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Efficacy of 10-Injection Induced Modified Rush Immunotherapy in Dogs with Atopic Dermatitis

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Abstract : Modified rush immunotherapy (IT), by combination of rush IT and conventional IT, provides a faster method to reach maintenance dose, leading to higher patient adherence when compared with conventional IT, decreasing systemic adverse reactions when compared with a standard rush IT. Ten atopic dogs of this study include 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 10 injections. Five 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. The efficacy of 10-injection induced mRIT was assessed using the canine atopic dermatitis extent and severity index (CADESI). During maintenance period, reduction rate from baseline scores varied between 3.2% and 60.9% and the after 6 months of therapy for CADESI-03 score in 6 of the 10 dogs. Adverse reactions were not observed in these dogs during induction period by mRIT with 10 injections. Based on these results, our modified rush IT protocol is considered to be a useful protocol to treat canine atopic dermatitis.

Key words **:** dog, atopic dermatitis, 10 injection, modified rush immunotherapy.

Introduction

Canine atopic dermatitis (CAD) has been recently defined as a genetically predisposed, inflammatory and pruritic allergic skin disease with characteristic clinical features, and is most commonly associated with immunoglobulins of the E class (IgE) to environmental allergens (9). Atopic dermatitis is a very common pruritic skin disease, believed to affect approximately 10% of the canine population (16). It is most commonly treated with glucocorticoids, cyclosporines, antihistamines and fatty acid supplementation, but most of these symptomatic therapy exhibits short- or long-term side effects (11).

Allergen specific immunotherapy (ASIT) is defined as 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 (1). In conventional IT the allergen extract is administered subcutaneously in steadily increasing volumes and concentrations during an induction period of several weeks to months (3). Thus, conventional IT in clinics demonstrate low compliance rates.

In humans rush immunotherapy (RIT) abbreviating the induction period to one or a few days have been reported (17). These protocols lead to a faster response rate although half the patients have been reported to show adverse effects. However, RIT carries an increased risk of systemic reaction. RIT has also been reported in dogs (6,7,13). Dogs are hospitalized for a day and premedicated with an antihistamine. Injections are administered every 30 minutes and the dogs are discharged on the maintenance dose.

Modified RIT (mRIT), by combination of RIT and conventional IT, provides a faster method to reach maintenance dose, leading to higher patient adherence when compared with conventional IT, decreasing systemic adverse reactions when compared with a standard RIT.

This study was designed to assess the efficacy of 10-injection induced mRIT in the treatment of dogs with atopic dermatitis.

Materials and Methods

Animals

The study included ten atopic dogs. The clinical diagnosis of canine atopic dermatitis as based upon the fulfillment by Favrot's criteria (2) and positive intradermal skin test (IDST) results except food allergy and flea bite hypersensitivity by compatible clinical signs. To exclude the food allergy, flea bite hypersensitivity, all dogs were fed an elimination diet during the study period and treated with long-acting anti-flea products such as fipronil or selamectin.

Allergens preparation for treatment

Individual allergens selected for immunotherapy had positive IDST results. The 3 allergens used in this study included house dust mites (HDM) allergen extract containing *Dermatophagoides farina* (10,000 PNU/ml), *Dermatophagoides pteronyssinus* (10,000 PNU/ml) and yeast allergen, *Malasse-*

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zia pachydermatis (20,000 PNU/ml). All the extracts were obtained from Greer Lab (Lenoir, North Carolina, USA) and all allergens are aqueous solutions.

Intradermal skin test (IDST)

IDST was performed by intradermally injecting 0.05 ml of aqueous allergen extracts (*D. farinae* 1:50,000 w/v, *D. pteronyssinus* 1:50,000 w/v, and *M. pachydermatis*, 1,000 PNU/ml) into a clipped area of the lateral thorax. Positive control was histamine phosphate 0.275 mg/mL (Histatrol®, Central Laboratories, Port Washington, USA) and negative control was 0.9% normal saline. Immediate skin test reactions were typically read 15 minutes after injection. Reactions were usually recorded with a score designated as 0, 1, 2, 3, or 4, where 0 is equal to the reaction of the negative control and 4 is equal to the reaction of the positive control. Any reaction of 2 (equal to halfway between negative and positive controls) or greater was regarded as positive (4).

