REVIEW

An in-depth analysis of the allergen α-gal: mechanisms, consequences and prospects

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Summary
The study aims to investigate the structural features of galactose-α-1,3-galactose (α-gal), mechanisms of its interaction with the immune system, clinical manifestations, diagnostic methods and approaches to the prevention and treatment of allergy to this antigen. A comprehensive study was carried out, including analysis of literature data, X-ray diffraction, electron microscopy and immunological studies. The study established that α-gal is a glycoprotein with a unique three-dimensional conformation determined by its glycan structure, which is recognised by the human immune system as a foreign antigen, causing the production of immunoglobulin E (IgE) antibodies. The antibodies bind to receptors on mast cells and basophils, which, upon repeated contact with α-gal, leads to the release of inflammatory mediators, including histamine. It causes skin rashes, swelling, gastrointestinal disorders, and in severe cases, anaphylaxis. A special feature is the delayed reaction associated with the slow release of α-gal from food into the bloodstream. Tick bites contribute to α-gal sensitisation due to the presence of this antigen in saliva. Diagnosis is based on clinical assessment, skin tests, IgE antibody levels and provocative tests. Prevention consists of avoiding foods with α-gal and preventing tick bites. Treatment includes epinephrine, antihistamines and promising immunotherapy.

Keywords
immunology; anaphylactic shock; hypersensitivity to meat; tick bite; antibodies

Galactose-α-1,3-galactose (α-gal) allergy is a form of allergy characterised by an immune response to a specific carbohydrate, which causes significant difficulties in diagnosis and treatment [1]. Given the serious health consequences of anaphylaxis, the study of the mechanisms and consequences of α-gal allergy is of paramount importance. According to the results of a study by Brzozowska et al. [2], α-gal syndrome can cause severe hypersensitivity reactions to food and drugs and often goes unnoticed due to low awareness of healthcare professionals and atypical symptoms. Furthermore, Rutkowski et al. [3] confirms that the α-gal epitope is present in glycoproteins and glycolipids of many mammals and parasites. Due to the absence of a functioning *ggta*1 gene, people develop antibodies against α-gal, which can cause allergic reactions, such as α-gal syndrome, which manifests itself as a delayed anaphylactic reaction to red meat [4].

The problem with the study is that many aspects of the pathogenesis and triggers of an allergic reaction to α-gal remain unclear. In particular, the question of why some people develop this allergy and others do not is relevant. Another significant problem is the lack of reliable diagnostic and treatment methods, which aggravates the situation for patients and doctors. Treatment methods provided from 2019 to 2024 were often not effective enough, which necessitates the search for new approaches.

Poziomkowska-Gęsicka [5] studied the prevalence of α-gal anaphylaxis in different regions and found that anaphylaxis to α-gal occurs after eating red meat and can manifest itself 5 h after eating. The introduction of molecular diagnostics has significantly reduced the number of cases of idiopathic anaphylaxis by helping to identify α-gal allergy. The average age of patients with α-gal anaphylaxis is 51 years. Lis et al. [6] analysed the immunological mechanisms underlying this allergy and concluded that antibodies against α-gal can cross-react with mammalian meat allergens. Patients with a positive result for α-gal immunoglobulin E (IgE) had allergic reactions after eating beef, but not poultry or fish. A study by Lis et al. [7] used standard and non-standard diagnostic methods to identify an allergic reac-

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tion to α-gal in a patient with no previous atopic history, but who developed a cross-reaction after a tick bite. High levels of IgE antibodies to α-gal and meat allergens were detected. The results confirmed that sensitisation to α-gal developed after a tick bite, leading to cross-allergy to mammalian meat allergens.

Despite significant efforts in this area, many issues remain unresolved. In particular, CONTRERAS et al. [8] pointed out the need for a more detailed study of the fact that tick bites increase the levels of IgE to α-gal glycan, which is associated with α-gal syndrome (AGS) or allergy to mammalian meat, which may be one of the mechanisms of α-gal syndrome development.

The study aims to analyse in detail the mechanisms of α-gal allergy, its health consequences and potential prospects for the development of new diagnostic and treatment methods. The objectives of the study were to critically analyse existing diagnostic and treatment methods and to propose new approaches based on the advances in immunology and genetics research over the period from 2020 to 2024.

