

## The future of immunotherapy for canine atopic dermatitis: a review

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Allergen specific immunotherapy (ASIT) is a foundation treatment for canine atopic dermatitis (CAD), though few critical studies have documented its effectiveness as a disease-modifying treatment in dogs. The mechanisms by which ASIT works in dogs have not been elucidated, although they are likely to parallel those known for humans. Current ASIT approaches in CAD focus on either subcutaneous or sublingual administration. Greater knowledge of major allergens in dogs, ideal dosage regimes and details of allergen admixture are likely to lead to better efficacy in CAD. Evaluation of biomarkers for successful therapy may also be of benefit.

Potentially important advances in human medicine, that have yet to be explored in dogs, include use of modified allergen preparations such as allergoids, recombinant major allergens or allergen peptides; modification with adjuvants; or packaging of the above in virus-like particles. Co-administration of immunomodulators such as CpG oligodeoxynucleotides or specific monoclonal antibodies might direct the immune response in the desired direction while calming the “cytokine storm” of active disease.

Initial trials of alternative routes of administration such as intralymphatic immunotherapy have yielded exciting results in humans, and continuing study in dogs is underway. Progress in ASIT of human food allergy may provide clues that will assist with improved diagnosis and patient management of CAD. Importantly, further study must be undertaken to clarify the conditions under which ASIT is a valuable treatment modality for dogs.

### Introduction: why allergen-specific immunotherapy?

In 1941, Wittich published the first report of using allergen-specific immunotherapy (ASIT) for the successful treatment of allergy in a dog.<sup>1</sup> Seventy five years later, it is appropriate to examine how far we have come and to where we might travel in the future, with regard to this important and foundational treatment for canine atopic dermatitis (CAD).

A significant number of studies in people, and a slowly increasing number in dogs, have documented the effectiveness of ASIT for allergic diseases. It is the only current treatment for allergy that can modify, or reverse, at least part of the pathogenesis of this condition, both alleviating clinical signs and preventing progression of disease.<sup>2</sup> This modification is accomplished without the possible long-term adverse effects of a lifetime of drug treatment, with minimal adverse effects, and with the potential of long-lasting effectiveness. Yet, there are a great many unresolved questions about ASIT, especially with regard to defining more clearly its efficacy in animals, and answering these is likely to result in even greater therapeutic efficacy in the future.

One key question revolves around differences in atopic dermatitis (AD) and other allergic syndromes such as

respiratory disease. The bulk of evidence for the effectiveness of ASIT in humans is for the management of allergic rhinitis and asthma; in fact, some authorities have considered its usefulness in human AD to be questionable. On the one hand, this position has been reinforced by systematic reviews concluding that the strength of recommendation for use of ASIT in human AD is weak;<sup>3</sup> on the other, some clinical trials and reports of patient experience have been highly encouraging, even in refractory cases.<sup>4–6</sup>

In dogs, this controversy seemingly never arose, perhaps due to early reports of success in CAD; as even in a placebo-controlled trial, results provided initial reason for optimism in allergic skin disease.<sup>7–9</sup> Based on these and other studies, “response rates” (typically quoted as percentage of dogs that experience at least 50% improvement in clinical signs) are typically quoted as 60–70%. Although not perfect, ASIT has a clear role as a useful and important part of multimodal therapy of CAD.

### Mechanisms: the known and the unknown

It is important to briefly review what is known about how ASIT works, to understand how proposed advances may exert their effects. The mechanisms by which ASIT works in dogs have not been completely elucidated, although they are likely to parallel those known in humans: early reduction in effector cell activity (eosinophils, basophils, mast cells) followed by a long-term immunologic shift from a T helper 2 (Th2) cell to a T helper 1 (Th1) cell response and development of immunological tolerance.<sup>10–12</sup> These shifts are accompanied by an increase in forkhead box P3 (FOXP3) + regulatory T (Treg)

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cells, and an increase in cytokines such as transforming growth factor beta (TGF $\beta$ ) and interleukin (IL)-10. As a result, there is an increase in allergen-specific immunoglobulin (Ig)G, especially IgG4 and, with extended treatment, a decrease in allergen-specific IgE. In dogs, although much less is known, a shift to a Th1 cell response, increases in IgG levels, the appearance of more Treg cells and increases in IL-10 levels have all been demonstrated, thus establishing the parallels to ASIT in humans.<sup>13–16</sup>

