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Efficacy of Modified Rush Allergen-Specific Immunotherapy on Canine Atopic Dermatitis

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Abstract : Modified rush ASIT protocol has been performed to identify the ideal schedule that allows the dose considered effective to be reached in the shortest possible time with the fewest adverse effects. Ten atopic dogs of this study includes fulfillment of Favrot's criteria. Offending allergens were identified by the use of IDST. During the induction period, the dogs were received a total of 15 injections. Ten injections were administrated every 30 minutes in a day with gradually increasing amounts and concentrations of allergens, and the last 5 injections were administered every 3 days. Disease severity was quantified by using the canine atopic dermatitis extent and severity index (CADESI). During induction period, reduction rate from baseline scores varied between 1% and 67% and the improvement of ≥ 50% was recorded after induction period of therapy for CADESI-03 score in 6 of the 10 dogs. This study of ten dogs with atopic dermatitis provide evidence for the efficacy and safety of modified rush ASIT for clinical improvement.

Key words **:** dog, atopic dermatitis, house dust mite, modified rush immunotherapy.

Introduction

Canine atopic dermatitis is a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated with IgE antibodies most commonly directed against environmental allergens (4). Symptomatic treatments include antihistamine, fatty acid supplementation, topical shampoos, glucocorticoid and cyclosporine (2,11). The only specific treatment for atopic dermatitis currently available is allergen-specific immunotherapy (ASIT) (3).

ASIT is the practice of administering gradually increasing quantities of an allergen extract to an allergic subject to ameliorate the symptoms associated with subsequent exposure to the causative allergen (9). ASIT requires repeated subcutaneous injections and may take months before clinical improvement can be observed (7). The clinical efficacy of subcutaneous ASIT with standardized allergen extracts for the treatment of canine atopic dermatitis is well documented (6,12,14).

Conventional ASIT is initiated with a low dose of the allergen extract with gradually increasing concentrations over a period of weeks (induction period), followed by long-term administration of high doses of allergen extract at specific regular intervals (maintenance period). Conventional ASIT schedules for the initial phase of incremental doses have the disadvantage of the time needed to reach the maintenance dose, with its attendant costs in terms of time and resources.

Rush ASIT is characterised by a reduced time interval between injections of increasing quantities of allergen, with a consequent decrease in the induction period to one day. However, rush ASIT schedules for subcutaneous allergens appear to be associated with a greater risk of adverse reactions such as severe pruritus and urticaria.

The aims of the present study were to determine the efficacy and safety of modified rush ASIT in the treatment of canine atopic dermatitis. Modified rush ASIT protocol has been performed to identify the ideal schedule that allows the dose considered effective to be reached in the shortest possible time with the fewest adverse effects.

Materials and Methods

Patients and diagnostic criteria

Ten dogs included in this study were patients of the Veterinary Medical Teaching Hospital at Chungnam National University. Diagnosis of canine atopic dermatitis are strongly dependent on acquiring accurate medical histories and assessing the corresponding clinical signs, exclusion of other pruritic disorders such as ectoparasite infestation, cutaneous adverse food reactions, pruritic bacterial folliculitis, *Malassezia* dermatitis and contact dermatitis (15). Canine atopic dermatitis of this study includes fulfillment of Favrot's criteria (1). Owners who selected to have allergen-specific immunotherapy administered to their atopic dogs were given schedule of modified rush immunotherapy. They were informed of the possible adverse effect of ASIT during the induction period.

Allergen preparation and intradermal skin test (IDST)

The allergens used in this study were house dust mites (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*) and yeast (*Malassezia pachydermatis*). All immunotherapy extracts were prepared in house with allergen extracts obtained from Greer Laboratories (Lenoir, USA). Offending allergens were identified by the use of IDST. The IDSTs

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were performed by intradermally injecting 0.05 ml of aqueous allergen extracts at concentrations of 50-100 protein nitrogen units (PNU)/ml into a clipped area of the lateral thorax. Positive control was histamine phosphate 0.0275 mg/ml (Hitatrol; Central Laboratories, Port Washington, USA) and negative control was 0.9% normal saline. The reactions were graded from 0-4 and compared to the reactions measured following challenge with the positive control and negative control. Wheal reactions considered positive responses were greater than grade 2 (median of positive and negative control) (5).

