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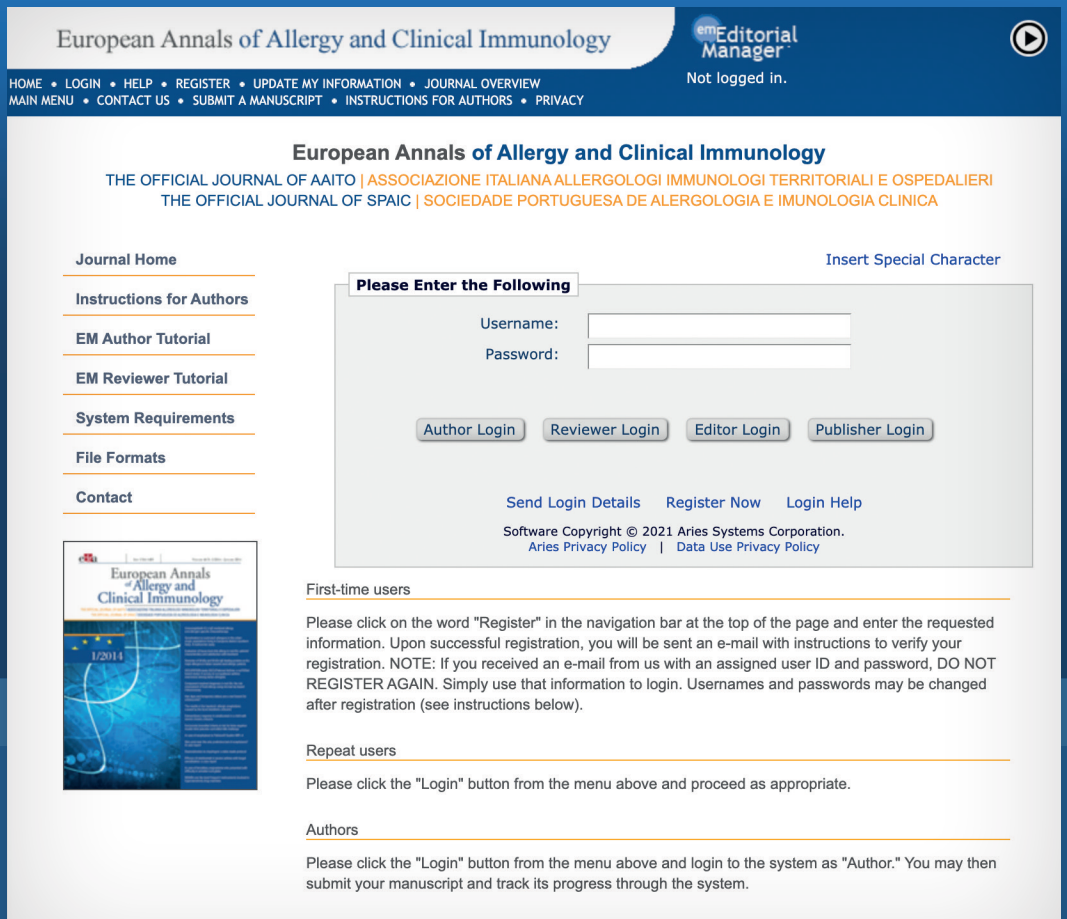
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Eosinophilic esophagitis as a side-effect of allergen immunotherapy: protocol for a systematic review and meta-analysis

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Key words
Eosinophilic esophagitis; allergen immunotherapy; oral desensitization.

Impact statement
Many cases of EoE development in patients following food desensitization protocols have been reported, as well as cases of EoE following sublingual immunotherapy to airborne allergens. The present paper describes the methodology adopted to examine the association and it is the first one produced by the relevant TF.

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Summary

Background. *Sensitization to food and airborne allergens is common in the majority of patients with eosinophilic esophagitis (EoE). Although there is not a direct cause-effect relationship of IgE-mediated allergy with the pathogenesis of EoE, there is growing evidence that oral desensitization to food and sublingual immunotherapy (SLIT) may induce the development of EoE as an adverse effect. As part of the "EoE and Allergen Immunotherapy (AIT)" Task Force funded by the European Academy of Allergy and Clinical Immunology (EAACI), a systematic approach will be followed to review the evidence from the published scientific literature on the development of EoE in children and adults under any type of AIT.* ***Methods.*** *This systematic review was carried out following the PRISMA statement guidelines. Studies were assessed for inclusion in the review according to the Population-Interventions-Comparators-Outcomes (PICO) criteria.* ***Results.*** *Expected outcomes will provide evidence on the AIT-EoE development connection.* ***Conclusions.*** *The findings from this review will be used as a reference to provide useful guidelines for physicians treating patients with EoE and/or are practicing AIT.* ***Study registration.*** *PROSPERO ID: CRD42023425917.*

Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease clinically characterized by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation (> 15 eosinophils per high power field) (1). Various EoE phenotypes have been proposed, based on response to therapy, atopic status and natural history of the disease, while three different endotypes have also been identified, based on histological, endoscopic and molecular features (2). Although EoE is not etiologically caused by an IgE-mediated pathomechanism, sensitization allergens is common with an underlying T-helper 2 (Th2) cell-mediated pathophysiology (3, 4).

Food allergens are considered common triggers for EoE, and this hypothesis has been sustained by the fact that elimination diets are often an effective treatment option. However, their effectiveness is not noticed in all EoE patients. It appears that EoE is a multifactorial disease caused by a combination of genetic predisposition, epithelial barrier dysfunction, environmental risk factors and allergen sensitization (5).

Airborne allergens have also been implicated in the pathogenesis of EoE, although there is no strong evidence of a cause-effect relationship. EoE has been developed experimentally in a murine model by initial intranasal sensitization to *Aspergillus fumigatus,* followed by challenging mice with the relative airborne allergen (6). Several single-center clinical observations have also found correlations between the onset or worsening of EoE symptoms with seasonal aeroallergen exposure (7-10). These findings have not been confirmed by other studies and no significant variations in the seasonal distribution of either the diagnosis of EoE or its clinical recrudescence throughout the year was reported by a systematic review and meta-analysis on this topic (11).

Regular contact of the esophageal mucosa with large amounts of food allergens and the minuscule exposure to airborne allergens have been involved in the development of EoE (12). This potential cause-and-effect relationship poses the question on whether allergen immunotherapy (AIT) administered per o.s. may represent a risk factor for the onset of EoE. There are case reports of biopsy-confirmed EoE developed in patients undergoing sublingual immunotherapy (SLIT) to pollen or house-dust mites, but the incidence rate is unknown (13-17).

The involvement of oral immunotherapy (OIT) to food allergens in the development of EoE has also been described (18, 19). OIT has emerged as a promising therapy for patients with IgE-mediated food allergy, with various tolerance induction protocols being developed and a variety of food allergens being addressed. The incidence of confirmed newly developed EoE as a side-effect of OIT has been reported in approximately 2.7-5.3% of patients, with a 5.6% OIT discontinuation rate due to a diagnosis of EoE (or symptoms possibly related to EoE) (18-20). The clinical and histological remission of EoE reported in case-series after the discontinuation of OIT is a further clue of this interaction.

Given the overarching principles of the European Academy of Allergy and Clinical Immunology (EAACI) to promote effective and safe medical care, EAACI created a Task Force (TF) to investigate the causal relationship between EoE and AIT, conducting a systematic review and meta-analysis. Subjects with active EoE would rather rarely undergo SLIT or OIT, so the systematic review aims to evaluate the ab initio manifestation of EoE in patients undergoing such treatments and to provide useful guidelines for physicians treating patients with EoE and/or practicing AIT. The protocol of the systematic review on the development of EoE as a side-effect in patients treated with AIT to airborne and food allergens is presented here.

Methods

Study design

The systematic review is going to follow the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analyses) statement guidelines (21, 22). The methodology has been reviewed and approved by all authors in a TF meeting held on December 2022.

Search strategy

The electronic search of the literature will be performed in three engines: PubMed, Scopus, and Embase. Grey literature (*e.g.*, conference abstracts) will also be searched, and the list of references of full-text articles will be screened to identify further relevant studies.

All databases will be searched from inception to March 31st, 2023. The following Medical Subject Heading (MeSH) terms and text words will be used in the queries: "eosinophilic esophagitis" OR "eosinophilic oesophagitis" OR "EoE" combined with ("AND") "Allergen immunotherapy" OR "Specific immunotherapy" OR "desensitization" OR "AIT" OR "Sublingual immunotherapy" OR "SLIT" OR "specific oral tolerance induction" OR "SOTI" OR "oral immunotherapy" OR "OIT" OR "airborne allergen" OR "respiratory allergen" OR "food allergen" OR "Epicutaneous immunotherapy" ("AND") "side effect" OR "adverse effect".

Eligibility criteria

Studies will be assessed for inclusion in the review according to the Population-Interventions-Comparators-Outcomes (PICO) criteria:

1. Population: human studies, without age, gender, or origin limits, will be included.
2. Intervention(s)/exposure(s): any type of AIT (probably only oral or sublingual) reported to cause or exacerbate, histologically and clinically diagnosed EoE, will be considered. Modalities used for AIT may include any protocol of food desensitization or sublingual AIT and any fresh food or extract used for these purposes.
3. Comparator(s)/control(s): studies comparing the assessment of EoE before and after AIT will be considered. A comparator can also be a group of AIT-treated patients that have been histologically and clinically assessed for the development of EoE, in parallel with the ones that developed EoE.
4. Main outcome(s)/additional outcome(s): there are two similar but not identical questions that will be addressed, both regarding the development of EoE after starting AIT. The first is the connection of EoE development after sublingual AIT using extracts of airborne allergens and the second is the connection of EoE development during oral desensitization to food allergens. The primary outcome for both will be any evidence on AIT-EoE development connection. Indicating AIT and OIT as the causal factor of EoE can be done with certainty only if patients have undergone an endoscopy prior to desensitization. The extended use of the non-invasive technique of sponge test, performed during endoscopy, has started facilitating the diagnostic procedure. Triggering the exacerbation of pre-existing EoE after AIT can be examined as a secondary outcome. Another secondary outcome is the course of EoE after the discontinuation of the culprit AIT, for both branches of the study.

Inclusion criteria

Observational (prospective and retrospective) and interventional studies examining the correlation of AIT with the development of EoE in humans will be included in this systematic review. Any type of AIT, including different protocols of food desensitization and any extract of SLIT, should have been performed in the primary studies. In order to confirm AIT as the trigger of EoE, confirmed histological diagnosis of EoE (> 15 eosinophils/high-power field) developed after the start of AIT will be considered. There will be no restrictions in terms of age, sex, and race. No language restrictions of the studies will be imposed.

Exclusion criteria

Publications that will be excluded are Case reports, Case series, Reviews, Opinion articles, Editorial articles, studies on laboratory animals, *in vitro-ex vivo* studies not directly referring to clinical data (EoE symptoms), studies that do not include AIT as described in the inclusion criteria and refer to other procedures (for example the use of food supplements or herbal infusions). Studies on the use of AIT for the treatment of EoE are subject of another project of our TF.

