https://doi.org/10.31925/farmacia.2019.1.6 **REVIEW**

DRUG ALLERGIES DUE TO IgE SENSITIZATION TO α-GAL

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Abstract

Serum specific IgE antibodies for non-primate mammalian carbohydrate galactose-α-1,3-galactose (α-Gal) are associated to α-Gal syndrome: delayed allergy to red meat manifested as anaphylaxis, angioedema or urticaria after ingestion of beef, pig or lamb meat, immediate-onset anaphylaxis at first parenteral exposure to drugs significantly containing α-Gal. IgE-mediated drug allergy in the α-Gal syndrome was reported for some therapeutic monoclonal antibodies, such as cetuximab, snake antivenom, and varicella-zoster vaccine, but there are risks also for colloid plasma volume substitutes, vaccines containing gelatine of porcine/bovine animal origin as an excipient, and drugs with porcine pancreatin or bovine-origin magnesium stearate.

Rezumat

Anticorpii IgE specifici serici pentru carbohidratul galactoză-α-1,3-galactoză (α-Gal) al mamiferelor non-primate sunt asociați cu sindromul α-Gal: alergie tardivă la carnea roșie manifestată ca anafilaxie, angioedem sau urticarie după ingerarea de carne de vită, porc sau miel, anafilaxie imediată la prima expunere parenterală la medicamente care conțin în mod semnificativ α-Gal. Alergia mediată de IgE la medicamente în sindromul α-Gal a fost raportată pentru anumiți anticorpi monoclonali terapeutici, cum ar fi cetuximabul, antiveninul de șarpe și vaccinul varicelo-zosterian, dar există riscuri și pentru substituenții plasmatici coloidali de volum, vaccinuri care conțin gelatină de origine animală porcină/bovină ca excipient și medicamente cu pancreatină porcină sau stearat de magneziu de origine bovină.

Keywords: α-Gal syndrome, allergy, anaphylaxis, drug allergy

Introduction

The galactose-α-1,3-galactose (α-Gal) represents a particular disaccharide antigen present in the chemical structure of glycolipids and glycoproteins of the nonprimate mammals (more than 10^6 epitopes *per* cell). Humans and superior primates have functionally lost in their evolution the α1,3-galactosyltransferase gene. The α-Gal is not expressed in the human tissues, therefore this epitope is highly immunogenic. In all non-immunocompromised human subjects, IgG antibodies against α-Gal are present, their continuous production being a response to intestinal bacteria expressing α-Gal [6, 18, 23, 24, 46, 47, 52, 57]. The α-Gal molecule is present in considerable amounts in red meat, such as pork, beef, mutton, horse and offal (e.g. kidney, liver), but ingestion of such animal food does not induce sensitization against α-Gal. IgE-mediated sensitization to the α-Gal epitope in humans was quite recently proved to be a consequence of hard tick bites. Patients with a personal history of multiple tick bites may experience IgE-mediated sensitization to α-Gal [9, 12, 13, 18, 20, 51, 52]. IgE reactivity to this epitope is common in endemic tick areas. In the case of discrete levels of serum specific IgE against α-Gal, sensitized subjects appear not to develop meat allergy [50-52, 57]. There is a close relationship between the tick bites personal history and the serum levels of specific IgE against α-Gal [56]. This epitope is present in some drugs of animal origin, excipients or ingredients, and therapeutic chimeric monoclonal antibodies.

The α-Gal epitope represents the mammalian cross-reactive carbohydrate determinant (CCD) with clinical significant involvement in the α-Gal syndrome. Other CCDs from glycosylated plant proteins and venoms of *Hymenoptera* insects are instead a usual cause of clinically irrelevant *in vitro* IgE testing positive results [1, 22, 59]. Although patients allergic to red meat with specific IgE response against α-Gal are considered not to have IgE antibody responses to CCDs from plants [2], a case of delayed food allergy to various red meats was reported in a Romanian adult patient with great tick bites and other arthropods exposure, associated with serum IgE against plant-derived CCD [39, 54].

The α-Gal syndrome

Serum specific IgE antibodies to the nonprimate mammalian epitope α-Gal are associated with the α-Gal syndrome: delayed allergy to the red meat manifested as late-onset anaphylaxis, urticaria or angioedema after ingestion of pig, beef or lamb meat, *anaphylaxis with immediate onset* at initial parenteral exposure to drugs significantly containing α-Gal, such as cetuximab [12, 13, 17, 55].

