

Efficacy and safety of rush immunotherapy with alum-precipitated allergens in canine atopic dermatitis

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Key words

Dog, allergy, desensitization, treatment

Summary

Objectives: Canine atopic dermatitis is a very common disease in small animal practice. Its only specific treatment is allergen immunotherapy. In rush-immunotherapy (RIT) increasing doses of allergen extract are injected subcutaneously in short intervals. Maintenance doses are achieved within one day compared to weeks or months with conventional immunotherapy. The aim of this study was to evaluate the safety and efficacy of RIT with alum-precipitated allergens.

Materials and methods: A series of 20 dogs with atopic dermatitis underwent RIT with alum-precipitated allergens. Pruritus and medications at the start of the immunotherapy and 12 months afterwards were compared and adverse effects were recorded. **Results:** Significant improvement in pruritus ($p = 0.0001$) and medication scores ($p = 0.0004$) was noted after approximately 12 months of treatment. The observed clinical response was good to excellent in 70% of the dogs, consistent with other published reports. One dog vomited once during the induction day, with no other clinical problems and completion of the normal protocol. The other 19 dogs showed no adverse effects at all during or after RIT. **Conclusion and clinical relevance:** RIT with alum-precipitated allergens seems to be a safe and efficacious method to treat dogs with atopic dermatitis.

Schlüsselwörter

Hund, Allergie, Desensibilisierung, Behandlung

Zusammenfassung

Gegenstand und Ziel: Die atopische Dermatitis des Hundes stellt eine häufige Erkrankung in der Kleintierpraxis dar. Die einzige ursächliche Therapie ist eine allergenspezifische Immuntherapie. Bei der Rush-Immuntherapie (RIT) werden aufsteigende Dosen von Allergenen in relativ kurzer Zeit bis zur Erhaltungsdosis subkutan appliziert. Die Erhaltungsdosis wird bereits nach einem Tag erreicht, während dies bei der konventionellen Methode Wochen bis Monate dauert. Ziel dieser Studie war, die Sicherheit und Wirksamkeit einer RIT mit alumpräzipitierten Allergenen zu prüfen. **Material und Methoden:** Insgesamt 20 Hunde mit atopischer Dermatitis wurden mit RIT unter Verwendung alumpräzipitierter Allergene behandelt. Pruritus und Medikationen vor und ungefähr 12 Monate nach Beginn der Therapie wurden verglichen und Nebenwirkungen dokumentiert. **Ergebnisse:** Eine signifikante Verbesserung des Juckreizes ($p = 0,0001$) und des Medikamentenscores ($p = 0,0004$) konnte nach einer Behandlungszeit von ungefähr 12 Monaten festgestellt werden. Die klinische Verbesserung war bei 70% der Hunde gut bis hervorragend, was mit bereits publizierten Daten übereinstimmt. Ein Hund erbrach während der Induktionsphase einmalig, konnte aber die RIT ohne weitere Probleme beenden. Die restlichen 19 Hunde hatten keine Probleme während oder nach der RIT. **Schlussfolgerung und klinische Relevanz:** Die RIT scheint eine sichere und wirksame Methode zur Behandlung der atopischen Dermatitis bei Hunden zu sein.

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Wirksamkeit und Sicherheit von Rush-Immuntherapie mit alumpräzipitierten Allergenen bei atopischer Dermatitis des Hundes

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Introduction

Canine atopic dermatitis is a common disease in small animal practice. There is no reliable diagnostic test for this disease, it is rather diagnosed by compatible history, clinical signs and exclusion of other pruritic differential diagnoses (5, 27, 32). Various diagnostic criteria have been reported (5, 28, 30). The newest set by Favrot et al. (5) has the highest sensitivity and specificity of all reported ones, but is still not reliable in every case. Thus, exclusion of differential diagnoses is still essential. After a confirmed diag-

nosis of atopic dermatitis there are two principal therapeutic options, symptomatic treatment and/or allergen-specific immunotherapy (14, 24). The former includes glucocorticoids (systemic or topical), ciclosporin, systemic or topical fatty acids, shampoo therapy, moisturizers, antihistamines, pentoxifylline or some combination thereof (24, 25).

