

Rush allergen specific immunotherapy protocol in feline atopic dermatitis: a pilot study of four cats

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Abstract Rush immunotherapy has been shown to be as safe as conventional immunotherapy in canine atopic patients. Rush immunotherapy has not been reported in the feline atopic patient. The purpose of this pilot study was to determine a safe protocol for rush immunotherapy in feline atopic patients. Four atopic cats diagnosed by history, physical examination and exclusion of appropriate differential diagnoses were included in the study. Allergens were identified via liquid phase immunoenzymatic testing (VARL: Veterinary Allergy Reference Labs, Pasadena, CA). Cats were premedicated with 1.5 mg triamcinolone orally 24 and 2 h prior to first injection and 10 mg hydroxyzine PO 24, 12 and 2 h prior to first injection. An intravenous catheter was placed prior to first injection. Allergen extracts (Greer Laboratories, Lenoir, North Carolina) were all administered subcutaneously at increasing protein nitrogen units (pnu) every 30 minutes for 5 h to maintenance dose of 15,000 pnus ml⁻¹. Vital signs were assessed every 15 minutes. Two cats developed mild pruritus and the subsequent injection was delayed 30 minutes. No changes in either cat's vital signs were noted, nor was there any further pruritus. All four cats successfully completed rush immunotherapy. Two cats developed a dermal swelling on the dorsal neck one week later. In these four cats, this protocol appeared to be a safe regimen to reach maintenance therapy. A larger sample of feline patients is needed to determine the incidence of adverse reactions and to follow the success of ASIT based upon this method of induction.

INTRODUCTION

Feline dermatitis that responded to hyposensitization and was thus characterized as atopic dermatitis was first reported in 1982.^{1,2} Clinical signs of feline atopic dermatitis include evidence of self trauma, noninflammatory alopecia, miliary dermatitis, otitis, and eosinophilic granulomas. Although many of these lesions are secondary to pruritus, some owners do not recognize that their cat is pruritic. The diagnosis of feline atopic dermatitis is based upon clinical history, physical examination and the exclusion of other diseases including flea related disease, food adverse reactions, dermatophytosis and other ectoparasites.^{1–3} Specific allergy testing may be performed via intradermal skin (IDST) or serum IgE testing.^{3–5} Allergy testing cannot confirm a diagnosis of atopic dermatitis; it merely identifies specific potential allergens to include in immunotherapy.

Allergen specific immunotherapy (ASIT) has been shown to be beneficial as a treatment for feline atopic dermatitis.^{1–5} Conventional ASIT requires a prolonged traditional induction period. While rush allergen specific immunotherapy (RIT) is a technique of advancing an allergic patient to a maintenance dose of an extract over a shorter period of time than that required for the traditional induction period.^{6–8} An effective and

safe RIT protocol has been reported for canines and humans.^{6–8} Additionally, in one blinded study comparing conventional ASIT and RIT in the canine, RIT was associated with a higher success rate than conventional ASIT.⁸ However, RIT has not been reported in the feline atopic patient.

Traditional ASIT, although effective, is associated with multiple potential impediments. Successful completion of the prolonged induction period requires both client and patient compliance.⁹ Clients may give up during the induction period due to frustration and cats may object to the injections when they are more frequent. Although the true impact of missed injections on the overall success rate of ASIT is unknown, missed injections may increase the failure rate and the incidence of adverse reactions. Multiple errors in the frequency and volume of shot administration may occur during the induction period due to client confusion. Additionally, some clients may be physically unable to administer the injections to their pets and may require help from their veterinarian or friend. Avoiding the induction period and proceeding directly to a consistent maintenance period would avoid or lessen all of the above mentioned obstacles.

In both humans and canines, RIT is associated with a low incidence of adverse reactions. Adverse reactions reported include localized injection site reactions, localized or generalized pruritus and anaphylaxis. Premedication of both human and canine patients further decreases the incidence of adverse reactions.^{6–8}

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Table 1. Patient signalment and presenting clinical signs

Cat	Age (year)	Breed	Gender	Pruritus score (+)	Clinical lesions
1	8	DSH	FS	10	Barbered alopecia, crusted milia
2	2	DSH	FS	4	Barbered alopecia
3	1.5	DSH	MN	7	Barbered alopecia, crusted milia
4	3	DSH	FS	10	Alopecia, erythroderma, crusted milia

FS, female spayed; MN, male neutered; DSH, Domestic Short Hair. Pruritus score is based on asking the client to assign a numerical value to their cat's level of pruritus based on a scale of 0–10, with 10 representing continuous pruritus and 0 representing a comfortable state.