10-injection induced mRIT

The allergens for the atopic dogs were identified by positive IDST results, an appropriate immunotherapy was carried out according to mRIT protocols (Table 1). Patients needed ten injections during the induction period. Five injections were administered every 30 minutes in a day with gradually increasing amounts and concentrations of allergens. The last 5 injections were administered an extract containing between 500 and 10,000 PNU every 3 days. During the maintenance period, some injections needed an extract containing between 5,000 and 10,000 PNU every 7 days since clinical signs disappeared. Subcutaneous injections are the standard route of administration for IT in dogs, which was used in this study.

Clinical evaluations and adverse reactions

The clinical outcome was documented using objective criteria. Canine atopic dermatitis severity was evaluated by the canine atopic dermatitis extent and severity index (CADESI). It was generated by combining an evaluation of the degree of severity (none (0), mild (1), moderate (2-3) and severe (4-5)) for each of the four cardinal signs of CAD (erythema, excoriation, lichenification and self-induced alopecia) on each of 62 different body areas (10). The maximum score of CADESI-03 was therefore 1240. Dogs were evaluated prior to the before administration, after induction period, in maintenance period. A reduction of 50% or higher of CADESI-03 was considered as a major outcome measure of treatment efficacy.

We observed adverse reactions including anaphylaxis, hives, facial swelling, vomiting, diarrhea for the first 30 minutes and preferably one hour after each injection.

Statistical analysis

Changes of CADESI-03 scores before and after mRIT with 10 injections were analyzed by Wilcoxon Signed Rank Test. Statistical analysis was performed with SPSS 19.0 for Windows. A value of $P < 0.05$ was considered statistically significant.

Results

Patients

Ten dogs included in this study. Seven were male and three were female. The breeds included cocker spaniel (3/10, 30%), maltese (2/10, 20%), shih-tzu (2/10, 20%), poodle (2/10, 20%), and mix (1/10, 10%). The age of dogs ranged from 2 years to 8 years and the mean age was 5.9 years. The onset of clinical signs was 1 month to 3 years. With respect to the prevalence of positive IDST reactions, there were a large number of cases including positive responses for *D. farinae* (5 dogs), *M. pachydermatis* (5dogs), *D. pteronyssinus* (4 dogs) (Table 2).

Efficacy and safety

The evaluation of CADESI-03 scores was carried out at the end of induction period and, at the end of maintenance period. All dogs receiving 10-injection induced mRIT, CADESI-03 score had decreased, compared with baseline score (Fig 1). The mean CADESI-03 score decreased significantly from 152.9 ± 70.8 to 110.2 ± 51.4 ($P < 0.01$) after induction phase of therapy and 152.9 ± 70.8 to 86.8 ± 39.6 ($P < 0.01$) during maintenance period. During maintenance period, reduction rate from baseline scores varied between

Table 1. Modified rush immunotherapy schedule with 10 injections

Dose no.	Time interval	Total allergen content (PNU)	
		Mal	Df, Dp
1	30 minutes	50	25
2	30 minutes	100	50
3	30 minutes	200	100
4	30 minutes	400	200
5	30 minutes	800	400
6	3 days	1000	500
7	3 days	2000	1000
8	3 days	4000	2000
9	3 days	8000	4000
10	3 days	10000	5000

Df, *Dermatophagoides farinae*; Dp, *Dermatophagoides pteronyssinus*; Mal, *Malassezia pachydermatis.*

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

No	Breed	Sex	Age (year)	Onset	Allergen
1	Cocker Spaniel	MC	5	3 year	Df, Dp, Mal
2	Cocker Spaniel	MC	4	2 year	Df, Dp
3	Maltese	MC	5	3 year	Df
4	Shih-Tzu	F	8	1 year	Dp
5	Shih-Tzu	MC	6	2 year	Df
6	Maltese	MC	2	1 year	Dp
7	Cocker Spaniel	F	8	1 mon	Mal
8	Mix	MC	4	4 mon	Mal
9	Poodle	MC	6	1 year	Mal
10	Poodle	FS	5	2 year	Df, Mal

