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Original article

Rush sublingual immunotherapy in canine atopic dermatitis: a prospective pilot study

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Abstract

Twenty dogs with canine atopic dermatitis (CAD) were treated with rush sublingual immunotherapy (SLIT), with a 48 hour build-up phase and 6 months maintenance phase (treated by antigen once every 3-4 weeks). The canine atopic dermatitis extent and severity index (CADESI)-4 was evaluated before treatment (baseline) and after 6 months. An open, non-controlled, non-randomized pilot trial was conducted to assess the effectiveness and safety of rush SLIT for environmental allergen extracts (*Dematophagoides pteronyssinus* and *D.farinae* mix and other). Three dogs dropped out and 17 dogs finished the trial. CADESI-4 at baseline was 60.6±27.1 (range 17-107, n=17). After 6 months of SLIT treatment, CADESI-4 was 37.4±36.0 (range 5-152, n=17) ($p < 0.01$), which was a 38.3% reduction. A significant improvement, defined as a CADESI-4 reduction of > 30%, was observed in 13 out of 17 dogs (76%). A moderate improvement, defined as a CADESI-4 reduction of ≦30%, was observed in 2 dogs (12%). In the other 2 dogs (12%), CADESI-4 worsened or showed no change. However, no severe adverse effects were observed during the trial.

Therefore, rush SLIT against environmental allergen extract for CAD showed effectiveness and safety as evidenced by the reduction of CADESI-4 after 6 months SLIT without severe adverse effects.

Key words: atopic dermatitis, dog, sublingual immunotherapy, rush

Introduction

In sublingual immunotherapy (SLIT), specific allergen extracts are delivered into the oral cavity, as opposed to subcutaneous immunotherapy (SCIT) (Bousquet PJ et al. 2009, Radulovic S et al. 2011). This treatment is widely used in Europe to treat allergic respiratory disease and atopic dermatitis in humans (Cadario G et al. 2007, Bousquet PJ et al. 2009). Furthermore, this treatment is being used to treat CAD in the United States (Olivry T et al. 2015, DeBoer DJ et al. 2016). Compared to SCIT, SLIT is considered a more convenient and safer approach for the treatment of allergies (Bousquet PJ et al. 2009, Radulovic S et al. 2011).

One of the disadvantages of SCIT is that it requires a long period of build-up phase and maintenance phase. There are some rush protocols to shorten the period of build-up phase and move into maintenance phase faster than the current standard protocol (Mueller SR et al. 2001, Trimmer AM et al. 2005).

To improve the current standard protocol, we tested the effectiveness and safety of rush SLIT against

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environmental allergen extract for CAD. CADESI-4 was used to measure effectiveness.

Materials and Methods

Animals

All dogs were diagnosed with canine atopic dermatitis at one clinic (Fujimura Animal Allergy Hospital, Osaka, Japan). The study started in January 2014 and concluded in June 2015 (Table 1).

Table 1. Rush SLIT with 48h build up phase and 6 months maintenance phase.

No.	Breed	Antigen	Adverse Effects	CADESI-4	
				PRE	POST
1	French Bulldog	HDM	Vomiting	77	54
2	Miniature Dachshund	HDM	None	68	38
3	Cavalier King Charles Spaniel	HDM	None	39	12
4	German Shepherd Dog	HDM	Itch	19	ND
5	Golden Retriever	HDM	Itch	83	152
6	Toy Poodle Mix	HDM	None	17	3
7	French bulldog	HDM, 7Grass mix and Velvet	Itch	99	740
8	Shiba Inu	HDM and Cotton	None	75	46
9	Shi Tsu	Mold	Itch	48	24
10	German Shepherd Dog	HDM	None	35	20
11	Shiba Inu	14 Grass mix	None	48	11
12	Toy Poodle	HDM	Itch	103	48
13	Papillon	HDM	None	25	ND
14	Shiba Inu	HDM and 7 Grass mix	None	44	15
15	Miniature Pinscher	HDM	Itch	31	ND
16	Golden Retriever	HDM	Itch	25	27
17	Shiba Inu	HDM	Itch (paw)	71	5
18	Toy Poodle	HDM	Itch	107	61
19	Chihuahua	HDM	Vomiting	54	32
20	Shiba Inu	7 Grass mix, Velvet and JC	Itch	38	14
	Mean ± SD			60.6 ± 27.1	37.4 ± 36.0

