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Allergen immunotherapy in people, dogs, cats and horses – differences, similarities and research needs

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Abstract

In human patients with seasonal allergic rhinoconjunctivitis sensitized to grass pollen, the first successful allergen immunotherapy (AIT) was reported in 1911. Today, immunotherapy is an accepted treatment for allergic asthma, allergic rhinitis and hypersensitivities to insect venom. AIT is also used for atopic dermatitis and recently for food allergy. Subcutaneous, epicutaneous, intralymphatic, oral and sublingual protocols of AIT exist. In animals, most data are available in dogs where subcutaneous AIT is an accepted treatment for atopic dermatitis. Initiating a regulatory response and a production of "blocking" IgG antibodies with AIT are similar mechanisms in human beings and dogs with allergic diseases. Although subcutaneous immunotherapy is used for atopic dermatitis in cats, data for its efficacy are sparse. There is some evidence for successful treatment of feline asthma with AIT. In horses, most studies evaluate the effect of AIT on insect hypersensitivity with conflicting results although promising pilot studies have demonstrated the prophylaxis of insect hypersensitivity with recombinant antigens of biting midges (*Culicoides* spp.). Optimizing AIT using allergoids, peptide immunotherapy, recombinant allergens and new adjuvants with the different administration types of allergen extracts will further improve compliance and efficacy of this proven treatment modality.

KEYWORDS
animal models, asthma, atopic dermatitis, clinical immunology, and tolerance induction

1 | ALLERGEN IMMUNOTHERAPY (AIT) FROM HUMAN BEINGS TO ANIMALS

The first successful subcutaneous allergen immunotherapy (SCIT) was reported in 1911 by Noon[1] in people with seasonal allergic rhinoconjunctivitis sensitized to grass pollen. Since then, allergen immunotherapy has been evaluated in many scientific studies. According to systematic reviews and meta-analyses, SCIT is helpful in alleviating symptoms and reducing medication in patients with allergic rhinoconjunctivitis and allergic asthma,[2,3] whereas its benefits for atopic dermatitis (AD) are still unclear.[4] However, some clinical trials and reports of AD patient experience have been highly encouraging.[5] Sublingual,[2] intralymphatic and epicutaneous immunotherapy have also been evaluated. Table 1 gives an overview on the efficacy of AIT by various routes.

In 1941, Wittich published the first report of allergen immunotherapy for an allergic dog.[6] Over the following decades, publications often noted the remarkable similarity of human and

Abbreviations: AD, atopic dermatitis; AIT, allergen immunotherapy; EPIT, epicutaneous immunotherapy; Ig, immunoglobulin; IL, interleukin; ILIT, intralymphatic immunotherapy; ILIT, intralymphatic immunotherapy; OIT, oral immunotherapy; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

TABLE 1 Allergen immunotherapy (AIT) in humans

Indication	Type of AIT	Dose	Allergens used and treatment duration	Success rate[§]	Adjuvants
Allergic rhinoconjunctivitis	SCIT	For example, 25 mcg Phl p 5	Mite, pollen, cat, dog allergens for 21-54 injections	20% TCS[a]	Alum, ca-phosphate, MPL, tyrosine
	SLIT	1.5-12 Amb a 1-U, or 75 000 SQ-T[d] or 6-12 SQ-HDM[e]	Mite-, pollen allergens daily for 0.5-5 years	12%-27% TCS[a], 20%-23% TCS 16-19% TCS[a]	Cellulose gelatin, mannitol
	ILIT	1000 SQ-U	3 injections of grass or birch pollen	16-28% TCRS[b]	Alum
	EPIT	21 mcg Phl p 5;−250 mcg peanut	Grass pollen or peanut	40-72% VAS[c] 25%	Petrolatum, 50% glycerol
Allergic asthma	SCIT	6-7 mcg	21-54 injections of mite antigen	Up to 40%	Allergoid, alum
	SLIT	6-12 SQ-HDM[e]	Mite antigens daily, for 0.5-5 years	25% TCS[a]	Cellulose
Atopic dermatitis	SCIT	1-1.2 mcg	Mite antigens for 12-18 months	19% ΔSCORAD[f,g]	Alum
	SLIT	0.4-4 mcg		n.s. modest[g]	Glycerol, cellulose

SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; ILIT, intralymphatic immunotherapy; EPIT, epicutaneous immunotherapy; n.s., not statistically significant.
[a]TCS, total combined scores.
[b]TCRS, total combined rhinitis score.
[c]VAS, visual analogue scale.
[d]SQ-T, standardized quality tablet.
[e]HDM, house dust mite.
[f]ΔSCORAD, changes in SCORing atopic dermatitis.
[g]Moderate and inconsistent results from heterogeneous studies.