ASIT protocol

During the induction period, the dogs were received a total of 15 injections. Ten injections were administrated every 30 minutes in a day with gradually increasing amounts and concentrations of allergens, starting with 0.05 ml of an extract containing 100 PNU/ml (*D. farina*), 110 PNU/ml (*D. pteronyssinus*) and 2,000 PNU/ml (*M. pachydermatis*). The last 5 injections were administered an extract containing 10,000 PNU/ml (*D. farina*), 11,000 PNU/ml (*D. pteronyssinus*) and 20,000 PNU/ml (*M. pachydermatis*) every 3 days (Table 1). All allergen extracts were administered subcutaneously in the dorsal neck area. The first 10 injections administered rush immunotherapy schedule and the last five injections utilized conventional immunotherapy schedule. A veterinarian was present at all times and continuously monitored the dogs during rush immunotherapy schedules until at least 1 hours after the last injection was administered.

Evaluation of efficacy and safety

Disease severity was quantified by using the canine atopic dermatitis extent and severity index (CADESI). This revised version was found to possess adequate content, construct, criteria, inter- and intraobserver reliability and sensitivity to change to justify its recommendation for assessment of atopic skin lesions in clinical trials (10). The CADESI-03 scores presently consists of the evaluation of the scales were assigned by participating investigators as described. Briefly, the severity scales (0 = none, 1 = mild, 2,3 = moderate and 4,5 = severe) of 4 clinical signs (erythema, lichenification, excoriations and self-induced alopecia) in atopic dermatitis was assessed at 62 sites on the body. Dogs were evaluated prior to the initiation of treatment and at the end of the induction period. Meaningful improvements in clinical signs could be detected during the study dogs were eligible for inclusion only if CADESI score decreased, compared with baseline score, by ≥ 50%.

A veterinarian was present at all times and continuously monitored the dogs during the first day of immunotherapy until at least 1 hour after the last injection was administered. Prior to each injection, heart rates, respiratory rates and rectal temperature were recorded, along with any changes identified during physical examination. When the heart or respiratory rate, rectal temperature increased to greater than the reference range, or abnormalities were detected during physical examination, the subsequent injection was discontinued. Dogs that had increased intensity of pruritus (manifested by frequent scratching or biting) and anaphylaxis as the only adverse effect were treated by administration of prednisolone (Prednisolone inj., 0.5 mg/kg, Sam-Woo Median, Korea) and epinephrine (Epinephrine inj., 0.02 mg/kg, Dai-Han Pharm., Korea).

Statistical analysis

Statistical analysis was performed with SPSS 19.0 for Windows using the Wilcoxon Signed Rank Test. A value of $P < 0.05$ was considered statistically significant.

Table 1. Schedule of modified rush allergen-specific immunotherapy

Injection No.	Time	Total allergen content (PNU)		
		Df	Dp	Mal
1	0 Min	5	5.5	10
2	30 Min	10	11	20
3	60 Min	20	22	40
4	90 Min	40	44	80
5	120 Min	50	55	100
6	150 Min	50	55	100
7	180 Min	100	110	200
8	210 Min	200	220	400
9	240 Min	400	440	800
10	270 Min	500	550	1000
11	4 Day	500	550	1000
12	7 Day	1000	1100	2000
13	10 Day	2000	2200	4000
14	13 Day	4000	4400	8000
15	16 Day	5000	5500	10000

PNU, protein nitrogen units
Df, *Dermatophagoides farinae*; Dp, *Dermatophagoides pteronyssinus*; Mal, *Malassezia pachydermatis*

Results

Patients

The breeds included in this study were Shih-Tzu (6 dogs)

