Evaluation of the safety of an abbreviated course of injections of allergen extracts (rush immunotherapy) for the treatment of dogs with atopic dermatitis

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Objective—To evaluate the safety of an abbreviated course of injections of allergen extracts (rush immunotherapy) for the treatment of dogs with atopic dermatitis.

Animals—30 dogs with atopic dermatitis examined at a veterinary dermatology referral practice for treatment with allergen-specific immunotherapy.

Procedure—A catheter was placed in a vein in each dog. Dogs were constantly observed throughout the procedure. Allergen extracts were administered in increasing concentrations every 30 minutes for 6 hours to a maintenance concentration of 20,000 protein nitrogen units/ml. Epinephrine, oxygen, and emergency treatment were available as needed.

Results—In 22 (73%) dogs, rush immunotherapy safely replaced the prolonged induction period (15 weeks) of weekly injections that consists of increasing concentrations of allergen extract. In 7 (23%) dogs, the induction period was abbreviated to 4 weeks. Of the 8 dogs that developed problems during rush immunotherapy, increased pruritus necessitated premature cessation of rush immunotherapy in 7, and 1 developed generalized wheals. Oral administration of prednisolone (1 mg/kg of body weight) resulted in resolution of adverse effects in all 8 dogs.

Conclusion and Clinical Relevance—Rush immunotherapy performed by personnel at a veterinary hospital is a safe method for treatment of dogs with atopic dermatitis. (*Am J Vet Res* 2001;62:307–310)

Atopy is a common skin disease in dogs.[1] It is defined as an inherited predisposition to develop IgE antibodies to environmental allergens resulting in clinical signs of atopic dermatitis after exposure to these allergens.[2] Palliative treatment for dogs with atopic dermatitis includes glucocorticoids, antihistamines, fatty acid supplements, and topical shampoos and moisturizers.[3-5] The only specific treatment for atopic dermatitis currently available is allergen-specific immunotherapy, whereby allergens involved in the patient's disease, as identified by intradermal skin testing or serum testing for allergen-specific IgE, are administered to the atopic patient. Allergen concentrations are increased gradually during the induction period, which takes place over the course of several weeks. Multiple schedules exist for the series of injections. Maintenance therapy involves administration of a specific concentration of allergens at a certain frequency, typically every few weeks,[6-8] and must be continuously provided for the lifetime of most patients, although some patients stay in remission after immunotherapy is discontinued.[6] Allergen-specific immunotherapy is more effective than antihistamines or fatty acids, has fewer adverse effects than use of glucocorticoids, and, thus, is an attractive alternative to palliative treatment.

Although some owners of atopic dogs opt to have their veterinarian administer the injections of the allergen extracts, most will choose to administer the injections themselves to decrease the financial burden associated with repeated veterinary visits. However, elderly or physically disabled people may not be able to give injections and may need their veterinarian to administer the injections to their pets. During the induction period, there is potential for misunderstanding and need to consult with a veterinarian because of the increasing amounts of allergens administered, which requires 2 or 3 vials with differing concentrations. In addition, in the experience of the authors, adverse effects such as increased pruritus and anaphylactic reactions are most common in the induction period. Thus, the first months of treatment are frequently the most stressful time of immunotherapy for dogs and owners. Circumventing the induction period and obtaining a quicker initial response would have an important impact on the well being of the dogs and be more convenient to owners.

An abbreviated course of injections of allergen (rush immunotherapy) is used to shorten the induction period by giving increasing amounts of allergen extracts during 1 or several days; this technique has been used extensively in human medicine.[9-14] It is considered a safe treatment in humans.[11,15-17] In a recent report of an evaluation of rush immunotherapy in 6 laboratory dogs with atopy and 5 client-owned atopic dogs, the author did not mention any adverse effects.[18] The purpose of the study reported here was to evaluate the safety of rush immunotherapy in a larger number of dogs with atopic dermatitis.

Materials and Methods

Owners who elected to have allergen-specific immunotherapy administered to their atopic dogs were given the choice of conventional immunotherapy (**Appendix 1**) or rush immunotherapy (**Appendix 2**). Owners were thoroughly educated about the background and scientific rationale of

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the study as well as the benefits and possible adverse effects of rush immunotherapy, particularly anaphylaxis, before giving authorization to include their dog in the study.

Atopic dermatitis was diagnosed on the basis of history, clinical examination, and exclusion of differential diagnoses such as food allergies or scabies, using tests or treatments described elsewhere.[3,5-7] Offending allergens were identified by use of an intradermal skin test.

All dogs included in the study were admitted to our veterinary hospital at 8 AM on Monday, Tuesday, or Wednesday to ensure availability of a veterinary dermatologist and local veterinarian during the first 2 to 3 days after initiation of rush immunotherapy. An indwelling catheter was placed in a cephalic vein of each dog, and patency of the catheter was maintained until 2 hours after cessation of rush immunotherapy. As a precautionary measure, epinephrine (0.02 mg/kg of body weight) for each dog was prepared in a labeled syringe and was available for immediate use during the day. An endotracheal tube and supplemental oxygen also were prepared for immediate use, if necessary.

