Current Treatment Options in Allergy
https://doi.org/10.1007/s40521-024-00371-y

REVIEW

Is Alpha-Gal an Emerging Allergen in Drug Allergy?

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Accepted: 18 July 2024

Abstract

Purpose of Review Galactose-alpha-1,3-galactose (alpha-gal) is a ubiquitous singular oligosaccharide and a relevant emergent allergen, first reported in 2008, which caused severe and even fatal allergic reactions to drugs such as the monoclonal antibody cetuximab. This article reviews the literature on drugs containing alpha-gal and on drugs acting such as compounding-factors in alpha-gal allergy and the concomitant risk of anaphylaxis, from the last 15 years.

Recent Findings On the one hand, contact with mammal-derived excipients or additives, could be an emergent cause of an alpha-gal hypersensitivity reaction. Previously, monoclonal antibodies (abs) and intravenous gelatins have been the most frequent culprits responsible for immediate alpha-gal drug allergic reactions regardless of the initially described cetuximab. On the other hand, drug co-factors such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Angiotensin Converting Enzyme (ACE) Inhibitors and Proton Pump Inhibitors (PPIs), have been reported to trigger alpha-gal allergy and increase the risk of anaphylaxis.

Summary This review provides the latest updates on Alpha-Gal Syndrome (AGS), focusing on drugs that contain alpha-gal, and emphasizing that certain medications can act as risky compounding-factors.

Data on prevalence, clinical presentation, current diagnosis and patient management are also reviewed, providing practical resources to support today´s best care including nutritional assessment. Future research should focus on improving effective treatment for managing AGS.

Keywords Alpha-gal · Drug allergy · Co-factors / Compounding factors · Anaphylaxis · Excipients · Additives

Introduction

Alpha-gal is a disaccharide, expressed on glycoproteins and glycolipids on the cell surface of non-primate mammals, certain invertebrates and microscopic organisms such as microbiota bacteria, helminths among others [1–6].

Throughout the evolution, primates and humans have lost the ability to synthesize alpha-gal. Human immune system naturally generates large amounts of anti-gal Immunoglobulin (Ig) G. Therefore, it is the major xenoantigen responsible for xenotransplant rejection [7]. Investigations of the classes of anti-alpha-gal antibodies (abs) revealed the presence of Ig G, Ig M, and Ig A abs in human serum and secretions [8]. Anti-alpha-gal Igs M and Igs G protect humans against malaria among others [3, 5]. Furthermore, not only the presence of specific IgE (sIgE) but also the quantification of additional specific Ig G against alpha-gal could be used as a risk marker for suffering mammalian meat allergy [9].

On the other hand, the alpha-gal antigen seems to represent a feasible target for developing glycan-based vaccines against multiple diseases including oncological ones [3, 10, 11].

Alpha-gal has a structure similar to blood group B. The presence of blood type B reduces the immune system´s capacity to produce anti-alpha-gal abs, presumably due to tolerance to alpha-gal. Therefore, individuals with blood group B and reduced levels of anti-alpha-gal abs, have a lower risk of developing Alpha- Gal Syndrome (AGS) [12–14].

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Published online: 09 August 2024

Chung et al. [15] in 2008, first reported allergy to alpha-gal due to immediate hypersensitivity reactions to the chimeric monoclonal ab cetuximab. Subsequently, Commins et al., identified 24 patients who had experienced delayed allergic symptoms after consuming beef, pork, or lamb due to alpha-gal, also suggesting a relationship between tick bites and the production of sIgE antibodies against alpha-gal [16], as reported by other authors later [17, 18]. It has been further observed that not only ticks but also other arthropods can elevate Ig E levels to alpha-gal [19]. Sensitization to wasp and bee venom has been reported to be common among mammalian meat-allergic patients [20, 21]. Additionally, Sánchez et al. described an anaphylactic reaction to a tick bite with a positive skin test result for cetuximab and specific Ig E for alpha-gal, suggesting the involvement of glycosylated allergens [22].

The alpha-gal moiety was found on the asparagine at position 88 in the murine heavy chain portion of cetuximab [9]. It is unknown whether the position of alpha-gal influences susceptibility to an allergic reaction. Our group described at least co-sensitization studied by Basophil Activation Test (BAT) to ramucirumab and cetuximab in a patient who experienced anaphylaxis during the first administration of ramucirumab. The patient had not been previously treated with cetuximab but had recently been bitten by ticks and sIgE to alpha-gal of 15.30 kUA/L was detected [23, 24]. Ramucirumab is produced in murine (NS0) cells using recombinant DNA technology [25] which suggests that it contains alpha-gal residues. Therefore, drug labels must specify whether they contain alpha-gal.

Alpha-gal not only induces immediate but also delayed severe allergic reactions [16]. Normally, if the administration is intravenous, the reaction will begin immediately. However, if the allergen is ingested orally, it may take about 3–8 h to develop a reaction [16]. Lipids and their transformation could be related to this time lag [19]. Additionally, cofactors not only seem to participate in the triggering but also in the increase of the severity of the reactions [18, 19, 26–29].

Due to its relevance, ubiquity, and particularities, alpha-gal has been intensively investigated in the last decade and a half, being considered a significant allergen present in different sources, such as medicines, drug excipients, additives, and food (mammalian meats, dairy, gelatins, gummies) [19], causing allergic reactions not only in adulthood but also in childhood [14, 19, 29–31].

Prevalence

Alpha-Gal Syndrome has shown a rising prevalence around the world, particularly in the southeastern United States (U.S.), Australia, and different locations of Europe [19, 32, 33]. Various studies have indicated that tick bites lead to sensitization to alpha-gal, contributing to AGS. Ticks such as the Lone Star tick (*Amblyomma americanum*) in the U.S., Ixodes species in Australia and Europe (particularly in countries like Sweden, Germany, and Spain, the *Ixodes ricinus* tick is the primary vector), and *Haemaphysalis species* in Japan, are significant vectors [16, 17, 19, 32–34].