Table 2. Animal characteristics and positive allergen using intradermal skin test

Patient no.	Breed	Sex	Age	Allergen
1	Maltese	MC	6	Df, Dp
2	Shih-Tzu	MC	7	Df, Dp
3	Shih-Tzu	F	10	Mal
4	Shih-Tzu	MC	7	Df, Dp
5	Shih-Tzu	F	3	Mal
6	Shih-Tzu	FS	8	Df, Dp
7	Shih-Tzu	F	10	Df, Dp
8	Maltese	FS	4	Df, Mal
9	Maltese	MC	7	Df, Dp
10	Maltese	F	2	Df, Dp

F, female; FS, female spayed; MC, male castrated
Df, *Dermatophagoides farinae*; Dp, *Dermatophagoides pteronyssinus*; Mal, *Malassezia pachydermatis*

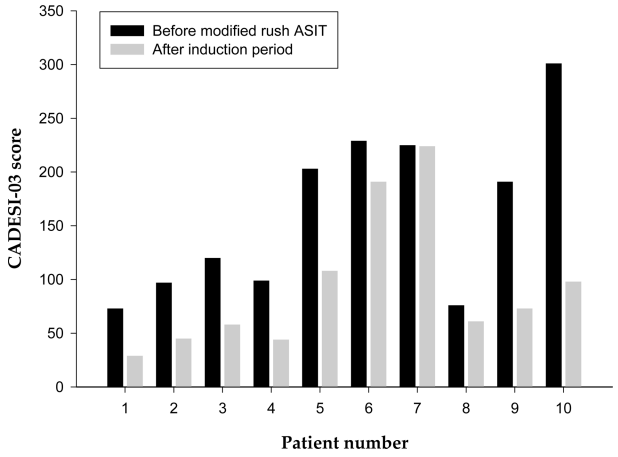

Fig 1. CADESI-03 scores prior to therapy and after induction period of modified rush immunotherapy.

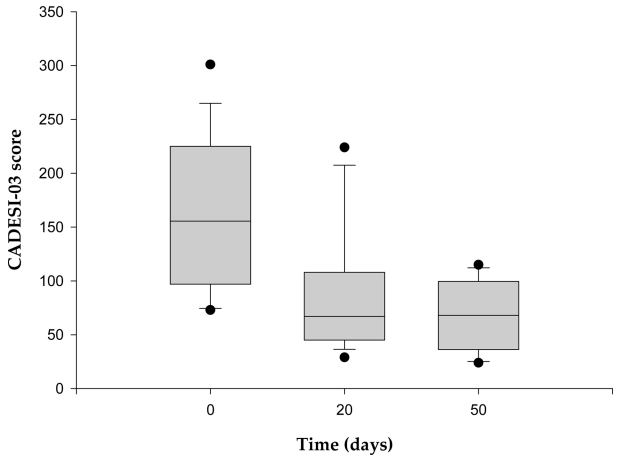

Fig 2. CADESI-03 scores for dogs with atopic dermatitis treated with modified rush ASIT. CADESI scores are significantly different among 0, 20 and 50 day ($P < 0.05$).

and Maltese (4 dogs). Dogs ranged from 2 to 10 years old and the average of age was 6.4 ± 3.2 years. Positive reactions identified by intradermal skin test were *D. farina*, *D. pteronyssinus* and *M. pachydermatis* (8/10 dogs, 7/10 dogs and 3/10 dogs) (Table 2).

Efficacy and safety

Dogs were evaluated prior to the initiation of treatment and at the end of induction period. All dogs receiving modified rush ASIT, CADESI-03 score had decreased, compared with baseline score (Fig 1). The mean CADESI-03 score decreased significantly from 161.4 ± 78.58 to 93.2 ± 65.38 ($P = 0.026$) after induction phase of therapy and 161.4 ± 78.58 to 69.7 ± 35.49 ($P = 0.018$) during maintenance period (Fig 2). During induction period, reduction rate from baseline scores varied between 1% and 67% and the improvement of ≥ 50% was recorded after induction period of therapy for CADESI-03 score in 6 of the 10 dogs (Table 3). Adverse reactions were not observed in these dogs during induction period by use of modified rush immunotherapy.