MATERIALS AND METHODS

This review was conducted using a systematic approach, including analysis and synthesis of data from various scientific sources. The search for scientific publications was conducted in leading bibliographic databases such as PubMed (National Center for Biotechnology Information, Bethesda, United States), Scopus (Elsevier, Amsterdam, Netherlands) and Web of Science (Clarivate Analytics, Philadelphia, USA). Keywords and phrases were used for the search: “allergy to α-gal”, “galactose-alpha-1,3-galactose”, “immunological mechanisms”, “allergy diagnosis”, and “allergy treatment”. The review includes publications from 2019 to 2024 to ensure that the data is up to date.

The inclusion and exclusion criteria were strictly adhered to. The review included articles describing the mechanisms of α-gal allergy development, molecular and immunological mechanisms underlying this pathology, clinical manifestations, and diagnostic and treatment methods. Publications not related to the research topic and duplicate data were excluded. All articles found were carefully analysed for content, methodology and results. The focus was on studies conducted under controlled conditions and with a high degree of evidence. Meta-analyses and systematic reviews that provide summarised data on the topic were also considered.

Data from various sources were synthesised to provide a holistic picture of the topic at hand. The main mechanisms underlying α-gal allergy were identified, clinical manifestations were discussed, and methods of diagnosis and treatment were proposed. Particular attention was devoted to the identification of gaps in existing research and promising areas for further research.

A critical analysis of the identified data was carried out to assess its reliability and practical significance. The possible reasons for the discrepancies in the results of different studies were discussed, as well as the limitations of current diagnostic and treatment methods. Based on the analysis, conclusions were drawn about the current state of knowledge on the topic of α-gal allergy. Recommendations for further research and practical applications in the field of diagnostics and treatment are proposed.

All sources used were obtained from open and accessible databases in compliance with copyright and scientific ethics. An important aspect of this study was the use of only peer-reviewed publications with a high degree of evidence. This minimises the impact of unreliable data and draws reasonable conclusions. The analysis was carried out by covering the latest advances in immunology, genetics and clinical medicine, which ensured a comprehensive approach to the study of α-gal allergy.

The focus was on identifying and analysing the immunological mechanisms underlying the allergic reaction to α-gal. The features of sensitisation, the role of various immune cells and mediators, as well as genetic factors that may contribute to the development of this allergy were discussed. The study also analysed the clinical manifestations of α-gal allergy, including symptoms and their variability depending on the individual patient.

To improve the diagnosis and treatment of α-gal allergy, methods and approaches were reviewed for the period 2010 to 2024, including molecular diagnostics, the use of specific biomarkers and new therapeutic strategies. Particular attention was devoted to the prospects of using personalised medicine, which can significantly improve treatment outcomes and the quality of life of patients.

RESULTS AND DISCUSSION

Structure and function of the allergen α-gal

The allergen α-gal is a component that causes allergic reactions in humans, especially after eating red meat and, in rare cases, after the admi-

nistration of certain medications and insect bites [8]. The breakdown of α-gal revealed its complex structure. It is a glycoprotein that includes a complex pattern of sugars, including the sugar residue α-gal, which serves as a specific allergenic epitope. A 2021 study by Román-Carrasco et al. [1] reported that the α-gal epitope, consisting of the disaccharide galactose-α-1,3-galactose (Gal-α-1,3-Gal), is usually supplemented with *N*-acetylglucosamine (GlcNAc) to form the trisaccharide Gal-α-1,3-Gal-β-1,4-GlcNAc. It is present in the glycoproteins and glycolipids of most mammals, except for Old World monkeys, great apes and humans. About 28 million years ago, the α(1,3)-galactosyltransferase (α1.3GT) gene responsible for the synthesis of α-gal was switched off in the ancestors of Old World primates. Instead of α-gal, humans produce antibodies against this epitope, which can cause hyperactive reactions during xenotransplantation due to activation of the complement system upon contact with α-gal on mammalian organs.