canine allergic diseases and speculated on *Canis familiaris* as an animal model for *Homo sapiens*.[7] In veterinary medicine, dermatologists preside over AIT treatments, as the most common allergic diseases in animals are cutaneous external parasite hypersensitivities and atopic dermatitis (AD). Allergic rhinitis and allergic asthma are much less common in dogs, although stabled horses are often affected by an asthma-like condition. Veterinary specialists generally view AIT as the only current treatment method for allergic diseases that can modify or reverse part of the condition's pathogenetic mechanism. This modification is associated with a reduction in the medication requirements and long-term improvements in clinical signs and is accomplished without the possible long-term effects of a lifetime of drug treatment. There is reportedly minimal chance for adverse effects and the potential for long-lasting efficacy. In animal AD, AIT is a common and accepted part of treatment (Table 2).

2 | MECHANISM OF AIT

2.1 | Mechanisms of AIT in human beings

Allergy is characterized by a dominance of T helper 2 cells and their cytokines and the formation of allergen-specific IgE with development of clinical hypersensitivity (Table 3). Interestingly, the described immune mechanisms of AIT in people are consistent among the various AIT regimens, dose escalations, application routes and type of allergens. Major immune changes include a shift from a Th2 towards a Th1 response, the induction of allergen-specific IgG4 "blocking" antibodies and T- and B-regulatory cells contributing immunosuppressive cytokines such as IL-10 and TGF-beta, the latter being responsible for IgA induction with a potential protective role at the mucosa.[8] The more recently described role of Th17 and Th22 cells is more complex and may involve pro-inflammatory as well as regulatory functions.[9] However, none of these changes can be used as biomarkers to predict clinical response to AIT in vivo, although a lack of allergen-specific IgG4 may be useful to indicate a lack of patient compliance.[10] Symptom and medication scores are used to monitor the clinical efficacy of AIT in human patients, but are in need of harmonization.[11]

2.2 | Mechanisms of AIT in animals

Among animals, the pathobiology of AD has been most extensively investigated in dogs (Table 3); a concise summary was recently published.[12] In other domestic animal species such as the cat and horse, little investigation has occurred. Generally, findings in dogs nearly or exactly parallel those in man, and our assumption is that AD is the "same disease" in both species. Early response is attributed to reduction in effector cell activity, followed by a long-term immunologic shift from a Th2- to Th1-biased response and development of immunologic tolerance. In dogs as in man, the shift to Th1 is accompanied by an increase in T-regulatory cells and IL-10 during successful AIT. Studies have demonstrated a rise in both total and allergen-specific IgG and decrease in allergen-specific IgE during AIT.[12-14] This supports the consideration of spontaneous atopic disease in dogs as a model for analogous conditions in human beings. With sublingual immunotherapy (SLIT) administration, the additional phenomenon of "oral tolerance" initiated by oromucosal dendritic cells is frequently discussed for SLIT in human patients. This mechanism is unexplored in companion animals.

TABLE 2 Allergen immunotherapy (AIT) in the dog, cat and horse

	Indication	Type of AIT	Dose	Allergens used	Success rate[a]	Adjuvants
Cat	Asthma	SCIT	200 mcg	Mites, pollens	64%-66%	CpG
	Atopic dermatitis	SCIT	1000-7500 PNU	Mites, pollens	50%-70%	Alum
Dog	Atopic dermatitis	SCIT	20 000 PNU	Mites, pollens, moulds	52%-77%	Alum, CpG
		SLIT	Not stated	Mites	40%	
		ILIT	2000 PNU	Mites, pollens	43%-54%	Alum
Horse	Atopic dermatitis	SCIT	20 000 PNU	Mites, pollens, moulds	54%	
	Urticaria	SCIT	20 000 PNU	Mites, pollens, moulds	50%	
	Culicoides hypersensitivity	SCIT	10-20 mg	*Culicoides* spp.	14-80%	
		ILIT	40 μg	*Culicoides* spp.	[b]	Alum, MPLA
		SLIT	[c]	*Culicoides* spp.	[b]	

SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; ILIT, intralymphatic immunotherapy; EPIT, epicutaneous immunotherapy; PNU, protein nitrogen units; W, weekly.

[a]Success rate was typically defined as a clinical improvement of at least 50%.

[b]Studies in normal horses measuring immune responses.

[c]Fed transgenic barley in 7 meals with a total of 500 g barley.