With sublingual administration, there is the additional effect brought about by oromucosal dendritic cells, frequently discussed for immunotherapy in people but unexplored in dogs. As with other dendritic cells, oromucosal dendritic cells are responsible for allergen uptake, processing and presentation to T-lymphocytes. They are abundant in the oral mucosa and have unique functional characteristics, being the key cell in induction of oral tolerance, the immunological function by which the immune system is set to a default of nonreactivity to substances placed in the mouth (e.g. foodstuffs).<sup>17,18</sup> Physician allergists take advantage of this normal, homeostatic process when attempting to desensitize a patient via the oromucosal route.

### **Review of current approaches to ASIT in dogs: how well does it work and can we do better?**

Current ASIT approaches in CAD focus on either subcutaneous (SCIT) or sublingual (SLIT) administration. Injectable immunotherapy has been conducted for decades and SLIT is a newer modality that has only recently become available for dogs in some countries. There are aspects of both methods that are poorly understood and elucidating these may facilitate improvements in therapy.

With regard to SCIT for dogs, two methods have evolved, predominantly based on availability and regulatory approvals in North America versus Europe. All SCIT in North America is undertaken with aqueous, saline-phenol preserved extracts provided by several manufacturers. Typically, two- or three-vial sets of increasing concentration are used, beginning with frequent injections of dilute extract and progressing to less frequent injections of concentrated extract as maintenance treatment. In Europe, use of alum-precipitated allergen extracts has been more common. Here, adsorption of the allergen molecules to an aluminium hydroxide adjuvant provides a slower-release formulation, which has the advantage of less frequent injections. However, concern is being increasingly raised regarding the possible adverse effects of chronic aluminium exposure, and the fate of aluminium-based adjuvants widely used in vaccine products is uncertain.<sup>19</sup>

Administration of SLIT has been a popular method of human ASIT for many years in European countries, in some regions eclipsing the use of SCIT. Most studies evaluating the efficacy of SLIT are therefore European. In the past, these studies have yielded conflicting results, which is predictable given that significantly different dosage and administration protocols have been used. More recently the World Allergy Organization has

published analyses and position papers which conclude that SLIT is an effective treatment with a favourable safety profile compared with SCIT.<sup>20</sup> The lower popularity of SLIT in the United States reflects that registered products have not been available until very recently and, with these, its use is increasing in human medicine. In dogs, use of SLIT has only recently been reported.<sup>21</sup>

There are numerous well-controlled studies of ASIT in human allergic disease that demonstrate efficacy, and critical reviews and meta-analyses that support this conclusion.<sup>22</sup> By contrast, in CAD very few studies have been published, and they are often small, uncontrolled and/or have confounding variables that make interpretation of results difficult. In a blind, placebo-controlled trial of 51 dogs, a response rate of 59% in allergen-treated dogs versus 21% in the placebo-treated group was reported.<sup>7</sup> More representative is another retrospective, uncontrolled study, where 60% of owners administering injections reported at least 50% improvement in their dogs. It should be noted that of the dogs receiving injections, 65% still required additional medication for control – which brings into question the ability of the owner to accurately judge the effectiveness of the ASIT itself.<sup>8</sup> Practice guidelines for treating CAD, employing a strength-of-recommendation taxonomy (SORT), continue to rate the quality of published evidence for efficacy of ASIT as limited, and at best based on inconsistent or limited quality patient-oriented evidence.<sup>23</sup>

With such limited evidence of efficacy, why then has a treatment so commonly used and recommended not been subjected to more frequent and rigorous study in dogs? Part of the reason, no doubt, is the high cost and time requirement for performing large, controlled studies of a complex disease that may require a year or more to respond to the intervention. Another part of the reason may be related to regulatory issues. Biological products (including allergenic extracts) are often subject to wholly different regulatory requirements than drugs, although the situation varies substantially between countries. In the United States, for example, veterinary biologicals are overseen by the US Department of Agriculture (USDA) under a different set of laws than drugs, which are overseen by the US Food and Drug Administration (FDA).<sup>24</sup> Historically, biologicals have been mainly evaluated for qualities such as safety, purity, sterility and consistency in manufacturing, and current veterinary allergen extracts received USDA licensure decades ago based on those standards. Dose-determination studies, short- and long-term safety analysis, and rigorous, large-scale controlled clinical trials in affected patients, as would be required for an FDA-regulated drug product, were not done – they were not required. This stands in contrast to allergenic extracts for human use, which are FDA-regulated and, therefore, were subjected to much more stringent standards and rigorous proof of efficacy.