Table 2. Breakdown of allergens by groups included in treatment sets

Cat	Trees	Weeds	Grasses	Epithelia	Insects	Moulds	House dust mites	Total no. allergens in treatment set
1	3	6		1				10
2	2	5	1	1	1		1	11
3	3	2		1				6
4	3	5	2				1	11

The purpose of this pilot study was to develop and evaluate the safety of a RIT protocol for feline atopic patients.

MATERIALS AND METHODS

Felines

The study included four atopic felines (Table 1). Atopic dermatitis was diagnosed on the basis of patient history, clinical examination and exclusion of differential diagnoses such as flea reactions, food adverse reactions, dermatophytosis or external parasites. All four cats had a history of non-seasonal pruritus with duration of greater than 1 year. Pruritus had not improved with flea control, treatment with selamectin or, when appropriate, systemic antibiotic therapy. None of the cats were on any medications prior to onset of pruritus except for topical flea preventative products and all four cats completed a food trial with a novel protein diet (duration 6 weeks) prior to entering the study. Owners were given the option to begin conventional ASIT or RIT. Owners were informed as to the experimental nature of the protocol, potential reactions and unknown impact of RIT on effectiveness of ASIT in the cat.

Allergen extracts

Allergen specific IgE antibodies were identified via liquid phase immunoassay testing (VARL: Veterinary Allergy Reference Laboratories, Pasadena, CA, USA). Individual allergens selected for immunotherapy had positive test results (defined as a score of ≥ 2 on the VARL test) and were chosen based upon history and environment for each feline patient (Table 2). All immunotherapy extracts were prepared in house with allergen extracts obtained from Greer Laboratories (Lenoir, NC, USA). The first six injections administered utilized antigens at a concentration range of 1500–2000 protein nitrogen units (PNU) mL⁻¹. The last five

Table 3. Specific breakdown of rush allergen specific immunotherapy protocol used

Injection	Time (min)	Dose (PNU)	Volume (mL)
1	0	150	0.1
2	30	300	0.2
3	60	600	0.4
4	90	900	0.6
5	120	1200	0.8
6	150	1500	1
7	180	1500	0.1
8	210	3000	0.2
9	240	4500	0.3
10	270	6000	0.4
11	300	7500	0.5

Dotted line indicates transition from the 1500 PNU mL⁻¹ vial to the 15 000 PNU mL⁻¹ vial.

injections utilized the maintenance concentration of approximately 15 000–20 000 PNU mL⁻¹.

RIT protocol

Each feline patient was premedicated with 1.5 mg triamcinolone (dose range of 0.11–0.19 mg kg⁻¹) per os 24 and 2 h prior to the first injection and 10 mg hydroxyzine (dose range of 0.74–1.2 mg kg⁻¹) orally 24, 12 and 2 h prior to the first injection. An intravenous catheter was placed prior to the first injection and flushed with heparinized saline every 4 h. All allergen extracts (Table 3) were administered subcutaneously (SQ) in the dorsal neck area at increasing PNUs every 30 min for 5 h to an average maintenance of 7500 PNU mL⁻¹ (0.5 mLs of 15 000–20 000 PNU mL⁻¹ vial). Vital signs (temperature, pulse and respiratory rate) and pruritus were assessed prior to the first injection and every 15 min thereafter. Additionally, the patients were monitored closely for signs of localized reactions at the injection site, angioedema or urticaria. Alterations of any variable were evaluated and, if deemed significant, the next injection was delayed by 30 min. At that time

the patient was re-assessed and if vital signs and pruritus had returned to previous levels, the injection was administered. Each feline patient was monitored in the hospital for at least 2 h after the final injection. A veterinarian or veterinary technician was present at all times. Owners were instructed at discharge to begin administering an average maintenance dose of 7500 PNU (0.5 mL of 15 000–20 000 PNU mL⁻¹ vial) SQ once every 7 days.

RESULTS

All four cats successfully completed the protocol attaining an average maintenance dose of 7500 PNU (0.5 mL of the 15 000–20 000 PNU mL⁻¹). Although none of the cats experienced any fluctuation in their vital signs, two out of the four cats displayed an increase in grooming behaviour and this was interpreted as a mild increase in pruritus. A reaction in cat #3 was noted following the injection of 900 PNU (fourth injection) and the reaction in cat #4 was noted after the injection at 1500 PNU (sixth injection). The following injection was delayed by 30 min in each cat. No further reactions were observed and each cat returned to the standard protocol of receiving an injection every 30 min. Neither cat reacted to any of the subsequent injections. No other adverse reactions during RIT were noted.