TABLE 3 Immunological data about allergy and allergen immunotherapy in humans, dogs and horses

Immunological parameters	Human	Dog	Horse
Changes with allergic disease	• CD4/CD8 ratio ↑ in blood • TARC ↑ in keratinocytes • CCR4+ T cells ↑ in blood • IL-5, IL-6, IL-10 IL-13, IFNγ ↑ in skin • IL-4, IL-31 ↑ in blood	• CD4+ T cells ↑ in dermis, CD8+ T cells ↑ in epidermis • CD4/CD8 ratio ↑ in blood • TARC ↑ in keratinocytes • CCR4+ T cells ↑ in blood • IL-5, IL-6, IL-10 IL-13, IFNγ ↑ in skin • IL-4, IL-31 ↑ in blood	• Mast cells ↑ in dermis • CD4+ T cells ↑ in dermis • Fox P3+/CD4+ T-cell ratio in dermis ↓ • IL-4, IL-13 ↑ in skin
Changes with AIT	• FoxP3+ CD4+ Treg ↑ • IL-10 ↑, IL-4 ↓ • IgE ↓, IgG4 ↑	• FoxP3+ CD4+ Treg ↑ • IL-10 ↑, IL-4 ↓ • IgE ↓, IgG4 ↑	Serum allergen-specific IgG and IgA ↑

3 | SUBCUTANEOUS ALLERGEN IMMUNOTHERAPY (SCIT)

3.1 | SCIT in human beings

AIT in people consists of an induction phase with increasing allergen doses followed by a maintenance phase over 3-5 years, to achieve tolerance at the highest possible safety level. Nevertheless, adverse effects occur (mostly during the induction phase) and include local reactions and systemic anaphylaxis.[15] These adverse effects are seen both in adults[15] and in children[16] and are more common with SCIT than with SLIT (Table 4) and with native allergens than allergoids.[15,16] The extended treatment times of AIT until clinical improvement, explained by the need to change an ongoing immune response, result in low patient compliance and high drop-out rates of both SCIT and SLIT.[17] Protocols for SCIT include classical (time-consuming) or abbreviated rush regimens. Efficacy of preseasonal treatments with grass and tree pollen was also documented.[18] A recent meta-analysis of venom allergen immunotherapy (VIT) indicated a substantial improvement of the quality of life in VIT-treated patients.[19] In VIT, a 3-day rush protocol is possible, although associated with a risk of local (42%) and systemic adverse reactions (10%).[20] The efficacy of subcutaneous immunotherapy for allergic rhinitis and asthma was recently confirmed by systematic reviews.[21] Patients with moderate asthma benefit most from SCIT, especially through a decreased use of inhaled glucocorticoids.[22] For pollen allergies, a rush schedule achieved efficacy even with intraseasonal application, although local adverse reactions were over 40%.[23] There is low-grade evidence that AIT could prevent new allergen sensitizations in people.[24] In human AD, there is only inconclusive evidence for the efficacy of SCIT.[4] Accordingly, current guidelines in children and adults recommend AIT only in selected AD patients sensitized to aeroallergens.[25] Similarly, so far there is no evidence for a beneficial use of SCIT for food allergies in human beings.[26]

3.2 | SCIT in the dog

Subcutaneous allergen immunotherapy has been conducted in dogs with AD for more than half a century.[27] Atopic dermatitis is diagnosed by history, clinical examination (Table 5) and exclusion of

TABLE 4 Comparison of different routes of AIT in humans and dogs

AIT route	Humans	Dogs
SCIT	Strengths • Long-standing expertise • Greatest number of clinical studies • SCIT allergoids have the lowest number of side effects in adults and paediatric patients Weaknesses • Patient compliance needed for injections (up to 70% dropout) • Different dosages, type of allergens, adjuvants, formulation, treatment duration in studies • Few paediatric studies available • No prophylactic population studies • No biomarker for the clinical success of AIT	Strengths • Extensive experience • Low rate of acute adverse effects • No long-term adverse effects • Established success rate Weaknesses • Although rare, anaphylactic reactions are possible • Regular visits to the veterinary clinic to administer injections
SLIT	Strengths • SLIT is easily administered by the patient • Immunological effect clearly demonstrated Weaknesses • Patient compliance needed for daily administration (up to 70% dropout)	Strengths • No anaphylactic reactions reported • Easily administered at home Weaknesses • Very limited data published • Unclear success rate as of yet
ILIT	Strengths • Strongest induction of immune response Weaknesses • Needs trained personnel • Few clinical studies available	Strengths • Most inexpensive AIT • Low rate of acute adverse effects Weaknesses • Limited data published • Unclear success rate as of yet • Unclear long-term adverse effects
EPIT	Strengths • Easy application • Commercially available for egg, milk and peanut Weaknesses • Strong local reactions, erythema, pruritus • Few studies so far available • Limited producers	• No data available, difficult and impractical in dogs and cats due to the need to fix patches for longer time periods to the skin