Gonzalez-Quintela et al. in 2014, conducted an investigation comparing the prevalence of alpha-gal sIgE abs in the general adult population of two separate European regions, Denmark and Spain. The study found that the prevalence of positive alpha-gal Ig E abs was 5.5% in Denmark and 8.1% in Spain. Factors such as pet ownership, specifically cat ownership, atopy (SPT positivity), and a history of tick bites were linked to alpha-gal Ig E positivity, associated with systemic anaphylaxis [34].

Five years later, Mateo-Borrega et al., focused on studying the prevalence of sIgE to alpha-gal in individuals with acute urticaria or anaphylaxis across different regions in Spain. They identified relevant demographic and lifestyle risk factors such as environmental exposure to ticks, outdoor activities, pet ownership and dietary habits like consumption of mammalian meats or innards before symptom onset [24]. The study found an overall prevalence of sIgE to alpha-gal of 15.7%, with significant differences between cases (26.3%) and controls (2.4%). The prevalence of alpha-gal sensitization specifically in Spain, shows marked geographical variations, with the highest rates observed in rural and Northern regions. Similar data was reported by Venturini et al., in 2018 in a group of foresters and forest workers in La Rioja, Spain, showing a higher prevalence of sIgE abs to alpha-gal compared to the control group, associated with the number of tick bites and length of exposure [33].

Demographics

Age

While AGS was initially reported more commonly in adults, recent studies have documented cases in pediatric and adolescent populations, suggesting the allergy affects a broader age range than previously understood [14, 19, 29–31].

Gender

Existing data do not indicate a significant gender preference for AGS, although some regional studies have shown slight variations, with AGS being more common in men compared to women due to their work environment [18, 33].

Tick exposure and risk factors

Tick Bites: Sensitization to alpha-gal is strongly associated with tick bites. Individuals residing in tick-endemic areas or

those with frequent outdoor activities, occupations involving wildlife, or a history of tick bites are at increased risk.

Climate and Tick Development: Temperate climates are generally considered to be more favorable for the development of ticks. Ticks thrive in environments with moderate temperatures and adequate humidity, which are characteristic of temperate regions. These conditions support their lifecycle and facilitate their survival and reproduction.

Environmental Factors: Changes in climate and land use patterns are influencing the distribution of tick populations, potentially expanding the regions affected by AGS.

Novel data and clinical presentation

Alpha-Gal Syndrome is characterized by immediate and/or pathognomonic delayed hypersensitivity reactions typically occur 3–8 h after ingesting mammalian meat, dairy or derivatives including excipients of various oral medications. Symptoms can range from gastrointestinal upset, itching, urticaria, angioedema, dyspnea to severe anaphylaxis [16, 19], with the most severe reactions described in cases involving cetuximab [35, 36].

Some patients exhibit isolated gastrointestinal symptoms such as abdominal pain, diarrhea, irritable bowel syndrome, or abdominal cramps [14, 16, 19, 26]. Clinical symptoms often manifest at night and can be greatly influenced by cofactors, primarily NSAIDs, exercise and alcohol intake [19] (See Fig. 1).

Despite common delayed allergic reactions, the study of alpha-gal reactions in some countries such as Germany and France began with immediate-type allergies following the consumption of pork kidney rich in alpha-gal, which is frequently consumed as a local delicacy or in sausages [36]. Additionally, the parenteral administration of drugs obtained from cells or tissue from mammals (e.g., cetuximab, abatacept, infliximab, vaccines, or gelatin-based colloids) has also resulted in immediate severe reactions such as anaphylaxis and anaphylactic shocks [19, 35, 37, 40–42]. Other gelatins used in medications, such as fenticonazole, may contain

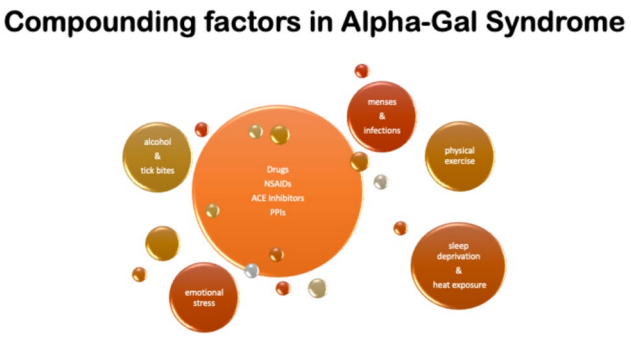

Fig. 1 Compounding factors involved in alpha-gal syndrome.

epitopes, and the use of these intravaginal capsules may also be associated with allergic reactions [43].

Heparins [44, 45], bioprosthetic heart valves [45], pancreatic enzymes [46, 47], thyroid hormones [48] and antivenoms [49] have also been described to produce allergic reactions in some alpha-gal patients including severe anaphylaxis.

Other components of medications such as arachidonic acid, arachidyl propionate, biotin, carrageenan, castoreum, glycerin, lanolin, latex, milk proteins, myristic acid, oleic acid and stearic acid can trigger AGS [19]. Therefore, it is important to be aware of these components as they appear to be hidden allergens (See Table 1).

A combination of exogenous and endogenous factors (e.g. emotional stress, lack of sleep, physical exercise, alcohol, NSAIDs, ACE Inhibitors, PPIs, infections, menses, intensive hot weather, tick bites, among others) [19, 26, 27, 36, 37] seem to play a role in increasing antigen recognition, intestinal absorption and the risk of anaphylaxis or anaphylactic shocks in alpha-gal patients [26, 27, 36, 37] (See Fig. 1).

Similar data have been reported on children´s symptoms including cofactors and increased allergic reactions [14, 29–31]. Vaccines such as measles-mumps-rubella and zoster virus contain a significant amount of gelatin, which includes alpha-gal, leading to basophil activation in patients with AGS [50].