Allergen immunotherapy (AIT) is the only specific treatment for canine atopic dermatitis. During the so-called induction phase, conventional allergen immunotherapy involves injecting increasing amounts and concentrations of allergens subcutaneously over

Table 1 Allergen concentration of the allergen immunotherapy.**Tab. 1** Allergenkonzentration bei der allergenspezifischen Immuntherapie

Parameter	Value
Average amount of allergens in therapy	4
Concentration for pollen allergens	250 NE/ml
Concentration for epithelia allergens	25 µg/ml
Sheep wool	2.5 µg/ml
Concentration for mould allergens	25 µg/ml
Concentration for mite/insect allergens	25 NE/ml

several weeks to months. In the subsequent maintenance phase a fixed dose of allergen extract is administered at regular intervals (7, 14). Adverse effects of immunotherapy occur more frequently in the induction phase. In addition mistakes regarding the amount of allergen injected are more common in the induction phase (7, 19, 29, 32). Rush immunotherapy (RIT) abbreviates the induction phase to one day; injections are administered every 30–60 minutes (17). The goal of RIT is to provide an efficacious therapy with a shorter time to clinical improvement. There are not many reports regarding RIT in veterinary medicine, the number of dogs evaluated is small and all reports evaluated aqueous allergens (15, 17, 19, 26). Data on RIT with alum-precipitated allergens is lacking. The purpose of this study was to evaluate the safety and efficacy of rush immunotherapy with alum-precipitated allergens in a retrospective case series of dogs with atopic dermatitis.

Materials and methods

Study objects and immunotherapy extract

Atopic dermatitis was diagnosed by history, clinical examination, and exclusion of other possible causes including flea bite hypersensitivity and adverse food reaction. The exclusion of the latter two was done by flea control and the exclusive feeding of a novel protein and carbohydrate source for at least 6–8 weeks. The offending allergens were identified with an intradermal test (ARTU Biologicals, Netherlands) or by measurement of allergen-specific

IgE in the serum with an ELISA using a recombinant Fcε-receptor (Heska Corporation, Fribourg, Switzerland). On average four allergens were selected for inclusion in the allergen extract (► Table 1) based on positive results of intradermal or serum testing and the clinical history of the dog as previously described (14). The most frequently used allergen was *D. farinae* (house dust mite), which is present the whole year and is regarded as major allergen in canine atopic dermatitis (9, 12, 16, 22).

Rush immunotherapy protocol

All dogs included in the study were hospitalized in the morning after a general and dermatologic examination, and monitored constantly until one hour after the last allergen injection. Fourteen dogs received an antihistamine and/or prednisolone prior to hospitalization (► Table 4). A prepared emergency kit containing intravenous formulations of adrenaline (Suprarenin® 1 mg/ml, Sandoz, Frankfurt) and prednisolone (Prednisolone ad. us. vet. 10 mg/ml, Albrecht, Aulendorf) was available and the hospital's staffed intensive care unit nearby.

Dogs were treated hourly with an alum-precipitated allergen extract (one solution, ARTU Biologicals, Netherlands) subcutaneously according to a predetermined schedule (► Table 2). Prior to each injection, dogs were examined and different parameters such as respiratory rate, heart rate, pulse quality and rate, mucous membrane colour, capillary refill time and rectal temperature were recorded. If any abnormalities were present, the next injection was postponed for one hour. If the problems resolved, the next injection was given at that time, otherwise the RIT was discontinued, medications were dispensed as needed, the dog discharged and allergen injections continued in form of conventional immunotherapy. After the RIT 1 ml of the AIT solution was given every third week subcutaneously and was further adapted depending on the pruritic behaviour directly after the injection (decrease of the dosage) or before the next injection (increase of the frequency).

Evaluation and efficacy

The study was conducted in 2012 and 2013. Efficacy of AIT was evaluated by regular phone calls and re-evaluations. Those re-evaluations varied from patient to patient depending on the clinical response and complications but occurred on average every 3–12 weeks. Owners graded pruritus at each visit with a visual analogue scale from 0 to 10 and additionally assessed the efficacy of AIT globally by stating no, mild, good or excellent improvement. For the study, pruritus and global assessment before and after one year of AIT were calculated.