PRE: Baseline, POST: After 6 months of treatment
ND: Not determined because Dog No. 4, 13 and 15 dropped out from trial due to lack of followup, poor client compliance or early discontinuation for mechanical reasons
JC: Japanese cedar pollen

Diagnosis of CAD and sensitized allergen

The diagnosis of CAD was made by ruling out other causes of the itch. All dogs received flea control and appropriate treatment for scabies mites. If bacterial pyoderma and yeast (*Malassezia dermatitis*) was diagnosed by cytology, it was treated mainly by shampoo therapy. All dogs underwent an elimination diet using „hypoallergenic" foods (Hill's prescription diet canine z/d Ultra: Hill's Pet Nutrition, Topeka, KS, USA; or Royal Canin Veterinary Diet Sensitivity Control: Royal Canin, Aimargue, France; or Iams Veterinary Formulas FP: Cincinnati, Ohio, USA) for at least 8 weeks. Diagnosis of CAD was based on compatible history and clinical signs of Favrot's criteria (Favrot C et al. 2010). To determine the identity of the sensitized antigens an intradermal allergy test was performed for 24 selected antigens. These antigens were subdivided into six environmental antigen groups (mite mix; *Dermatophagoides farina* and *Dermatophagoides pteronyssinus,* dust, epithelia, tree, weed, grass, mold) and flea antigen. The majority of commercial allergen preparations were purchased from Greer Laboratories (Lenoir, USA). The remainder (Japanese cedar) was obtained from Torii Medicine (Tokyo, Japan). The mixed house dust mite extract was used at a concentration of 1,000 PNU/ml and 200 PNU/ml. House dust extract was used at a concentration of 100 PNU/ml and other antigens were at a concentration of 1,000 PNU/ml. All extracts were prepared and diluted as sterile diluents. During the intradermal allergy test, dogs were premedicated with atropine sulfate (0.04 mg/kg, subcutaneously) and sedated with xylazine (0.15 mg/kg, intravenously).

Canine Atopic Dermatitis Extent and Severity Index (CADESI)-4

CADESI-4 was used to assess lesion severity (Olivry T et al. 2014). A severity of erythema, lichenification, excoriations/alopecia was assessed at 20 body

sites using a scale from 0-3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe). Benchmarks for mild, moderate and severe AD skin lesions are 10, 35 and 60, respectively. CADESI-4 was evaluated before treatment (baseline) and after 6 months treatment. No other therapies (e.g., oral corticosteroids, cyclosporine, or antimicrobial) were allowed during the 6 months treatment period.

Sublingual rush immunotherapy

Twenty dogs were treated with rush SLIT with the following antigens.14 dogs were treated only with HDM (*Dermatophagoides farina* and *Dermatophagoides pteronyssinus*), 1 dog with HDM, 7 Grass mix (*Poa pratensis, Dactylis glomerata, Agrostis alba, Phleum pratense, Anthoxanthum odoratum, Festuca elatior, Lolium perenne*) and Velvet extracts, 1 dog with HDM and Cotton extract, 1 dog with Mold extracts (*Penicillium notatum*), 1 dog with 14 Grass mix extracts (7 Grass mix, Cypress bald, Velvet, Bermuda, Dandelion, Mugwort, Plantain english and Ragweed short), 1 dog with HDM and 7 Grass mix extracts and 1 dog with 7 Grass mix, Velvet and Japanese cedar pollen (Table 1). All antigen extracts were diluted in sterile diluents (containing 0.4% phenol preservative). No antigens contained 50% glycerin saline.

Rush sublingual immunotherapy (SLIT) consisted of a 48 hour build-up phase (Table 2) and 6 months maintenance phase (treated with antigen once every 3-4 weeks). Sublingual administration was performed by a veterinarian. Exclusion criteria included treatment with systemic or highly potent systemic corticosteroids or immunosuppressant agents. For concomitant therapies, temporary use of corticosteroid spray or ointment was allowed.

Results

Out of 20 dogs, 3 dogs (No.4 German Shepherd Dog, No.13 Papillon, and No.15 Miniature Pinscher) dropped out before the end of the 6 months of treatment. The reasons for the drop out were as follows: Dog No.4 showed poor response to SLIT and had to switch to SCIT after 3 months of maintenance phase. Dog No. 13 showed low compliance to the treatment. Dog No. 15 was excluded due to severe itch requiring oral steroid treatment. These 3 dogs were excluded from the data.