Alpha-gal has been associated not only to gastrointestinal morbidity but also to cardiovascular disease. Wilson et al., explored the relationship between coronary artery disease (CAD) and Ig E sensitization to alpha-gal [51]. In a study involving 118 subjects undergoing cardiac catheterization and intravascular ultrasound, 26% of the participants tested positive for sIgE to alpha-gal. These individuals exhibited a higher atheroma burden and less stable plaque characteristics. This association was particularly strong in subjects aged 65 or younger. IgE to alpha-gal was specifically correlated with atherosclerosis even after adjusting for factors such as sex, diabetes, hypertension, and statin use. These findings suggest potential new targets for preventing or treating CAD in specific subpopulations with alpha-gal sensitivity.

Another study conducted by Vernon et al., confirms that alpha-gal sensitization is linked to a higher burden of non-calcified plaques and obstructive CAD, and is significantly associated with increased rates of ST-segment–elevated myocardial infarction (STEMI) [52]. This finding suggests the need for further research into the role of alpha-gal sensitization in heart disease, particularly in tick-endemic regions.

Patients with both alpha-gal allergy and Mast Cell Hyperactivity (MCH) appear to have higher incidence of gastroesophageal reflux disease (GERD), migraines, psychiatric conditions, and multiple other atopic conditions compared to those with alpha-gal allergy alone [53]. Another uncommon symptom noted in AGS is joint pain [14, 19].

Table 1 Medications containing Alpha-Gal (AG)

Biological Drugs containing AG	Excipients Containing AG	Medications Containing AG
Cetuximab	Gelatin	Heparins Antiplatelets (Lactose, magnesium sterate)
Infliximab	Gelatin based products	Propofol (Glycerol)
Abatacept	Carmine	Gel capsules
Natalizumab	Carrageenan	Gelatins
Ramicirumab	Glycerin (Lanolin) Glycerol	Vaccines
	Whey proteins	Pancreatic Enzymes
	Arachidonic acid	Thyroid hormones
	Arachidyl propionate	Vasopresin (Lactic acid)
	Castoreum	Bioprosthetic heart valves
	Biotin (milk)	Anti Venoms
	Latex (casein /milk proteins)	Thrombin
	Myristic acid	Milrinone (Lactic acid)
	Oleic acid	Clevidipine (Glycerin, oleic acid)
	Stearic acid	Epoprostenol (Metabolite of arachidonic acid)
	Magnesium sterate	Hydromorphone intravenous (Lactic acid, sodium lactate)
		Hydromorphone oral (Glycerin, lactose, magnesium sterate, stearic acid)
		Acetaminophen (Gelatin, glycerin, lactose monohydrate, magnesium stearate, stearic acid, oleic acid, stearic acid)

In this sense, it appears that alpha-gal may contribute to mast cell activation. One patient studied in Vitoria-Gasteiz (Basque Country, Spain) with colorectal tumor, presented an anaphylaxis after the first administration of cetuximab. He had not sIgE to alpha-gal but his basal tryptase was higher than eleven. He tolerated cetuximab with cromoglicate as a pretreatment. (Unpublished data).

Current diagnosis

Alpha-Gal Syndrome is typically diagnosed through a compatible medical history, assessing the prior intake of medications containing alpha-gal, inquiring about the concurrent use of other drugs or implicated cofactors, and a positive blood test (> 0.1 IU/mL) for sIgE to alpha-gal. This blood test has a reported specificity of 92.3% and sensitivity of 100% among patients with AGS [19]. However, the titer of sIgE to alpha-gal does not predict the severity of the reaction [14, 19].

The diagnosis can be confirmed by observing that symptoms lessen or disappear when the patient follows a diet that avoids mammalian meat.

Other diagnostic tools

Mammalian skin tests: Skin prick and intradermal tests using mammalian meat extracts can be included for diagnosis. Skin tests with commercial meat extracts have shown low sensitivity. Patients often exhibit doubtful or negative reactions in skin prick tests using commercial meat extracts [16, 18]. However, Izaguirre et al., achieved better results not only with skin prick tests using commercial meat extracts but also with tests using cooked mammalian meats and raw lamb kidneys in a study involving 14 patients [54]. Apart from this study, globally, skin tests are generally considered unreliable [16].

Total cow milk prick tests have been reported to show limited positivity in a series of 10 patients allergic to alpha-gal [18]. In these cases, milk fractions tested negative. Subsequently, in a larger series of 47 AGS patients, only one patient exhibited a definitive positive result in a commercial milk prick test [55]. Therefore, skin tests using mammalian milk are not considered helpful for diagnosing AGS.

Cetuximab skin prick tests: It is noteworthy that there are no commercial skin tests for alpha-gal, and before the

availability of alpha-gal sIgE tests, cetuximab skin tests were the only available method for rapidly diagnosing patients. Cetuximab skin prick tests have showed high sensitivity and specificity for AGS at 5 mg/mL [18, 56]. An intradermal test at 5 µg/mL can be conducted in patients with smaller papule diameter pricks (3–4 mm). Ramucirumab has also demonstrated a positive skin intradermal result in a patient sensitized to alpha-gal. An undiluted prick test and intradermal test at a 1/10 dilution (1 mg/mL) with ramucirumab were performed, resulting in a positive intradermal test [24].

Gelatin prick and intradermal tests have been valuable in confirming the diagnosis of AGS [37, 42].

BATs can be used to confirm allergy to alpha-gal due to previously demonstrated positive results [18]. BAT is capable of detecting cetuximab and alpha-gal-sensitized patients and assessing their potential risks, although the technique is not readily available for routine clinical care. BAT results are evaluated by measuring CD63 expression by basophils following in vitro allergen-specific stimulation with different concentrations of cetuximab covering various log scales, simulating in vivo concentrations (0.25, 0.125, and 0.025 mg/mL). The procedure should be carried out without bovine serum albumin. A monoclonal anti-IgE antibody (Sigma-Aldrich) at 1 mg/mL and N-formyl-methionyl-leucyl-phenylalanine (fMLP) (Sigma-Aldrich) at 1 mmol/L are utilized as positive controls. Samples are analyzed using a BD FACS flow cytometer (BD Biosciences), with a minimum of 500 CD123highHLA-DRdim basophils per sample studied. Activated basophils are also identified as CD63-positive. In our experience, optimal results have been achieved at 0.025 mg/mL [18, 23, 37].