Study selection and risk of bias assessment strategy

Two investigators will independently scrutinize the eligibility of the identified titles and abstracts based on the elements of the "EoE as a side-effect of SLIT with airborne allergens" question. A third author will help resolve disagreements between the first two authors and reach consensus. Two investigators will also work on the identified search results on "EoE due to the specific oral tolerance induction/food immunotherapy" question, with a third investigator helping as a referee. The Rayyan QCRI web tool will be used to assist in the study selection (23). Data extraction will be done twice. Excluded papers will be published as an online supplementary appendix.

Detailed information on the included studies will be provided in a table describing study participants (number and age groups), research designs, interventions (allergy testing), comparators, and outcomes. The sources of funding for the studies included in the review will be reported.

Two investigators will carry out an independent quality assessment on each eligible study of the final list. AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) will be used to assess the quality of all studies that will be extracted from the literature research, offering an accurate and comprehensive summary of the results (21, 22). Moreover, different assessment tools will be used for different study designs. The risk of bias (RoB) of the included randomized controlled trials will be evaluated using the Cochrane Collaboration RoB Tool (24). To assess the quality of evidence in non-randomized interventions, ROBINS-I will be used (25). Two investigators will review the results.

Data extraction, analysis and synthesis

Separate analyses for each one of the outcomes will be undertaken. When possible, subgroup analyses by age group, food allergens, airborne extracts, study design and risk of bias will be performed to investigate potentially different effects on risk. The heterogeneity of pooled results will be examined using the Cochran's Q test, with a 0.10 level of significance and the I^2 statistic, which describes the percentage variation across studies due to heterogeneity rather than chance (26, 27). A narrative synthesis of the data will also be done.

Ethics

Ethical approval and consent were not required as this study was based on publicly available data.

Discussion

There are still unmet needs regarding our knowledge on the development of EoE as a side-effect of AIT: age as a risk factor, the implication of each of the two different food desensitization modalities (sublingual and oral) to the development of EoE, the possibility that the practice of spitting (not swallowing) the allergen during SLIT is a safer (still efficacious) option, whether preliminary anamnesis of symptoms posing the suspicion of EoE is enough or whether endoscopy should be performed before the start of desensitization protocols and if the treatment protocols of EoE in the cases related to AIT should be the same with the already followed ones.

In a meta-analysis regarding patients undergoing OIT, the overall rates per patient for symptoms possibly related to EoE were 34% for general gastrointestinal symptoms, including 32% of reported symptoms related to abdominal pain and 12% of reported vomiting. The overall rate of OIT discontinuation was 14%, with 4.7% of these reporting symptoms potentially attributable to EoE (19).

In general, EoE clinically and histologically resolves after food OIT discontinuation. Food desensitization protocols are proposed in cases of IgE-mediated food allergy, mainly to patients that have a history of anaphylaxis, so it is clear that a decision to stop OIT has to be followed by an updated anaphylaxis action plan.

It is certainly important to offer evidence-based guidelines on whether EoE related to AIT prohibits any future effort to desensitization, either to food or to airborne allergen, using the oral route. Although it appears apparently irrelevant, it should be clear whether desensitization can be performed using other AIT routes for the same patients.

In conclusion, in this paper we described the protocol of the systematic review that has been planned. This systematic review will mainly focus on existing evidence: 1) on whether the severity and frequency of EoE presented during AIT is similar to a comparator population without AIT, and 2) how cessation or prolongation of AIT affects the clinical course of EoE. The described option to treat EoE (with proton pump inhibitors and swallowed corticosteroids) and continue the desensitization protocol will be also assessed (20).

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Contributions

CP, CMR, IT, AC: conceptualization. GKN: methodology. EA, CP: writing – original draft. MV, AB, GNK, DA-A, GKN, OP, EH, AA-P: writing – review & editing.

Conflict of interests

GKN received an honorarium from the EAACI for his advice on the methodology of this systematic review. The rest of the authors declare that they have no conflict of interest to declare with the current protocol's publishing.

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Contact sensitization in pediatric patients with atopic dermatitis: a purpose for a new patch testing series for the Portuguese population

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Key words

Atopic dermatitis; allergic contact dermatitis; prevalent allergens; baseline series; pediatric patients.

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Impact statement

Children with and without atopic dermatitis have similar contact sensitization rates however to different allergens. An adapted baseline series with the most relevant allergens is proposed for the pediatric population with atopic dermatitis.

Summary

Background. *Atopic dermatitis is a prevalent condition in the pediatric population, with affected children exhibiting a susceptibility to cutaneous sensitization due to skin barrier dysfunction and immune dysregulation. Recent studies have highlighted an increased prevalence of certain allergens, which identification may be clinically relevant, with direct implications for the management of atopic dermatitis.* ***Methods.*** *We retrospective reviewed pediatric patients patch tested due to suspected contact dermatitis. Patients were divided according the diagnosis of AD, with subsequent comparison of positive results for both groups.* ***Results.*** *A total of 145 pediatric patch testing were analyzed, 44.1% (n = 63) with the diagnosis of atopic dermatitis. There were notable differences in sensitization rates of relevant allergens between groups and when compared to other European studies. Based on the most prevalent and relevant allergens, we proposed an adapted hapten series for assessing portuguese pediatric patients with AD and suspicion of concomitant allergic contact dermatitis.* ***Conclusions.*** *Our findings confirmed the geographic sensitization variability and emphasize the need for pediatric adaptation and "individualized baseline series".*

Introduction

Atopic dermatitis (AD) is a common illness in pediatric population. In contrast, allergic contact dermatitis (ACD) used to be considered a rarity (1-3). Children with AD are prone to develop cutaneous sensitization due to several factors, due to skin barrier disruption, immune dysregulation, and consequent increased penetration of allergens (1-3). Children with AD are exposed to several allergens from an early age. The frequent application of numerous topical treatments such as emollients and topical drugs may determine a characteristic sensitization profile (1, 3, 4).

Recent studies have shown that sensitization rates are similar between children with and without AD, although certain al-

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lergens have a higher prevalence in AD patients. Despite this, the interrelation of AD and ACD is complex, and controversy remains over whether AD increases the risk of contact allergy in children or determines different contact sensitization profiles (1, 2).

Epicutaneous patch testing is the gold standard test for the diagnosis of ACD. It is a specific, relatively inexpensive and safe procedure, even for preschool children however, one of the main limitations is the limited body surface area available for adhesive application (4). Therefore, a selection of allergens based on the exposures and clinical examination are recommended but difficult to standardize (1, 4).

The identification of clinically relevant allergen sensitization in a patient with AD may have important implications for AD disease management and symptom control (3-5). According to the European Academy of Allergy and Clinical Immunology (EAACI) position paper published in 2015 and other recent reviews (1, 4, 6), epicutaneous patch testing is recommended in patients with AD with:

- a suspicion of specific ACD;
- difficult-to-control AD;
- new-onset dermatitis in patients with AD;
- prior to initiating systemic therapy for severe AD.

Considering the difficulty in identifying relevant allergens and their standardization, several research groups have proposed a "baseline series" for the pediatric population, based on sensitization rates in Europe and specific regions (4, 7, 8). Regarding the Portuguese population, few data is available (1, 3), therefore the aim of this study was the creation and subsequent application of a "baseline series" for pediatric AD patients with suspected ACD, difficult-to-control AD, new-onset dermatitis and prior to initiating systemic therapy for AD, or when no specific exposure is identified, in order to improve AD management and treatment in pediatric patients.

Materials and methods

Study design

The authors performed a retrospective, descriptive and inferential review of pediatric patients (< 18 years old) patch tested at the Contact Allergology Unit of the Dermatology and Venereology Department in a tertiary hospital, between 2005 and 2021 (17 years). Patients were divided into two groups: those diagnosed with AD and those without AD, with subsequent comparison of positive results. Based on the analysis of the relevant findings, we proposed an adapted series for assessing portuguese pediatric patients with AD.

All legal guardians of pediatric patients received written informed consent. This paper was written considering the ethical and legal principles and following the recommendations of the Declaration of Helsinki of the World Medical Association. The anonymity of all the participants in this work was guaranteed.

Subjects

Patients were characterized according to demographic data, personal and family history of atopy, and clinical and diagnostic parameters such as allergen series applied, positive reactions, and relevance. Atopic dermatitis was diagnosed according to the criteria of Hanifin and Rajka (9).

All patients included were routinely tested with the European baseline series and/or with the cosmetic series. The allergens used were from Chemotechnique Diagnostics®, Vellinge, Suécia; Trolab Allergens®, Smartpractice GmBH, Alemanha; Bial Alergénios®. Although, each series has been selected and adapted following the European Society of Cutaneous Allergy and Contact Dermatitis (ESCD) recommendations. Additionally, and in accordance with the available body surface and clinical history, supplementary series or specific allergens were applied. Allergen chambers were from (Epitest Ld®) or IQUltra chambers (Chemotechnique diagnostics®). The allergen chambers were applied on intact upper back and kept in occlusion for 48 hours. Readings were carried out on day(D) 3 or D4, and, in specific cases, associated with a second reading on D7. The reactions were scored according to the recommendations of the International Contact Dermatitis Research Group (ICDRG) and ESCD (10).

It was assessed the sensitization prevalence rates for the population as a whole and stratified for children with and without AD. Allergens patch tested < 20 times were excluded from this analysis to avoid non-inferential results. A value of 20 was chosen to reach a comparable number of patients tested with at least substances in the European baseline series.

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 24.0®. Descriptive statistics were analyzed as measures of central tendency and dispersion. The comparison of proportions was made using the chi-square test. Fisher's exact test was used in cases of low sample sizes. A Type I error of 0.05 was considered.

Results

Demographic and clinical characteristics

In a total sample of n = 145 pediatric patients, 68.3% (n = 99) females, with a median 13.0 years old (interquartile range 10-15), corresponding to 4.1% (n = 6) with < 6 years, 35.2% (n = 11) with 6-12 years, and 60.7% (n = 88) with > 12 years, were included in the analysis. AD patients corresponding to 43.4% (n = 63) of the total sample. Patient characteristics are summarized in **table I**.

Table I *- Demographics of pediatric patients referred for Patch Testing due to ACD suspicion.*

Characteristic	Total	With atopic dermatitis	Without atopic dermatitis	P-value
Number, % (n)	100.0 (145)	43.4 (63)	56.6 (82)	
Sex (female), % (n)	68.3 (99)	65.1 (41)	70.7 (58)	0.472
Age (years), median (IQR)	13.0 (10.0-15.0)	12.0 (9.0-14.0)	14.5 (11.0-16.3)	**0.015**
Group age				
< 6 years, % (n)	4.1 (6)	4.8 (3)	3.7 (3)	> 0.99
6-12 years, % (n)	35.2 (51)	44.4 (28)	45.1 (23)	0.467
>12 years, % (n)	60.7 (88)	50.8 (32)	63.6 (56)	0.104
Asthma, % (n)	25.5 (37)	28.6 (18)	23.2 (19)	0.463
Rhinitis, % (n)	25.5 (37)	38.1 (24)	15.9 (13)	**0.02**
Atopy, % (n)	50.3 (73)	76.2 (48)	30.5 (25)	**0.001**
Atopy family history, % (n)	31.7 (46)	42.9 (27)	23.2 (19)	**0.011**
Major location of suspected ACD				
Face, % (n)	40.0 (58)	42.9 (27)	37.8 (31)	0.232
Hands, % (n)	28.2 (41)	17.5 (11)	36.6 (30)	**0.001**
Upper or lower extremities, % (n)	13.1 (19)	12.7 (8)	13.4 (11)	0.648
Generalized, % (n)	6.8 (10)	9.5 (6)	4.9 (4)	> 0.99
Flexures, % (n)	6.2 (9)	7.9 (5)	4.9 (4)	> 0.99
Torso, % (n)	2.8 (4)	3.2 (2)	2.4 (2)	> 0.99
Periumbilical, % (n)	2.8 (4)	6.3 (4)	0 (0)	**0.046**
≥ 1 positive patch test result, % (n)	48.3 (70)	49.2 (31)	47.6 (39)	0.868
≥ 2 positive patch test result, % (n)	20.0 (29)	17.5 (11)	21.2 (18)	0.537
≥ 3 positive patch test result, % (n)	11.7 (17)	7.9 (5)	14.6 (12)	0.299

P-value is result of differences between patients with and without atopic dermatitis groups. Statistically significant values were marked bold.