other causes of pruritus.[28] Following diagnosis, intradermal or serum testing is used to identify relevant allergens in the light of the animal's history.[29] Relevant allergens in veterinary allergology include mites, moulds and pollens and were recently reviewed.[30] Allergen immunotherapy is recommended in dogs with clinical signs extending over most of the year or for dogs with seasonal clinical signs that are severe and nonresponsive to symptomatic medication.[31] Clinical contraindications for AIT in veterinary medicine are not known.[27]

Neither uniform recommendations nor solid scientific data exist regarding the optimal amount of individual allergen or the optimal number of allergens included in the extract used for AIT.[31] Retrospective studies evaluating high- and low-dose protocols and immunotherapy with a large number vs few antigens showed similar success rates.[27] However, the number of dogs included in the studies was universally low and well-powered, double-blind, randomized studies are lacking.[27] One study showed a decreased success rate of immunotherapy when pollens and mould spores were mixed in the same vial.[32] Separating mould spores and pollens into two vials (as recommended in human allergology)[33] led to an increase in treatment success and was recommended in a subsequent study.[34] However, this recommendation is not uniformly accepted and is probably most relevant for aqueous extracts.

With classical AIT in veterinary medicine, the allergen extract is injected subcutaneously in increasing volume/concentration during the induction period of four weeks to four months (Figure 1), until a maintenance dose is reached and subsequently administered, typically every three to four weeks.[31,34] The allergen dose and frequency of administration are adapted to the individual animal based on the pruritus observed.[35] Therapy is continued for at least 12 months before the outcome is evaluated. Some patients will require lifelong therapy; other patients will have sustained benefit for months to years after cessation of AIT. Success rates vary, but in most studies over half of the dogs have a good-to-excellent response.[27,31] The first studies of SCIT with recombinant, adjuvanted Der f2 antigens showed promising results in experimentally sensitized atopic Maltese-beagle crossbred dogs.[36]

Mueller et al reported rush immunotherapy in 30 dogs, 22 of which completed the 6-h rush protocol without problems.[37] In seven dogs, the protocol was discontinued prematurely due to increased pruritus; one dog developed generalized urticarial wheals. All adverse effects responded to the administration of oral

TABLE 5 Clinical signs of allergy in dogs, cats and horses

	Dogs	Cats	Horses
Cutaneous signs	• Pruritus affecting face, ears, distal limbs, ventrum, perianal and inguinal area leading to alopecia, excoriations, lichenification and hyperpigmentation • Secondary infections with *S. pseudintermedius* and *Malassezia pachydermatis* • Urticaria and angioedema	• Pruritus leading to alopecia, excoriations and ulcers • Linear granulomas • Eosinophilic plaques • Indolent ulcers • Crusted papules (miliary dermatitis) • Secondary infections with *S. aureus* or *S. pseudintermedius*	• Pruritus leading to alopecia, lichenification and excoriations • Urticaria and angioedema • Eosinophilic granuloma
Respiratory signs	• Not recognized as a problem	• Asthma	• Recurrent airway obstruction

prednisolone. In a subsequent double-blind, randomized study, subcutaneous RIT was compared to conventional immunotherapy.[38] A significant decrease in lesion, pruritus and medication scores was seen with RIT; there was, however, no difference long term between conventional and RIT outcomes. There was also no statistically significant difference in the time to maximal improvement (6.8 months with RIT and 9.2 months with conventional immunotherapy). Adverse effects were not seen. In a more recent case series, RIT was also reported with alum-precipitated allergens with significant improvement in pruritus and medication scores.[39] In a review of allergen immunotherapy in animals,[27] RIT in dogs was deemed a safe and effective alternative to conventional immunotherapy. However, well-powered, double-blind, randomized studies are urgently needed to confirm those preliminary findings.