BAT involving cetuximab has exhibited positive outcomes within a high percentage range of stimulation, varying between 39% and 93.7% [18]. Interestingly, a patient with 0.14 kUA/L sIgE to pork displayed a notably high positive BAT result (89%) with cetuximab. The BAT results with cetuximab surpassed those previously observed with extracts from mammalian meats [57].

Mehlich et al., reported that establishing thresholds of BAT parameters indicating heightened basophil reactivity and sensitivity may assist clinicians in selecting appropriate doses for oral provocation tests in patients with AGS. This approach can also help in advising patients to avoid foods and medications containing even trace amounts of alpha-gal [58].

Diagnostic challenges may arise in patients without clear clinical symptoms or seronegativity. Some patients may have a negative study (negative sIgE to alpha-gal despite clinical symptoms), requiring alternative diagnostic strategies like food challenges and surrogate marker testing [19]. Patients must sign an informed consent due to the potential risk of a severe allergic reaction.

Treatment and management

Pathology information

It is essential for patients to be well-informed about their condition, considering that cofactors can contribute to triggering and exacerbating reactions [14, 19, 26, 27, 29, 36]. For this reason, patients should carry a rescue kit containing epinephrine, antihistamines, and oral corticosteroids. They should also be educated on how to self-administer epinephrine effectively.

Arthropod bites avoidance

To prevent arthropod bites, particularly tick and hymenoptera bites, individuals should use repellents and wear clothing that covers their body. Blood levels of sIgE to alpha-gal and the risk of allergic reactions often decrease in patients who avoid repeated tick bites, although the rate of decline can vary among patients [19].

Food avoidance and nutritional assesment

Alpha-Gal Syndrome involves avoidance of mammalian meat (and visceral organs), some patients (about 10–20%) also need to avoid dairy products and mammalian-derived gelatins, gummies and other derivatives. It seems that high-fat dairy may be more problematic than light milk [19]. Other dairy products such as low-fat yogurt, may contain gelatin to improve consistency.

On the other hand, whey proteins such as lactoferrin, gamma- globulin and lactoperoxidase, as well as cow and sheep dairy derivatives, have been identified to contain alpha-gal and should be avoided if patients exhibit clinical symptoms. Conversely, pure goat's milk and cheese have been shown to be well-tolerated in a recent study involving 47 AGS patients [55].

It is crucial to minimize the consumption of products containing alpha-gal and compounding factors wherever possible. While some AGS patients may occasionally tolerate mammalian meat with few or no symptoms, they may experience severe reactions on other occasions. These differences have been linked to cofactors and recent tick bites [19].

Collaboration with dietitians is also important to ensure a well-rounded nutritional plan. In terms of nutritional assessment, Sacristan-Arias et al., documented deficiencies in calcium, vitamin D, and iron in AGS patients [59].

Drugs avoidance

Regarding medications, cetuximab, gelatin-containing colloidal fluids, bioprosthetic heart valves, and high dose intravenous heparins pose a high-risk for AGS patients due to the significant quantity of alpha-gal and their direct administration [15, 19, 35–37, 41, 42, 44, 45]. Vaccines containing gelatin should be avoided or administered with caution in an allergy department [40]. Conversely, other medications such as certain heparins, pancreatic enzymes [46, 47], thyroid hormones [48] and anti-venoms [49] have been reported to cause allergic reactions in only a few alpha-gal patients, hence individual recommendations are necessary. Unfortunately, the alpha-gal content of many medications, varies between manufacturers and is not consistently disclosed. However, alpha-gal is often well-tolerated in small daily amounts [19].

Biological treatments such us abatacept [38], infliximab, an anti-tumor necrosis factor monoclonal antibody also synthesized in the SP2/0 murine-derived cell line [39] and ramucirumab [23, 24] have been described to produce allergic reactions in AGS. There is a potential risk of natalizumab also eliciting an allergic response [60]. Nevertheless, panitumumab could serve as a therapeutic alternative to cetuximab since it lacks the alpha-gal epitope [61].

The potential utilization of cell lines that do not glycosylate proteins with alpha-gal, such as Chinese hamster ovary (CHO) cells, for the production of biological products like cetuximab, infliximab, and natalizumab, can help reduce the risk of anaphylactic reactions in patients with Alpha-gal [60].

Drugs such as NSAIDs, ACE inhibitors, and PPIs have been implicated in triggering allergic reactions in AGS patients and must be avoided as much as possible [19, 26].

Managing AGS in the perioperative setting requires heightened awareness of medications containing alpha-gal and potential co-factors. Recently, Leder et al. proposed an interesting comprehensive safety profile of medications for AGS patients [62].

It appears that carrageenan, a high molecular weight polysaccharide sourced from red seaweed and containing alpha-gal, has emerged as a potential trigger for IgE-mediated hypersensitivity symptoms in individuals with AGS due to its widespread presence. Carrageenan can be found in various products such as toothpaste, lubricants, shampoos, certain food items like dairy products, frozen desserts, beer, canned and cured meats, emulsified sauces, jelly candies, and some powdered goods. This highlights the importance of recognizing carrageenan as a possible allergen for individuals with AGS when assessing their exposure risks and managing their condition [19, 63].

Other excipients referred before (Table 1) can also produce alpha -gal symptoms [19, 62].

Avoiding certain excipients, additives, drugs, mammalian meats, and dairy products is currently the primary treatment option for individuals with AGS. There is a possibility that desensitization to beef and milk could become a future treatment approach. It has been observed in clinical settings that individuals with AGS who can tolerate small amounts of dairy are more likely to see an improvement in their allergic symptoms [19, 60].

For refractory cases, allergy medications or even alpha-gal free biologics such as omalizumab may be considered. Additionally, treatments such as metformin, cromoglicate, daily antihistamine use, and leukotriene receptor antagonists have shown potential in improving symptoms associated with AGS. It is important to work with healthcare providers to determine the best treatment plan for managing AGS symptoms effectively [19].