Major location of suspected ACD

Regarding the affection of suspected ACD body areas (**table I**), the face corresponded to the main suspected body area in both groups. Particularly, the body area corresponding to the hands was more representative in the group of patients with AD; AD group 17.5% (n = 11) *vs* non-AD group 36.6% (n = 30), p < 0.001. Suspicion of ACD associated with the periumbilical location has only been described in patients with AD; AD group 6.3% (n = 4) *versus* non-AD group 0.0% (n = 0), p < 0.046.

Patch-testing results

The presence of allergic sensitization was similar in both groups. At least the presence of one allergic sensitization was demonstrated in 48.3% (n = 70), corresponding to 49.2% (n = 31) to AD patients (**table I**).

In **table II** the allergens tested and their sensitization prevalence rates for the total sample, AD patients group and non-AD patients group are shown. In **table III** the 20 most common sensitization prevalence rates for each group are listed. The most prevalent allergen for both groups was nickel sulfate. Between the two groups evaluated, there were variable prevalences among the different allergens tested.

In the AD group there was a higher prevalence of sensitization to quaternium 15, parthenolide, diazolidinyl urea, 2-hydroxyethyl methacrylate, hidroperoxide of limonene, compositae mix II, 1,2-dibromo-2,4-dicyanobutane, caine mix II, sesquiterpene lactone mix, and epoxy resin, sensitizations that were not prevalent in the non-AD group. In AD group, none of the most prevalent allergens were included in cosmetic series.

In contrast, allergens such as hydroperoxide linalool, methylchloroisothiazolinone/methylisothiazolinone, fragance mix I, amerchol l-101, disperse orange 3, p-phenylenediamine, imidazolidinyl urea, formaldehyde, and n-isopropyl-n′-phenyl-phenylenediamine had a similarly high prevalence in both analyzed groups.

Table II *- Overview of all routinely tested allergens (European baseline series and cosmetic series), and distribution of positive patch test reactions in the total pediatric population and in with and without atopic dermatitis.*

Allergen	Total (n = 145)	With atopic dermatitis (n = 63)		Without atopic dermatitis (n = 82)		P-value
	% (n positive/n tested)	% (n positive/n tested)	% PRPP	% (n positive/n tested)	% PRPP	
Baseline series						
Nickel sulfate 5% pet	16.0 (23/144)	16.1 (10/62)	70	15.9 (13/82)	62	> 0.99
MCI/MI 0.02% aq	8.3 (12/144)	6.5 (4/62)	100	9.8 (8/82)	88	0.578
Hydroperoxide linalool 1/0.5% pet	6.8 (3/44)	7.4 (2/27)	50	5.6 (1/18)	100	> 0.99
Methylisothiazolinone 0.2% aq	6.3 (9/144)	1.6 (1/63)	100	9.9 (8/81)	88	**0.046**
Amerchol L-101 50% pet	4.9 (7/143)	4.8 (3/62)	67	4.9 (4/81)	25	> 0.99
Cobalt chloride 1% pet	4.9 (7/142)	0.1 (4/62)	50	3.8 (3/80)	33	0.699
Benzisotiazolinona 0.1% pet	4.9 (2/41)	0 (0/21)	NA	10.0 (2/20)	100	0.232
Fragance mix I 8% pet	4.8 (7/145)	4.8 (3/63)	100	4.9 (4/82)	75	> 0.99
Caine mix III 10% pet	4.3 (6/141)	0 (0/60)	0	7.4 (6/81)	17	**0.038**
p-Phenylenediamine 1% pet	4.3 (6/140)	3.3 (2/61)	100	5.1 (4/79)	100	0.697
Disperse Orange 3 1% pet	3.8 (4/106)	4.8 (2/42)	50	3.1 (2/64)	0	0.648
Formaldehyde 2% aq	3.5 (5/143)	3.2 (2/62)	50	3.7 (3/81)	67	> 0.99
Parthenolide 0.1% pet	3.4 (1/29)	6.3 (1/16)	100	0 (0/13)	NA	> 0.99
Diazolidinyl urea 2% pet	2.8 (4/144)	4.8 (3/63)	100	1.2 (1/81)	100	0.319
Quaternium 15 1% pet	2.8 (4/141)	6.7 (4/60)	100	0 (0/81)	NA	**0.031**
Sodium disulfite 1% pet	2.8 (1/36)	0 (0/18)	NA	5.6 (1/18)	0	> 0.99
N-Isopropyl-N′-phenyl-pphenylenediamine 0.1% pet	2.2 (3/138)	1.7 (1/59)	100	2.5 (2/79)	0	> 0.99
Hidroperoxide of limonene 0.2/0.3% pet	2.2 (1/46)	3.7 (1/27)	100	0 (0/19)	NA	> 0.99
Lanolin alcohols 30% pet	2.1 (3/144)	1.6 (1/63)	0	2.5 (2/81)	50	> 0.99
Fragance mix II 14% pet	2.1 (3/144)	0 (0/63)	NA	3.7 (3/81)	67	0.257
Imidazolidinyl urea 2% pet	2.1 (3/141)	3.3 (2/61)	100	1.3 (1/80)	100	0.578
2-Hydroxyethyl methacrylate 1% pet	2.0 (1/49)	4.2 (1/24)	100	0 (0/25)	NA	0.49
Peru balsam 25% pet	1.4 (2/143)	1.6 (1/62)	0	1.2 (1/81)	100	> 0.99
Compositae mix II 2.5% pet	1.1 (1/87)	2.6 (1/38)	100	0 (0/49)		0.437
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (lyral) 5% pet	1.0 (1/98)	0 (0/47)	NA	1.9 (1/51)	100	> 0.99
Propolis 10% pet	0.9 (1/109)	0 (0/46)	NA	1.6 (1/63)	100	> 0.99
1,2-Dibromo-2,4-dicyanobutane 0.3% pet	0.8 (1/129)	1.8 (1/55)	100	0 (0/74)	NA	0.426
Caine mix II 10% pet	0.8 (1/128)	1.8 (1/55)	100	0 (0/73)	NA	0.43
Parabens 12% pet	0.7 (1/142)	1.6 (1/61)	100	0 (0/81)	NA	0.43
Potassium dichromate 0.5% pet	0.7 (1/142)	1.6 (1/62)	100	0 (0/80)	NA	0.437
Sesquiterpene lactone mix 0.3% pet	0.7 (1/139)	1.7 (1/59)	100	0 (0/80)	NA	0.424
Epoxy resin 1.0% pet	0.7 (1/137)	1.7 (1/59)	0	0 (0/78)	NA	0.431

→

Allergen	Total (n = 145)	With atopic dermatitis (n = 63)		Without atopic dermatitis (n = 82)		P-value
	% (n positive/n tested)	% (n positive/n tested)	% PRPP	% (n positive/n tested)	% PRPP	
Mercaptobenzothiazole 2% pet	0 (0/144)	0 (0/62)	NA	0 (0/82)	NA	NA
Thiuram mix 1% pet	0 (0/144)	0 (0/62)	NA	0 (0/82)	NA	NA
Colophonium 20% pet	0 (0/144)	0 (0/62)	NA	0 (0/82)	NA	NA
Neomycin sulfate 20% pet	0 (0/142)	0 (0/60)	NA	0 (0/82)	NA	NA
p-tert-Butylphenol formaldehyde resin 1% pet	0 (0/140)	0 (0/61)	NA	0 (0/79)	NA	NA
Budesonide 0.1% pet	0 (0/140)	0 (0/60)	NA	0 (0/80)	NA	NA
Mercapto mix 2% pet	0 (0/139)	0 (0/60)	NA	0 (0/79)	NA	NA
Tixocortol-21-pivalate 1% pet	0 (0/137)	0 (0/59)	NA	0 (0/78)	NA	NA
Disperse blue 106 1% pet	0 (0/137)	0 (0/59)	NA	0 (0/78)	NA	NA
Panthenol 5% pet	0 (0/131)	0 (0/57)	NA	0 (0/74)	NA	NA
Hydrocortisone-17-butyrate 0.1% pet	0 (0/110)	0 (0/43)	NA	0 (0/67)	NA	NA
Primin 0.01% pet	0 (0/97)	0 (0/38)	NA	0 (0/59)	NA	NA
Carba mix 3% pet	0 (0/95)	0 (0/45)	NA	0 (0/50)	NA	NA
Farnesol 5% pet	0 (0/91)	0 (0/36)	NA	0 (0/55)	NA	NA
Clioquinol 5% pet	0 (0/90)	0 (0/36)	NA	0 (0/54)	NA	NA
Textile dye mix 6.6% pet	0 (0/49)	0 (0/24)	NA	0 (0/25)	NA	NA
DMDM hydantoin 1% pet	0 (0/47)	0 (0/25)	NA	0 (0/22)	NA	NA
Lidocaine 15% pet	0 (0/45)	0 (0/22)	NA	0 (0/23)	NA	NA
Cosmetic series*						
Cocamidopropyl betaine 1% aq	2.3 (1/44)	0 (0/21)	NA	4.3 (1/23)	100	> 0.99
Octyl gallate 0.25% pet	2.1 (1/47)	0 (0/22)	NA	4.0 (1/25)	100	> 0.99
Phenoxyethanol 1% pet	2.0 (1/49)	0 (0/23)	NA	3.8 (1/26)	100	> 0.99
Cetearyl alcohol 20% pet	1.9 (1/52)	0 (0/24)	NA	3.6 (1/28)	100	> 0.99
Triethanolamine 2.5% pet	0 (0/56)	0 (0/25)	NA	0 (0/31)	NA	NA
Ethylenediaminetetraacetic acid 1% pet	0 (0/55)	0 (0/24)	NA	0 (0/31)	NA	NA
Chlorocresol 1% pet	0 (0/54)	0 (0/24)	NA	0 (0/30)	NA	NA
Oxybenzone 10% pet	0 (0/52)	0 (0/23)	NA	0 (0/29)	NA	NA
Sorbic acid 2% pet	0 (0/51)	0 (0/24)	NA	0 (0/27)	NA	NA
Chloroxylenol 1% pet	0 (0/50)	0 (0/23)	NA	0 (0/27)	NA	NA
Hexahydro-1,3,5-tris-(2-hydroxyethyl) triazine (Grotan BK) 1% aq	0 (0/49)	0 (0/23)	NA	0 (0/26)	NA	NA
Chloroacetamide 0.2% pet	0 (0/49)	0 (0/23)	NA	0 (0/26)	NA	NA
Propylene glycol 5% pet	0 (0/48)	0 (0/23)	NA	0 (0/25)	NA	NA
Butyl hydroxy toluene 2% pet	0 (0/47)	0 (0/22)	NA	0 (0/25)	NA	NA
Triclosan 2% pet	0 (0/47)	0 (0/21)	NA	0 (0/26)	NA	NA
Abietic acid 10% pet	0 (0/46)	0 (0/22)	NA	0 (0/24)	NA	NA
Butylhidroxianisole 2% pet	0 (0/43)	0 (0/20)	NA	0 (0/23)	NA	NA

Numbers in parentheses represent the number of times that a positive reaction was found to allergen, divided by the total number of times that the allergen was tested. PRPP: Present Relevant per positives; MCI/MI: methylchloroisothiazolinone/methylisothiazolinone; NA: not applicable. P-value is result of differences between patients with and without atopic dermatitis groups. Statistically significant values were marked bold. *Allergens patch tested < 20 times were excluded to avoid non-inferential results (excluded ones are presented in supplementary information).

