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ALLERGEN-SPECIFIC IMMUNOTHERAPY IN DOGS: CURRENT STATE AND PERSPECTIVES

Abstract

Allergen-specific immunotherapy (ASIT) is the only treatment that directly affects the pathogenic mechanisms of canine atopic dermatitis by modifying the immune response rather than providing symptomatic control. With the growing prevalence of allergic diseases in companion animals, the study of ASIT efficacy, safety, and immunomodulatory properties has become increasingly relevant.

The aim of this review is to summarize current data on the clinical efficacy, immunological changes, and new technological approaches in the application of ASIT in dogs with atopic dermatitis.

The review analyzes recent clinical and experimental studies that evaluate the effects of subcutaneous, intralymphatic, and sublingual immunotherapy, the use of polymerized, mannan-conjugated, and recombinant allergens, as well as laboratory biomarkers for assessing treatment effectiveness.

In most dogs, ASIT promotes stable clinical remission, reduces pruritus and skin inflammation, and decreases the need for corticosteroids and antihistamines. Successful ASIT is accompanied by increased interleukin-10 production, normalization of transforming growth factor $\beta 1$ levels, expansion of regulatory T lymphocytes, and reduced expression of pro-inflammatory cytokines. The use of glutaraldehyde-modified or mannan-bound allergens lowers the risk of adverse reactions, while recombinant allergens provide high specificity and stability of the immune response.

ASIT has proven to ensure long-term remission even in refractory cases, such as allergic otitis media, thereby improving the quality of life of affected dogs. Promising directions for further development include the improvement of allergen production technologies for ASIT – including polymerized, mannan-conjugated, and recombinant forms — and the implementation of biomarkers for monitoring treatment effectiveness, which will enhance therapy personalization and the duration of clinical stabilization.

Keywords: dogs, skin, dermatitis, itching, allergen, immunotherapy, ASIT, cytokines, remission.

Introduction. Canine atopic dermatitis is a polyetiological chronic skin disease of allergic origin that significantly affects the quality of life of both animals and their owners and is a fairly common skin condition in dogs in world and in Ukraine [1, 2]. A similar trend has been observed in Ukraine: based on our own study conducted in Kyiv, the proportion of dogs diagnosed with AD was 16.5% in 2021 and 23.1% in 2022 among patients with chronic dermatological disorders [3]. Comparable results were reported by Zhak et al. (2024), who found that in the city of Vinnytsia, atopic dermatitis accounted for over 20% of all chronic dermatoses in dogs, highlighting its high prevalence among allergic skin diseases [4]. These findings emphasize the growing clinical relevance of the problem and the need for therapeutic strategies targeting the etiopathogenetic mechanisms of AD.

Despite the availability of effective anti-inflammatory drugs, complete recovery can only be achieved by modulating the immune response of the organism. Therefore, allergen-specific immunotherapy is considered the only etiopathogenetic treatment method [4, 5]. According to Kotnik (2023), dogs receiving allergen-specific immunotherapy showed markedly greater improvement in quality of life compared with those treated symptomatically, underscoring the clinical importance of this therapeutic approach [6].

The subcutaneous route of ASIT administration remains the most commonly used, and its efficacy has been confirmed in large retrospective studies, where more than 60% of dogs demonstrated clinical improvement [7, 8]. At the same time, alternative routes of administration are being investigated, such as intralymphatic immunotherapy, which is characterized by a shorter induction period, a potentially faster onset of clinical improvement, and fewer injections, although it requires specialized equipment and operator training [9, 10].

Significant progress has been achieved in the development of novel allergen formulations. The modification of allergens with glutaraldehyde and conjugation with mannan allows for a reduction in allergenicity while stimulating dendritic cells, thereby promoting the induction of immune tolerance [11]. Furthermore, the use of recombinant allergens provides new opportunities for standardization and increased specificity of immunotherapy [12, 13].

The aim of this review is to summarize current data regarding the efficacy, mechanisms of action, and future perspectives of allergen-specific immunotherapy in dogs with atopic dermatitis.