Unal et al., reported two cases of successful beef desensitization in adult patients with AGS using a 27-day desensitization protocol [64]. Additionally, another case report documented successful beef desensitization in a pediatric patient from Turkey [65].

Furthermore, Unal et al., conducted a study focusing on the long-term safety and efficacy of red meat (RM) oral immunotherapy (OIT) for alpha-gal allergy in adults. All patients who underwent OIT developed tolerance to RM. During the 5-year follow-up, patients desensitized to RM exhibited a gradual decrease in alpha-gal sIgE concentrations, contrasting with the control group where these levels remained stable. The study highlighted tick bites as triggers for hypersensitivity reactions in some instances. It underscored the safety and effectiveness of alpha-gal OIT and proposed the potential use of alpha-gal sIgE as a biomarker for monitoring OIT (66).

Conclusion

Alpha-gal has emerged as a significant allergen, leading to severe allergic reactions in response to drugs such as cetuximab.

Excipients and additives derived from mammals have been identified as potential instigators of alpha-gal hypersensitivity reactions.

Drug-cofactors such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Angiotensin Converting Enzyme (ACE) Inhibitors, and Proton Pump Inhibitors (PPIs) have been associated with triggering alpha-gal allergy and increasing the risk of anaphylaxis.

The review emphasizes the importance of understanding drugs containing alpha-gal and the use of medications as compounding-factors in alpha-gal allergy.

Data on prevalence, clinical presentation, diagnosis, and management of alpha-gal syndrome have been reviewed,

providing insights into effective treatment strategies and the need for improved management practices.

These conclusions shed light on the complexities of alpha-gal allergy, highlighting the critical need for effective treatment strategies and ongoing research to enhance the management of this emerging allergen in drug allergy.

Acknowledgements Ana Martínez-Arcediano would like to thank her family for their support.

Author Contributions Ana Martínez-Arcediano (the corresponding author) produced and designed the manuscript and did the final revision. All authors were involved in the acquisition of data, including the search, analysis, and interpretation of data and the critical revision of the manuscript for important intellectual content.

Declarations

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Competing interests The authors declare no competing interests.

Permissions Table 1 and Fig. 1 are original.

References

1. Román-Carrasco P, Hemmer W, Cabezas-Cruz A, Hodžić A, de la Fuente J, Swoboda I. The α-Gal Syndrome and Potential Mechanisms. Front Allergy. 2021;16(2):783279. https://doi.org/10.3389/falgy.2021.783279.
2. Rydberg L, Holgersson J, Samuelsson BE, Breimer ME. Alpha-Gal epitopes in animal tissue glycoproteins and glycolipids. Subcell Biochem. 1999;32:107–25. https://doi.org/10.1007/978-1-4615-4771-6_5.
3. Cabezas-Cruz A, de la Fuente J. Immunity to α-Gal: The Opportunity for Malaria and Tuberculosis Control. Front Immunol. 2017;4(8):1733. https://doi.org/10.3389/fimmu.2017.01733.
4. Yilmaz B, Portugal S, Tran TM, Gozzelino R, Ramos S, Gomes J, et al. Gut microbiota elicits a protective immune response against malaria transmission. Cell. 2014;159:1277–89. https://doi.org/10.1016/j.cell.2014.10.053.
5. Galili U. Significance of the evolutionary α1,3-galactosyltransferase (GGTA1) gene inactivation in preventing extinction of apes and old world monkeys. J Mol Evol. 2015;80:1–9. https://doi.org/10.1007/s00239-014-9652-x.
6. Murangi T, Prakash P, Moreira BP, Basera W, Botha M, Cunningham S, Facey-Thomas H, Halajian A, Joshi L, Ramjith J, Falcone FH, Horsnell W, Levin ME. Ascaris lumbricoides and ticks associated with sensitization to galactose α1,3-galactose and elicitation of the alpha-gal syndrome. J Allergy Clin Immunol. 2022;149(2):698-707.e3. https://doi.org/10.1016/j.jaci.2021.07.018.
7. Sandrin MS, McKenzie IF. Gal alpha (1,3)Gal, the major xenoantigen(s) recognised in pigs by human natural antibodies. Immunol Rev. 1994;141:169–90. https://doi.org/10.1111/j.1600-065x.1994.tb00877.x.
8. Hamadeh RM, Galili U, Zhou P, Griffiss JM. Anti-alpha-galactosyl immunoglobulin A (IgA), IgG, and IgM in human secretions. Clin Diagn Lab Immunol. 1995;2(2):125–31. https://doi.org/10.1128/cdli.2.2.125-131.1995.
9. Joral A, Azketa N, Sanchez P, Vélez-Del-Burgo A, Aranzabal-Soto MA, Lizarza S, Martínez J, Postigo I. The Quantification of IgG Specific to α-Gal Could Be Used as a Risk Marker for Suffering Mammalian Meat Allergy. Foods. 2022;4(11):466. https://doi.org/10.3390/foods11030466.
10. Galili U. Autologous tumor vaccines processed to express alpha-gal epitopes: a practical approach to immunotherapy in cancer. Cancer Immunol Immunother. 2004;53(11):935–45. https://doi.org/10.1007/s00262-004-0524-x.
11. Tanemura M, Miyoshi E, Nagano H, Eguchi H, Matsunami K, Taniyama K, Hatanaka N, Akamatsu H, Mori M, Doki Y. Cancer immunotherapy for pancreatic cancer utilizing α-gal epitope/natural anti-Gal antibody reaction. World J Gastroenterol. 2015;21(40):11396–410 (**28**).
12. Hamsten C, Tran TAT, Starkhammar M, Brauner A, Commins SP, Platts-Mills TAE, et al. Red meat allergy in Sweden: Association with tick sensitization and B-negative blood groups. J Allergy Clin Immunol. 2013;132(6):1431-4.e6.
13. Apostolovic D, Rodrigues R, Thomas P, Starkhammar M, Hamsten C, van Hage M. Immunoprofile of α-Gal- and B-antigen-specific responses differentiates red meat-allergic patients from healthy individuals. Allergy. 2018;73(7):1525–31.
14. Wilson JM, Schuyler AJ, Workman L, Gupta M, James HR, Posthumus J, et al. Investigation into the α-Gal Syndrome: Characteristics of 261 Children and Adults Reporting Red Meat Allergy. J Allergy Clin Immunol Pract. 2019;7(7):2348-58.e4.
15. Chung CH, Mirakhur B, Chan E, Le QT, Berlin J, Morse M, Murphy BA, Satinover SM, Hosen J, Mauro D, Slebos RJ, Zhou Q, Gold D, Hatley T, Hicklin DJ, Platts-Mills TA. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. N Engl J Med. 2008;358(11):1109–17. https://doi.org/10.1056/NEJMoa074943. (**13**).
16. Commins SP, Satinover SM, Hosen J, Mozena J, Borish L, Lewis BD, Woodfolk JA, Platts-Mills TA. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-alpha-1,3-galactose. J Allergy Clin Immunol. 2009;123(2):426–33. https://doi.org/10.1016/j.jaci.2008.10.052.
17. Nunez R, Carballada F, Gonzalez-Quintela A, Gómez-Rial J, Boquete M, Vidal C. Delayed mammalian meat-induced anaphylaxis due to galactose-α-1,3-galactose in 5 European patients. J Allergy Clin Immunol. 2011;128:1122–4.
18. Martínez Arcediano A, Audicana Berasategui MT, Longo Areso N, Ibáñez EF, Balza de Vallejo OV, Velasco Azagra M, Reyes Dominguez SM, Muñoz Lejarazu D. Allergy to galactose-alpha-1,3-galactose: Clinical features and the diagnostic value of cetuximab. J Investig Allergol Clin Immunol. 2014;24(6):450–2.
19. Commins SP. Diagnosis & management of alpha-gal syndrome: lessons from 2,500 patients. Expert Rev Clin Immunol. 2020;16(7):667–77. https://doi.org/10.1080/1744666x.2020.1782745.
20 Choudhary S, Jerath MR, Commins SP. Venom allergy is increased in alpha-gal allergy: shared environmental or immunologic factors? J Allergy and Clin Immunol. 2018;141(2):AB199. https://doi.org/10.1016/j.jaci.2017.12.631.
21 Kutlu A, Unal D. Mammalian Meat Allergy Accompanied by Venom Allergy: A Review of 12 Cases. Iran J Allergy Asthma Immunol. 2019;18(5):584–8. https://doi.org/10.18502/ijaai.v18i5.1928.
22. Sánchez M, Venturini M, Blasco A, Lobera T, Bartolomé B, Oteo JA. Tick bite anaphylaxis in a patient allergic to bee venom. J Investig Allergol Clin Immunol. 2014;24(4):284–5.
23. Martínez- Arcediano A, Longo-Areso N, Audícana- Berasategui MT, Ollo Morales P, Martel Martin C, Fernández- Ibañez E, Araba University Hospital (HUA), Gasteiz, Spain1591, Cross reactivity between Cetuximab and Ramucirumab in an alpha-gal