Table III - *Top 20 most common sensitization prevalence rates for allergens from European baseline series and cosmetic series.*

Top 20 Total	Top 20 with atopic dermatitis	Top 20 without atopic dermatitis
Nickel sulfate 5% pet	Nickel sulfate 5% pet	Nickel sulfate 5% pet
MCI/MI 0.02% aq	Hydroperoxide linalool 1/0.5% pet	**Benzisotiazolinona 0.1% pet**
Hydroperoxide linalool 1/0.5% pet	**Quaternium 15 1% pet**	**Methylisothiazolinone 0.2% aq**
Methylisothiazolinone 0.2% aq	MCI/MI 0.02% aq	MCI/MI 0.02% aq
Amerchol L-101 50% pet	**Parthenolide 0.1% pet**	**Caine mix III 10% pet**
Cobalt chloride 1% pet	Fragance mix I 8% pet	Hydroperoxide linalool 1/0.5% pet
Benzisotiazolinona 0.1% pet	**Diazolidinyl urea 2% pet**	**Sodium disulfite 1% pet**
Fragance mix I 8% pet	Amerchol L-101 50% pet	p-Phenylenediamine 1% pet
Caine mix III 10% pet	Disperse Orange 3 1% pet	Fragance mix I 8% pet
p-Phenylenediamine 1% pet	**2-Hydroxyethyl methacrylate 1% pet**	Amerchol L-101 50% pet
Disperse Orange 3 1% pet	**Hidroperoxide of limonene 0.2/0.3% pet**	**Cocamidopropyl betaine 1% aq***
Formaldehyde 2% aq	p-Phenylenediamine 1% pet	**Octyl gallate 0.25% pet***
Parthenolide 0.1% pet	**Imidazolidinyl urea 2% pet**	**Cobalt chloride 1% pet**
Diazolidinyl urea 2% pet	Formaldehyde 2% aq	**Phenoxyethanol 1% pet***
Quaternium 15 1% pet	**Compositae mix II 2.5% pet**	Formaldehyde 2% aq
Sodium disulfite 1% pet	**1,2-Dibromo-2,4-dicyanobutane 0.3% pet**	**Fragance mix II 14% pet**
Cocamidopropyl betaine 1% aq*	**Caine mix II 10% pet**	**Cetearyl alcohol 20% pet***
N-Isopropyl-N′-phenyl-pphenylenediamine 0.1% pet	N-Isopropyl-N′-phenyl-pphenylenediamine 0.1% pet	Disperse Orange 3 1% pet
Hidroperoxide of limonene 0.2/0.3% pet	**Sesquiterpene lactone mix 0.3% pet**	**Lanolin alcohols 30% pet**
Lanolin alcohols 30% pet	**Epoxy resin 1.0% pet**	N-Isopropyl-N′-phenyl-pphenylenediamine 0.1% pet

Allergens are shown from most to least frequent. Different top 20 allergens between with and without atopic dermatitis groups were marked bold. *Allergens from Cosmetic series. MCI/MI: methylchloroisothiazolinone/methylisothiazolinone.

Considering the clinical relevance, based on the criteria mentioned above, **table IV** shows the 20 main relevant allergens for each group separately. The most prevalent allergen, nickel sulfate, was considered among the 20 most relevant tested allergens however, it assumed a minor position due to its high prevalence.
The tested allergens methylchloroisothiazolinone/methylisothiazolinone, fragrance mix I, diazolidinyl urea, p-Phenylenediamine, imidazolidinyl urea, methylisothiazolinone, nickel sulfate, and hydroperoxide linalool proved to be relevant in both groups studied. In the AD group, the tested allergens quaternium 15, parthenolide, 2-Hydroxyethyl methacrylate, hydroperoxide of limonene, compositae mix II, 1,2-Dibromo-2,4-dicyanobutane, caine mix II, N-Isopropyl-N′-phenyl-phenylenediamine, sesquiterpene lactone mix, potassium dichromate, parabens, and amerchol L-101 differ from the non-AD group. Based on the results presented, **figure 1** shows the new proposed baseline series for AD patients with a recommendation for ACD evaluation.

Discussion

In this study, we report the experience of our hospital in patch test evaluation in the pediatric population. In our study, most patch-tested patients were aged between 10 and 15 years old. The AD group included significantly younger patients, with most patients aged between 9 and 14 years old. These findings support the notion that ACD increases with age in general and that ACD affects AD patients at an earlier age. They are in line with the probability that AD patients, whose disease presentation appears at a younger age, may have an increased risk of ACD (1, 3). However, the percentage of positive tests in different age groups was similar. In addition, although the safety of patch testing has been verified in children from 6 months of age, the reduced number of children tested at ages below 6 years may reflect the lack of knowledge of the safety profile in this age group (10). Therefore, it is important to the awareness of health professionals for early recognition of this clinical presentation.

Figure 1 *- Purpose for the adapted baseline series for children with AD, with suspected ACD, difficult-to-control AD, new-onset dermatitis and prior to initiating systemic therapy for AD, or when no specific exposure is identified.*

ADAPTED SERIES FOR CHILDREN WITH ATOPIC DERMATITIS WITH RECOMMENDATION TO ACD EVALUATION		
Allergens	**48 h**	**72-96h**
1. Quaternium 15 1% pet		
2. MCI/MI 0.02% aq		
3. Parthenolide 0.1% pet		
4. Fragance mix I 8% pet		
5. Diazolidinyl urea 2% pet		
6. 2-Hydroxyethyl methacrylate 1% pet		
7. Hidroperoxide of limonene 0.2/0.3% pet		
8. p-Phenylenediamine 1% pet		
9. Imidazolidinyl urea 2% pet		
10. Compositae mix II 2.5% pet		
11. 1,2-Dibromo-2,4-dicyanobutane 0.3% pet		
12. Caine mix II 10% pet		
13. N-Isopropyl-N′-phenyl-phenylenediamine 0.1% pet		
14. Sesquiterpene lactone mix 0.3% pet		
15. Methylisothiazolinone 0.2% aq		
16. Potassium dichromate 0.5% pet		
17. Parabens 12% pet		
18. Nickel sulfate 5% pet		
19. Amerchol L-101 50% pet		
20. Hydroperoxide linalool 1/0,5% pet		

Table IV *- Top 20 most common relevant allergens from European baseline series and cosmetic series. Allergens are shown from most frequently relevant in number to least frequent.*

Top 20 with atopic dermatitis	Top 20 without atopic dermatitis
Quaternium 15 1% pet	**Benzisotiazolinona 0.1% pet**
MCI/MI 0.02% aq	Hydroperoxide linalool 1/0.5% pet
Parthenolide 0.1% pet	p-Phenylenediamine 1% pet
Fragance mix I 8% pet	**Cocamidopropyl betaine 1% aq***
Diazolidinyl urea 2% pet	**Octyl gallate 0.25% pet***
2-Hydroxyethyl methacrylate 1% pet	**Phenoxyethanol 1% pet***
Hidroperoxide of limonene 0.2/0.3% pet	**Cetearyl alcohol 20% pet***
p-Phenylenediamine 1% pet	**Hydroxyisohexyl 3-cyclohexene carboxaldehyde (lyral) 5% pet**
Imidazolidinyl urea 2% pet	**Propolis 10% pet**
Compositae mix II 2.5% pet	Imidazolidinyl urea 2% pet
1,2-Dibromo-2,4-dicyanobutane 0.3% pet	Diazolidinyl urea 2% pet
Caine mix II 10% pet	Peru balsam 25% pet
N-Isopropyl-N′-phenyl-pphenylenediamine 0.1% pet	Methylisothiazolinone 0.2% aq
Sesquiterpene lactone mix 0.3% pet	MCI/MI 0.02% aq
Methylisothiazolinone 0.2% aq	Fragance mix I 8% pet
Potassium dichromate 0.5% pet	**Fragance mix II 14% pet**
Parabens 12% pet	**Formaldehyde 2% aq**
Nickel sulfate 5% pet	Nickel sulfate 5% pet
Amerchol L-101 50% pet	**Lanolin alcohols 30% pet**
Hydroperoxide linalool 1/0.5% pet	**Cobalt chloride 1% pet**

Different top 20 allergens between with and without atopic dermatitis groups were marked bold. *Allergens from Cosmetic series. MCI/MI: methylchloroisothiazolinone/methylisothiazolinone.

Despite the interrelation between AD and ACD is controversial, the failure to identify a culprit allergen can have important consequences for the evolution and management of AD. Some of the most common allergens shown in our sample, such as nickel, cobalt, methylchloroisothiazolinone/methylisothiazolinone, hydroperoxide linalool, fragrances, p-phenylenediamine, quaternium 15 and formaldehyde, have been similarly described in the literature as having a high prevalence (11). Regarding patients with and without atopic dermatitis, contact sensitization rates were similar however, after nickel, main allergens were different, mostly related to preservatives (formaldehyde releasers) and plant extracts (parthenolide) that may be present in topical products used in the management of AD. Pointing out particular allergens, nickel as the most prevalent allergen for both groups, is a known commonly identified allergen in many studies of ACD in children and adolescents, likely attributable to the increased use of jewelry, children's toys, metallic components of children's clothing, electronic equipment, and dental appliances (12). Sensitizations to methylisothiazolinone and cobalt were more prevalent in the non-AD group. Although methylchloroisothiazolinone/methylisothiazolinone was one of the most prevalent in both groups, the individual sensitization to methylisothiazolinone showed to be more frequent in non-AD group, which is described in previous studies as a frequent allergen in ACD of hands and face due to its presence in cosmetic and hygiene products, before its ban in 2017 (13). Regarding the prevalence of sensitization to cobalt, our data diverges from some studies published

(11, 14). For example, in China it was found that sensitization to cobalt was higher in patients with AD and was dependent on geographic exposures, not being necessarily related to the coexistence of sensitization to other metals such as nickel (14).

Our study has some limitations that are considered transversal to the other works presented on this topic, namely the possibility of differences in reading techniques between observers. However, in our work, reading and interpretation of patch test results was perfomed always by the same person, to limit this bias. Another limitation may be the difficulty distinguishing between allergic or irritant reactions. The data collected in this work involved children from the same region and a considerable period of time, which may influence the results. We need to consider the high variability of allergen expression in the environment, changes in European legislation, modifications in components of topical products, and lifestyle habits.