Literature Review. Canine atopic dermatitis (AD) is considered a complex multifactorial disease in which genetic, immunological, and environmental factors play an important role. Hensel et al. (2024), in the report of the International Committee on Allergic Diseases of Animals (ICADA), indicated that a combination of hereditary predisposition, alterations in the skin microbiome, and exposure to aeroallergens are key factors in the development of AD [14]. Marsella (2021) also emphasized the importance of these mechanisms, noting that understanding the interaction between environmental factors and the immune response determines the effectiveness of therapeutic strategies [15].

The efficacy and safety of allergen-specific immunotherapy. Allergen-specific immunotherapy remains the only method that modifies the course of AD by influencing immune mechanisms. Flanagan et al. (2021) emphasized the role of veterinarians in referring patients for ASIT and the impact of owner compliance on the final outcome [16]. Kotnik (2023) demonstrated that ASIT significantly improves the quality of life of animals, while Suici et al. (2021) confirmed that uncontrolled AD substantially reduces the quality of life of both dogs and their owners, highlighting the importance of effective treatment [17]. Mueller et al. (2023), in a systematic review, concluded that immunotherapy remains the most effective method for controlling AD in dogs and cats, showing stable clinical results without significant complications [18].

Immunological mechanisms of action. The efficacy of ASIT is explained by its ability to restore immune tolerance through the stimulation of regulatory T cells and the shift of the immune response from a Th2- to a Th1-dominant profile. Martini et al. (2022) demonstrated increased IL-10 and TGF- β 1 levels during treatment, indicating activation of anti-inflammatory mechanisms [19]. A. Majewska et al. (2022) observed a cytokine profile shift toward regulatory dominance, and in a subsequent study, A. Majewska et al. (2023) found transcriptomic changes that indicate suppression of pro-inflammatory gene expression [20, 21].

Modern technologies of allergen design. The development of allergen-specific immunotherapy is closely associated with continuous improvement of allergen extract composition, aimed at reducing allergenicity while maintaining immunogenicity. Modification of proteins with glutaraldehyde is a well-established method to stabilize allergens and minimize the risk of adverse reactions. Guzmán-Fulgencio et al. (2017) demonstrated that such modification in children and adults reduces both local and systemic adverse effects without compromising clinical efficacy, supporting its potential applicability for veterinary analogues [22]. Similar approaches have been adapted in veterinary dermatology, where polymerized and mannan-modified allergenic extracts are employed.

González et al. (2018) found that conjugation of *Dermatophagoides farinae* allergens with mannan enhances their uptake by dendritic cells through mannose receptors, thereby reducing IgE-binding activity while maintaining a specific T-cell response. This was confirmed in pilot study where the mannan–Der f 2 allergoid induced less pruritus and erythema while retaining clinical efficacy in 74% of dogs after 12 months [23].

Another direction of ASIT development focuses on producing recombinant allergens with a high degree of standardization. Olivry et al. (2017) were the first to demonstrate the preventive efficacy of high-dose recombinant immunotherapy with Der f 2 in sensitized dogs [12]. In a recent study, Nagata et al. (2025) employed a pullulan–Der f 2-conjugated allergen that reduced the need for concurrent anti-inflammatory medications and achieved superior clinical control without significant adverse effects [13].

Pali-Schöll and colleagues (2020) emphasized in their interdisciplinary review that polymerized allergens, recombinant proteins, DNA vaccines, and mannan

conjugates form the basis for the next generation of personalized veterinary immunotherapy, tailored to each animal's sensitization profile [11].

Molecular and cellular biomarkers of efficacy. The search for objective markers of ASIT efficacy remains one of the central directions of current research. Martini, Rostaher and Favrot (2022) reported increased plasma levels of IL-10 and TGF- β 1 in dogs during treatment, indicating activation of regulatory immune pathways [19]. Majewska et al. (2022) confirmed dynamic changes in cytokine profiles and lymphocyte proportions during therapy, reflecting a shift from Th2-mediated response toward tolerance. Further transcriptomic analysis (Majewska et al., 2023) revealed downregulation of genes associated with inflammatory processes and upregulation of those involved in immune regulation [20, 21]. Favrot and colleagues (2021) proposed the level of C-reactive protein as a simple clinical biomarker that correlates with symptom reduction in dogs responding well to therapy [24]. Marsella (2021) highlighted that integrating clinical outcomes with laboratory parameters could improve prediction of ASIT success and help standardize monitoring approaches in veterinary practice [15].