The structure of α-gal has been studied in detail using X-ray crystallography, which determines the exact three-dimensional structure of the protein, and electron microscopy, which gives us an idea of its morphology at the level of individual molecules [9]. As such, the complex three-dimensional conformation of α-gal is due to its glycan structure and distribution of functional groups, which determines its interaction with the immune system. Perusko et al. [9], noted that the α-gal epitope is highly immunogenic for humans, great apes and Old World monkeys, which produce anti-gal antibodies (IgM, IgA and IgG). Due to the intestinal microbiota expressing α-gal, these antibodies account for 0.2–1.0 % of all immunoglobulins in humans. Anti-gal antibodies predominantly use genes of the V3 family in the heavy chain, where tryptophan at position 33 is important for binding to α-gal. The formation of anti-gal antibodies begins in the first months of life, with IgM growing faster than IgG and IgA. In the appendix, Galili [10] notes that the production of anti-gal antibodies is a natural process that occurs in response to the presence of α-gal like epitopes on gastrointestinal bacteria, contributing to the immune system's development and function.

The α-gal oligosaccharide is structurally similar to the blood group B antigen, with the difference being the α1-2 linked fucose residue. Anti-gal antibodies can cross-react with blood group B antigen. People with blood type B or AB do not have such cross-reactive antibodies, which may protect them from α-gal allergy [11]. The molecular mechanisms of this protection require further study. Patients with α-gal allergy rarely have IgE antibodies to other mammalian carbohydrate epitopes.

Due to the widespread distribution of α-gal on glycolipids and glycoproteins in mammals, many of these molecules can cause allergic reactions to food and animal products [12]. Several proteins, such as beef laminin γ-1, collagen α-1(VI) and bovine gamma globulin (BGG), have been found to contain α-gal and bind IgE in patients with beef allergy. Of particular note are pig kidneys, which contain the highest amount of α-gal and are the strongest trigger of AGS symptoms. In addition, α-gal is present in pharmaceuticals and vaccines, which poses a risk to patients with AGS. α-gal is also found in mites, which contributes to allergic reactions. Therefore, patients with AGS should strictly avoid all products and goods of animal origin [6]. The α-gal epitope plays a crucial role in allergic reactions, activating the immune system and provoking the production of IgE antibodies. This occurs in people whose bodies have developed an allergic sensitivity to α-gal. Such allergic reactions can manifest themselves in a variety of symptoms, including skin rashes, itching, swelling and, in some cases, anaphylaxis. It is important to note that, in addition to its content in meat, α-gal is present in some medicines and bee venom. This means that allergic reactions can occur not only after eating but also after a medical procedure or an insect bite.

The allergen α-gal is a component that triggers allergic reactions in humans, particularly after consuming red meat or certain medications, and occasionally following insect bites. Structurally, α-gal is a glycoprotein featuring a complex sugar pattern, including the sugar residue α-gal, which acts as a specific allergenic epitope. This epitope is present in most mammals but is absent in Old World monkeys, great apes, and humans due to the evolutionary inactivation of the α1.3GT gene. The absence of α-gal in humans leads to the production of antibodies against this epitope, which can cause hyperactive reactions during xenotransplantation. The complex three-dimensional conformation of α-gal, determined by its glycan structure, is crucial for its interaction with the immune system, making it highly immunogenic. Understanding this structure is a key to developing effective diagnostic and therapeutic strategies for managing α-gal-related allergies.

Mechanisms of interaction with the immune system

The interaction of α-gal with the human immune system is a complex process that leads to the development of allergic reactions. According

to SHARMA et al. [13], there are 2 main types of response to α-gal: natural anti-gal response and induced anti-gal response. The natural anti-gal response is a natural immune response in which an anti-gal antibody is produced against α-gal-like epitopes present on the walls of normal gastrointestinal (GI) bacteria. The level of anti-gal in the blood changes with age: in newborns, it is presented in the form of maternal IgG, and children and adults in the form of IgG, IgM and IgA [14]. This antibody is naturally present in all humans due to the evolutionary absence of α-gal epitopes in their bodies. In addition, the anti-gal antibody binds to α-gal epitopes on xenograft cells (e.g. pig organs), which leads to hyperacute rejection of transplants. Induced anti-gal response is an activated immune response in which anti-gal B cells are activated upon encountering α-gal epitopes on xenografts or in experimental conditions, such as injection of 3T3 mouse cells [15]. This causes a significant increase in the titre of anti-gal antibodies. This response involves an increase in the number of anti-gal B cells and an increase in antibody affinity through affinity maturation.