Beyond consideration of efficacy, it is clear that ASIT protocols for dogs lack standardization and are subject to substantial variation. Veterinary clinicians use different allergen dosage regimes with unstandardized allergen extracts that vary in composition and potency between manufacturers and from batch to batch, using different

schedules of administration, differing concurrent treatments and with different 'rules' about how to mix extracts together. Given this, there are many steps that could theoretically be taken to examine and compare these procedures, and more carefully optimize protocols to produce maximal patient efficacy. Many of these may be completely impractical, given the difficulty and expense of conducting large-scale clinical trials. However, some important measures may be possible to accomplish with coordinated effort.

An important example would be to establish the major allergenic epitopes for dogs, especially for common allergens, and use this information to provide some measure of standardization to allergen extracts.<sup>25</sup> This information would permit standardized dosing, preparation of recombinant allergens, determination of T-cell epitopes, use of peptide immunotherapy and other advances. This has certainly been the course in human ASIT, as guidelines from the European Medicines Agency and other regulatory bodies – which increasingly mandate standardization of extracts – have prompted more clinical studies on optimal dose-finding for both safety and efficacy. The body of clinical evidence will increase and lead to more products with documented efficacy and safety. In veterinary medicine, central to the above is answering the question "what is the optimal dose of allergen extract in dogs?" Dose-dependency of ASIT efficacy has been long-observed in human trials and recent mouse models.<sup>26,27</sup> Not only the absolute dose, but also the dosing intervals have measurable effects on efficacy under some circumstances. Unfortunately, these effects remain unstudied for ASIT in animals.

Extending these thoughts further, what will be the role of rush immunotherapy in CAD in the future? At present, it appears that rush protocols are used by comparatively few veterinary clinicians, although they are the one specific administration schedule that has been examined in dogs and found to be equally effective to a conventional injection protocol.<sup>28</sup> Rush immunotherapy has a clear advantage of limiting the number of injections that an owner must give at home when initiating ASIT, although safety concerns are higher as well as the cost for a brief hospitalization under observation.

Likewise, it is hoped that veterinary clinicians will be able to employ a more scientific approach to allergen prescription formulation. With the marked variation among clinicians in how, and how many, extracts of different types are mixed together, it is not surprising that there is a variable outcome. Should the number of extracts in a mixture be limited from eight to ten to 12 or unlimited? Should protease-containing extracts such as moulds be admixed, or administered only by separate injection? Should the mixture be based upon results of intradermal testing or serological testing or both? Or made uniform for each dog, based on what allergens are predominant in a region? In humans, these debates are controversial, although recent large-scale studies have provided some guidance. Evidence suggests that in polysensitized humans, treatment with a single, dominant allergen is as effective as multi-allergen ASIT, even though polysensitization is more prevalent.<sup>29,30</sup> This "less is more" approach – prevalent in Europe – is unpopular in the United States

among physician allergists. The evidence for limiting the number of allergen extracts used in treatment is in contrast to protocols used by most veterinary clinicians and, if applicable to dogs, will require a modification to our thinking. Authoritative guidelines specify that mould extracts should not be mixed in the same vial as pollens, as there is clear evidence that pollen allergens will be degraded by mould proteases during storage.<sup>31</sup> Despite similar (though less) evidence in dogs,<sup>32</sup> many veterinary clinicians continue to recommend this practice. Further research is clearly indicated to answer this question, among many others.