Mechanisms for inducing IgE-mediated sensitization to α-Gal are complex. Ticks with hard shells belonging to the *Ixodidae* family, including *Ixodes ricinus* in Europe and *Amblyomma americanum* in North America, are important arthropod agents involved in human IgE-mediated sensitization to α-Gal [57]. Tick bites represent the major cause of the specific IgE responses to this epitope, saliva of *Ixodidae* ticks being contaminated with nonprimate mammalian blood group α-Gal carbohydrate [12, 13, 57], and α-Gal being detected in the *Ixodes ricinus* tick gastrointestinal tract [20, 21]. Moreover, α-Gal is present at the site of the tick bite. Local immunomodulator factors, such as phospholipase A2, prostaglandin E2, and lipocalins, promote Th_2 cell responses and IgE isotype switching [7]. The α-Gal chemical structure is similar to the human blood group B antigen, therefore B-positive blood group is associated with a lower production of specific IgE against it [3, 21]. In subjects presenting IgE sensitization to the epitope α-Gal, clinical allergic reactions having immediate onset may be induced by first parenteral exposure to drugs containing this epitope. After ingesting oral drugs of bovine/porcine origin or red meat, the allergic reactions have a late onset, in 3-6 hours. Allergenic α-Gal is stable to heat and pepsinolysis and has a prolonged chylomicron transport from the intestine through mesenteric lymph nodes in circulation [3, 4, 12, 13, 57].

IgE-mediated drug allergy in α-Gal syndrome

Although this special type of drug hypersensitivity in patients presenting IgE-mediated sensitization to α-Gal oligosaccharide was reported for some therapeutic monoclonal antibodies, antivenoms, and vaccines (Table I), there are also potential risks for colloidal plasma volume substitutes and other drugs containing gelatin of porcine/bovine origin, or drugs with porcine pancreatin. Moreover, because most such adverse reaction reports are recent, to our knowledge there is no published updated comprehensive review from a pharmaceutical and pharmacological perspective, and allergy information and education of physicians and pharmacists regarding this drug allergy are crucial.

Table I

Drug allergy cases reported in patients with IgE sensitization to α-Gal

Therapeutic class	Drug	Hypersensitivity reactions	Publications year(s)	References
Chimeric anti-EGFR monoclonal antibody	cetuximab	severe, even fatal, anaphylaxis, at first infusion, series of cases	2007-2017	[11, 25, 37, 38, 55]
Chimeric anti-TNFα monoclonal antibody	infliximab	anaphylaxis, at first dose, case report	2017	[10]
Snake antivenom	crotalid polyvalent immune Fab ovine	generalized urticaria, case report	2017	[42]
Colloidal plasma volume substitutes	modified fluid gelatin	intraoperative anaphylaxis, case reports	2012-2014	[35, 41, 43]
Vaccines and other drugs containing gelatin and/or other proteins of porcine/bovine origin	herpes zoster vaccine; MMR, varicella, DTaP/IPV vaccination	anaphylaxis, case reports (adult, child)	2017-2018	[47, 48]
	oral drug formulations with magnesium stearate of bovine origin as an inactive ingredient	systemic allergic reactions, case report	2015	[34]
	vaginal capsules with porcine gelatin cover	anaphylaxis, case report	2016	[53]

IgE-mediated allergy to therapeutic monoclonal antibodies in α-Gal syndrome

Hypersensitivity to some monoclonal antibodies has been associated with the existence of specific IgE antibodies against α-Gal epitopes present on the molecules.

Cetuximab is a recombinant human/mouse chimeric monoclonal antibody which binds with specificity to the extracellular region of the human

epidermal growth factor receptor (EGFR), authorized as intravenous infusion for the therapy of EGFR-expressing, RAS wild-type metastatic colorectal cancer and head and neck squamous cell carcinoma. Cetuximab is obtained in mammalian murine myeloma cell culture. Cetuximab contains Fv domains of a murine anti-EGFR antibody and human IgG_1 heavy and kappa light chain constant regions. The Fab region of the heavy chain is glycosylated at Asn88 position with carbohydrates, including α-Gal. The presence of this epitope on both Fab segments allows cross-linking of the IgE molecules on the mast cells, with degranulation and thus releasing of hypersensitivity mediators involved in the pathogenesis of anaphylaxis [11, 28, 40, 45, 60].