allergic patient, detected by Basophil Activation Test. Abstracts Poster. Allergy. 2023;78:56–716. https://doi.org/10.1111/all.15616.
24. Ollo Morales P, Audicana Berasategui MT, Longo Areso MN, Martel Martin C, Gutierrez Niso M, Velasco Azagra M, Girao Popolizio IN, Uriel Villate O, Villarreal Balza De Vallejo MO, Martínez Arcediano A, Araba University Hospital, Gasteiz, Spain. 001370, Anaphylaxis due to ramucirumab allergy in a patient sensitized to alpha-gal. Abstracts Poster. Allergy. 2023;78:56–716. https://doi.org/10.1111/all.15616.
25. https://www.ema.europa.eu/en/documents/product-information/cyramza-epar-product-information_en.pdf
26. Martínez-Arcediano A, Audícana Berasategui MT, Longo Areso MN, Villarreal Balza De Vallejo MO, Velasco Azagra M, Campandegui Lecuona A, Marquínez Ruíz De Arbulo MD, Ollo Morales P, Fernandez Ibañez E. The relevance of compounding factors and the risk of anaphylaxis in 63 patients allergic to alpha-gal. Allergy: Eur J Allergy Clin Immunol. 2021;76(SUPPL 110):546–7. https://doi.org/10.1111/all.15096.
27. Morisset M, Richard C, Astier C, Jacquenet S, Croizier A, Beaudouin E, Cordebar V, Morel-Codreanu F, Petit N, Moneret-Vautrin DA, Kanny G. Anaphylaxis to pork kidney is related to IgE antibodies specific for galactose-alpha-1,3-galactose. Allergy. 2012;67(5):699–704. https://doi.org/10.1111/j.1398-9995.2012.02799.x.
28. Mateo Borrega MB, Garcia B, Larramendi CH, et al. IgE-Mediated Sensitization to Galactose-α-1,3- Galactose (α-Gal) in Urticaria and Anaphylaxis in Spain: Geographical Variations and Risk Factors. J Investig Allergol Clin Immunol. 2019;29(6):436–43. https://doi.org/10.18176/jiaci.0373.
29. Martínez-Arcediano A, Audícana-Berasategui MT, Velasco-Azagra M, Villarreal-Balza De Vallejo O, Gutierrez-Niso M, De La Viuda-Camino E, Fernández-Ibañez, E. Allergy to alpha-gal, compounding factors and the risk of anaphylaxis in 4 European pediatric and adolescent patients. Página 176; Volumen 78: Abstracts from the EAACI Hybrid Congress. 2022. https://doi.org/10.1111/all.15616.
30. Kennedy JL, Stallings AP, Platts- Mills TA, Oliveira WM, Workman L, James HR, Tripathi A, Lane CJ, Matos L, Heymann PW, Commins SP. Galactose-α-1,3-galactose and delayed anaphylaxis, angioedema, and urticarial in children. Pediatrics. 2013;131:e1545–52.
31. Martín-Lázaro J, Núñez-Orjales R, González-Guzmán LA, González MT, Boquete M, Carballada F. Galactose-α-1,3-galactose (alpha-gal) allergy: first pediatric case in a series of patients in Spain. Allergol Immunopathol (Madr). 2020;48(3):251–8. https://doi.org/10.1016/j.aller.2019.07.004.
32. Levin M, Apostolovic D, Biedermann T, et al. Galactose alpha-1,3-galactose phenotypes: Lessons from various patient populations. Ann Allergy Asthma Immunol. 2019;122(6):598–602.
33. Venturini M, Lobera T, Sebastián A, Portillo A, Oteo JA. IgE to α-Gal in Foresters and Forest Workers From La Rioja, North of Spain. J Investig Allergol Clin Immunol. 2018;28(2):106–12. https://doi.org/10.18176/jiaci.0218.
34. Gonzalez-Quintela A, Dam Laursen AS, Vidal C, Skaaby T, Gude F, Linneberg A. IgE antibodies to alpha-gal in the general adult population: relationship with tick bites, atopy, and cat ownership. Clin Exp Allergy. 2014;44(8):1061–8.
35. Pointreau Y, Commins SP, Calais G, Watier H, Platts-Mills TA. Fatal infusion reactions to cetuximab: role of immunoglobulin E–mediated anaphylaxis. J Clin Oncol. 2012;30:334–5. https://doi.org/10.1200/JCO.2011.38.4701.
36. Fischer J, Yazdi AS, Biedermann T. Clinical spectrum of α-Gal syndrome: from immediate-type to delayed immediate-type reactions to mammalian innards and meat. Allergo J Int. 2016;25:55–62. https://doi.org/10.1007/s40629-016-0099-z.