Allergen extracts of commercially available allergens[a] were formulated for each dog on the basis of each dog's test results. Intradermal injections of allergen extract at increasing concentrations were administered every 30 minutes (Appendix 2). The last 2 injections were administered subcutaneously because of the large volume of allergen extract injected (0.8 and 1.0 ml). Prior to each injection, dogs were examined, and heart and respiratory rates, rectal temperature, and capillary refill time were recorded, along with any changes identified during physical examination. When the heart or respiratory rate increased by > 30%, rectal temperature increased to greater than the reference range, capillary refill time was > 2 seconds, or abnormalities were detected during physical examination, the subsequent injection was postponed, and the dog was reevaluated 30 minutes later. If values for the monitored variables had returned to acceptable limits at that time, the next injection was administered. If they had not, additional injections were not given that day, and the dog was discharged to the owner and assigned to receive conventional immunotherapy (Appendix 1). A veterinarian or a veterinary technician was present at all times and continuously monitored the dogs during the first day of rush immunotherapy until at least 2 hours after the last injection was administered. Dogs that had increased intensity of pruritus (manifested by frequent scratching or biting) as the only adverse effect were treated by administration of prednisolone (1 mg/kg, PO, q 24 h for 4 days). When a substantial decrease in the signs of pruritus were evident within 2 hours after administration of prednisolone, rush immunotherapy was continued. Dogs that did not respond favorably to prednisolone administration were discharged to their owners and were assigned to receive weekly increases in injected allergen extracts in accordance with the schedule for conventional immunotherapy, beginning at the last dose given during rush immunotherapy.

Results

Thirty dogs were included in the study. Twenty-two (73%) dogs did not have adverse effects during or following rush immunotherapy, but premature discontinuation of rush immunotherapy was necessitated in 8 dogs. Seven of these dogs had signs of increasingly severe pruritus that did not resolve within 60 minutes after injection of allergen extracts. Rush immunotherapy was discontinued at 0.08 ml (160 **protein nitrogen units [PNU]**; 1 dog), 0.1 ml (2,000 PNU; 1), 0.2 ml (4,000 PNU; 2), 0.4 ml (8,000 PNU; 2), and 0.8 ml (16,000 PNU; 1), respectively. One dog, a 2.5-year-old neutered male Jack Russell Terrier, developed edematous eyelids and generalized wheals at 0.1 ml (2,000 PNU). All dogs in which rush immunotherapy was discontinued had values for monitored variables that did not return to acceptable limits within 30 minutes after the previous injection, and, thus, were administered prednisolone. All responded to prednisolone treatment, were discharged to their owners, and were assigned to receive conventional immunotherapy. Complications were not observed in these dogs during subsequent induction by use of conventional immunotherapy.

Discussion

Dogs with atopy may receive palliative treatments such as glucocorticoids, antihistamines, or fatty acids. Allergen-specific immunotherapy is an alternative that combines a low risk of adverse effects with a high rate of clinical improvement. Success rates in animals vary between 45 and 100%,[6-8,19-21] reflecting various definitions of success, numbers of animals included in each study, and variations in follow-up periods. The mechanism of action of allergen-specific immunotherapy in humans and other animals is not clear. Several hypotheses proposed for humans include a decrease in allergen-specific IgE production,[22,23] an increase in allergen-specific blocking IgG antibodies,[13,24,25] and changed T-cell reactivity.[26-28]

Clinical improvement can be evident as early as 4 weeks after initiation of immunotherapy in some dogs. However, most dogs will not have much improvement for the first 4 to 6 months,[6] and some dogs do not improve until 8 to 12 months after beginning treatment.[7] This delay in response can cause substantial distress for pruritic dogs and be of great concern to owners. A more rapid response would be of great benefit to patients and owners. The predominant reason for rush immunotherapy in humans is the need or desire to quickly achieve hyposensitization and, thus, clinical improvement. This is of particular relevance in patients with hypersensitivity against wasps or bees, when a sting may cause a life-threatening reaction,[9-11] but it also may be needed in patients who are allergic to dust mites[12,13] and mold allergens.[14]

In animals, owners usually administer the injections to their own pets for financial and convenience reasons. Multiple vials with differing concentrations are dispensed. Allergen extracts are administered in increasing concentrations, and the amount injected is removed from various vials during the induction period. Thus, additional reasons for rush immunotherapy in veterinary medicine are increased convenience and decreased incidence of administration of an incorrect concentration of an allergen extract.

In humans, injections have been given in accordance with various protocols.[11,12,29-32] Induction periods of 1, 2, 3, 7, and 14 days have been cited. We chose a 1-day induction protocol for 2 reasons. First, a high allergen load that is orally administered is associated with T-cell anergy in mice,[33-35] and similar changes may be expected after intradermal or subcutaneous injection of a high allergen load in dogs. Furthermore, this protocol is associated with minimal inconvenience for

owners that have to travel long distances to bring their animals to our clinic. The duration of the hospital stay is short, and animals do not need to be hospitalized overnight.