A central problem in answering many of these questions is that most studies in veterinary medicine evaluating the parameters of successful ASIT have been clinical trials. In conducting such trials, there is significant difficulty in obtaining reproducible, objective data based on validated scoring systems; the patient variability that confounds analysis; the pervasive and prominent placebo effect; and the very large number of dogs necessary to study effect sizes that may be small, but important. Turning again to the human ASIT experience, studies rely not only on clinical criteria, but also on biomarkers of successful treatment. Most studies report not only subjective patient response, but also objective changes in parameters such as ventilatory mechanics and changes in specific immunoglobulin levels. Objective changes that could be measured are notably under-researched in veterinary medicine. The initial proof-of-concept demonstration that accelerometer based "activity monitors" could provide objective measures of pruritus in dogs has not yet been adopted in clinical trials, although advances in this technology may facilitate such in the future.<sup>33</sup> Over 10 years ago, it was demonstrated that total serum IgG1 concentrations increased with successful ASIT in dogs,<sup>13</sup> and the IgG response of dogs during dust mite ASIT has been studied in even more detail.<sup>15</sup> The nature and functional characteristics of canine IgG subclasses have recently been described in much greater detail.<sup>34</sup> Significant increases in Treg cells and IL-10 have been demonstrated in dogs undergoing successful ASIT.<sup>16</sup> Yet, none of these findings has been extended or explored to the extent that these or other biomarkers could be useful, objective and perhaps more rapid measures of ASIT success with which to study different interventions.

### New approaches: animal models are shedding light

Canine AD appears to have marked similarity to human and murine models of AD, and new research findings in people may bring forth ideas about useful management strategies for dogs. Important advances in human medicine that have yet to be explored in dogs include 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 or specific monoclonal antibodies could direct the immune response in the

desired, nonallergic direction while calming the “cytokine storm” of active disease, thus allowing ASIT to work more effectively. Combining any of the above therapies with new methods of ASIT administration such as intralymphatic injection could be potentially effective for dogs.

Modified allergen preparations have substantial potential for the enhancement of ASIT. Allergoids are the simplest of these modifications in concept: native allergen is chemically treated to either polymerize it or, in some cases, render it monomeric. The resulting allergoids retain immunological activity, yet have lower ability to activate mast cells and other potential mediators of immediate-type hypersensitivity reactions.<sup>35</sup> Their major advantage in human medicine is safety, with less chance of a life-threatening anaphylactic reaction. Because these reactions are relatively uncommon and typically not life-threatening, allergoids may be a less exciting concept in dogs.

Conversely, recombinant allergens and allergen peptides may have greater potential in veterinary dermatology. Recombinant allergens, where an entire major allergen molecule such as Der f 1 is produced synthetically, have their major advantage in purity and consistency resulting in precise and uniform dosing. Of course, a significant issue here is that most individuals, canine or otherwise, are sensitized against a number of major allergens of each substance, such that a very large number of recombinant products might need to be manufactured and tested; not to mention the need for determining the best way to combine them. Peptide immunotherapy carries this principle a step further; major allergens are examined to find specific, even smaller amino acid sequences within the allergen to which T-lymphocytes may react (“T-cell epitopes”), yet are far too small to trigger anaphylaxis. A combination of these peptides can be created that equals the full immunological potency of the native allergen, without the risk of adverse reaction. Peptide allergen desensitization is currently at its most impressive in human cat dander allergy, where initial trials demonstrated a beneficial and long-lasting effect (years) after administering only four doses over a few months.<sup>36,37</sup>

Beyond modifying the specific allergen molecule; non-specific enhancement of its desensitizing effect is another active area of research. Adjuvanting the allergen to enhance its delivery such as packaging in VLPs prior to injection, or in a mucoadhesive polymer to prolong oromucosal contact in SLIT, is promising.<sup>38–41</sup> Immunomodulating substances that direct the immune system towards a Th1 cell response and/or tolerance – again as a nonspecific action that could be administered along with any specific allergen – have been studied, but principally in mouse models.<sup>42,43</sup> Administration of CpG oligodeoxynucleotides either as sole therapy or along with specific allergen may have benefit, including in dogs.<sup>40,44</sup>

New routes of administration of the desensitizing allergen(s) have dazzling potential for future success. Particularly notable in human allergic patients is the recent use of epicutaneous or intralymphatic administration. Epicutaneous immunotherapy can be accomplished with synthetic allergen molecules that are

modified such that they cause no cutaneous or systemic reaction, yet trigger a profound desensitizing effect as demonstrated in murine models.<sup>45</sup> Clinical trials of intralymphatic ASIT in human allergic disease are impressive; a few, very small doses of allergen painlessly injected into lymph nodes can produce a dramatic and long lasting therapeutic effect with complete safety (see review by Senti *et al.*<sup>46</sup>). Preliminary studies in dogs have been reported.<sup>47–49</sup>