The immune response to xenotransplantation and infection is also an example of an induced anti-gal response. The introduction of xenografts or infection with protozoa bearing α-gal-like epitopes leads to increased anti-gal activity, which causes complement-dependent lysis of infectious agents or xenograft cells. Both types of immune responses play a key role in the body's reactions to foreign antigens, whether bacterial epitopes or xenograft cells. Studies show that immunisation against α-gal can activate the complement system and cytotoxic T cells. This can significantly improve the effectiveness of cancer therapy. FANG et al. [16] concluded that the use of neoantigens, such as α-gal, enhances the immune response to tumour cells during immunotherapy by modulating the T-cell response and increasing phagocytosis in the tumour site.

The antibody response to α-gal has positive effects, including protection against infections by pathogens such as *Plasmodium falciparum*, *Trypanosoma cruzi*, and *Leishmania*, as well as prevention of adhesion of some bacteria to mucous membranes, highlighting its potential role in immune defence at the level of mucosal surfaces. According to a study by BERNTH JENSEN et al. [17], IgG anti-α-gal antibodies, which are widely present in human plasma, bind to most sepsis pathogens. The study showed that these antibodies have a high specificity for Galα3Gal and bind to 56 out of 100 pathogens, mainly Gram-positive bacteria (39 out of 52 strains). Even though IgG anti-α-gal make up only about 0.1 % of antibodies in the body, they target a significant proportion of pathogens that cause invasive diseases. It is believed that this may be determined by the fact that carbohydrate antigens, which are oligosaccharides of 3 units or more (e.g. ABO antigens and α-gal epitope), can bind to B cells through the corresponding B cell receptor (BCR), but do not bind to T cell receptors, which does not cause the production of specific IgG and IgA.

Ticks such as *Amblyomma americanum* (lone star tick) carry α-gal in their saliva [18]. When a tick bites a person, it injects saliva containing α-gal into the bloodstream. The immune system recognises α-gal as a foreign substance and begins to produce IgE antibodies against α-gal [19]. MITCHELL et al. [20] determined that people who had been bitten by *Amblyomma americanum* ticks were significantly more likely to have elevated levels of anti-α-gal IgE compared to those who had not been bitten. The association between tick bites and increased levels of anti-α-gal IgE was not time-dependent. There was also a tendency to increase the level of anti-α-gal IgE with an increase in the number of tick bites, although this relationship was not statistically significant. KIM et al. [21] examined the effect of tick bites on the level of IgE antibodies specific for α-gal in patients with α-gal syndrome. The results showed that the level of these antibodies decreased over time in patients who avoided tick bites. In contrast, patients exposed to repeated bites were more likely to demonstrate an increase in IgE to α-gal. This confirmed the link between tick bites and the pathogenesis of α-gal syndrome, emphasising the importance of preventing tick bites for disease management.

After the initial contact, the immune system continues to produce IgE antibodies to α-gal. These antibodies bind to receptors on the surface of mast cells and basophils, "preparing" them for possible repeated contact with α-gal. With subsequent tick bites, α-gal re-enters the bloodstream. Pre-existing IgE antibodies recognise α-gal and bind to it, activating mast cells and basophils. This leads to the release of various inflammatory mediators such as histamine.

The release of inflammatory mediators causes various allergic symptoms, ranging from skin rashes to anaphylactic shock. In the case of α-gal syndrome, this reaction often occurs several hours after eating mammalian meat (beef, pork, lamb), as α-gal is present in the glycolipids and glycoproteins of these products. Thus, tick bites can lead to sensitisation of the body to α-gal and the develop-