In conclusion, confirmed allergic contact dermatitis was relatively common in our sample. It appeared to increase with age, however, the rates of positive tests were similar between age groups. As expected, there were notable differences in sensitization rates of relevant allergens when compared to other European studies, confirming the geographic sensitization variability and need for pediatric adaptation and custom "baseline series".

Patients with and without atopic dermatitis had similar contact sensitization rates however the main allergens were different. We propose the first Portuguese Pediatric Baseline Series adapted for AD patients, based on only the most common and relevant allergens. Overall, this study provides key information on the relationship between AD and ACD in pediatric patch-tested patients in Portugal. Further studies on a national scale are necessary to validate this new series proposal for the Portuguese pediatric population.

Fundings

None.

Contributions

JCC, IAC: conceptualization, project administration, methodology, formal analysis, writing - original draft, writing - review & editing. CL: writing - review & editing. ACC, LR: data collection, resources. MG: data collection, resources, project administration, formal analysis, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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The role of skin tests with polyethylene glycol and polysorbate 80 in the vaccination campaign for COVID-19: results from an Italian multicenter survey

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Key words

PEG; skin test; vaccines; anaphylaxis; COVID-19.

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Impact statement

The study, consistently with the latest guidelines, demonstrates that after adequate diagnostic work-up, the positivity of skin test with PEG and or PS before vaccination is rare and mostly replaceable by an accurate clinical history.

Summary

Background. *International guidelines suggested skin tests with Polyethylene-glycol (PEG) and polysorbate 80 (PS-80), to investigate a possible hypersensitivity to these excipients either to identify subjects at risk of developing allergic reactions to COVID-19 vaccines, or in patients with suspected IgE mediated hypersensitivity reactions (HR) to the COVID-19 vaccine. The main purpose of this study was to investigate the prevalence of PEG and PS sensitization in patients with a clinical history of HR to drugs containing PEG/PS and in patients with a suspected COVID-19 vaccine immediate HR.* ***Methods.*** *This was a multicenter retrospective study conducted by allergists belonging to 20 Italian medical centers. Skin testing was performed in 531 patients with either a clinical history of suspected hypersensitivity reaction (HR) to drugs containing PEG and/or PS-80 (group 1: 362 patient) or a suspected HR to COVID-19 vaccines (group 2: 169 patient), as suggested by the AAIITO/SIAAIC guidelines for the "management of patients at risk of allergic reactions to COVID-19 vaccines".* ***Results.*** *10/362 (0.02%) had positive skin test to one or both excipients in group 1, 12/169 (7.1%) in group 2 ($p < 0.01$). In group 2 HRs to COVID-19 vaccines were immediate in 10/12 of cases and anaphylaxis occurred in 4/12 of patients.* ***Conclusions.*** *The positivity of skin test with PEG and or PS before vaccination is extremely rare and mostly replaceable by an accurate clinical history. Sensitization to PEG and PS has to be investigated in patients with a previous immediate HR to a COVID-19 vaccine, in particular in patients with anaphylaxis.*

Introduction

In December 2020, at the beginning of the COVID-19 vaccination campaign, 2 anaphylaxes were reported after the administration of the first 500 BNT162b2vaccines. For this reason, the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA) temporarily contraindicated this vaccine in patients with a severe allergic background (1).

This contraindication was revoked in January 2021 and more recent data on the safety of COVID-19 vaccines show that severe hypersensitivity reactions are rare even in patients with an allergic background (2-4).

In mRNA vaccines (Comirnaty by Pfizer BioNTech and Spikevax by Moderna) the components suspected of being the cause of IgE-mediated hypersensitivity reactions (HR) are the excipient Polyethylene glycol (PEG or macrogol, with a molecular weight of 2000 kDa) and Trometamol (contained at time only in Spikevax), while in the adenoviral vector vaccines (Vaxzeviria by AstraZeneca and Jcovden by Janssen) polysorbate 80 (PS-80), a substance chemically correlated with PEGs has been incriminated. Non-IgE mediated mechanisms with activation of immunological mechanisms triggered by complement activation (CARPA, Complement Activation-Related PseudoAllergy) have also been hypothesized (5).

According to current national and international guidelines, an allergological evaluation in still needed in individuals with suspected hypersensitivity to excipients of COVID-19 vaccines, PEG and PS-80.

An evaluation by allergy specialist is recommended also in patients with a suspected HR to COVID-19 vaccination, in order to evaluate the indication to a further vaccine dose and which vaccine could be administered (5-7).

According to the aforementioned guidelines, individuals with allergy to foods, inhalants, Hymenoptera venom and drugs (with the exception of PEG/PS containing injective drugs) can be vaccinated in a standard setting and don't need a "preventive" allergological evaluation.
Among these patients, even those with a history of anaphylaxis can be vaccinated in a standard setting with a prolonged observation period (60 minutes according to Italian guidelines).
Instead, an allergy evaluation is needed in subjects with a previous reaction to drugs containing PEG or PS. In these patients, skin tests with PEG and/or PS are suggested as a useful test to evaluate a possible contraindication to vaccination. Trometamol was contained at that time as an excipient only in Spikevax. This substance may have an irritative effect, and for this reason, is not recommended for skin testing.
In individuals with a severe anaphylactic reaction to prior doses of COVID-19 vaccines, both in case of positive and negative tests, it is preferable not to administer the following dose of the same vaccine.
It should be emphasized that data on skin tests currently available in the literature indicate their low positive and negative predictive value and the need for the diagnostic procedure to be entrusted to the allergy specialist.
These guidelines highlight the central role of allergist in the evaluation of subjects with suspected hypersensitivity to COVID-19 vaccines or to the excipients contained in these preparations.
The main purpose of this study was to investigate the prevalence of PEG and PS sensitization in Italian patients with a clinical history of HR to drugs containing PEG/PS and in patients with a suspected COVID-19 vaccine immediate HR.

Materials and methods

This was a multicenter retrospective study conducted, from March to December, 2021, by allergists belonging to 20 Italian medical centers located either in hospitals (n = 9) or outpatient clinics (n = 13).
Skin testing was performed in patients with either a clinical history of suspected hypersensitivity reaction (HR) to drugs containing PEG and/or PS 80 (group 1) or a suspected HR to COVID-19 vaccines (group 2), as suggested by the AAIITO/SIAAIC guidelines for the "management of patients at risk of allergic reactions to COVID-19 vaccines" (7).
Skin tests were performed in 6 steps: 3 steps for prick tests followed by 3 steps for intradermal tests using increasing concentrations of PEG and PS, as suggested by national and international guidelines (6, 7). Demographic and clinical data were collected: age, previous anaphylaxis or HR to drug or vaccine (either containing or not containing PEG and PS), allergic comorbidities. Data were collected by means of an anonymous survey, filled out online by an allergist. No data on gender and ethnicity were collected. The approval by the ethical committee was not requested being an anonymous survey.

Statistical analysis

Microsoft Excel 2019®, OpenEpi online (www.openepi.com, accessed on 25 January 2022), and JASP 0.16.0.0 were used for statistical analysis. The distribution of categorical variables among groups were compared using the chi-square test. Categorical variables are reported as absolute numbers (percentage). P-values < 0.05 were considered significant.

Results

531 patients were enrolled: 362 (68.2%) were referred to carry out the skin tests to exclude PEG/PS hypersensitivity before vaccination (group 1), and 169 (31.8%) for a suspected HR to the first or second dose of COVID-19 vaccine (group 2).
10/362 (0.02%) scored positive on skin test to one or both excipients in group 1 *vs* 12/169 (7.1%) in group 2 ($p < 0.01$). All patients of group 1 had a previous drug anaphylaxis and 50% had a previous HR to drugs containing PEG. In group 2, HRs to COVID-19 vaccines occurred after the first dose in all patients. HRs were immediate in 10/12 (83%) patients and anaphylaxis occurred in 4/12 (33%) patients.

Patients with a history of adverse reactions to drugs containing PEG

Demographic and clinical features

362 patients were enrolled. Patients between 40 and 70 years old represented the most numerous age group. 160 patients had a clinical history of anaphylaxis (128 induced by drugs, 15 by vaccines, and 6 by Hymenoptera stings). 41 patients (11,7%) had a clinical history of multiple anaphylaxis (≥ 2). Antibiotics, NSAIDs and vaccines were the most common causes of previous anaphylaxis. 50.6% (n = 179) had a clinical history of multiple drug reactions (most caused by antibiotics and NSAIDs). 165 patients reported adverse reactions to drugs or vaccines containing PEG (most commonly amoxicillin/clavulanate, paclitaxel, ciprofloxacin, methylprednisolone, and docetaxel).
253 (72.5%) showed allergic or pseudoallergic comorbidities (asthma, rhinitis, conjunctivitis, dermatitis, chronic spontaneous urticaria), and 60% of the population suffered from extra-allergological comorbidities (cardiovascular diseases, endocrinopathies, hyperuricemia, osteoporosis).

Characteristics of patients with positive skin test to PEG/polysorbate

10 patients scored positive on skin test with PEG and PS (**table I**): 2 patients (PT n. 204, 351) scored positive only to skin test with PS (antipneumococcus vaccine and Optive plus).

Table I *- Demographic and clinical features of patients with a clinical history of HRs to drugs containing polyethylene-glycol (PEG) or/and polysorbate (PS).*

PT	Age	Past anaphylaxis	Drug anaphylaxis	Multiple anaphylaxis	Multiple drugs reactions	Past reactions to PEG and or PS containing drugs	Tolerance to PEG containing drugs	Allergic comorbidities	AntiFlu vaccine	Positive skin test (PEG)	Positive skin test (PS)
9	71-80	Yes	Yes	Yes	Yes	Yes (Pantoprazole, amoxicillin/ clavulanate)		No	No	ID MPDa 0.04 mg/ml	
32	41-50	Yes	Yes	No	Yes	Yes (Cetrizine)			No	SPT Macrogol 1:1	
89	41-50	Yes	Yes (Lidocaine + MPDa)	No	Yes	No		Yes (Rhinitis, conjunctivitis)	No	SPT MPDa 40 mg/ml, ID MPDa 0.04/0.4/4 mg/ml	
168	41-50	Yes	Yes (Betamethasone)	No	No	No	Yes	Yes (asthma, rhinitis)	No	SPT MPDa 40 mg/ml, SPT MPD 40 mg/ml, ID MPD (control) 0.04/0.4/4 mg/ml, ID MPDa 0.04/0.4/4 mg/ml	
204	41-50	Yes	Yes	No	No	No			No		SPT and ID antipneumococcus vaccine
265	51-60	Yes	Yes	No	No	No		Yes (Rhinitis, conjunctivitis)	No	ID MPDa 0.4 mg/ml	
346	41-50	Yes	Yes	No	No	Yes (MPDa)	Yes	No	No	ID MPDa 4 mg/ml	SPT and ID Optive plus™
351	51-60	No	No	No	Yes			No	No		ID Optive plus™
359	51-60	Yes	Yes	No	No	Yes (Paclitaxel)			No	ID MPDa 0.4 mg/ml	ID Triam 4 mg/ml
360	61-70	Yes	Yes	No	No	Yes (Macrogol)	No		No	SPT Macrogol 1:1, SPT MPDa 40 mg/ml, ID MPDa 4 mg/ml	SPT Triam 40 mg/ml, SPT Optive plus™

PT: patient; PEG: polyethylene-glycol; PS: polisorbate; Triam: triamcinolone; MPDa: methylprednisolone acetate (Depomedrol®); MPD: methylprednisolone (Urbason).