Allergen-specific immunotherapy for food allergy is an exciting topic in human medicine, in part due to the social difficulties and potentially lethal consequences of this condition in people. In the past, ASIT for food allergens such as peanut or shellfish was generally considered prohibitive due to the risk to the patient. Molecular diagnostics (i.e. identifying the specific epitopes to which the individual patient reacts), modified treatment allergens and alternate methods of administration have now made this ASIT feasible. Large-scale trials of sublingual immunotherapy, in particular, have shown success with peanut allergy.<sup>50,51</sup> Although food allergy is more readily managed and of less serious consequence in dogs than in humans, the progress with ASIT for the management of food allergy in people may assist with better diagnosis and patient management of canine AD.

One cannot discuss the future of ASIT in dogs without considering future treatments that may render ASIT archaic or unnecessary. Highly effective drugs such as ciclosporin or oclacitinib,<sup>23</sup> or biologicals such as anti-IL-31 therapeutic monoclonal antibody,<sup>52</sup> may obviate some of the “need” for ASIT, as the former treatments may control clinical signs very well over long periods of time. However, they are still treatments that require lifetime administration; they only reduce clinical signs rather than reversing pathogenesis; their long-term safety is not always established; and they carry no hope of permanent “cure” as can sometimes be achieved with ASIT. Therefore, this author believes that there will always be a place for ASIT in our armamentarium for CAD.

There are many lines of investigation of ASIT that are yielding exciting results in humans and bode well for the future of this fundamental mode of treatment in animals. Importantly, ASIT has historically been viewed by some general-practice veterinarians as a “last-resort” treatment – after all other efforts have been exhausted, the pet is finally referred for evaluation for “allergy shots.” At this point, the patient often has chronic and unremitting disease that is challenging for any treatment. If the veterinary profession encourages greater knowledge on how and when to use ASIT, and fosters improvement in our methods and technology, one hopes that veterinary clinicians and clients will consider ASIT as an early choice for treatment of AD, rather than as a last resort; modifying both clinical signs and the course of the disease over the patient’s lifetime should be a primary and early goal. As new, more effective, and safer drug and biological treatments are developed and become more commonplace, we must also continually ask where ASIT fits in, in the world of multimodal allergy treatment.

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## Résumé

L'immunothérapie spécifique d'allergènes (ASIT) est un traitement de fond de la dermatite atopique canine (CAD) depuis que des études critiques ont documenté son efficacité comme traitement agissant sur la maladie des chiens. Les mécanismes par lesquels l'ASIT fonctionne chez le chien n'ont pas été élucidés bien qu'il y ait un parallèle avec ceux de l'homme. Les approches actuelles de l'ASIT dans la CAD se focalisent soit sur l'administration sous cutanée soit sur l'administration sublinguale. De meilleures connaissances des allergènes majeurs chez le chien, les dosages idéaux et les détails des mélanges d'allergènes permettraient une meilleure efficacité dans la CAD. L'évaluation de biomarqueurs pour un traitement efficace pourrait aussi être utile. Des avancées potentiellement importantes en médecine humaine qui doivent encore être explorées chez le chien comprennent l'utilisation d'allergènes modifiés tels que les allergènes, les allergènes majeurs recombinants ou les peptides d'allergènes; modification avec adjuvants; ou un package des précédents avec des particules virus-like. La co-administration d'immunomodulateurs tels que CpG oligodeoxynucleotides ou les anticorps monoclonaux spécifiques pourraient diriger la réponse immunitaire dans la direction voulue pour calmer la tempête cytokinique de la maladie active. Les essais préliminaires des routes alternatives d'administration tels que l'immunothérapie intralymphatique ont donné des résultats encourageants chez l'homme et des études de longue durée chez le chien sont en cours. Le progrès d'ASIT dans l'allergie alimentaire de l'homme peut fournir des données qui aideront à améliorer le diagnostic et la gestion du chien atopique. En outre, des études supplémentaires doivent être réalisées pour clarifier si l'ASIT est une modalité de traitement valable chez le chien.