Medications given during the 2 weeks before the initial and last visit were recorded using a modification of a medication score previously reported (18). No medication scored 0 points, each topical therapy 5 (with exception of tacrolimus and hydrocortisone aceponate), antihistamine and/or fatty acid supplementation 10 points. If glucocorticoids were used, the score depended on

Table 2 Injection schedule for the first day of rush immunotherapy.**Tab. 2** Injektionsschema für den ersten Tag der Rush-Immuntherapie

Hour	Volume (ml)				
	0.2	0.4	0.6	0.8	1
0	X				
1		X			
2			X		
3				X	
4					X

the daily dose. A dose of > 1 mg/kg of prednisolone scored 40, 0.5–1 mg/kg 30, 0.2–0.5 mg/kg scored 20 and < 0.2 mg/kg or topical hydrocortisone aceponate scored 10 points. Similarly, if cyclosporine was used, a dose of 5 mg/kg daily scored 40, a dose of 2.5 or more, but less than 5 mg/kg 30, a daily dose of 1.25 or more but less than 2.5 mg/kg scored 20 and < 1.25 mg/kg or topical tacrolimus scored 10 points.

Pruritus and medication scores before and after 12 months of RIT were compared with a paired t-test (or in case of data not normally distributed a Wilcoxon matched-pairs signed rank test) and a two-sided p-value of less than 0.05 was considered significant.

Results

Study objects

Twenty dogs (14 male and 6 female) were included in the study. Five of those dogs were Labrador or Golden Retrievers, three were mixed breeds, two were German Shepherd dogs, all other breeds

were only represented once (► Table 3). In 15 dogs (75%) the onset of pruritus was between 1 and 3 years of age. A quarter of the dogs showed seasonal clinical signs, a quarter had clinical signs constantly and the residual half of the dogs was affected all year round, but deteriorated seasonally.

Adverse effects and efficacy

Nineteen dogs (95%) did not have any adverse effects during or after the RIT. One dog (5%) vomited once during the induction phase but could complete RIT with no further problems.

The follow-up time post RIT for all dogs besides one was approximately 12 months. One dog died suddenly 4 months unrelated to the atopic dermatitis and/or desensitization. Mean **pruritus score** went from 7.8 (95% confidence interval [CI] 7.0–8.5) before RIT to 3.1 (CI 1.9–4.3) after RIT. This decrease was significant (Wilcoxon matched-pairs signed rank test, $p = 0.0001$). In 14 of the 20 dogs (70%) the pruritus resolved or the residual pruritus was only mild. Five dogs (25%) were completely itch-free and eight more (40%) showed a decrease of more than 50% in pruritus. One

Table 3 Signalment and pruritus of dogs undergoing rush immunotherapy with alum-precipitated allergens.

Tab. 3 Signalement und Juckreiz der Hunde mit einer Rush-Immuntherapie mit alumpräzipitierten Allergenen

Dog	Breed	Age (years)	Gender ¹	Onset (years)	Course ²	Pruritus before AIT (0 to 10) ³	Pruritus after AIT (0 to 10) ³	Global owner assessment on improvement
1	Small Muensterlaender	5.4	fc	1.5	sw	3	0	excellent
2	Labrador Retriever	7.1	mc	2	sw	8	7	mild
3	West Highland White Terrier	7.8	m	2	ns	9	4	good
4	Mixed breed	6.1	mc	2	sw	8	7	mild
5	Labrador Retriever	7.5	mc	2	s	8	4	good
6	Labrador Retriever	2.1	f	1	sw	8	7	no
7	German Shepherd	5.2	m	1	ns	9	3	excellent
8	Cairn Terrier	7.1	mc	4	sw	9	5	mild
9	Jack Russell Terrier	5.9	f	2	s	5	0	excellent
10	French Bulldog	3.2	mc	1.5	ns	7	7	mild
11	Jack Russell Terrier	10.5	mc	1	s	9	2	excellent
12	Mixed breed	10.1	mc	9	sw	8	0	excellent
13	Magyar Vizsla	7.8	mc	6	s	8	2	excellent
14	Mixed breed	5.1	fc	3.5	ns	8	2	mild
15	Golden Retriever	4.1	m	1	s	10	4	good
16	Golden Retriever	9.1	mc	6	sw	9	1	excellent
17	Afghan	2.1	m	1	sw	7	0	excellent
18	Havanese	5.1	m	1.5	ns	7	4	excellent
19	Bullterrier	4	f	3	na	8	0	good
20	German Shepherd	5,1	fc	1.5	sw	7	3	good

¹ f = female, m = male, c = castrated

² sw: pruritus during the whole year but seasonally worse; s: pruritus only during some months of the year; ns: non seasonal; na: not available

³ Pruritus before AIT: pruritus before desensitization (begin of the study); pruritus after AIT: pruritus after one year of desensitization

Table 4 Medication overview.