One week following RIT two cats (cat #2 and #3) developed a firm, dermal, alopecic nodule measuring 1 cm in diameter on their dorsal necks. The owners would not consent to a biopsy. Fine-needle aspiration revealed multiple inflammatory cells but no organisms were seen. Aerobic and anaerobic cultures of both the allergen solution and aspirate were performed. Neither culture yielded organism growth. Tacrolimus was applied topically to the nodules once daily and both resolved within 3 weeks.

DISCUSSION

All four cats successfully completed the RIT protocol. However, this was a pilot study that was designed to establish the basis for a RIT protocol in feline atopic patients only and further studies are needed to evaluate the true safety of RIT in the feline patient. Two out of the four cats displayed a mild increase in grooming behaviour, which was interpreted as a mild increase in pruritus. However, whether or not this reaction was a result of RIT is questionable. Although delayed injection site reactions occurred in two cats 1 week after completing the protocol we suspect that this reaction may have been avoided by altering the injection locations in the fourth cat.

Allergen specific immunotherapy is a safe and effective therapy for feline atopic dermatitis. It has reported success rates as high as 70%.^{1–5} Owner compliance is a significant factor in the successful management of feline atopic dermatitis and use of ASIT. At this time the study of RIT as a method for treating atopic felines

is limited. However, RIT in the feline patient minimizes the owner's burden and may result in improved compliance. In this study all four cats successfully completed rush immunotherapy with no significant complications. As in the canine patient, the application of RIT may increase the long-term success rate of ASIT in the feline atopic patient. However, this was not evaluated in this initial pilot study.

Successful RIT protocols have been reported for both human and canine atopic patients.^{6–8} In all previously reported protocols, human patients have been premedicated with a myriad of medications including glucocorticoids, antihistamines and leukotriene inhibitors.⁶ With the exception of leukotriene inhibitors, similar medications have been utilized in canine premedication protocols.^{7,8} In this pilot study, the owners administered both a glucocorticoid and antihistamine to each cat beginning 24 h prior to the first RIT injection.

Although two of the four cats in the study experienced a mild increase in grooming behaviour, their vital signs did not fluctuate. Moreover, both cats exhibited this behaviour at low concentrations of the allergy serum. Thus, it is unclear whether this change in behaviour can be attributed to the RIT injections. Alternatively, it may have been an unrelated symptom of active atopic disease. The abnormal grooming behaviour resolved without the aid of further medication and both cats completed the protocol without exhibiting any further evidence of pruritus. Nevertheless, these data do not indicate that no reaction took place. Increases in pruritus have been reported by owners of feline and canine patients undergoing traditional ASIT at low serum concentrations, and pruritus has been reported in humans during RIT at similarly low serum concentrations.^{1,6}

The localized injection site reactions that developed in the second and third feline patients may be a consequence of RIT. Localized reactions have not been reported in canines; however, the localized reactions in this study are similar to those reported in human patients.^{2,6} Arthus type III reactions have been reported in human patients after injections of allergy serum, vaccines, insulin and multiple other injectable medications. Arthus type III reactions are characterized by the formation of a nodule at the injection site 6 to 8 h following the injection and persist for at least 48 h. On cytology and histopathology these are characterized as granulomatous reactions due to the preponderance of macrophages viewed.¹⁰ Although the nodules were not noted until 1 week after RIT, cytological and clinical findings suggested that the nodules were injection site reactions similar to those documented in human patients, and were treated accordingly. The owners' refusal to allow biopsies to be performed prevented histopathological confirmation. As the owners did not administer an injection for 1 week following RIT it is possible that the nodules were present and went unnoticed by the owners as the cats were asymptomatic.

The mildly fractious nature of these two cats required them to be restrained by the nape of the dorsal neck each time an injection was administered. Thus, the

injections were clustered in one centralized area in both of these cats possibly creating more severe localized inflammation. The injections in the fourth cat were more widely distributed in the dorsal neck area in an attempt to avoid further recurrence. Previous canine studies have shown that administering allergen injections intradermally may cause a localized reaction and an accidentally administered intradermal injection may have caused the dermal nodules in these cats as well.