Table 3. Reduction rate of CADESI-03 score after induction period

Patient no.	CAESI-03 score		Reduction rate (%)
	Before the therapy	After induction period	
1	73	29	60
2	97	45	54
3	120	58	52
4	99	44	55
5	203	108	47
6	229	191	17
7	225	224	1
8	76	61	20
9	191	73	62
10	301	98	67

Discussion

The present study provides evidence for the efficacy of modified rush ASIT as treatment for canine atopic dermatitis. The safety and convenience of the induction period of modified rush ASIT has been verified in this study.

Modified rush ASIT induction protocol was designed for two reasons. Firstly, rapid clinical response could have significant impact on the well-being of the animal. The advantage of modified rush immunotherapy schedule is that it permits patients attained a therapeutically effective response more rapidly than with a conventional schedule. Protocol of this study was associated with minimal inconvenience for owners that have to visit frequently to bring their animals to a dermatologist. The success rate of ASIT in dogs varies from 59 to 72% in the previous study (14,17,19). The results of these studies seem to be influenced by a number of factors including the allergy testing method, the type of allergen and allergen source, induction protocol, dose and concentration of allergen and response criteria. In the present study, 60% of dogs treated with modified rush ASIT were confirmed clinical improvement (reduction rate of CADESI-03 score ≥ 50%).

Secondly, the disadvantages of rush immunotherapy induction schedule has a potentially higher risk of systemic reactions. In a previous study, 8/30 (27%) dogs had adverse effects during or following rush immunotherapy and seven of those dogs were discontinued immunotherapy at high concentrations of allergen extracts (6). The most common adverse reaction is increased pruritus, angioedema, urticaria and anaphylaxis after administration of increasing concentrations of immunotherapy. Modified rush schedule compared with rush schedule reduced complications such as severe pruritus, urticaria and angioderma at high concentrations.

The house dust mites have been identified in previous study as major allergen in canine atopic dermatitis in Korea (16,19). Secondary infection with *Malassezia* is common in dogs with atopic dermatitis and previous studies have shown significantly greater IgE responses in atopic dogs to *Malassezia* antigens (8). Dogs sensitized to *Malassezia* antigens could require specific immunotherapy. Thus, in the present study,

the major allergens utilized in the IDST were two species of house dust mites (*D. farinae* and *D. pteronyssinus*) and yeast (*M. pachydermatis*).

Immunotherapy protocols consist of initial loading dose and maintenance dose. In previous studies, the initial dose of were 100-200 PNU/ml (15) and 200 PNU/ml (6,13,19) during induction period. High allergen dose with a concentration of the allergen 20,000 PNU/ml was applied during maintenance period (6,13,15,19). In the present study, the allergen concentrations for the initial dose and maintenance dose were 100-200 PNU/ml and 10,000-20,000 PNU/ml respectively. However, confirmation of efficacy and safety based on the optimal dose of allergen for immunotherapy schedules is still needed.

The present study has proven that modified rush ASIT might lead to a significant improvement in subjective and objective clinical symptoms after induction period. Modified rush ASIT schedules would have lower rate of adverse effects in comparison with rush ASIT schedules. Obtaining a more rapid clinical response than that of conventional ASIT would have an important impact on the treatment of the atopic dogs and be more convenient to owners.

Modified rush ASIT may be a useful approach to the treatment of canine atopic dermatitis which should be evaluated in further clinical studies. To determine the efficacy of modified rush ASIT in canine atopic dermatitis required to large collectives of atopic patients in the future.

This study of ten dogs with atopic dermatitis provide evidence for the efficacy and safety of modified rush ASIT for clinical improvement. The modified rush ASIT had the advantages of a more rapid clinical response and decreasing of adverse reaction.

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