ment of a specific immune response that causes allergic reactions when foods containing α-gal are subsequently consumed. The effect of α-gal on immune cells, such as B-lymphocytes and mastocytes, activates signalling pathways, resulting in the synthesis and release of inflammatory mediators such as histamine. These mediators cause characteristic allergic symptoms such as itching, swelling, skin rashes and, in severe cases, anaphylaxis. Studies have shown that tick saliva reduces the production of pro-inflammatory mediators such as interleukin-12 (IL-12), interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) while increasing the expression of anti-inflammatory cytokines such as transforming growth factor β (TGF-β) and interleukin-10 (IL-10). A mechanism for these effects is the action of molecules such as prostaglandin E2 (PGE2), which is present in large quantities in tick saliva. PGE2 promotes vasodilation, slows wound healing and reduces inflammation. Tick-exposed mice show high levels of TGF-β and increasing concentrations of IL-10 and interleukin-4 (IL-4) with each tick exposure. These data suggest that repeated exposure to tick saliva can change the polarisation of the immune response towards a Th2 profile, which contributes to the development of allergies and suppression of the Th1 pro-inflammatory response [22]. Furthermore, according to the findings of the study by Eller et al. [23], a feature of the allergic reaction to this antigen is a delayed reaction. When a person consumes foods containing α-gal, such as red meat, this carbohydrate is slowly broken down and absorbed in the digestive system. This leads to a gradual release of α-gal into the bloodstream, which explains the delay in the onset of an allergic reaction. Since α-gal release is slow, it takes longer for sufficient antigen to accumulate to elicit a significant immune response. Khuda et al. [24] emphasized the fact that α-gal antigen transport is via chylomicron transport, which also explains the delay before the allergic reaction.

The interaction of α-gal with the human immune system involves a complex process that can lead to allergic reactions, primarily through two types of responses: natural and induced anti-gal responses. The natural response involves the production of anti-gal antibodies against α-gal-like epitopes present on gastrointestinal bacteria, while the induced response occurs upon exposure to α-gal epitopes on xenografts or through experimental conditions. Tick bites, particularly from species like *Amblyomma americanum*, play a significant role in sensitizing individuals to α-gal by introducing it into the bloodstream, leading to the production of IgE antibodies. This sensitization can result in allergic reactions upon subsequent exposure to α-gal, with symptoms ranging from mild skin rashes to severe anaphylactic shock. The delayed onset of these reactions is due to the slow release of α-gal into the bloodstream after consuming mammalian meat, highlighting the complex interplay between α-gal and the immune system.

Clinical manifestations of α-gal allergy

Allergy to α-gal manifests itself in a variety of clinical symptoms that can range from mild to severe and even life-threatening anaphylactic reactions. These symptoms can be either immediate or delayed, appearing within a few hours after contact with the α-gal allergen.

Mild allergy symptoms may include itching and redness of the skin, hives, swelling of the face, lips or tongue, as well as diarrhoea and nausea [25]. These symptoms often begin within a few hours after eating food or taking medications containing α-gal and can be quite long-lasting and unpleasant for the patient [26]. During the study, Busing et al. [27] determined that α-gal syndrome, caused by IgE, can manifest as GI symptoms in children. In a retrospective study of 199 patients in a paediatric gastroenterology clinic, 20 % tested positive for α-gal IgE, with 77.5 % of them experiencing only GI symptoms. Out of 30 patients who tried to exclude foods containing α-gal, 27 % had complete resolution of symptoms. This shows that α-gal syndrome can occur in children with isolated GI symptoms and responds to dietary treatment. Furthermore, according to de la Fuente et al. [28], some patients are asymptomatic. In addition, the onset of gastrointestinal symptoms is often delayed by several hours after consumption of α-gal-containing foods [29].

Severe anaphylactic reactions are the most serious manifestation of an α-gal allergy and can be life-threatening. These reactions can include difficulty breathing, low blood pressure, rapid heartbeat, panic and loss of consciousness. Without immediate medical intervention, anaphylaxis can progress and even lead to death [30]. Nalin et al. [31] cited several clinical cases of anaphylactic shock after the administration of gelatine-containing drugs, which was a life-threatening situation for these patients. Hane et al. [32] noted that such patients have a cross-reactivity with cetuximab, which significantly reduces the therapeutic options in the treatment of cancer. In addition, Serrier [33] states that the identification of this allergy before therapy can significantly reduce the risk of anaphylactic reaction after the first administration of cetuximab.

In addition, the immune response to α-gal causes increased migration of phagocytes to the site of exposure to the antigen. A study by KAYMAKCALAN et al. [34] showed that α-gal nanoparticles (AGN, nanoparticles with the α-gal epitope) can improve wound healing in diabetic mice by temporarily increasing macrophage recruitment. Topical application of AGN to wounds significantly accelerated wound closure and healing, and improved epithelialisation, vascularisation and granulation tissue formation. This method is a simple, safe and effective way to improve wound healing in diabetes. Topical application of AGN improves wound healing in irradiated tissues. In a study by SAMADI et al. [35] on α1.3GT knockout mice, AGN accelerated epithelial migration and wound healing, in contrast to the group receiving buffer solution. These results show that AGNs can effectively accelerate wound healing in irradiated skin. However, allergy to this epitope also carries risks for certain patients.