3 patients (PT n. 346, 359, 360) scored positive on both PS (Kenacort® "Triamcinolone acetonide" and/or Optive plus) and PEG (Depomedrol® "Methylprednisolone acetate" and Macrogol) testing.
5 (PT n. 9, 32, 89, 168, 265) patients showed a PEG positive skin test (one with macrogol 1:1 on SPT, and the others ID with Depomedrol® (doubtful SPT result)).
Patient n. 168 scored positive on SPT with both to Depomedrol® "Methylprednisolone acetate" and Urbason® "Methylprednisolone", suggesting methylprednisolone rather than PEG hypersensitivity.
5 patients experienced a previous reaction to PEG-containing drugs (Cetirizine, Paclitaxel, Augmentin® "Amoxicillin/Clavunate", Pantoprazole, Movicol® "Macrogol").
3 patients showed allergic comorbidities (rhinitis, asthma, conjunctivitis).
9/10 patients had a clinical history of drug anaphylaxis: 1 patient to Depomedrol® and Lidocaine "Methylprednisolone acetate", 1 to Bentelan® "Betamethasone". The drug is not known for the other 7. mRNA vaccines have been discouraged to patient with PEG skin test positivity.

Patients with suspected hypersensitivity reactions to COVID-19 vaccines

Demographic and clinical features (**table IIA**)
A total of 169 patients with suspected hypersensitivity reactions to COVID-19 vaccine were registered in the participating centers and subsequently submitted to skin testing with vaccine excipients (7). 14% of subjects had a clinical history of allergic reactions at least to 2 different drugs and 17% had a clinical history of anaphylaxis. Other allergic comorbidities were reported in 57% of subjects. Among patients with previous anaphylaxis there was a significantly higher percentage of subjects with positive skin tests than in patients without anaphylaxis (17% *vs* 5%, $p < 0.01$) while there was not a significative difference in patient with multiple drug hypersensitivity.

Details of the suspected HR (**table IIB**)
147/169 (95%) of suspected HRs to COVID-19 vaccines occurred after the 1st dose, 8/169 (4.7%) after the 2nd dose and 14/169 (8.2%) after both doses. This means that globally 22 patients had HRs after the 2nd dose. 104/161 (64%) of HRs

Table II - (A) *Demographic and clinical features of patients with HRs to COVID-19 vaccines;* ***(B)*** *Demographic and clinical features of patients with HRs to COVID-19 vaccines and positive skin tests.*

A

Clinical and demographic features	n	%
Age group	169	100
20-30	15	9
31-40	39	23
41-50	36	21
51-60	31	18
61-70	26	15
71-80	12	7
> 80	3	2
Previous anaphylaxis	29	17
Drug	9	5
Vaccine	13	8
> 1 anaphylaxis	5	3
> 1 drug HR	25	15
HR to PEG/ polysorbate containing drug	26	15
Allergic comorbidities	96	57
AntiFlu vaccine (2020/2021)	21	12

B

Clinical and demographic features	n	%
Age range	12	100
31-40	2	16.7
41-50	2	16.7
51-60	5	41.7
61-70	2	16.7
71-80	1	8.3
Past anaphylaxis	5	41.7
Drug anaphylaxis	4	33.3
Multiple anaphylaxis	3	25
Multiple drug reactions	3	25
Past reactions to PEG-containing drugs	4	33.3
Tolerance to PEG-containing drugs*	5	41.7
allergic comorbidities	5	41.7
AntiFlu vaccine	2	16.7

HR to anti-SARS-CoV-2 vaccines					
	n	**%**		**n**	**%**
HR D1	161	95	HR D2	19	18
Immediate	104	62	Immediate	13	68
Local reactions	8	8	Local reactions	5	26
Diffuse itching	41	39	Diffuse itching	5	26
Urticaria	14	13	Urticaria	2	11
Rash (other)	45	43	Rash (other)	7	37
Angioedema	41	39	Angioedema	4	21
Skin (total)	107	103	Skin (total)	12	63
Pharyngeal disclosure	17	16	Pharyngeal disclosure	2	11
Asthma/ bronchospasm	21	20	Asthma/ bronchospasm	4	21
Anaphylaxis/ glottic edema	11	7	Anaphylaxis/glottic edema	2	11
Paresthesia	28	27	Paresthesia	1	5
Drugs to treat HR	106	66	**Drugs to treat HR D2**		
AntiH1	89	86	Antih1	10	53
GC	65	63	Gc	8	42
Epinephrine	9	9	Epinephrine	2	11
			HR 1 and 2D	12	63
			Positive skin test	12	63

HRs to COVID-19 vaccine		
HR 1D	12	100
HR immediate	10	83.3
HR not immediate	2	16.7
HR: symptoms		
Local reactions	1	8.3

*Tolerance to PEG containing drugs before COVID-19 vaccines.

after first dose and 13/22 (68%) of HRs after 2nd dose were immediate (> time of onset within 4 hours from vaccination). Skin reactions were the most common HRs, occurring in 69.6% of patients. 12/169 of HR were classified as anaphylaxis according to modified WAO grading system (6). Antihistamines were used in 57% of cases, corticosteroids in 41%, and epinephrine in 11% of cases.

***Positive skin tests in patients with suspected hypersensitivity reactions* (table III)**

Among the 169 patients with suspected HRs, 12 (7.1%) had positive skin test results. 7 patients showed positive tests for PEG (PT n. 1, 3, 4, 5, 8, 11, 12) and 3 for PS (PT n. 2, 6, 10), while only 2 (PT n. 7, 10) patient had positive tests for both excipients.

In this subgroup HRs to COVID-19 vaccines occurred after the first dose in all patients.

HRs were immediate in 10/12 (83%) of cases and anaphylaxis occurred in 4/12 (33%) of patients.

5/12 (41%) had both a history of anaphylaxis and allergic comorbidities.

Only 2 patients out of 12 received the 2nd dose of vaccine:

Patient n. 8 received the 2nd dose of the same vaccine (BNT162b2) despite HR to the first dose and reported the same reaction (dyspnea and bronchospasm).

Patient n. 12, who developed a generalized urticaria after the first dose of mRNA vaccine and was positive to PEG received the 2nd dose with adenoviral vaccine, administered in fractioned doses, reported no adverse events.

Considering the medical history of those patients, 4/12 (33%) reported past reactions to PEG-containing drugs, while 5/12 (41,7%) reported, before COVID-19 vaccination, the tolerance of at least one PEG- containing drug. HRs to PEG- containing vaccines in subjects who tolerated PEG- containing drug could be explained by the role of lipidic nanoparticles. Those nanoparticles, when conjugated to PEG, may determine an HR mediated by complement activation.

Discussion

The study, consistently with the latest national and international guidelines (1, 2) demonstrates that after adequate diagnostic work-up, the positivity of skin test with PEG and or PS before

Table III *- Patients with positive skin tests and hypersensitive reaction to COVID-19 vaccine.*

Patient	Age	Previous anaphylaxis	Allergic comorbidities	HR 1D	Type of vaccine	Time of onset	Therapy of HR	Received 2nd dose	HyPR2D	Time of onset	Therapy HyPR2D	Positive skin test (PEG)	Positive skin test (polysorbate)
1	51-60	No	No	Local wheal and rush, angioedema	ND	< 1 h	AntiH1, GCs	ND	No	NA	NA	Macrogol 3350 ID 0.4 mg/ml	No
2	61-70	vaccine	ACD	Angioedema, dyspnea, bronchospasm (A)	ND	< 1 h	Epi	ND	No	NA	NA	No	p80 Triam ID 0.4 mg/ml
3	51-60	Food	Drugs allergies	Pharyngeal discomfort, mouth paresthesia	ND	< 1 h	GCs	ND	No	NA	NA	MPD ID 40 mg/ml	No
4	31-40	Other drugs	Rhinoconjuctivitis	Apnea, bronchospasm, anaphylaxis without hypotension (A)	ND	< 1 h	Epi	ND	No	NA	NA	SPT Macrogol 3350 1:10, SPT MPDa 40 mg/ml	No
5	51-60	No	No	Diffuse itching, mouth paresthesia	ND	< 1 h	AntiH1, GCs	ND	No	NA	NA	SPT Macrogol 3350 1:10, ID MPDa 0.4 mg/ml, ID MPDa 4 mg/ml	No
6	41-50	No	No	Angioedema, dyspnea, bronchospasm (A)	Adenovirus (ChAdOx1 nCoV-19)	1-4 h	AntiH1, GCs	ND	No	NA	NA	No	SPT p80 Triam 40 mg/ml, ID p80 Triam 40 mg/ml
7	71-80	No	No	Angioedema, glottic edema (A)	ND	< 1 h	AntiH1, GCs	ND	No	NA	NA	SPT Macrogol 3350 1:10	ID p80 Triam 0.4 mg/ml
8	51-60	vaccine, other drugs	Asthma	Dyspnea, bronchospasm	mRNA (BNT162b2)	< 1 h	Epi	yes, mRNA (BNT162b2)	Dyspnea, bronchospasm	< 1	AntiH1, GCs	SPT Macrogol 3350 1:100	No
9	61-70	No	No	Angioedema	Adenovirus (ChAdOx1 nCoV-19)	> 4 h	AntiH1, GCs	ND	No	NA	NA	No	ID p80 eye drops 1:10

Patient	Age	Previous anaphylaxis	Allergic comorbidities	HR 1D	Type of vaccine	Time of onset	Therapy of HR	Received 2nd dose	HyPR2D	Time of onset	Therapy HyPR2D	Positive skin test (PEG)	Positive skin test (polysorbate)
10	31-40	No	No	Urticaria, itching	ND	> 4 h	AntiH1, GCs	No	NA	NA	NA	ID MPDa 0.4 mg/ml	ID p80 eye drops 1:11
11	51-60	Other drugs	Rhinoconjuctivitis	Diffuse itching, angioedema, maculopapular rash, hypotension, dyspnea, bronchospasm, rhinitis (A)	mRNA (BNT162b2)	< 1 h	AntiH1, GCs, Epi	ND	No	NA	NA	ID MPDa 4 mg/ml	No
12	41-50	No	No	Urticaria	mRNA (BNT162b2)	< 1 h	ND	Yes*	No	NA	NA	SPT Macrogol 3350 1:100	No

PT: patients; HR: hypersensitivity reactions; antiH1: antihistamines; GCs: glucocorticoids; Epi: epinephrine; ID: intradermal; SPT: skin prick test; Triam: triamcinolone; MPDa: methylprednisolone acetate; (A): anaphylaxis; ND: no data, NA: not applicable; *adenovirus vaccine, fractioned doses.

vaccination is extremely rare and mostly replaceable by an accurate clinical history. In particular, we found a significatively lower prevalence of positive skin tests in group 1 than in group 2. Sensitization to PEG and PS has to be investigated in patients with a previous immediate HR to a COVID-19 vaccine, in particular in patients with anaphylaxis. Nonetheless, it is important to underline that the vast majority of patients who experience a suspected HR at the first dose of COVID-19 vaccine should not be automatically precluded from being re-vaccinated, in particular in patients with non-severe reactions and negative test, after an accurate allergological evaluation. This is also underlined by the latest Italian guidelines and recent review and meta-analysis of the available literature regarding immediate reactions to the first dose of COVID-19 vaccine, where the incidence of severe immediate reactions to re-vaccination with the second dose of COVID-19 vaccine was very low (0.16%) in the absence of related deaths (3, 7, 8). From our data, patients with previous anaphylaxis have also a major probability of scoring positive on skin tests. This further supports the importance of a complete anamnesis in the screening and management of these reactions. Only patients who received a new diagnosis of allergy to PEG/PS, ascertained by skin test, would not be suitable for the administration of the second dose. On this point, the Italian guidelines highlight the fact that skin tests seem to have a low positive and negative predictive value (9).