37. Martel Martin C, Martínez Arcediano A, Longo Areso MN, Audícana Berasategui MT, Ollo Morales P, De La Viuda Camino E, Frias Jiménez M, Bernedo Belar N, Fernández Ibañez E. Anaphylaxis due to a hidden allergen in an intraoperative surgery Páginas 175–176 del Volumen 78: Abstracts from the European Academy of Allergy and Clinical Immunology Hybrid Congress. Allergy. 2022;78:56–716. https://doi.org/10.1111/all.15616.
38. Bosques CJ, Collins BE, Meador JW 3rd, Sarvaiya H, Murphy JL, Dellorusso G, Bulik DA, Hsu IH, Washburn N, Sipsey SF, Myette JR, Raman R, Shriver Z, Sasisekharan R, Venkataraman G. Chinese hamster ovary cells can produce galactose-α-1,3-galactose antigens on proteins. Nat Biotechnol. 2010;28(11):1153–6. https://doi.org/10.1038/nbt1110-1153.Erratum.In:NatBiotechnol.2011;29(5):459.
39. Chitnavis M, Stein DJ, Commins S, Schuyler AJ, Behm B. First-dose anaphylaxis to infliximab: a case of mammalian meat allergy. J Allergy Clin Immunol Pract. 2017;5(5):1425–6. https://doi.org/10.1016/j.jaip.2017.04.044.
40. Stone CA Jr, Commins SP, Choudhary S, Vethody C, Heavrin JL, Wingerter J, Hemler JA, Babe K, Phillips EJ, Norton AE. Anaphylaxis after vaccination in a pediatric patient: further implicating alpha-gal allergy. J Allergy Clin Immunol Pract. 2019;7(1):322-324.e2. https://doi.org/10.1016/j.jaip.2018.06.005.
41. Uyttebroek A, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Anaphylaxis to succinylated gelatin in a patient with a meat allergy: galactose-α(1, 3)-galactose (α-gal) as antigenic determinant. J Clin Anesth. 2014;26(7):574–6. https://doi.org/10.1016/j.jclinane.2014.04.014.
42. Serrier J, Khoy K, Ollivier Y, Gervais R, Le Moel G, Lafosse M, Johnson A, Le Mauff B, Mariotte D. Recurrent anaphylaxis to a gelatin-based colloid plasma substitute and to cetuximab following sensitisation to galactose-alpha-1,3-galactose. Br J Anaesth. 2021;126(6):e200–2. https://doi.org/10.1016/j.bja.2021.02.013.
43 Vidal C, Méndez-Brea P, López-Freire S, González-Vidal T. Vaginal Capsules: An Unsuspected Probable Source of Exposure to α-Gal. J Investig Allergol Clin Immunol. 2016;26(6):388–9. https://doi.org/10.18176/jiaci.0105.
44. Commins SP. Invited Commentary: Alpha-Gal Allergy: Tip of the Iceberg to a Pivotal Immune Response. Curr Allergy Asthma Rep. 2016;16(9):61. https://doi.org/10.1007/s11882-016-0641-6.
45. Mozzicato SM, Tripathi A, Posthumus JB, Platts-Mills TAE, Commins SP. Porcine or bovine valve replacement in 3 patients with IgE antibodies to the mammalian oligosaccharide galactose-alpha-1,3-galactose. J Allergy Clin Immunol Pract. 2014;2(5):637–8. https://doi.org/10.1016/j.jaip.2014.04.016.
46. Swiontek K, Morisset M, Codreanu-Morel F, Ollert M, Eberlein B, Hilger C, et al. Drugs of porcine origin- a risk for patients with α-gal syndrome? J Allergy Clin Immunol In Practice. 2019;7(5):1687–90. https://doi.org/10.1016/j.jaip.2018.12.005.
47. Kuravi KV, Sorrells LT, Nellis JR, Rahman F, Walters AH, Matheny RG, et al. Allergic response to medical products in patients with alpha-gal syndrome. J Thorac Cardiovasc Surg. 2022;164(6):411–24. https://doi.org/10.1016/j.jtcvs.2021.03.100.
48 Slayden TA, Shakir MKM, Hoang TD. A bull in a pill shop: alpha-gal allergy complicating treatment options for postprocedural hypothyroidism. AACE Clin Case Rep. 2020;6(3):e101–4. https://doi.org/10.4158/ACCR-2019-0495. (11).
49. Fischer J, Eberlein B, Hilger C, Eyer F, Eyerich S, Ollert M, Biedermann T. Alpha-gal is a possible target of IgE-mediated reactivity to antivenom. Allergy. 2017;72(5):764–71. https://doi.org/10.1111/all.13073.
50. Schmidle P, Mehlich J, Brockow K, Darsow U, Biedermann T, Eberlein B. Gelatin-Containing Vaccines for Varicella, Zoster, Measles, Mumps, and Rubella Induce Basophil Activation in Patients with Alpha-Gal Syndrome. Int Arch Allergy Immunol. 2021;182(8):716–22. https://doi.org/10.1159/000514263.