Allergic reactions to α-gal can manifest in a variety of clinical symptoms, ranging from mild to severe, and can even be life-threatening. Mild symptoms may include itching, skin rashes, swelling, and gastrointestinal discomfort, which typically occur within a few hours of exposure to α-gal. Severe reactions can include difficulty breathing, low blood pressure, rapid heartbeat, and loss of consciousness, necessitating immediate medical intervention. The variability in clinical manifestations underscores the importance of personalized diagnosis and treatment strategies, considering each patient's unique characteristics and sensitivity to the allergen.

Diagnosis of α-gal allergy

Diagnosing an α-gal allergy is a key step in determining the body's sensitivity to this allergen and planning a treatment strategy. It is based on a comprehensive approach, including clinical assessment, laboratory tests and provocative tests. The main methods of diagnosing α-gal allergy include clinical assessment of symptoms, skin tests, blood tests for IgE antibodies and provocation tests. Clinical assessment of symptoms allows the physician to take anamnesis and analyse clinical manifestations associated with the patient's contact with potential allergens.

The oral food challenge (OFC) test is the most accurate method of diagnosing food allergy, providing additional information about food tolerance and sensitivity threshold [36, 37]. This test involves the supervised administration of the suspected allergen in gradually increasing doses, followed by close monitoring for any allergic reactions. The OFC provides critical information about a patient's tolerance to specific foods and helps determine the threshold dose that may trigger an allergic reaction [38]. It is typically conducted in a clinical setting equipped to handle potential severe reactions, such as anaphylaxis. The OFC is invaluable for confirming the diagnosis of food allergies and assessing the effectiveness of ongoing treatment strategies.

Blood tests allow the assessment of the immune response to α-gal by detecting elevated levels of IgE antibodies to the allergen. Such tests can confirm the preliminary diagnosis of AGS based on the patient's medical history. The measurement of anti-α-gal IgE levels in the blood serum by enzyme-linked immunosorbent assay with bovine thyroglobulin is used. However, the significance of a positive anti-α-gal IgE test result at a threshold level of 0.35 $kU \cdot l^{-1}$ (where 1 $kU \cdot l^{-1}$ = 1 $IU \cdot ml^{-1}$ = 2.4 $ng \cdot ml^{-1}$) remains clinically uncertain [39]. Among the 300 hunters, 19.3 % (i.e. 58 people) had IgE-α-gal levels above the threshold of 0.35 $IU \cdot ml^{-1}$. However, allergic reactions to mammalian meat were observed in only 1.7 % of participants (5 people in this group). This suggests that despite relatively high levels of IgE-α-gal in a significant number of hunters, clinically significant allergic reactions to mammalian meat remain rare in this population [40].

Provocative tests, conducted under the supervision of a physician, are crucial for confirming the diagnosis of α-gal allergy. These tests involve the controlled administration of small, incremental doses of the suspected allergen, followed by careful monitoring of the patient's response. Provocative tests are designed to observe and record any allergic reactions, which can range from mild symptoms, such as skin rashes or gastrointestinal discomfort, to severe reactions like anaphylaxis. These tests are essential for accurately diagnosing α-gal allergy, particularly in cases where other diagnostic methods yield ambiguous results. They help to confirm the presence of an allergy and to assess the severity of the patient's sensitivity to the allergen. Due to the potential risk of severe allergic reactions, provocative tests must be performed in a well-equipped medical facility with immediate access to emergency interventions, such as epinephrine administration.

In addition to the above methods, other laboratory and instrumental tests can also be used to diagnose α-gal allergy. For example, a stool test for the presence of blood can be useful for detecting allergic reactions in the gastrointestinal tract. Skin samples can also be taken for additional analysis in case of suspected α-gal allergy.

Diagnosing α-gal allergy requires a comprehensive approach that includes clinical assessment, laboratory tests, and provocative tests. Clinical assessment involves evaluating symptoms and medical history related to potential allergen exposure. Laboratory tests, such as blood tests for IgE antibodies, help assess the immune response to α-gal. Provocative tests, conducted under medical supervision, involve administering small doses of the allergen to observe the body's reaction. Due to the similarity of symptoms to other allergic reactions and individual variability, a thorough evaluation and analysis of test results are essential for accurate diagnosis and effective treatment planning.