Safety and clinical observations. The safety of ASIT remains a crucial factor for its widespread clinical application. The study by Weitzer and Mueller (2023), involving more than 200 dogs, confirmed that accelerated ("rush") immunotherapy protocols rarely cause adverse reactions, with most being mild and self-limiting [25]. Kim et al. (2024) described a unique case of successful management of refractory otitis media in a dog using ASIT, highlighting the therapeutic potential of this approach even in atypical clinical scenarios [26]. Similar observations emphasize the universality and safety of modern immunotherapy protocols [18]. Ramio-Lluch and colleagues (2020) noted that the main factor limiting treatment efficacy is not adverse reactions but poor adherence to prescribed schedules, underscoring the importance of close collaboration between veterinarians and pet owners [27].

Clinical efficacy and compliance. Flanagan et al. (2021) surveyed practicing veterinarians and found that only a portion of clinicians consistently recommend ASIT, although the satisfaction rate among those who prescribe it is high [16]. Fennis and colleagues (2022), in a large retrospective study of 664 dogs, reported that clinical improvement is usually observed within a few months of treatment, with maximum efficacy achieved after approximately one year of continuous therapy [7]. Tham and Olivry (2022) clarified that the average time to reach a stable clinical response is around five months, although duration may vary depending on allergen type and prior treatments [8].

Perspectives on ASIT development. Further advancement of allergen-specific immunotherapy focuses on improving delivery methods, standardizing allergen preparations, and incorporating molecular indicators of immune response. In a recent systematic review, Mueller et al. (2023) summarized data on ASIT efficacy in dogs and cats, confirming a consistently high proportion of positive clinical responses in both species [18]. DeBoer (2017) emphasized the necessity of developing novel immunomodulatory strategies aimed at inducing tolerance without triggering

hypersensitivity reactions [5]. Pali-Schöll et al. (2020) predicted that the use of recombinant and polymerized allergens could lead to formulations with improved safety profiles and long-lasting immune memory [11].

Materials and Methods. The review was conducted between 2024 and 2026 at the Department of Vertebrate Physiology and Pharmacology, National University of Life and Environmental Sciences of Ukraine (Kyiv). The aim of the study was to systematize current scientific data on the efficacy, safety, and development trends of allergen-specific immunotherapy (ASIT) in canine atopic dermatitis (AD), as well as to summarize diagnostic and preventive approaches applied in modern veterinary dermatology.

The study involved the analysis of scientific publications focused on the mechanisms of action, clinical efficacy, diagnostic methods, and preventive strategies for canine atopic dermatitis. To achieve the stated objective, the following scientific methods were applied: review and systematization of academic sources, comparative analysis of the effectiveness of various ASIT approaches, critical evaluation of methodological quality in reviewed studies, and synthesis of the obtained data.

The analysis included peer-reviewed scientific articles published over the past 10 years in journals indexed in Scopus, Web of Science, PubMed, and CrossRef databases. The main focus was on studies addressing the pathogenesis, laboratory diagnostics, clinical efficacy, and innovative developments in the implementation of ASIT for dogs.

The research utilized materials from international and national scientific journals, as well as official reports of expert groups, including the International Committee on Allergic Diseases of Animals (ICADA) and leading research institutions specializing in veterinary immunotherapy.

Results and Discussion. A review of recent studies confirms that allergen-specific immunotherapy (ASIT) remains the only treatment for canine atopic dermatitis (AD) capable of modifying the disease's underlying pathophysiological mechanisms and establishing long-term immunological tolerance. According to Marsella (2021), the efficacy of ASIT is determined by its influence on key immunological mechanisms – maintaining the Th1/Th2 cell balance, activating regulatory T cells, and reducing IgE-mediated inflammation [15]. Unlike symptomatic therapies aimed merely at suppressing pruritus or inflammation, ASIT modulates the immune response itself, shifting from a Th2-predominant profile toward regulatory balance, thereby reducing hypersensitivity and clinical signs. The combined molecular and clinical data demonstrate consistent upregulation of anti-inflammatory cytokines and suppression of proinflammatory gene pathways, confirming a genuine immunomodulatory effect [19-21].

