy need to be selected on the basis of the test results and the clinical history of the individual dog (Mueller and Jackson 2003, Scott and others 2001).

Mould proteases have been reported to degrade pollen allergens rapidly when they are stored in the same vial (Esch 1992, Rosenbaum and others 1996), and this is the basis for the recommendation in human medicine to store mould allergens separately from pollen allergens (Joint Task Force on Practice Parameters 2003, Nelson 2004). However, it is not known whether this is due to the destruction of relevant epitopes, thus decreasing the immunogenicity of individual allergens. In a previous study, the success rate of immunotherapy with extracts containing mould antigens was much less than that with extracts containing only pollen or dust mite allergens (Mueller and Bettenay 1996), suggesting that the immunogenicity of extracts containing mould spores may have been reduced. As a result, at the author's practice mould antigens for immunotherapy have been subsequently dispensed in separate vials. In the present study, the success rate of the extracts containing mould antigens was comparable with that of the other types of allergen, suggesting that the separation of the antigens may have prevented them from being degraded.

In a German study the combination of pollens, moulds and dust mites led to a lower success rate than the administration of only one type of allergen (Heil-Franke and Hunsinger 2002), but there was no significant difference between the results obtained with extracts containing exclusively dust mite antigens or exclusively pollen antigens. In a British study, there was no difference between the responses to allergen extracts containing either dust mite antigens or pollen antigens (Nuttall 1998). In the present study there were also no significant differences between the results of immunotherapy with different types of antigen.

In a study by Walton Angarano and MacDonald (1992), a larger volume of allergens led to an increased success rate, but the dogs were followed for only eight months and the difference was not significant. In contrast, three other studies reported a lower response in dogs treated with a larger number of allergens (Nesbitt and others 1984, Heil-Franke and Hunsinger 2002, Zur and others 2002); the studies by Nesbitt and others (1984) and Zur and others (2002) were evaluated statistically. It was not clear whether the lower response rates were due to the dogs reacting to the large number of allergens, or to the quantity of allergens in the extracts used to treat them. Nesbitt and others (1984) suggested that the amount of PNU was more relevant than the number of allergens included in the extract. In the present study, the dogs treated with a large number of allergens were compared first with the dogs treated with a smaller number of allergens, and then with the dogs that had a large number of positive reactions on serum or intradermal testing but were treated only with the allergens that were considered the most relevant for them. The number of allergens included in the extract seemed to have no significant influence on the therapeutic outcome; because the number of allergens was equivalent to a larger number of PNU, this result conflicts with the results of Nesbitt and others (1984). However, more recent studies have had similar results to the results reported here (Walton Angarano and MacDonald 1992, Scott and others 1993, Nuttall 1998).

The age of the dogs when the disease developed, and their age when their treatment began, did not seem to affect the response rate (Tables 5 and 6), in agreement with the results of Mueller and Bettenay (1996), Nuttall (1998) and Zur and others (2002) for the age of onset, and with Nesbitt (1978), Scott (1981), Schulz and Nagylaki (1990) and Mueller and Bettenay (1996) for the age when treatment began. In contrast, Scott and others (1993) reported that dogs more than five years old when the clinical signs developed had a worse prognosis than dogs in which the signs developed earlier. The reason for this difference is not clear. However, in none of the studies was there many dogs in which the disease developed when they were older, and in one of them the poorer response in the older dogs was not statistically significant (Zur and others 2002). Heil-Franke and Hunsinger (2002) reported a lower success rate in dogs between nine and 10 years of age, but in dogs older than 10 years there were increases in the numbers of dogs that responded to immunotherapy and also in the numbers that deteriorated; the authors speculated that an ageing immune system may have been responsible for this finding.

Nuttall (1998) reported that dogs that had shown clinical signs for more than 61 months responded less well to immunotherapy. In contrast, the present study provides evidence that the period for which the dogs had shown clinical signs before their treatment began had no influence on the success rate (Table 7), in agreement with the results of studies by Gosselin and others (1983) and Zur and others (2002).

A rapid improvement with immunotherapy is important for the owner's compliance and has a significant impact on the wellbeing of the animal. The majority of the dogs improved after two to five months, in agreement with the results of Scott (1981) and Gosselin and others (1983). Short and intense courses of immunotherapy (rush protocols) have been shown to lead to a more rapid response in human beings and have been introduced in veterinary dermatology (Macdonald 1999, Mueller and others 2001). In a double-blinded, randomised study, rush immunotherapy led to a more rapid clinical response than conventional immunotherapy (Mueller and others 2004). However, none of the dogs in the present study was treated by a rush protocol.

A reduction or cessation of glucocorticoid therapy is widely accepted as a desirable outcome of allergen-specific

immunotherapy (Scott and others 2001). The average dose of prednisolone was reduced from 1.2 mg/kg per week to 0.4 mg/kg per week, and the number of dogs requiring prednisolone at the completion of the study was reduced to nearly half of the original number, indicating that the immunotherapy had beneficial effects even in the dogs that did not achieve remission. The weekly dose used in most of the dogs was much lower than the dose usually considered to be effective for the treatment of atopic dermatitis (Scott and others 2001), possibly because many of them were also treated with antihistamines and fatty acid supplements, treatments that have been reported to decrease the requirement for glucocorticoids (Paterson 1995, Scott and Miller 1990).

The results suggest that it would be prudent to separate mould antigens from pollen antigens when treating atopic dogs with allergen-specific immunotherapy. The response rate of the dogs treated in this way was better than the response of dogs treated with identical allergens by similar protocols, and in which the improvements were graded in the same way (Mueller and Bettenay 1996); in addition, there is good evidence that mould proteases can degrade pollen antigens (Esch 1992, Rosenbaum and others 1996). Immunotherapy with pollen, mould and dust mite antigens appeared to have the same response rate. The study also provides further evidence that the type of testing (serum testing for allergen-specific IgE or intradermal testing), the age of the dog when the disease develops and when the immunotherapy is introduced, and the period for which it has suffered clinical signs do not influence the therapeutic outcome significantly. Similarly, increasing the number of allergens included did not seem to lead to a significantly higher success rate. On the basis of new evidence from human and veterinary medicine, it may be possible to achieve higher success rates by modifying the treatment protocols (Mueller and others 2001), but further studies will be needed to establish this possibility.

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