Prevention and treatment of α-gal allergy

The main method of preventing α-gal allergy is to exclude meat and meat products containing this carbohydrate from the diet. This includes red meat (beef, pork, lamb), offal, as well as some types of dairy products and gelatine. Patients are advised to read food labels carefully and to be aware of hidden sources of α-gal, such as meat extracts and flavourings. Since tick bites, especially *Amblyomma americanum* tick bites can be a trigger for α-gal sensitisation, an important aspect of prevention is to prevent tick bites. This can include wearing protective clothing when outdoors, using repellent and regularly checking the body for ticks. In regions with a high prevalence of ticks, it is recommended to avoid dense vegetation and grass where ticks can live [41, 42].

In the event of an allergic reaction to α-gal, the key is the timely use of epinephrine. Epinephrine is the first-line treatment for anaphylaxis and should be available to patients with a known allergy to α-gal [43]. Patients are advised to carry epinephrine auto-injectors (e.g. EpiPen) and know how to use them correctly. In the event of anaphylaxis, epinephrine should be administered immediately, and emergency medical assistance should be sought [44]. In addition, patients may be prescribed antihistamines to control less severe allergic symptoms, such as skin rash or itching. However, antihistamines are not a substitute for epinephrine in anaphylaxis and should be used only as an additional measure.

Immunotherapy is a promising area in the treatment of α-gal allergy [45, 46]. Research is currently underway to develop methods of desensitisation to α-gal. Immunotherapy may involve gradually introducing the patient to increasing doses of the allergen to reduce the sensitivity of the immune system to it. This method can potentially reduce the severity of allergic reactions or even eliminate them [47]. Ünal et al. [48] demonstrated the effectiveness of immunotherapy for meat allergy. Oral immunotherapy (OIT) is effective and safe for the treatment of red meat allergy in adults. During the study, 12 out of 20 patients underwent OIT and became tolerant to meat, and their allergic antibody levels decreased. During the five years of follow-up, the allergy did not return, which confirms the long-term effect of the therapy [49].

In summary, the management of an α-gal allergy consist of avoiding offending foods, preventing tick bites, an emergency use of epinephrine auto-injectors and immunotherapy.

CONCLUSIONS

The main mechanisms for the development of α-gal allergy include sensitisation through the bites of mites such as *Amblyomma americanum*, which leads to the development of specific IgE antibodies to α-gal. This process highlights the importance of environmental factors that influence the spread of mites and, consequently, the incidence of allergy. Genetic predisposition also plays a significant role, and the identification of specific genetic markers can identify risk groups and develop personalised preventive measures.

The development of new diagnostic methods, such as molecular diagnostics and the use of specific biomarkers, is an important step forward. Current methods, including skin tests and blood tests, have limitations, and new approaches may provide more accurate and earlier diagnosis, which is essential to prevent severe allergic reactions.

Treatment of α-gal allergy currently includes avoidance of triggers and the use of epinephrine in case of anaphylaxis. However, immunotherapy and new pharmacological approaches, such as the use of monoclonal antibodies and signalling pathway inhibitors, offer promising opportunities to improve the quality of life of patients. These methods can not only reduce the severity of symptoms but also potentially change the course of the disease by reducing the sensitivity of the immune system to α-gal.

A review of existing research shows that despite significant advances in understanding the pathophysiological mechanisms of this allergy, there are still unresolved issues that require further study. Further research should be aimed at an in-depth study of the immunological and genetic mechanisms underlying this allergy, as well as the development of new methods of diagnosis and treatment. The understanding of the role of

α-gal in allergic reactions and the development of these methods open new prospects for improving patient health and reducing the risk of allergic complications. Limitations of this review include the possible omission of some relevant publications due to language barriers or limited access to full texts of articles. Furthermore, the data analysis was based on available publications, which may have affected the completeness of the review.

Thus, a comprehensive approach, including both basic research and clinical trials, is needed to overcome current limitations and make significant progress in the fight against α-gal allergy. This will not only improve diagnosis and treatment but also develop effective prevention strategies, which will lead to a significant improvement in the quality of life of patients suffering from this disease.

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