## Resumen

La inmunoterapia específica para alérgenos (ASIT) es un tratamiento básico para la dermatitis atópica canina (CAD), aunque pocos estudios críticos han documentado su eficacia como tratamiento modificador de la enfermedad en perros. Los mecanismos por los que funciona el ASIT en perros no han sido aclarados, aunque es probable que sean paralelos a los conocidos para los seres humanos. Las pautas actuales de ASIT en CAD se centran en la administración subcutánea o sublingual. Un mayor conocimiento de los principales alérgenos en los perros, los regímenes de dosificación ideal y detalles de la mezcla de alérgenos es probable que conduzcan a una mejor eficacia en el tratamiento de la CAD. La evaluación de biomarcadores para una terapia exitosa también puede ser beneficiosa. Los avances potencialmente importantes en la medicina humana que todavía no se han explorado en perros incluyen el uso de preparaciones alérgicas modificadas tales como alergenoides, alergenos principales recombinantes o péptidos alérgicos; modificación con adyuvantes; o empaquetamiento de las anteriores moléculas en partículas similares a virus. La coadministración de inmunomoduladores tales como oligodeoxinucleótidos de CpG o anticuerpos monoclonales específicos podría dirigir la respuesta inmune en la dirección deseada mientras se estabiliza la "tormenta de citoquinas" de la enfermedad activa. Los ensayos iniciales de vías alternativas de administración, tales como la inmunoterapia intralinfática, han producido resultados emocionantes en humanos, y estudios continuados en perros están en marcha. El progreso en la ASIT en la alergia alimentaria humana puede proporcionar información que ayudarán con un mejor diagnóstico y manejo del paciente de CAD. Es importante destacar que se deben realizar más estudios para aclarar si ASIT es una modalidad de tratamiento valiosa para los perros.

## Zusammenfassung

Die Allergen-spezifische Immuntherapie (ASIT) ist ein fester Bestandteil der Behandlung der atopischen Dermatitis des Hundes (CAD), obwohl nur wenige kritische Studien ihre Wirksamkeit als Krankheits-modifizierende Behandlung bei Hunden dokumentiert haben. Die Mechanismen, durch welche ASIT bei Hunden funktioniert, wurden noch nicht abgeklärt, obwohl es wahrscheinlich ist, dass sie parallel zu jenen des Menschen verlaufen. Die derzeitigen ASIT Protokolle bei CAD konzentrieren sich entweder auf die subkutane

oder die sublinguale Verabreichung. Besseres Wissen über die Hauptallergene bei Hunden, ideale Dosismodes und Details über die Allergenmischungen werden wahrscheinlich zu einer besseren Wirksamkeit bei CAD führen. Mögliche wichtige Fortschritte in der Humanmedizin, die bei Hunden noch untersucht werden müssen, beinhalten die Verwendung von modifizierten Allergenpräparaten wie Allergoide, rekombinante Hauptallergene oder Allergenpeptide; Modifizierung mit Adjuvantien; oder ein Verpacken der obengenannten in Virus-ähnliche Partikel. Eine gleichzeitige Verabreichung von Immunmodulatoren wie CpG Oligodeoxynukleotide oder spezifische monoklonale Antikörper könnten direkt die Immunantwort in die gewünschte Richtung weisen, während der „Zytokinsturm“ der akuten Erkrankung beruhigt wird. Anfängliche Versuche alternativer Administrationswege wie eine intralymphatische Immuntherapie haben aufregende Ergebnisse beim Menschen erzielt, weiterführende Studien beim Hund werden gerade durchgeführt. Der Fortschritt der ASIT bei der Ernährungallergie des Menschen könnte Hinweise liefern, die bei einer verbesserten Diagnose und beim Patientenmanagement der CAD helfen werden. Es ist wichtig, dass weitere Studien durchgeführt werden, um klarzustellen, ob ASIT eine wichtige Behandlungsmodalität für Hunde darstellt.