The most common adverse effect with SCIT is increased pruritus. This adverse effect is typically addressed by use of concurrent antipruritic medication and modification of the dose and frequency of allergen extract administration. Systemic reactions have been reported to occur in approximately 1% of the dogs and include weakness, depression, sleepiness, panting, diarrhoea, vomiting, urticaria and angioedema and anaphylaxis.[27]

4 | SUBLINGUAL IMMUNOTHERAPY (SLIT)

4.1 | SLIT in human beings

In SLIT, allergen extracts in liquid or tablet form are placed under the tongue to boost tolerance to the allergens and relieve clinical symptoms. SLIT is considered a convenient way to treat allergic rhinitis[40] with fewer systemic reactions than SCIT (0.056% vs 1%).[41] Different protocols and dosages are found on the market. Compared to SCIT, SLIT has been associated with a decreased compliance, possibly due to the necessary daily administration.[17,41] Meta-analyses and reviews demonstrate a well-documented efficacy for SLIT in particular for pollen and house dust mite allergens in patients suffering from allergic rhinitis.[11] Recently published clinical trials in asthmatic subjects with house dust mite SLIT in tablet form led to the implementation of AIT as official treatment algorithm of the Global Initiative for Asthma Management and Prevention.[42]

For desensitization with food antigens, oral and sublingual routes (Table 4) are chosen most often. Oral AIT against IgE-mediated food allergens was effective in raising the threshold of reactivity with sustained benefit,[43] but was associated with an increased risk of systemic reactions and substantially increased risk of local adverse reactions. Oral AIT showed a higher efficacy but systemic adverse events were also higher than with SLIT and epicutaneous immunotherapy.[44]

At present, SLIT is the only AIT administered without adjuvants in Europe, while in the United States, SCIT usually is based on aqueous extracts without adjuvants. However, vector and carrier systems that enhance allergen uptake into dendritic cells, while improving its mucosal targeting and safety, are a focus of research.[45]

4.2 | SLIT in dogs

A pilot study and subsequently a placebo-controlled trial using SLIT in a dust mite–sensitized beagle model with homogenized mite paste being administered by smearing on the gums once weekly failed to demonstrate either efficacy or a change in allergen-specific IgE levels.[46] In a small, uncontrolled 6-month pilot study in mite-sensitive dogs, using a twice-daily protocol adapted from human SLIT, clinical improvement with reduced pruritus, lesions and a decreased medication score occurred in the majority of dogs.[14] Improvement was accompanied by reductions in mite allergen-specific IgE and increases in allergen-specific IgG. An unpublished larger, open, uncontrolled study reported a "good-to-excellent" response in approximately 60% of the dogs, using the same treatment protocol.[47] In this study, SLIT was reported to be effective in half of the animals that had failed SCIT, and was used safely in dogs with prior anaphylactic reactions to SCIT. SLIT may be a useful alternative to SCIT in the dog and is becoming more available worldwide.

In pets with food allergy, avoidance of offending allergens is often accomplished with commercial limited-ingredient or hydrolysed-protein diets. Most animals are happy to eat the same food every day, despite protests to the contrary from their owners. However, especially in families with small children and with finicky eaters such as cats, avoidance is not always possible. In contrast to symptoms in people, dietary hypersensitivity in animals predominantly manifests with nonfatal cutaneous and gastrointestinal signs. Food-related

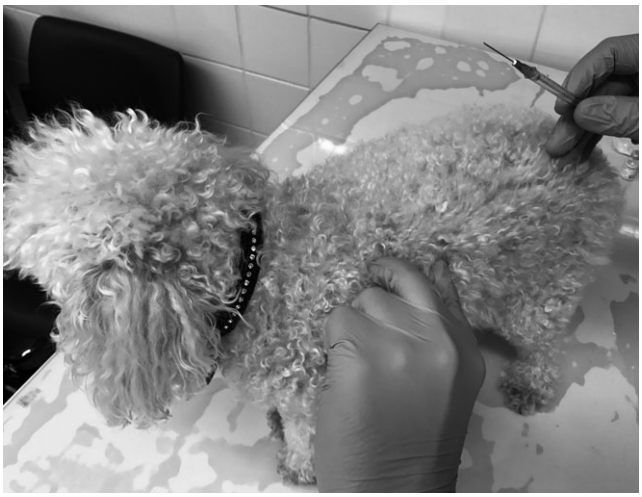

FIGURE 1 Subcutaneous injection of allergen extract during a SCIT protocol in a 5-year female Toy Poodle

anaphylaxis is virtually nonexistent. Thus, AIT for food allergy has limited relevance in pets. Nevertheless, one study has evaluated the feasibility and safety of using food allergen–based SLIT in dogs.[48] This may be well worth studying as a model for food allergen AIT in people.