Overall response rates of 60–75% have been reported across different populations and protocols, indicating reproducibility and clinical reliability [18, 28]. However, therapeutic failures are often linked to irregular treatment schedules and poor owner compliance rather than lack of efficacy [27]. Kotnik (2023) demonstrated that

quality of life indicators significantly improve following one year of ASIT, including reduced pruritus and enhanced behavioral activity [1].

Safety and tolerability remain among the key criteria for ASIT success. In their multicenter study, T. Weitzer and R. S. Mueller (2023) evaluated 230 cases of accelerated (“rush”) ASIT and demonstrated a favorable safety profile even under intensive dosing conditions, confirming that individualized adjustment of protocols is feasible depending on disease severity and patient tolerance [25].

The evolution of immunotherapeutic technologies has led to the introduction of new allergen-delivery routes. Fischer et al. (2020) compared subcutaneous, sublingual, and intralymphatic ASIT, finding that the intralymphatic route achieved clinical effect faster and required fewer injections [9].

The evolution of ASIT is closely related to advances in allergen design. Chemical and structural modifications, such as glutaraldehyde polymerization and mannan or pullulan conjugation, have been shown to reduce allergenicity while preserving immunogenicity [22, 23]. Recombinant allergens, such as Der f 2, demonstrated efficacy in both therapeutic and prophylactic protocols [12]. These findings support the transition from crude allergen extracts toward standardized formulations. Traditional extracts containing natural protein mixtures are progressively being replaced by standardized and modified forms that ensure greater reproducibility and a lower risk of adverse reactions. Pali-Schöll et al. (2020) emphasize that polymerized, recombinant, and carbohydrate-conjugated allergens may form the foundation for next-generation veterinary immunotherapy products with individualized safety and efficacy profiles [11].

One of the most promising examples is the study by Nagata et al. (2025), which utilized a pullulan-conjugated recombinant Der f 2 (dust-mite allergen). This preparation exhibited pronounced anti-inflammatory activity, reduced glucocorticoid requirements, and provided stable clinical control in dogs with severe AD. According to the authors, this allergen form minimizes the risk of systemic reactions, making ASIT feasible even for hypersensitive patients [13].

The work of Mueller et al. (2023) underscored that the standardization of allergen extracts and implementation of molecularly modified or recombinant allergens represent key milestones in the development of personalized veterinary immunotherapy. These technologies enable more precise selection of vaccine components according to each patient’s sensitization profile [18].

A major research direction in recent years has been the search for adjuvants that enhance immune responses while simultaneously reducing allergenicity. Pignard et al. (2024) described the potential use of mannan-, virus-like-particle (VLP)-, and flagellin-based adjuvants in allergen-specific vaccines. These technologies activate pattern-recognition receptors (PRRs) of innate immunity, thereby promoting a more balanced Th1/Th2 response. Such approaches open new prospects for developing safe next-generation veterinary vaccines that can not only increase therapeutic efficacy but also promote a more stable and balanced immune response in allergy-prone animals. Innovative allergen-design technologies, including nanoparticles and biopolymers,

create opportunities for controlled antigen release. Such platforms enable modification of allergen pharmacokinetics, ensuring gradual systemic exposure and minimizing the risk of anaphylactic reactions. In their review, Pignard et al. (2024) noted that combining VLP adjuvants with polymerized proteins can significantly enhance therapeutic efficacy without increasing the dose [29].

Alongside allergen development, the optimization of diagnostic methods remains crucial. The results of Stotska (2023) and Morales-Romero et al. (2025) confirm that integrating serological, cytological, and molecular approaches substantially improves diagnostic accuracy and facilitates targeted allergen selection prior to ASIT initiation [30, 31].

An emerging focus in ASIT research involves identifying objective biomarkers of therapeutic success. Quantification of acute-phase proteins such as C-reactive protein [24], together with cytokine profiling and transcriptomic monitoring [21], offers new opportunities for predicting responsiveness and tailoring protocols. This aligns with the broader concept of personalized immunotherapy, in which clinical progress is integrated with immunological and molecular monitoring to guide treatment adjustments.