51. Wilson JM, Nguyen AT, Schuyler AJ, Commins SP, Taylor AM, Platts-Mills TAE, McNamara CA. IgE to the Mammalian Oligosaccharide Galactose-α-1,3-Galactose Is Associated With Increased Atheroma Volume and Plaques With Unstable Characteristics-Brief Report. Arterioscler Thromb Vasc Biol. 2018;38(7):1665–9. https://doi.org/10.1161/ATVBAHA.118.311222.
52. Vernon ST, Kott KA, Hansen T, Finemore M, Baumgart KW, Bhindi R, Yang J, Hansen PS, Nicholls SJ, Celermajer DS, Ward MR, van Nunen SA, Grieve SM, Figtree GA. Immunoglobulin E Sensitization to Mammalian Oligosaccharide Galactose-α-1,3 (α-Gal) Is Associated With Noncalcified Plaque, Obstructive Coronary Artery Disease, and ST-Segment-Elevated Myocardial Infarction. Arterioscler Thromb Vasc Biol. 2022;42(3):352–61. https://doi.org/10.1161/ATVBAHA.121.316878.
53. Browning R, Le V, Jerath M. Alpha-gal allergy and mast cell hyperactivity overlap. J Allergy Clin Immunol. 2022;149(2):Ab201.
54. Izaguirre Ayestarán Y, Ruiz García P, Navajas B, Soriano AM, Garcia Lirio E, Jauregui Presa I. Rentabilidad diagnóstica de las pruebas cutáneas e IgE específica en adultos alérgicos a alfa-gal. Poster of the Basurto University Hospital presented in the 30th Allergology and Clinical Immunology Spanish Congress, San Sebastian, España. 2016.
55. Martínez- Arcediano A, De la Viuda Camino E, Audícana Berasategui MT. Dairy products and its clinical relevance in a series of Alpha gal allergic patients. Abstract D1 128. EAACI Congress 2024 31 May - 03 June 2024 Valencia, Spain. https://eaaci.org/agenda/eaaci-congress-2024/sessions/food-allergy
56. Jacquenet S, Moneret-Vautrin DA, Bihain BE. Mammalian meat-induced anaphylaxis: clinical relevance of anti-galactose- alpha-1,3-galactose IgE confirmed by means of skin tests to cetuximab. J Allergy Clin Immunol. 2009;124:603–5.
57. Kim JH, An S, Kim JE, Choi GS, Ye YM, Park HS. Beef-induced anaphylaxis confirmed by the basophil activation test. Allergy Asthma Immunol Res. 2010;2:206–8.
58. Mehlich J, Fischer J, Hilger C, et al. The basophil activation test differentiates between patients with alpha-gal syndrome and asymptomatic alpha-gal sensitization. J Allergy Clin Immunol. 2019;143(1):182–9. https://doi.org/10.1016/j.jaci.2018.06.049.
59. Sacristan-Arias M, Audícana-Berasategui MT, Martínez-Arcediano A. Nutritional assessment in a series of nine patients allergic to mammalian meats and dairy, due to alpha gal. Universidad del Pais Vasco, Gasteiz, Spain. Abstract D2 119. EAACI Congress 2024 31 May - 03 June 2024 Valencia, Spain. https://eaaci.org/agenda/eaaci-congress-2024/speakers/ana-martinez-arcediano/
60. Macdougall JD, Thomas KO, Iweala OI. The Meat of the Matter: Understanding and Managing Alpha-Gal Syndrome. Immunotargets Ther. 2022Sep;15(11):37–54. https://doi.org/10.2147/ITT.S276872.
61. Marti A, Fauconneau A, Ouhabrache N, Beylot-Barry M, Pham-Ledard A. Complete Remission of Squamous Cell Carcinoma After Treatment With Panitumumab in a Patient With Cetuximab-Induced Anaphylaxis. JAMA Dermatol. 2016;152(3):343–5. https://doi.org/10.1001/jamadermatol.2015.4134.
62 Leder J, Diederich A, Patel B, Bowie M, Renwick CM, Mangunta V. Perioperative Considerations in Alpha-Gal Syndrome: A Review. Cureus. 2024;16(1):e53208. https://doi.org/10.7759/cureus.53208. (30).
63. Borsani B, De Santis R, Perico V, et al. The role of carrageenan in inflammatory bowel diseases and allergic reactions: where do we stand? Nutrients. 2021;13(10):3402.
64. Unal D, Coskun R, Demir S, Gelincik A, Colakoglu B, Buyukozturk S. Successful beef desensitization in 2 adult patients with a delayed-type reaction to red meat. J Allergy Clin Immunol Pract. 2017;5(2):502–3.
65. Yucel E, Sipahi Cimen S, Varol S, Suleyman A, Ozdemir C, Tamay ZU. Red meat desensitization in a child with delayed anaphylaxis due to alpha-Gal allergy. Pediatr Allergy Immunol. 2019;30(7):771–3.
66. Unal D, Eyice-Karabacak D, Kutlu A, et al. Oral immunotherapy in alpha-gal red meat allergy: could specific IgE be a potential biomarker in monitoring management? Allergy. 2023;78(12):3241–51. https://doi.org/10.1111/all.15840.