In addition to considering excipients as the cause of IgE-mediated allergic reactions to the currently approved COVID-19 vaccines, alternative non-IgE pathways for activating mast cells and other inflammatory cells must be considered, because they can lead to a similar clinical presentation. For example, activation of the complement system leads to the generation of C3a, C4a, and C5a, which are potent activators of inflammation and are called anaphylatoxins due to their ability to cause non-IgE-mediated mast cell degranulation (1).

Depletion of complement levels and production of C3a and C5a have been seen in both mouse models of anaphylaxis and in clinical studies. C5a is the most potent anaphylatoxins and can contribute to vascular permeability as well as activation and chemotaxis of neutrophils, basophils, and mast cells. Infection and tissue injury can lead to activation of the complement system resulting in the generation of C3a and C5a, and these mediators can lead to anaphylaxis. PEG IgM and IgG can cause complement-activation-related pseudoallergy, a nonspecific immune response to PEGylated, nanoparticle-based medicines (1).

Clearly, it is important to consider both IgE and alternative mechanisms for the current reactions. Measurement of serum tryptase and complement may help elucidate the mechanism of the drug-induced reactions in patients following COVID-19 vaccination (1).

For this reason, the panel of experts suggests not to limit the allergy evaluation to the result of skin tests, but to carry out an

integrated evaluation for each patient based on: 1) the precise allergological history, 2) the severity of the reported reactions, and 3) the evaluation of the risk/benefit ratio deriving from vaccination (SIAAIC/AAIITO).

In conclusion, the survey demonstrates that the onset of symptoms suggestive for a HR to the first dose of COVID-19 vaccine should not automatically prevent the citizen from receiving the second dose but requires an adequate allergy assessment that include a detailed clinical history associated with skin tests, when indicated by the allergist.

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Contributions

The authors contributed equally to this work.

Conflict of interests

The authors declare that they have no conflict of interests.

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Can dose reduction be made in patients with allergic bronchopulmonary aspergillosis receiving high-dose omalizumab treatment?

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Key words

Omalizumab; ABPA; asthma; asthma control; omalizumab dose reduction.

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Impact statement

Decreasing the total monthly omalizumab dose either by the same or extended time interval does not cause clinical deterioration in patients with ABPA after the disease is controlled.

Summary

Background. *Allergic bronchopulmonary aspergillosis (ABPA) is an endotype of severe asthma which frequently needs biologics for their steroid sparing effect. We aimed to evaluate the outcomes of reducing the omalizumab dose in patients with ABPA who were on long-term omalizumab treatment.* ***Methods.*** *Once asthma was controlled, two approaches were used to reduce total monthly omalizumab dose: 1) both extending dose intervals from 2 to 4 weeks and decrease omalizumab dose, 2) to reduce omalizumab dose while keeping dose intervals stable.* ***Results.*** *Thirteen patients with ABPA (8F/5M, mean age 53.4 ± 13.0 years) were included. Pre-omalizumab, mean numbers of attacks and hospitalizations were 2.5 ± 1.5 and 1.3 ± 0.8, mean oral corticosteroid (OCS, as methylprednisolone) dose was 12.2 ± 10.4 mg daily. First omalizumab dose reduction was made to all patients at a median time of 35 months (min 13, max 47). The 2nd dose reduction was made in four patients at median of 23.5 months. Mean OCS decreased to 0.69 ± 0.95 mg/day (p = 0.001) in the 1st year of omalizumab, could be stopped in 11 patients in last evaluation. Attacks/hospitalizations decreased significantly to 0.31 ± 0.86 and 0, respectively, in the 1st year of omalizumab. Total omalizumab dose was reduced by median 40% (min 20, max 60) in 1st intervention and 50% (min 20, max 67) after 2nd intervention. After omalizumab dose reduction, asthma control did not deteriorate and there was no need to increase the omalizumab or OCS-dose.* ***Conclusions.*** *Decreasing the total omalizumab dose does not cause clinical deterioration in ABPA after the disease is controlled.*

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a lung disease with a wide clinical spectrum: asthma, bronchiectasis, and if left untreated, it results in pulmonary fibrosis to destructive pulmonary disease (1). ABPA treatment aims to achieve asthma control, to prevent attacks and the development of bronchiectasis and pulmonary fibrosis (2). In ABPA, which is associated with high IgE levels, one of the current treatment alternatives is omalizumab especially in oral corticosteroid (OCS)-dependent patients with adverse effects due to steroid use. Omalizumab (Xolair; Genentech and Novartis, South San Francisco, CA) is the first approved biological in patients with severe allergic asthma because of established efficacy and safety in this group (3, 4). Published data demonstrated that omalizumab was also effective in reducing exacerbations and OCS requirements and improving asthma symptoms and pulmonary function parameters in patients with asthma and ABPA

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who had previously shown an unsatisfactory response to inhaled corticosteroids (ICS) and OCS (2, 3, 5, 6).
We started using omalizumab since 2008, first in the treatment of severe allergic asthma and then in patients with ABPA. In keeping with that, we reported our first experience with omalizumab on 14 patients with a diagnosis of ABPA (6). In this study, patients were on omalizumab for a mean of 31.5 months, which was the longest follow-up period reported to date. Since then, we continued prescribing omalizumab in new patients with ABPA. Further considering the high cost, we attempted to reduce the omalizumab dose in patients with ABPA who were on long-term omalizumab treatment. In the present paper, we aimed to share our experience with this approach.

Materials and methods

Study population

The study was conducted as a retrospective chart review of patients with asthma and ABPA who were treated with omalizumab at the Department of Chest Diseases, Division of Clinical Immunology and Allergy, Faculty of Medicine. The charts were reviewed by three physicians. The local Ethics Committee of Faculty of Medicine approved the study and informed consent was obtained from all the subjects (Ethics Committee Approval no: I4-230-20, date: April 29, 2020).
In the diagnosis of ABPA, the diagnostic criteria determined by Agarwal *et al*. were used (2). A total of 13 patients with ABPA, who had undergone treatment with omalizumab injections between December 2008 and March 2020 were included in the study. The patients were being followed up regularly and had complete health care coverage. Demographics and disease characteristics were recorded from patient files (**table I**). All patients were receiving OCS (as methylprednisolone) with other controller medications including high-dose ICS and long-acting beta 2 agonist.

Measurements

After treatment with omalizumab was started, data including forced expiratory volume in first second (FEV1), asthma control test (ACT) scores, eosinophil count and dose of OCS, for asthma were collected at baseline, first year, and the last evaluation. Outcome measurements are detailed in **figure 1**. The number of asthma exacerbations and hospitalizations for 1 year prior to omalizumab and yearly after starting omalizumab were also recorded. To evaluate the response to omalizumab treatment, patients with ABPA were classified as "complete responders", "partial responders" and "non-responders". If the patient's asthma was under control, with no asthma attack or asthma-related hospitalization in the last 1 year of treatment, and ACT ≥ 20 and this was accompanied by a at least 25% decrease in OCS dose or an improvement at least 200 ml increase in FEV1, these patients were accepted as "complete responders". If at least one of complete control parameters could not be reached, they were accepted as "partial responders". Patients who did not meet any of complete control parameters were considered "non-responders".

Table I *- Demographic and clinical characteristics of the patients before initiation of omalizumab treatment for the first time.*

Variables	Mean ± SD (min-max)
n	13
Sex (female)	8
Age, year	53.4 ± 13.0 (31-69)
Disease duration of asthma, years	19.4 ± 8.4 (9-34)
ABPA diagnosis time, years	10.2 ± 3 (3.5-13)
Body weight, kg	74.5 ± 18.8 (49-105)
Total IgE, IU/mL	821.9 ± 494.8 (356-2,030)
Blood eosinophil count, (cells/mcL)	723.1 ± 547.1 (100-2,200)
FEV1, %	63.0 ± 17.0 (40-100)
FEV1, mL	1876.2 ± 606.7 (1,000-2,970)
FEV1/FVC, %	67.7 ± 13.1 (49-90)
ACT score	15.7 ± 3.5 (11-22)
OCS dose (mg) (methylprednisolone)	12.2 ± 10.4 (4-40)
Number of asthma attacks/year (in the previous year before starting omalizumab treatment)	2.5 ± 1.5 (1-6)
Number of hospitalizations/year (in the previous year before starting omalizumab treatment)	1.3 ± 0.8 (0-2)
Duration of omalizumab treatment, months	64.8 ± 24.2 (38-99) (median 63)
Total monthly omalizumab dose	median 750 (min 300-max 900)
300 mg (patient #9)	1
450 mg (patient #4)	1
600 mg (patient #1, 10)	2
750 mg (patient #2, 3, 6, 7, 8, 11, 12)	7
900 mg (patient #5, 13)	2

SD: standard deviation; min: minimum; max: maximum; ABPA: allergic bronchopulmonary aspergillosis; IgE: immunoglobulin E; FEV1: forced expiratory volume in first second; FVC: forced vital capacity; ACT: asthma control test; OCS: oral corticosteroid.

Study design

During omalizumab treatment, at least one year treatment with omalizumab, if once the disease was controlled, then one of the two approaches was initiated in order to reduce the total monthly dose of omalizumab. The first was to extend dose intervals from 2 weeks to 4 weeks and to decrease the total omalizumab dose used per month, the second approach was to reduce the omalizumab dose while keeping the dose interval stable. In some patients, two approaches were used sequentially if the patient tolerated the dose reduction and/or dose interval extension (**table II**, **figure 1**). If the patient was still a complete responder at the end of the third year of the treatment at the earliest, omalizumab could be discontinued. If the disease became uncontrolled after treatment cessation, omalizumab was restarted.

Statistical analysis

The statistical analysis was performed by using the SPSS version 22 software (SPSS Inc., Chicago, IL, USA). As descriptive statistics, quantitative variables were stated as mean ± standard deviation (SD) and median (minimum-maximum) values, and qualitative variables as number (n) and percentage (%). To examine the difference between two dependent quantitative variables, the paired-samples t-test was used if the assumptions of normal distribution were met, and the Wilcoxon Sign test was used if not. A value of $p < 0.05$ was considered statistically significant.

Results

Data from the total of 13 patients with ABPA who were treated with omalizumab and underwent dose reduction were evaluated. The baseline demographic and clinical characteristics of the patients are summarized in **table I** and patients with corresponding approaches along with current situation are summarized in **table II**. The clinical characteristics of each subject are shown in **table III**.