From the standpoint of immune monitoring, Morales-Romero et al. (2025) stressed that future progress will depend on multiplex panels capable of simultaneously quantifying cytokines, immunoglobulins, and cellular markers. These systems will allow treatment personalization based on the immune profile of each patient [31].

Collectively, available evidence supports ASIT as a pathogenetically justified and well-tolerated treatment for canine AD, offering sustained clinical remission, reduced reliance on anti-inflammatory drugs, and improved quality of life for affected dogs. Future research should focus on standardizing treatment protocols, validating immunological biomarkers, and integrating molecular technologies to optimize individualized therapeutic strategies in veterinary allergology.

Conclusions. Allergen-specific immunotherapy remains the only therapeutic approach capable of influencing the immunopathogenesis of canine atopic dermatitis and achieving long-term clinical remission. Current studies suggest that its efficacy may be associated with the induction of regulatory cytokines such as IL-10 and TGF- β 1, a reduction in Th2-mediated responses, and partial restoration of immune balance; however, these mechanisms require further investigation.

Chemical and structural allergen modifications, including glutaraldehyde polymerization, mannan or pullulan conjugation, as well as the development of recombinant allergens, appear to enhance the safety profile of ASIT while maintaining its immunogenic potential and clinical benefit.

Accordingly, the available data confirm the high clinical efficacy and safety of modern ASIT protocols.

In summary, modern ASIT should be viewed not merely as a treatment modality but as a comprehensive immunomodulatory strategy integrating diagnosis, monitoring, and a preventive approach to allergic disorders. The further advancement of this field is linked to the implementation of personalized therapeutic schemes, innovative

adjuvant systems, and multi-biomarker diagnostic tools – developments that are expected to increase therapeutic efficacy, prolong remission, and enhance the quality of life in dogs affected by atopic dermatitis.

Conflict of Interest: The author declares no conflict of interest.

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АЛЕРГЕН-СПЕЦИФІЧНА ІМУНОТЕРАПІЯ У СОБАК: СУЧАСНИЙ СТАН І ПЕРСПЕКТИВИ

Анотація

Алерген-специфічна імунотерапія (АСІТ) є єдиним методом лікування, що впливає на патогенетичні механізми атопічного дерматиту у собак, спрямованим на модифікацію імунної відповіді замість симптоматичного контролю. В умовах зростання частоти алергічних захворювань у тварин, дослідження ефективності, безпеки та імуномодельовальних властивостей АСІТ набуває особливої актуальності.

Мета роботи – узагальнення сучасних даних про клінічну ефективність, імунологічні зміни та нові технологічні підходи у проведенні АСІТ у собак з атопічним дерматитом.

Проведено огляд сучасних клінічних та експериментальних досліджень, що оцінюють вплив підшкірної, інтралімфатичної та сублінгвальної імунотерапії, використання полімеризованих, манан-кон'югованих та рекомбінантних алергенів, а також лабораторних маркерів ефективності лікування.

У більшості собак застосування АСІТ сприяє стійкій клінічній ремісії, зниженню інтенсивності свербіжу та запалення шкіри, зменшенню потреби у кортикостероїдах та антигістамінних препаратах. Встановлено, що успішна АСІТ супроводжується підвищенням продукції інтерлейкіну-10, нормалізацією рівнів трансформувального фактора росту $\beta 1$, збільшенням кількості регуляторних Т-лімфоцитів та зменшенням експресії прозапальних цитокінів. Використання модифікованих глутаральдегідом або манан-зв'язаних алергенів знижує ризик побічних реакцій, а рекомбінантні алергени забезпечують високу специфічність та стабільність імунної відповіді.

Алерген-специфічна імунотерапія довела здатність забезпечувати тривалу ремісію навіть у рефрактерних випадках, зокрема при алергічному середньому отиті, покращуючи якість життя тварин. Перспективним напрямом розвитку є вдосконалення технологій створення алергенів для АСІТ – полімеризованих, манан-кон'югованих та рекомбінантних форм і впровадження біомаркерів контролю ефективності лікування, що підвищить персоналізацію терапії та тривалість клінічної стабілізації.

Ключові слова: собаки, шкіра, дерматит, свербіж, алерген, імунотерапія, АСІТ, цитокіни, ремісія.

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