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

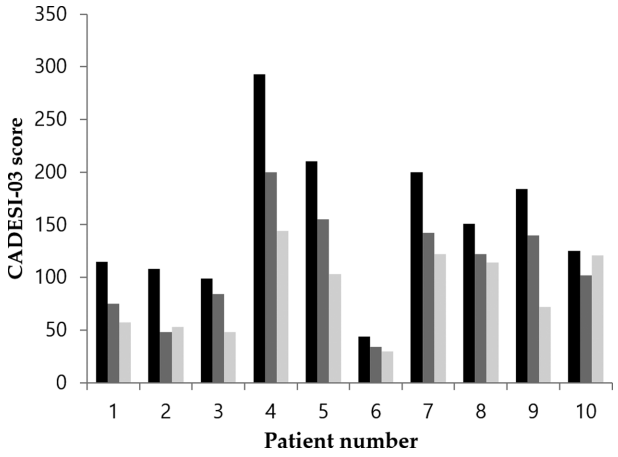

Fig 1. CADESI-03 scores before administration (■), after induction period (■), after 6 months in maintenance period (■) of modified rush immunotherapy with 10 injections.

3.2% and 60.9% and the improvement of ≥ 50% was recorded after 6 months of therapy for CADESI-03 score in 6 of the 10 (Table 3). Adverse reactions were not observed in these dogs during induction period by mRIT with 10 injections.

Discussion

The goal of our protocol modification was to increase compliance while decreasing injections using an initial dose of 25-50 PNU. Five injections of low target dose were administered with rush protocol, and 5 injections of high target dose were followed conventional protocol. Table 1 describes the protocol for our modified RIT.

IT has been used for years to treat dogs with atopic dermatitis. Despite the clear benefits of IT, only a small percentage of allergic patients were subscribed to this treatment. There were two important disadvantages of existing conventional IT protocols. Inconvenience is one of the primary reasons for discontinuation of IT. Some clients may complain of the increased financial burden associated with repeated veterinary visits and give up during the induction period due to frustration, and dogs may object to the injections when they are more frequent. RIT was proposed to reduce the time required to reach the higher maintenance dose, and thus, possible time to maximal efficacy was reduced. It needs at least fifteen injections for an induction period and, an effective and safe RIT protocol has been reported for dogs (5). The optimal dosing interval for loading and maintenance allergen injections has not been established in controlled studies, and can be highly variable between individual patients.

Ten-injection induced mRIT is regarded as an alternative therapeutic protocol. This protocol has little injections comparable with other protocols which needs at least 15 injections during induction phase (5). Thus, little injections during inductions are associated with less labor for veterinarian and time required for owners that spend more time during induction period. In addition, little injections might reduce stress for dogs which do not tolerate injections. This method is also more cost effective.

In this study, a reduction rate of CADESI-03 score ≥ 50% of dogs treated with mRIT was noted in six of 10 dogs ($P = 0.005$). Its efficacy was comparable with previous study, in which 50-100% (9,12,14,18).

Adverse reactions to IT were reported as uncommon to rare in dogs. Previous study reported an incidence of 5% (1), in another study of 100 dogs undergoing ASIT, one suffered from anaphylaxis, five had facial angioedema, and seven other dogs had milder adverse reactions (15). RIT was used to shorten the induction period by giving increasing amounts of allergen. It may be associated with adverse effects such as increased pruritus and anaphylactic reactions. This study had no adverse effect (0/10 dogs).

Ten-injection induced mRIT schedule offers a solution that optimizes convenience and safety. Further studies are needed to define appropriate patients for this form of therapy, the optimal therapeutic target dose. Based on these results, our mRIT protocol is considered to be a useful protocol to treat canine atopic dermatitis.

Acknowledgements

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Table 3. Reduction rate of CADESI-03 score during maintenance period modified rush immunotherapy with 10 injections

No.	Before therapy	After induction	During maintenance (after 6 months)	Reduction rate (%)	Adverse effect
1	115	75	57	50.4	No
2	108	48	53	50.9	No
3	99	84	48	51.5	No
4	293	200	148	50.9	No
5	210	155	103	50.9	No
6	44	34	30	31.8	No
7	200	142	122	39.0	No
8	151	122	114	24.5	No
9	184	140	72	60.9	No
10	125	102	121	3.2	No

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