Initial evaluations of severe hypersensitivity allergic reactions to this therapeutic monoclonal antibody considered that these occur in about 3% of subjects, but studies in particular regions in the United States (Tennessee and North Carolina) revealed that 22% of patients treated with such chimeric monoclonal antibodies have severe hypersensitivity reactions. In most subjects, serum IgE antibodies to cetuximab were detectable before treatment, and these were specific for the α-Gal epitope [37]. It is considered nowadays that severe infusion-related adverse reactions to cetuximab, including anaphylaxis, may commonly appear, in several cases with fatalities. A severe reaction related to the infusion of this drug requires urgent and permanent cessation of the treatment, and necessitates emergency appropriate therapy. Anaphylactic reactions may occur quickly within minutes of the initial infusion, attributable to preformed specific IgE antibodies reacting with the α-Gal present in cetuximab. Such reactions can happen regardless of the use of premedication. The risk for anaphylaxis is increased in subjects with a personal history of hypersensitivity to the red meat or tick bites or positive *in vitro* testing results for specific IgE to cetuximab α-Gal [11, 25, 37, 60].

Panitumumab, which is a recombinant completely human IgG_2 anti-EGFR monoclonal antibody, without α-Gal epitope on its Fab portion, is indicated as intravenous infusion for the therapy of adults with the RAS wild type metastatic colorectal cancer. This drug was tolerated as parenteral monotherapy, in a case series small trial, in subjects with previous severe infusion-related adverse reactions to cetuximab [29]. *Tomuzotuximab* is a glycoengineered second generation antibody of cetuximab, with the elimination of the previously mentioned α-Gal molecule, thus having improved tolerability [15].

Chimeric (human/murine) monoclonal IgG_1 antibodies with α-Gal epitopes on their intact Fc domains, such as the anti-CD25 *basiliximab* and anti-respiratory syncytial virus fusion protein *palivizumab*, does not bind specific IgE to the α-Gal molecule, probably because of the steric interference of a polypeptidic structure around the disaccharide [28, 44].

Other therapeutic monoclonal antibodies derived from cell lines that glycosylate with galactose-α-1,3-galactose, besides cetuximab, are anti-α4-integrin *natalizumab* and anti-TNFα *infliximab*. Recently, a first dose IgE-mediated anaphylaxis to *infliximab* due to α-Gal sensitization was reported in a Crohn's disease patient with allergy to mammalian meat [10]. To avoid recurrence of allergic symptoms with subsequent treatment, *vedolizumab*, a humanized therapeutic monoclonal antibody binding the $\alpha_4\beta_7$ integrin, blocking the interaction of this heterodimeric molecule with MAdCAM-1, may be an option, being a non-glycosylated monoclonal antibody [10].

Risk of IgE-mediated allergy to antivenoms in α-Gal syndrome

North American crotalid snake polyvalent immune Fab *ovine* antivenom was reported to induce generalized urticaria during intravenous infusion in a patient with a history of tick exposures, bitten by the *Agkistrodon contortrix* snake [42].

The α-Gal disaccharide may also be involved in IgE-mediated adverse reactions to *equine* antivenoms, being detected by immunoblot technique in viper (e.g. Malayan Pit Viper Antivenom), cobra (e.g. Indian Snake Venom Antiserum) and scorpion (e.g. Brazil Soro Antiscorpionico) [16].

Risk of IgE-mediated allergy to plasma volume substitutes in α-Gal syndrome

Intraoperative anaphylaxis to bovine-derived gelatine colloid plasma volume substitutes was reported, including in α-Gal allergy [35, 41, 43]. The colloidal solution for infusion with succinylated gelatine contains about 0.52 μg α-Gal *per* gram, similar to the colloidal intravenous infusion solution with polygeline or degraded gelatine polypeptides cross-linked *via urea bridges* (about 0.44 μg α-Gal *per* gram), both containing about 4000 times less α-Gal compared to cetuximab (10.2 μg α-Gal *per* 5 mg in 1 mL solution for infusion) [35].

Risk of IgE-mediated allergy to gelatine-containing vaccines in α-Gal syndrome

Vaccines that contain gelatine or bovine calf-serum may induce anaphylaxis in patients sensitized to α-Gal, although not all subjects have adverse reactions. There is a report of immediate anaphylaxis to injected herpes zoster vaccine with Oka varicella-zoster virus and hydrolysed gelatine as an

ingredient, in an adult with α-Gal IgE sensitization and recurrent anaphylaxis [48]. The content of hydrolysed gelatine as vaccine stabilizer *per* dose was reported as 15580 mg porcine gelatine in 0.65 mL of a varicella-zoster vaccine, 14500 mg bovine gelatine in 0.5 mL of a measles, mumps, rubella vaccine, and 7500 mg porcine gelatine in 0.5 mL of a yellow fever vaccine [36, 48].