CADESI-4 at baseline was 60.6±27.1 (range 17-107, n=17). After 6 months of SLIT, CADESI-4 was significantly reduced to 37.4±36.0 (range:3-152, n=17) ($p<0.01$). This was a 38.3% reduction compared to baseline. The dogs were divided into 3 groups as defined by their improvement rate (Cadario et al. 2007). A significant improvement defined as a CADESI-4 reduction of > 30%, was observed in 13 out of 17 dogs (76%). A moderate improvement defined as a CADESI-4 reduction of ≦30%, was observed in 2 cases (12%). In the last 2 cases (12%), CADESI-4 worsened or showed no change (Table 1).

No severe adverse effects were observed during the trial. In the build-up phase, weak itch was seen in 10 dogs and vomiting was seen in 2 dogs. There was moderate itch on the paws which disappeared in a short time (Table 1). In the maintenance phase, vomiting was seen in 1 dog (data not shown). None of the dogs had to stop the trial due to adverse effects. However, Dog Nos. 2, 5 and 9 received steroid ointment or spray once a week.

Table 2. Sublingual rush immunotherapy protocol 48 hour build-up phase.

	Antigen concentration		
	200 PNU/mL	2,000 PNU/mL	20,000 PNU/mL
Day 1 (9 : 00)	0.05 mL		
Day 1 (10 : 00)	0.1 mL		
Day 1 (11 : 00)	0.2 mL		
Day 1 (12 : 00)	0.4 mL		
Day 1 (13 : 00)		0.05 mL	
Day 1 (14 : 00)		0.1 mL	
Day 1 (15 : 00)		0.2 mL	
Day 1 (16 : 00)		0.4 mL	
Day 2 (9 : 00)			0.05 mL
Day 2 (10 : 00)			0.1 mL
Day 2 (11 : 00)			0.2 mL

PNU: protein nitrogen units

Maintenance phase: SLIT administration threshold concentration on day 2, thereafter each 3-4 weeks. The threshold concentration varied according to dog. Most threshold concentration was 20,000 PNU/mL and administration volume was 0.2 mL (4,000 PNU).

Statistical Analysis

Statistical analysis was performed using a Wilcoxon signed-rank test, and statistical significance was defined as $p<0.01$.

Discussion

In this trial, rush SLIT showed effectiveness for the treatment of CAD. Administration frequency of maintenance phase was once every 3-4 weeks. This administration frequency was based on the maintenance phase of SCIT (Olivry T et al. 2015). In human study, administration frequency of the maintenance phase is once per day (Cadario G, et al. 2007), but, as for our method, an effectiveness for dogs were clear.

There was itch and vomiting in the 48 hour build-up phase and vomiting in the maintenance phase. However, these were not severe. This study shows that rush SLIT is safe. The mild adverse effects can readily be treat dog by owner at home. However, further investigation using a greater sample size may be needed to confirm these results.

Eighty-eight percent of the dogs showed improvement, which was higher than that of a previous trial of 60% (Olivry T et al. 2015). The major difference of two trials is who administered the treatment. In our trial, a trained veterinarian treated the dogs. In contrast, dog owners administered the treatment in the previous trial. This is probably the reason for the difference in improvement rate since a trained professional can more easily handle the dogs.

Dog No. 4 (G. Shepherd) dropped out before end of the trial, because SLIT was not effective and SCIT had to be used. In this case, the dog showed drivel and it appeared that the G. Shepherd was not suitable for SLIT. Moreover, 3 dogs which did not show improvement after 6 months SLIT, did improve with SCIT. But changing from SLIT to SCIT raises concern about adverse effects. Anaphylactic shock was observed in one dog who switched from SLIT to SCIT (data not shown). Also in a previous trial, in dogs which showed no response after SCIT, 49% of them showed improvement after changing to SLIT. These results indicate that, in non-responsive cases, changing from SLIT to SCIT or vice versa might be beneficial.

Conclusion

Rush SLIT is effective and safe for CAD sensitized to environmental allergens. Future research will be needed to compare side-by-side the effectiveness of rush SLIT to SCIT with a large sample size.

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