5 | INTRALYMPHATIC IMMUNOTHERAPY (ILIT)

5.1 | ILIT in human beings

ILIT is an evolving form of allergen immunotherapy that includes three injections of allergen extract directly into the lymph node over a period of 12 weeks.[49,50] ILIT introduces lower doses of allergen to a large number of highly immunocompetent lymphocytes to maximize probabilities for tolerance induction, while reducing the risk for adverse effects. The cumulative dose is approximately 1000 times lower than with SCIT. Its first human clinical application was with a fusion protein (MAT-Fel d 1) consisting of the major cat dander allergen 1, the translocation sequence (TAT) of human immune deficiency virus protein and a truncated peptide of the invariant chain, named MAT-Fel d 1) that was administered with alum as adjuvants intralymphatically and significantly improved the clinical symptoms of allergic rhinitis,[49] presumably by induction of T-cell nonresponsiveness. ILIT has been effective in birch– and grass pollen–allergic patients.[50] In a recent study of patients with allergic rhinitis, the effects lasted for one year, but two anaphylactic episodes were recorded, questioning the postulated safety of ILIT.[51] However, clinical improvement in human patients was described to be greater with ILIT than with SCIT.[52]

5.2 | ILIT in dogs

Intralymphatic immunotherapy in dogs was first reported more than 30 years ago,[53] when some dogs not responding to conventional immunotherapy improved with the allergen extract administered intralymphatically. Recently, intralymphatic immunotherapy (Figure 2) with alum-precipitated allergens was reported in dogs with a comparable efficacy to conventional immunotherapy.[54] Well-powered, double-blind and randomized studies evaluating intralymphatic immunotherapy are needed. In addition, long-term effects of intralymphatic immunotherapy are not known in any species.

6 | EPICUTANEOUS IMMUNOTHERAPY (EPIT)

6.1 | EPIT in human beings

EPIT as a new route of AIT is interesting for high-risk food allergic patients as only low doses of allergens are applied (EPIT: 250-500 mcg, compared to 300 mg-4 g in OIT, or 2.5-7.5 mg in SLIT).[44] In a multicenter, double-blind, randomized, placebo-controlled study with peanut-allergic patients, EPIT lead to a tenfold or greater tolerance in almost half of the patients.[55] Even in the patients with a high risk of adverse effects, mostly local (patch) reactions were observed. EPIT induced peanut-specific IgG4 with a trend towards a reduction in the Th2 bias.[55] Products for egg and milk EPIT are also available commercially. Overall, the epicutaneous route seems promising in terms of safety and efficacy.

6.2 | EPIT in dogs and other animals

Epicutaneous immunotherapy has not been reported in animals to date.

7 | AIT IN THE CAT

The most common feline allergic diseases are probably confined to the skin. In contrast to dogs, where very good clinical diagnostic criteria for AD exist,[56] cats exhibit a large variety of disparate cutaneous reaction patterns that are attributed, often without proof, to an allergic aetiology.[57] "Feline atopic dermatitis" is a diagnosis of exclusion. Cats are the only domestic animal species that exhibits asthma in a fashion very similar to the human disease.[58] As in human asthma, it is not always clear whether hypersensitivity to environmental allergens plays a role in the disease. Limited studies of intradermal testing in asthmatic cats provide some evidence that sensitization may be present in some cases.[59]

AIT is used commonly as a treatment for presumptive atopic skin disease in cats with success rates similar to those in dogs.[57] Likewise, AIT has been proposed as treatment for feline allergic asthma, but studies to date are limited to experimentally sensitized cats in the laboratory.[60] Results of these initial studies are encouraging, however, and AIT for feline respiratory allergy deserves to be studied further. As in human beings, the shock organ of cats is the lung and as such AIT should be undertaken with epinephrine at hand.

FIGURE 2 Intralymphatic injection of allergen extract in the popliteal lymph node of an 8-year, male French bulldog