The diagnosis of feline atopic dermatitis is based upon clinical history, physical examination and the exclusion of other diseases. Atopy is a rule out diagnosis and often the clinical history provided by the owner may be misleading. It is important that the clinician rule out other differentials through complete patient evaluations and appropriate diagnostic testing. Skin scrapings, cytology, fungal cultures, biopsies and elimination diets should be considered in many cases to rule out major differentials. Specific allergy testing may be performed via intradermal skin (IDST) or serum IgE testing.^{1-4,11} However, allergy testing cannot confirm a diagnosis of atopic dermatitis; it merely identifies allergens to include in immunotherapy.

In the feline, IDST is associated with multiple impediments and even some controversy. Intradermal skin testing in the feline is often difficult to interpret and for the novice to perform.^{11,12} Additionally, there is disagreement as to the concentration at which allergens should be tested in the cat.¹³ Gilbert and Halliwell demonstrated that antisera specific for feline IgE could detect IgE in the sera of cats in which allergen specific IgE to *Dermatophagoides farinae* was induced experimentally under controlled conditions. All cats underwent both ELISA and IDST. An IgE response was seen in all cats and in some instances IgE antibodies were detected prior to the development of a positive skin test reaction. In this report it appears ELISA is a sensitive, specific and reliable method to detect allergen specific IgE in cats.¹⁴ A direct comparison between IDST and serum allergy testing was performed on 22 allergic cats and seven normal cats. None of the seven normal cats exhibited positive reactions to either IDST or serum allergy testing. In contrast, the study showed that when the positive results for each allergic cat were compared the tests showed good agreement.¹⁵

Although serum IgE testing is associated with some false positive results it is easier on both the patient and clinician to perform. A questionnaire-based review of felines who underwent radioallergosorbent testing and then were treated with ASIT based upon this testing method indicated that serum IgE testing has value in the cat.⁵ Additionally, a small unpublished study was performed in cats by one of the authors to assess VARL testing. This is the type of liquid phase immunoenzymatic testing used in this study and previously validated in humans.¹⁶ Blinded blood samples were submitted for VARL testing from eight normal cats and 10 atopic cats. Additionally the normal cats were subjected to IDST for house dust mite and flea antigen. Only one of the eight normal cats had a positive reaction on the VARL. None

of the normal cats reacted to the intradermal injection of house dust mite antigen and only one reaction was noted with the flea antigen injections. Five of the 10 atopic cats had positive scores based on VARL testing.^{12,17} VARL testing provides a reliable and straightforward means of allergy testing in the feline atopic patient.

In these four cats, this RIT protocol appeared to be a safe and effective regimen to reach maintenance therapy. Although the patients in the pilot study experienced relatively few reactions, RIT is not without risk and the clinician must be certain of his/her diagnosis and fully educate the client as to the potential risks associated with RIT before subjecting a feline patient to this route of therapy. The pilot study design did not include a control group of normal cats. The sole purpose of the pilot study was to establish the reaction patterns of RIT in atopic cats. A larger sample of feline patients is necessary to determine the incidence of adverse reactions and to follow the success of ASIT based upon this method of induction.

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Résumé L'immunothérapie rapide s'est avérée aussi sûre que l'immunothérapie classique chez le chien. L'immunothérapie en rush n'a pas été décrite chez le chat. Le but de cette étude pilote était de déterminer un protocole sécuritaire d'immunothérapie en rush pour les chats atopiques. Quatre chats diagnostiqués comme atopiques par l'anamnèse, l'examen clinique et l'exclusion des autres diagnostics différentiels ont été inclus dans l'essai. Les allergènes ont été identifiés par dosage sérologique (VARL: Veterinary Allergy Reference Labs, Pasadena, CA). Les chats ont été prémédiqués avec 1.5 mg de triamcinolone par voie orale 24 et 2 h avant la première injection et 10 mg d'hydroxyzine PO 24, 12 et 2 h avant la première injection. Un cathéter a été mis en place avant la première injection. Les extraits allergéniques (Greer Laboratories, Lenoir, North Carolina) ont été administrés par voie sous cutanée à doses progressivement croissantes toutes les 30 minutes pendant 5 heures pour atteindre la dose de maintenance de 15,000 pnu/ml. Un examen clinique était réalisé toutes les 15 minutes. Deux chats ont montré un prurit modéré et l'injection suivante a été différée de 30 minutes. Aucune modification grave n'a été observée. Tous les quatre chats ont terminé leur désensibilisation rapide. Deux chats ont eu un gonflement dermique sur la peau du cou une semaine plus tard. Chez les quatre animaux, ce protocole est apparu sans risque pour atteindre la dose de maintenance. Un échantillon plus important de chats est nécessaire pour déterminer l'incidence des réactions secondaires et l'efficacité de l'ASIT selon cette méthode d'induction.