Tab. 4 Überblick zur Medikation

Dog	Prednisolone (mean dose in mg/kg/day)		Topical tacrolimus (T), ear medication (EM), hydro-cortisone aceponate (HA)		Antihistamines (AH)		Shampoo (S), lotion (L) or ear cleaner (EC)		Oral (OFA) or topical fatty acids (TFA)	
	Pre AIT	Post AIT	Pre AIT	Post AIT	Pre AIT	Post AIT	Pre AIT	Post AIT	Pre AIT	Post AIT
1										
2			T, EM, HA	HA			S, EC	S, EC	TFA	TFA, OFA
3					AH		S	S	TFA	
4	0,2				AH	AH	S		TFA	
5			HA	HA	AH	AH	S, EC	EC		
6		0,1	EM		AH	AH	S, EC	EC	OFA	OFA
7							S, EC	S	TFA	
8	0,1	0,1	HA		AH		S, EC		OFA	
9			HA		AH				OFA	
10	0,3	0,5	HA		AH	AH	S, EC	S, EC		TFA
11				HA	AH	AH	S, L	S		
12	0,1		HA		AH	AH	S, EC	S	OFA	OFA
13	0,16		HA		AH		S		OFA, TFA	TFA
14							S	S		
15			HA	HA	AH	AH	S, EC	S, EC	TFA	
16							S, EC	S, EC	TFA	
17	0,12	0,05	HA				S, EC	S, L	OFA, TFA	TFA
18	0,08		HA	HA	AH	AH	S, L	L		
19		0,17			AH		S			
20			HA		AH	AH	S, EC	EC	OFA	OFA

Before AIT: before desensitization (begin of the study); after AIT: after one year of desensitization

dog did still have severe pruritus (5%). **Medication scores** decreased significantly from 31 (CI 24–38) to 18 (CI 12–24) (Wilcoxon matched-pairs signed rank test, $p = 0.0004$).

Concurrent medications before and after AIT are listed in ► Table 4. Most dogs received less medications after AIT than before. Two dogs (10%) did not receive any additional medications, in eight dogs (40%) the medication score improved by more than 50%. More than one third of the dogs (7/20) were on oral prednisolone at various doses before AIT, after AIT one quarter (5/20) of the dogs received oral glucocorticoids. Similarly, more than half of the dogs (11/20) were on topical hydrocortisone aceponate before rush AIT, after AIT a quarter (5/20) of the dogs received this topical glucocorticoid. When combining pruritus and medication, two dogs (10%) did not receive any medications and were completely free of pruritus, 10 dogs (50%) improved by more than 50% in pruritus or medication score or both. In dogs with an improvement of > 50% in only one parameter, the other one improved as well or stayed approximately the same. The improvement of AIT

was considered by owners to be good to excellent in 14 dogs (70%) and mild in 5 (25%).

Discussion

Twenty dogs with atopic dermatitis underwent RIT with alum-precipitated allergens. Adverse effects were only observed in one dog (which completed the RIT nonetheless) and the observed clinical response to AIT was comparable to that reported in the literature (14).

Allergen immunotherapy is a safe and efficacious treatment option for canine atopic dermatitis with a reported success rate of 45–100% (2, 23, 29, 31). The mechanism of action is not completely elucidated. After one allergen injection a decreased activity and enzyme production of mast cells and basophils was seen in humans. In humans and dogs the pruritus threshold was increased and specific regulatory T (T_{reg}) cells producing interleukin-10

Table 5 Medication score before and after 12 months of rush immunotherapy (RIT).**Tab. 5** Medikamentenscore vor und 12 Monate nach der Rush-Immuntherapie (RIT)

Dog	Medication score	
	Before RIT	After RIT
1	0	0
2	45	35
3	20	5
4	40	10
5	30	25
6	40	35
7	15	5
8	50	10
9	30	0
10	50	45
11	20	25
12	40	25
13	50	5
14	5	5
15	35	30
16	15	10
17	45	25
18	40	25
19	15	10
20	40	25

(IL-10) were induced (1, 11). However, a decrease of allergen-specific serum IgE with a corresponding increase in blocking IgG antibodies (IgG1 and IgG4) is only seen after months to years of therapy (6, 8, 10, 11, 13, 26).