Another recent report was published regarding a paediatric subject with a pre-existing α-Gal IgE-mediated hypersensitivity, who presented anaphylaxis rapidly after administration of the usual 5-year vaccination with measles, mumps, and rubella (MMR), varicella, and diphtheria, tetanus, and acellular pertussis, and inactivated polio vaccine (DTaP/IPV). Both varicella and MMR vaccines contain significant quantities of gelatine (*per* dose: 12,500 mg in 0.5 mL and 14,500 mg in 0.5 mL, respectively). Moreover, DTaP/IPV, MMR, and varicella vaccines also include bovine serum ingredient in unreported amounts [47].

Risk of allergy to other drugs with ingredients of porcine/bovine origin

Although α-Gal is not present on heparin molecules, being derived from porcine intestinal mucosa there is a potential of contamination with this epitope in the manufacturing process, with a theoretical risk in patients with α-Gal allergy [27].

The α-Gal carrying proteins were instead recently detected by immunoblot technique in porcine-derived oral medications, such as gastro-resistant capsules with *porcine* pancreatin (amylase, lipase, protease) microspheres, used in the therapy of exocrine pancreatic insufficiency in chronic pancreatitis, pancreatic cancer, cystic fibrosis or post-pancreatectomy, and gastro-resistant coated tablets with porcine pepsin as supportive medication for gastrointestinal malfunction [49].

Vaginal capsules may also represent a hidden source of exposure to the α-Gal epitope, a case of anaphylaxis was reported in a female patient diagnosed with α-Gal allergy, after application of an intravaginal capsule with gelatine cover with collagen of porcine origin [53].

A case report of α-Gal allergy associated with an allergic reaction to drugs containing magnesium stearate probably of bovine origin was also published, underlying that medical practitioners and pharmacists should be aware of potential cross-reactivity between α-Gal and drugs with meat byproducts, considering that inappropriate avoidance is correlated with a risk of anaphylaxis [34]. Bovine-based magnesium stearate may be used as a lubricant excipient to facilitate tablets ejection [19].

Allergy diagnosis for drug allergy in α-Gal syndrome

Allergological diagnosis approach includes, besides a detailed patient history, *in vivo* and *in vitro* allergy testing. *In vivo* diagnosis in α-Gal allergy may include allergy skin testing and challenge tests with meat or meat extracts, but not all are usually recommended for ethical reasons, related to standardization or biological safety. Skin prick tests with selected meat extracts may be equivocal or negative. Allergy skin testing performed with cetuximab is more sensitive and it is performed as skin prick test with cetuximab solution for infusion 5 mg/mL, followed by an intradermic test with cetuximab solution for infusion 0.05 mg/mL (1: 100 dilution) [33].

Serum specific IgE to α-Gal *in vitro* detection using immunoenzymatic ELISA as a commercially sensitive test must take into consideration that it can also be positive in patients with parasitic infections and in a tick-endemic population. Serum specific IgE to bovine thyroglobulin may be determined by singleplex fluorescence immune-enzymatic assay (FEIA) with activated cellulose solid phase. Patients with α-Gal syndrome have elevated levels of serum specific IgE against bovine thyroglobulin, a protein containing 5.6 μg α-Gal *per* gram. Serum specific IgE to cetuximab by ELISA or FEIA immunoenzymatic methods, using biotinylated anti-IgE antibodies and streptavidin-alkaline phosphatase conjugate is also useful, because patients with α-Gal syndrome have high concentrations of serum specific IgE to cetuximab, a monoclonal antibody containing 2.04 μg α-Gal *per* mg [30, 31].

The basophil activation test (BAT) with cetuximab (CD203c) or porcine pancreatin (CD63) is an alternative *in vitro* evaluation of α-Gal sensitization [5, 31 33, 49]. The assessment of $CD63^+$ basophils induced by α-Gal and after stimulation with anti-FcεRI may be used to distinguish asymptomatic sensitization from α-Gal syndrome [32].

The most used diagnostic methods in the α-Gal syndrome are the intradermal test for cetuximab allergy and the detection of specific IgE against α-Gal for the allergy to red meat [55]. Implementing BAT beyond research poses some questions about reproducibility [58].

Conclusions

It is noteworthy to mention that the lack of universal awareness of drug allergy due to IgE sensitization to α-Gal may lead to misdiagnosis or delayed diagnosis, and puts allergic patients at risk for anaphylaxis [8, 14, 26]. Because manufacturers do not commonly assess the α-Gal content in pharmaceutical products, it is important for

allergists and pharmacists to be aware of this problem [34, 51] and to identify the risk medications, such as the drugs with mammalian sources having the potential for contamination with α-Gal, and the pharmaceutical products with ingredients containing α-Gal epitopes, that may provoke a potentially severe allergic reaction in patients with α-Gal IgE sensitization.

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