Typically, injections are administered subcutaneously. However, best results would be expected at sites that have maximal exposure of antigen to T-cells. Supporting this hypothesis, intralymphatic immunotherapy reportedly is more effective than conventional immunotherapy in dogs.[b] However, intralymphatic immunotherapy is associated with technical difficulties. Dermal T-cells express cutaneous lymphocyte antigen and the ligand for E-selectin expressed by endothelial cells of the postcapillary venules in the dermis; also, there is a high concentration of memory T-cells located perivascularly in the dermis.[36] This rationale led to our protocol for intradermal injection of allergen extract, except for the final 2 injections, because the volume of each of the final 2 injections prohibited intradermal administration.

The safety of rush immunotherapy in humans has been evaluated in several studies.[11,15,16] Adverse effects included mild exacerbation of clinical signs and, less commonly, anaphylactic shock. However, none of the patients had to be admitted to an intensive care unit, and rush immunotherapy was considered a therapy that could be safely used in an ambulatory setting. The incidence of adverse effects was significantly reduced when patients were medicated with antihistamines[16] or glucocorticoids prior to rush immunotherapy.[37] In another study,[17] reactions were much more common during the induction period for rush immunotherapy and were rare during maintenance injections; adverse effects were seen within the first 45 minutes after injection of the allergen extract.

Similar to the study reported here, MacDonald[18] used a protocol with an induction period of 1 day for rush immunotherapy in atopic dogs. He did not report any adverse effects in 6 laboratory dogs and 5 privately owned dogs after rush immunotherapy instituted by him or in another 9 dogs after rush immunotherapy instituted at other veterinary hospitals. This is in contrast to our study in which we were forced to discontinue rush immunotherapy prematurely in 8 of 30 (27%) dogs as a result of unacceptable adverse effects, most notably increased pruritus. Allergen extracts were obtained from the same source[a] in both studies, and the amount of allergen extract administered also was the same. A possible reason for the reported difference, other than the larger number of dogs in our study, is that intradermal injection of allergens may have led to increased degranulation of mast cells after cross-linking of surface-bound allergen-specific IgE by injected allergens and release of proinflammatory mediators. Another possible explanation may have been a difference in tolerance to pruritus of the atopic dogs between the investigators. In our study, dogs were intensively monitored and closely observed for signs of increased pruritus. This increase in pruritus may not have been evident in dogs in the other study, or it may not have been detected or reported, because monitoring may have concentrated on severe signs of anaphylaxis. Although not reported, some of the dogs in the other study may have been medicated with antihistamines or glucocorticoids prior to initiation of rush immunotherapy. However, all dogs with adverse effects in our study responded readily to oral administration of prednisolone and completed the induction period in a conventional manner without further complications.

Rush immunotherapy can be used to replace or substantially reduce the induction period. It should be administered at a veterinary hospital by veterinarians or veterinary technicians, and dogs should be monitored closely. Whether rush immunotherapy is associated with a more rapid decrease or resolution of pruritus or a higher overall response rate, compared with conventional immunotherapy, will need to be clarified in other studies.

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[a]Allergenic extracts of various grass, weed and tree pollens, dust mites, insects and molds, Greer Laboratories, Lenoir, NC.

[b]Juillard GJF, Bubbers JE. Experimental intralymphatic immunotherapy (ILI) of canine allergic disease (abstr). *Fed Proceed* 1983;42:441.

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Appendix 1

Concentration of allergen extracts and frequency of administration during induction achieved in accordance with a schedule for conventional immunotherapy

	Injection*														
Variable	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
ml	0.1	0.2	0.4	0.8	1.0	0.1	0.2	0.4	0.8	1.0	0.1	0.2	0.4	0.8	1.0
PNU†	20	40	80	160	200	200	400	800	1,600	2,000	2,000	4,000	8,000	16,000	20,000

*Injections administered at weekly intervals. †Injections 1 to 5 were of a solution containing 200 PNU/ml, injections 6 to 10 were of a solution containing 2,000 PNU/ml, and injections 11 to 15 were of a solution containing 20,000 PNU/ml.
PNU = Protein nitrogen units.

Appendix 2

Concentration of allergen extracts and frequency of administration during induction achieved in accordance with an abbreviated course of injections of allergen extracts (rush immunotherapy)

	Injection*											
Variable	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
ml	0.2	0.4	0.08	0.1	0.2	0.4	0.08	0.1	0.2	0.4	0.8	1.0
PNU†	40	80	160	200	400	800	1,600	2,000	4,000	8,000	16,000	20,000

*Injections administered at 8:30, 9:00, 9:30, 10:00, 10:30, and 11:00 AM, noon, and 12:30, 1:00, 1:30, and 2:00 PM. †Injections 1 and 2 were of a solution containing 200 PNU/ml, injections 3 to 6 were of a solution containing 2,000 PNU/ml, and injections 7 to 12 were of a solution containing 20,000 PNU/ml.