With conventional AIT it can take up to one year before improvement of clinical signs (29). In humans the goal of RIT is a more rapid alleviation of clinical signs and possibly a higher success rate. In dogs a double-blinded study comparing rush and conventional immunotherapy with aqueous allergens showed a shorter period to maximal improvement with RIT than with conventional immunotherapy, but the difference was not statistically significant (19). It was impossible to judge the time to maximal clinical improvement in our study and a control group was lacking, but the efficacy of this treatment after approximately 12 months of therapy seems comparable to what is published in the literature.

In two previous studies (15, 19) evaluating RIT in dogs, adverse effects were not reported although Mueller et al. (19) premedicated the patients either with glucocorticoids or antihistamines prior to the trial. In another pilot study (17) adverse effects occurred in a

quarter of the dogs and included oedema, wheal formation and increased pruritus, but injections were administered intradermally and not as in the other studies subcutaneously (15, 19). Intradermal injections of allergens may have a higher rate of adverse effects than subcutaneous AIT (3). In our study one patient vomited once during the first day of treatment, but could complete the induction period of RIT. If the vomiting was due to the allergen injections or other reasons is impossible to say, but the dog showed no further adverse effects with subsequent injections.

For conventional immunotherapy with the alum-precipitated allergens used in this study, the manufacturer recommends five injections initially 14 days and then 21 days apart increasing from 0.2 ml to 1.0 ml, reaching maintenance dose after 64 days. The time to final dose thus was decreased by 9 weeks. The additional costs of hospitalisation for RIT need to be balanced against the cost of four individual visits for allergen injection. In addition, other benefits such as potential earlier benefit need to be balanced against the risk of nosocomial infections during hospitalisation in each individual patient for each practice.

Many dogs on AIT in this study received concurrent antipruritic therapy. Multimodal therapy is commonly needed in canine atopic dermatitis (4, 24, 25). However, after rush AIT in most dogs those were restricted to medications with few and mild adverse effects. Only one quarter of the dogs received oral glucocorticoids at lower doses. In all of those dogs the prednisolone dosage decreased with AIT. This decrease in medication dose may be interpreted as a positive effect of the AIT, however, this was a retrospective study without control group. To avoid seasonal influences on the results, almost all dogs (95%) were evaluated after approximately one year on therapy, thus the influence of seasonal variations was minimized but other factors also may have influenced the need for medical therapy. In veterinary dermatology the effect of antipruritic medications on the success rate of AIT is not well established. Particularly systemic glucocorticoids could influence the outcome of immunotherapy. However, such drugs may be necessary due to the patient's intense pruritus. If glucocorticoids dosages are kept low and the course of medication is short (over a few days), it probably does not affect the outcome of desensitization (7).

Conclusion for practice

As a conclusion this study provides evidence that rush immunotherapy with alum-precipitated allergens seems to be safe. The evidence for efficacy is more limited due to the retrospective nature of the study and the concurrent medications tailored to the individual patient's needs, but the number and dose of concurrent medications could be decreased in most dogs and the degree of improvement corresponds to other retrospective studies in the literature. Further studies are needed comparing the efficacy of rush AIT with alum-precipitated allergens and to identify factors influencing treatment outcome in prospective, double-blinded and randomised protocols.

In contrast to most studies on AIT in veterinary medicine, in our study alum-precipitated and not aqueous allergens were used. In humans, alum-precipitated allergens show slower allergen release, increased immunogenicity, decreased allergenicity, less adverse effects, a higher concentration of blocking antibodies, and fewer needed injections than aqueous allergens (20, 21). It is not clear, if these findings also hold true in veterinary medicine. In dogs comparative studies are rare and RIT has not been reported with alum-precipitated allergens.

Conflict of interest

The intradermal test solution used to determine the allergen extracts for the patients in this study was supplied by ARTU Biologicals, Netherlands. No other conflict of interest was present.

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