## 要約

アレルギー特異免疫療法は、犬アトピー性皮膚炎(CAD)の基礎治療であるが、犬において、根治治療としての効果を検証した決定的な報告はほとんど存在しない。犬におけるASITの効果発現機序は、人で知られているものに相似している可能性が高いが、いまだ明らかにはなっていない。現在、CADに対するASITは皮下投与あるいは舌下投与に焦点を当てている。犬における主要アレルゲンへのより広い知識、最適な用法用量、アレルゲン混合の詳細を解明することが、CADに対するより良い効果につながると期待される。治療効果を評価するバイオマーカーの開発も有用であると考えられる。人医療における潜在的に重要な進歩でありながら、犬ではいまだ実施されていない治療として、アレルゴイド、組み換え主要アレルゲンやペプチドアレルゲンなどの変形アレルゲンの使用、免疫賦活剤の添加、および、上記アレルゲンのウィルス様粒子によるパッケージングなどがある。CpGオリゴデオキシヌクレオチドや特異的モノクローナル抗体などの免疫調整剤との同時投与によって、免疫応答を好ましい方向へと導く一方で、活動的状態にある疾患の“サイトカインの嵐”を抑える効果も期待される。人では、リンパ節内免疫療法などの異なる投与経路を検証した初期試験が非常に興味深い結果を出しており、犬においても研究が進められている。人の食物アレルギーに対するASITの進歩が、CADの診断および治療を向上させる手がかりになると期待される。犬において、ASITが妥当な治療法であることを明確にする更なる研究の実施が重要である。

## 摘要

虽然有少数批判性研究表示,过敏原特异性免疫治疗法(ASIT)对疾病恢复无效,但它仍是一种用于治疗犬异位性皮炎(CAD)的基础方法。目前还阐述不清ASIT对犬机体的作用机制,尽管可能与人体已知的类似。目前用于CAD的ASIT法主要是皮下注射或者口服。进一步了解犬的主要过敏原、理想的剂量方案和详细的过敏原混合,都有可能使其治疗CAD的效果更好。生物标记的评价有助于成功的治疗。对于还没在犬上开发的人用药物,有可能做出重大改进,包括使用改进的过敏原制剂,例如类过敏原、主要过敏原重组或者抗原多肽;改良的佐剂;或将上述成分用类病毒粒子包装。联合使用免疫调节剂的,例如CPG寡聚脱氧核苷酸可以在需要的方面直接作出免疫应答,同时使活跃疾病的“细胞因子风暴”平静下来。改变给药途径的初期试验,例如淋巴管注射免疫治疗,在人体方面已经得到了积极的结果,而犬的研究仍在进行。用于人食物过敏的ASIT过程可以提供线索,这会帮助改进CAD的诊断和病例管理。更重要的是,进一步的研究必须去证明ASIT是否对犬是有价值的治疗方法。

## Resumo

Imunoterapia alérgenos específica (ASIT) é um tratamento base para a dermatite atópica canina (DAC), ainda que poucos estudos tenham documentados a sua eficácia como um tratamento modificador da doença em cães. Os mecanismos pelos quais ASIT funciona em cães não foram elucidados, apesar de serem provavelmente paralelos aos conhecidos para humanos. As abordagens atuais de ASIT são focadas em administrações subcutâneas, bem como sublinguais. Conhecimento mais aprofundado a respeito dos principais alérgenos em cães, dosagem e protocolo ideal e formulação dos frascos tendem a gerar melhores resultados de ASIT. A avaliação de biomarcadores de terapia bem sucedida pode ser benéfica para a ASIT em cães. Avanços potencialmente importantes na medicina humana que podem ainda ser explorados em cães incluem o uso de preparações de alérgenos modificados como os alergóides, principais alérgenos recombinantes ou peptídeos alergênicos; modificação com adjuvantes; ou embalagem dos anteriores em partículas *vírus-like*. Administração conjunta com imunomoduladores como a CpG oligodeoxinucleotídeos ou anticorpos monoclonais específicos podem direcionar a resposta imune na direção desejada e acalmar a tempestade de citocinas da doença ativa. Estudos preliminares de vias alternativas de administração como a imunoterapia intralinfática demonstraram resultados animadores, e estudos em cães estão a caminho. Progressos na ASIT para alergia alimentar em humanos podem gerar indícios que auxiliarão no diagnóstico e manejo de pacientes com DAC. É muito relevante que estudos sejam conduzidos para esclarecer se ASIT é ou não uma modalidade de terapêutica válida para o tratamento de cães com DAC.