8 | EQUINE AIT

Reports regarding AIT in horses are largely anecdotal.[61] While equine asthma is a frequent condition in stabled horses, AIT has not been widely used to date for this condition perhaps because the causative allergens are often not identified.[62] Most of the prospective studies evaluating AIT were conducted in horses with insect hypersensitivity. Equine hypersensitivity against biting midges (*Culicoides* (*C.*) spp.) is observed worldwide and can cause both severe dermatitis and affect performance. A placebo-controlled, double-blind trial evaluating equine AIT was reported in 14 horses with *Culicoides* hypersensitivity.[63] Half of those horses were treated with 7500 protein nitrogen units of *Culicoides* whole body extract every three weeks, half with placebo. Only one horse in each group improved. In another study, ten horses with chronic long-standing *Culicoides* hypersensitivity were treated with a crushed body extract of 10-20 mg of *C. variipennis*.[64] Eight of the ten horses improved in the first season, and six of those maintained their improvement in the second summer after starting immunotherapy, while control horses showed severe clinical signs in both seasons. Whether those differing results are due to the different study designs, dose or type of allergen is unclear. *Culicoides* hypersensitivity does not occur in Iceland but has a high prevalence in horses imported from Iceland into Europe.[65] With the aim of developing a preventive therapy against *Culicoides* hypersensitivity, and in contrast to past studies which used whole body extracts of *Culicoides* spp., Icelandic horses were vaccinated with four recombinant *C. nubeculosus* allergens (rCul n 1, rCul n 2, rCuln 5 and rCul n 9, 10 μg each) intralymphatically or intradermally in the presence or absence of adjuvant (TLR-9 agonist, IC31®).[66] An increase in specific IgG was observed, more markedly in the adjuvant groups, accompanied by increased IL-10. In a subsequent study comparing intralymphatic immunization with four recombinant *C. nubeculosus* allergens in aluminium hydroxide alone or combined with monophosphoryl lipid A (MPLA) as adjuvant, a significant increase in allergen-specific IgA and IgG, but no production of allergen-specific IgE was noted during the 32-week trial for both adjuvant groups. Furthermore, the induced IgG antibodies had the capacity to block IgE-binding to the allergen in vitro, an important feature of successful AIT. A clinical rechallenge with *Culicoides* midges was not performed in those studies. Interestingly, immunization with recombinant allergens in alum/MPLA but not in alum only induced a significant increase in IL-10 and IFN-γ.[67] Another interesting approach in horses is the development of preventive oral immunotherapy (OIT) by application of transgenic barley flour expressing *Culicoides* allergens. In a pilot study, Icelandic horses treated by OIT with transgenic barley expressing the *Culicoides* allergen Cul n 2, a hyaluronidase, developed a Cul n 2-specific IgG response. The induced antibodies cross-reacted with the corresponding allergen derived from another *Culicoides* species, *C. obsoletus* (Cul o 2), and were able to block binding of Cul n 2- as well as Cul o 2-specific IgE from horses affected with *Culicoides* hypersensitivity. This approach might be a useful alternative for prevention and treatment of *Culicoides* hypersensitivity.[68] Only one retrospective study was published looking at the success rate of AIT in 32 horses with environmental allergies.[69] An improvement of clinical signs with AIT was reported by 84% of the owners; more than half of the owners could cease concurrent medications. AIT was discontinued by 75% after an average of two years; two-thirds of those horses did not show recurrence of clinical signs after ceasing AIT.

9 | AIT IN OTHER SPECIES

Allergen immunotherapy has been evaluated in a number of studies using mouse models of human atopic asthma or atopic dermatitis, but discussing those models is beyond the scope of this paper. However, therapeutic AIT has also been used anecdotally in a number of other species. One of the authors (RSM) has used this treatment modality in an allergic seal, a parrot and a snow leopard, and case reports have been published in a black leopard[70] and a camel.[71]

10 | THE FUTURE OF AIT

10.1 | The future of human AIT

The most urgent need is to improve safety and achieve shorter treatment periods to improve patient compliance (Table 6).[17] This can be accomplished by Th1 adjuvants such as monophosphoryl lipid A,[72] instead of aluminium hydroxide. SCIT using allergoids was shown to be safer than injections with native allergens.[15,16] SCIT is, however, not optimal for antigen uptake and transport to regional lymph nodes. ILIT may be a promising future option due to its efficacy and relative safety. EPIT utilizes even lower allergen dosages (approximately half of SCIT) and may be an additional safe treatment option in the future, especially for patients at high risk for anaphylaxis. However, pruritus

and eczematous lesions at the patch site may demoralize patients and decrease compliance. SLIT would benefit from improved delivery systems increasing antigen uptake by dendritic cells[45] and enhanced safety by entrapping the allergens, for example into biodegradable particles.[73] A continuous release of allergen from biodegradable particles may increase patient compliance with SCIT due to the need for fewer injections. Allergen extracts generally have a heterogeneous composition, are difficult to standardize and do not fulfil the more recent legislative requirements of medicinal products. This has led to a dramatic reduction in available human allergen therapeutics, which currently is a major concern in human allergy medicine.[74]

10.2 | The future of veterinary AIT

Protocols for AIT in animals are largely nonstandardized and subject to enormous variation. These protocols need to be compared and optimized to produce maximal efficacy (Table 6). Given the difficulty and expense of conducting large-scale clinical trials, this will be a challenge. However, some important measures may be accomplished with coordinated effort. The International Committee on Allergic Diseases of Animals (www.icada.org) is one group attempting to promote such efforts.