Resumen La inmunoterapia rápida ha demostrado ser tan segura como la inmunoterapia convencional en perros con atopia. El uso de esta inmunoterapia en gatos no ha sido publicado hasta el momento. El propósito de este estudio piloto fue determinar un protocolo seguro para inmunoterapia rápida en gatos atópicos. Cuatro gatos con atopia diagnosticados mediante historia clínica, examen físico y exclusión de los diagnósticos diferenciales apropiados se incluyeron en este estudio. Los alérgenos fueron identificados mediante prueba líquida inmunoenzimática (VARL: Laboratorios Veterinarios de Referencia en Alergia, Pasadena, CA). Los gatos fueron previamente medicados con 1.5 mg de triamcinolona vía oral 24 y 2 horas antes de la primera inyección, y con 10 mg de hidroxizina vía oral 24, 12 y dos horas previas a la primera inyección. Asimismo se colocó un catéter intravenoso antes de la primera inyección. Los extractos de alérgenos (Laboratorios Greer, Lenoir, North Carolina) fueron administrados vía subcutánea a dosis crecientes de unidades de nitrógeno proteico (pnu) cada 30 minutos durante 5 horas, para mantener una dosis de 15,000 pnu/ml. Los signos vitales se evaluaron cada 15 minutos. Dos gatos desarrollaron mínimo prurito, por lo cual la inyección siguiente se retrasó 30 minutos. No se observaron cambios en los signos vitales de ninguno de los dos gatos, y tampoco se observó más prurito. En todos los gatos se completó con éxito el protocolo rápido de inmunoterapia. Dos gatos desarrollaron hinchazón en la piel del dorso del cuello una semana después. En los cuatro gatos, este protocolo demostró ser un régimen seguro para alcanzar una terapia de mantenimiento. Un mayor número de gatos sería necesario para determinar la incidencia de reacciones adversas, así como para valorar éxito de ASIT basado en este método de inducción.

Zusammenfassung Bei caninen atopischen Patienten konnte gezeigt werden, dass Rush Immuntherapie (Schnellsteigerung) ebenso sicher ist wie konventionelle Immuntherapie. Beim felineen atopischen Patienten wurde Rush Immuntherapie bisher nicht dokumentiert. Das Ziel dieser Pilotstudie war es, ein sicheres Protokoll für Rush Immuntherapie bei felineen atopischen Patienten zu ermitteln. Vier atopische Katzen, diagnostiziert mittels Anamnese, klinischer Untersuchung und Ausschluss von entsprechenden Differentialdiagnosen, wurden in die Studie aufgenommen. Die Allergene wurden mittels 'Liquid Phase Immunoenzymatic Testing' (VARL: Veterinary Allergy Reference Labs, Pasadena, CA) identifiziert. Die Katzen erhielten eine Prämedikation per os mit 1.5 mg

Triamcinolon 24 und 2 h, sowie mit 10 mg Hydroxyzin 24, 12 und 2 h vor der ersten Injektion. Ein intravenöser Katheter wurde vor der ersten Injektion gesetzt. Die Allergen Extrakte (Greer Laboratories, Lenoir, North Carolina) wurden alle 30 Minuten in zunehmenden Protein Nitrogen Units (pnu) über einen Zeitraum von 5 Stunden bis zur Erhaltungsdosis von 15,000 pnu ml^{-1} subkutan verabreicht. Die Vitalzeichen wurden alle 15 Minuten beurteilt. Zwei Katzen entwickelten milden Juckreiz und die nächste Injektion wurde um 30 Minuten verzögert. Bei keiner der Katzen wurden Veränderungen der Vitalzeichen bemerkt, es bestand auch kein weiterer Juckreiz. Alle vier Katzen beendeten die Rush Immuntherapie erfolgreich. Bei zwei der Katzen entstand nach einer Woche eine dermale Schwellung am dorsalen Nacken. Bei diesen vier Katzen stellte sich dieses Protokoll als sicheres Dosierungsregime heraus, um die therapeutische Erhaltungsdosis zu erreichen. Eine größere Anzahl an feline Patienten ist notwendig, um das Auftreten von Nebenwirkungen zu eruieren und um den Erfolg der allergenspezifischen Immuntherapie (ASIT), die auf dieser Induktionsmethode beruht, zu verfolgen.