Biological products for use in animals in the United States are overseen by the U.S. Department of Agriculture (USDA) under a different set of laws than drugs which are overseen by the U.S. Food and Drug Administration (FDA). Dose-determination studies, short- and long-term safety analysis, and rigorous, large-scale controlled clinical trials in affected animals, as would be required for an FDA-regulated drug product, are cost-prohibitive for veterinary medicine. However, a reasonable increase in regulatory efforts by FDA or the European Medicine Agency (EMA) may lead to an increased number and quality of clinical studies evaluating AIT in animals.

Major allergenic epitopes for animals are not necessarily the same as those for human beings.[30] For example, dogs may or may not be sensitized to Der f 1 or Der f 2, but are frequently sensitized to a high-molecular weight, heat-stable epitope designated Der f 15.[75] Thus, the use of recombinant allergens developed for humans will not necessarily help animals. Defining the important major allergens for common substances could be a first step for providing some measure of standardization to veterinary allergen extracts. This would in turn permit standardized dosing, preparation of recombinant allergens, determination of T-cell epitopes, use of peptide immunotherapy and other advances. Dose dependency of AIT efficacy has long been observed in humans.[11] Unfortunately, animal studies evaluating varying doses are of low quality and revealed conflicting results.[27] Thus, the important question of the optimal dose remains unanswered in animals.

TABLE 6 Future research needs in human and veterinary allergen immunotherapy

Human AIT	Veterinary AIT
• Reduction of numbers of injections • Reduction of daily SLIT • Development of vaccine concept with long-term memory • Improvement of adjuvants • Employment of Th1 or immunomodulating adjuvants instead of Th2 adjuvants like alum • Prophylactic vaccination against most important allergens in predisposed/atopic individuals • Family planning: AIT before pregnancy for next-generation prophylaxis	• Identification of major allergenic epitopes for different mammalian species • Standardization of allergen preparations intended for veterinary use • Dose-optimization studies in animals for both SCIT and SLIT • Optimizing allergen delivery via different adjuvants or immunomodulators for both SCIT and SLIT

Clinical trials have attempted to evaluate parameters of successful AIT in veterinary medicine. Despite the development of validated clinical scoring systems for dogs,[76,77] objective data are lacking due to the pervasive and prominent placebo effect and the small number of animals in previous reports. Studies in human patients rely not only on clinical criteria, but also on biomarkers of successful treatment such as ventilatory mechanics and changes in specific immunoglobulin levels. Objective changes that could be measured are notably under-researched in veterinary medicine. Over 10 years ago, it was demonstrated that total serum IgG1 concentrations increased with successful AIT in dogs,[78] the IgG response of dogs during dust mite AIT has been studied and the nature and functional characteristics of canine IgG subclasses have recently been described in much greater detail.[79] Significant increases in Treg cells and IL-10 have been demonstrated in dogs undergoing successful AIT.[13] Yet, none of these findings has resulted in useful, objective biomarkers that perhaps could be more rapid measures of AIT success.

Canine AD has a remarkable similarity to human AD. This allows veterinarians to examine new research findings in people for ideas about what might be useful in dogs, and vice versa physician allergists may be able to use research in animals. Potentially important advances in human beings that have yet to be well explored in dogs include the use of modified allergen preparations, such as allergoids, recombinant major allergens or allergen peptides. Enhancing the effect of allergens using adjuvant-like manipulations such as IL-10 inducers, packaging in virus-like particles (VLPs) or, in the case of SLIT, mucoadhesive polymers, holds promise. Co-administration of immunomodulators such as CpG oligodeoxynucleotides, MPLA or specific monoclonal antibodies might "push" the immune response in the desired, nonallergic direction, thus possibly allowing AIT to work more effectively. The first pilot studies using CPG oligodeoxynucleotides in vitro[80] and in vivo[81] for canine atopic dermatitis or local application of gelatin nanoparticle–bound CPG-ODNs by inhalation for equine asthma[82] have been reported in veterinary medicine with promising results. Efficacy may be increased by combining any of the above with new methods of administration such as intralymphatic injection in companion animals. OIT with transgenic foods as explored in horses[68] may also be of interest particularly in infants and young children as early allergen exposure associated with decreased development of clinical signs. However, larger controlled studies are needed to provide data about optimal allergen

concentrations and type of immunomodulating adjuvants as well as their success rate.

Despite its limitations, allergen immunotherapy remains a viable treatment option for mammalian allergies of all types. The mechanism of action of allergen immunotherapy seems to be similar in all types of mammals. Sharing and comparing our experiences among all species is an important way we can potentially advance the field.

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CONFLICT OF INTEREST

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