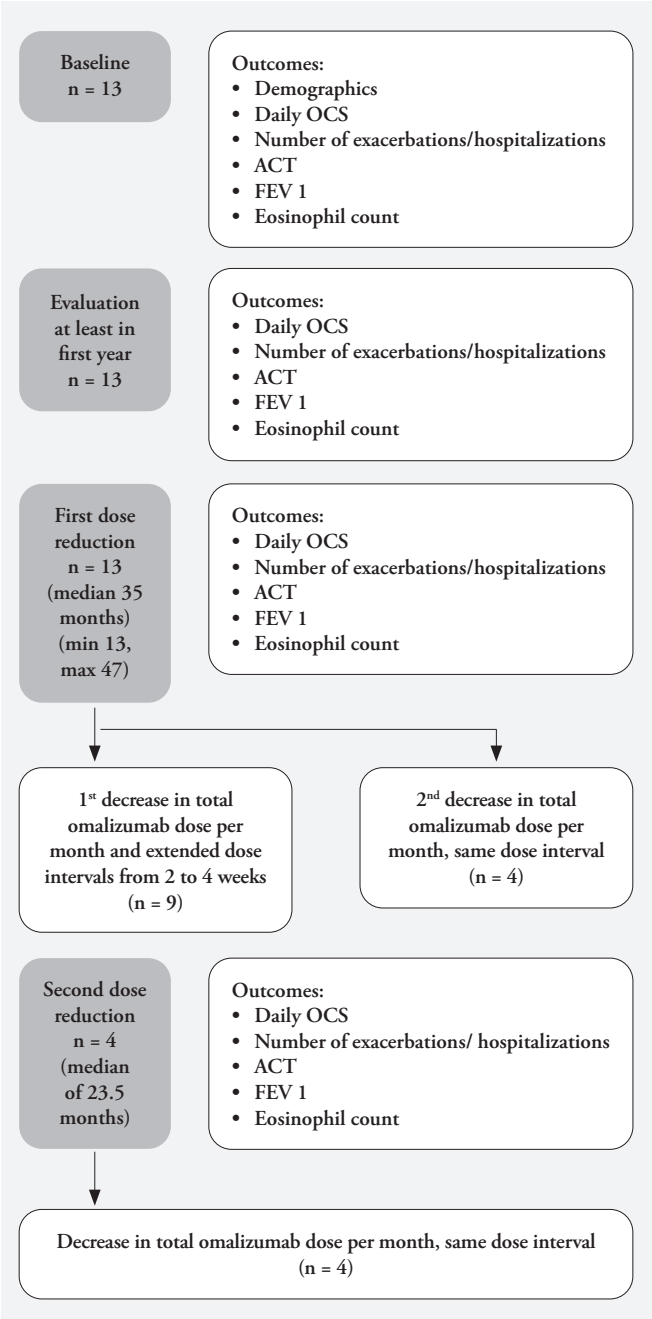
The mean time of dose reduction in omalizumab treatment was 33 ± 9.57 (median 35, minimum 13, maximum 47) months. The OCS used by the 13 patients before omalizumab treatment was 12.2 ± 10.4 mg/day. In the first year of omalizumab, the methylprednisolone dose decreased to 0.69 ± 0.95 mg/day with a mean dose of 0.25 ± 0.63 mg/day in the last evaluation of the dose-reduced patients, and methylprednisolone treatment could be stopped in 11 patients. Before omalizumab, the mean number of attacks was 2.5 ± 1.5 and the mean number of hospitalizations was 1.3 ± 0.8. In the first year of the treatment, the mean number of attacks decreased to 0.31 ± 0.86, and the mean number of hospitalizations decreased to 0. In the first year of omalizumab treatment, four patients (patient 1, 6, 9, 11) were complete responders, the remaining nine patients were partial responders.

The first approach, extension of dose intervals from 2 weeks to 4 weeks and decreasing the total omalizumab dose used per month, was used in patients 2, 3, 4, 5, 6, 8, 10, 12, 13. The second approach was used in patients 1, 7, 9, 11. In some patients (2, 5, 6, 13) two approaches were used sequentially if the patients tolerated the dose reduction and/or dose interval extension (**tables II**, **III**). The earliest dose reduction was done at 13th month (patient 5) in dose interval extended group (maximum 47th, median 35 months) in first dose reduction. The patient was receiving her omalizumab injections in her family physician's office because of the pandemic and had one asthma attack

Table II *- Details of management approaches.*

Approaches	Patients n at first attempt	Patients n at second attempt	Current situation in patients (n = 13)
Decrease in total omalizumab dose per month and extended dose intervals from 2 weeks (wk) to 4 weeks	n = 9 (#2, 3, 4, 5, 6, 8, 10, 12, 13)	-	n = 5 (#3: still in remission after omalizumab cessation for 18 months (last dose 300 mg/4 wk) #4: remission in 300 mg/4 wk #8: remission in 300 mg/4 wk #10, 12: in remission with 450 mg/4 wk omalizumab)
Decrease in total omalizumab dose per month, same dose interval	n = 4 (#1, 7, 9, 11)	n = 4 (#2, 5, 6, 13)	n = 8 (#1: remission in 450 mg/4 wk #2, 5, 6, 13: Remission in 300 mg/4 wk #7: was still in remission after omalizumab cessation for 10 months (last omalizumab dose was 300 mg/2 wk), then lost to follow-up from our clinic since 2014, but in her recent medical records she was not restarted omalizumab, she does not use oral steroid #9: remission in 150 mg/4 wk #11: remission in 300 mg/2 wk)

Figure 1 *- Flowchart of the study.*



requiring OCS, but she was devoid of OCS dose at 13th month. A second dose reduction was made in four patients (2, 5, 6, 13) at the minimum sixth month (patient 5) of the treatment (maximum 42nd, median 23.5 months).

In essence, the total omalizumab dose given per month was reduced in all 13 patients in both interventions. The total omalizumab dose given per month was reduced by a median of 40% (min 20, max 60%) in first intervention. After second intervention, the total dose reduction was a median 50% (min 20, max 67%).

In four patients (patients 4, 7, 9, 10), omalizumab was stopped before the fifth year. For patient 4, omalizumab was stopped at the third year, and two months after treatment cessation, OCS had to be restarted, so omalizumab was also restarted. For patient 7, omalizumab was stopped at the third year, and the patient was stable after treatment cessation, then she was lost to follow up, but from her electronic medical records, we learned that she was stable after omalizumab cessation. For patient 9, omalizumab was stopped at the third year of the treatment. Nineteen months after treatment cessation, the patient had three attacks, so omalizumab was restarted. For patient 10, omalizumab was stopped at the fourth year. Four months after treatment cessation, asthma control deteriorated, and OCS needed to be increased and omalizumab had to be restarted. In two patients, omalizumab treatment was given for longer than five years. For patient 6, omalizumab was stopped at the sixth year of the treatment, three months after treatment cessation asthma control was lost. Patient 8 discontinued omalizumab after the fifth year, four months after discontinuation of omalizumab he had dyspnea and deterioration in pulmonary function tests. In these two patients, omalizumab was again restarted and the patients responded well.

Discussion

In the present study, omalizumab treatment has been shown effective in treating patients with ABPA. Pre-omalizumab, mean OCS dose was 12.2 ± 10.4 mg daily, decreased to 0.69 ± 0.95 mg ($p = 0.001$) in the 1st year of omalizumab and could be stopped in 11 patients. 1 year prior to omalizumab, the mean numbers of attack and hospitalization were 2.5 ± 1.5 and 1.3 ± 0.8, respectively, and attacks and hospitalizations decreased to 0.31 ± 0.86 ($p < 0.001$) and 0 ($p = 0.003$), respectively, in the first year of omalizumab. Given the high cost of the drug and uncertainty in the long-term approach for omalizumab treatment in patients with ABPA, once the disease is under control, we attempted to decrease the dose of omalizumab by either extended intervals between doses or decreasing total doses or using both approaches. In these 13 patients whose omalizumab dose was reduced, there was no need to increase the omalizumab dose again, no need to increase the OCS dose, and despite that asthma remained under control.

Omalizumab was first licensed for severe allergic asthma patients with a total IgE level between 30-700 IU/mL at a maximum dose of 375 mg every two weeks (7). As a result of research on its use for higher IgE values (700-1,500 IU/mL) (7, 8) the dose table was updated for a maximum dose of 600 mg every 2 weeks

Table III *- Details of individual patients.*

Patient #, age, sex	Total IgE level	Initial number of attacks/ hospitalizations/ OCS (mg) (methylprednisolone)	Initial omalizumab dose	Dose reduction time 1 (months)	Reduced omalizumab dose time 1	Number of attacks/ hospitalizations/ OCS (mg) at first dose reduction	Dose reduction time 2 (months)	Reduced omalizumab dose time 2	Number of attacks/ hospitalizations/ OCS (mg) at second dose reduction or last evaluation
#1 61 y, M	567	2/0/8 mg	600 mg/4wk	37	450 mg/4wk	0/0/0 mg	Not done	-	0/0/0 mg
#2 61 y, F	400	2/2/6 mg	375 mg/2wk	35	450 mg/4wk	0/0/0 mg	35	300 mg/ 4wk	0/0/0 mg. Last evaluation 0/0/0 mg
#3 68 y, M	1512	4/1/20 mg	375 mg/2wk	45	300 mg/4wk	0/0/0 mg	Not done		0/0/0 mg
#4 43 y, F	356	1/1/40 mg	225 mg/2wk	42	300 mg/4wk	0/0/0 mg	Not done		0/0/0 mg
#5 53 y, F	1042	2/2/20 mg	450 mg/2wk	13	450 mg/4wk	1/0/0 mg	6	300 mg/ 4wk	0/0/0 mg
#6 33 y, M	588	2/2/16 mg	375 mg/2wk	22	300 mg/4wk	0/0/0 mg	42	150 mg/ 4wk	0/0/0 mg
#7 43 y, F	2030	1/1/4 mg	375 mg/2wk	27	300 mg/2wk	0/0/0 mg	Not done	Stopped	0/0/0 mg Then lost to follow up
#8 59 y, M	909	2/2/5 mg	375 mg/2wk	33	300 mg/4wk	0/0/0 mg	Not done		0/0/0 mg Then lost to follow-up
#9 57 y, F	482	4/2/10 mg	300 mg/4wk	24	150 mg/4wk	0/0/0 mg	Not done		0/0/0 mg
#10 69 y, F	491	4/2/5 mg	300 mg/2wk	37	450 mg/4wk	0/0/2 mg	Not done		0/0/2 mg
#11 31 y, M	1110	1/1/16 mg	375 mg/2wk	47	300 mg/2wk	0/0/2 mg	Not done		0/0/0 mg
#12 69 y, F	489	6/3/4 mg	375 mg/2wk	35	450 mg/4wk	1/1/0 mg	Not done		1/0/0 mg
#13 47 y, F	709	2/0/4 mg	450 mg/2wk	32	450 mg/4wk	0/0/0 mg	12	300 mg/ 4wk	1/0/0 mg Last evaluation 0/0/0 mg

(9, 10). Omalizumab for the treatment of ABPA has been evaluated in clinical studies (4, 11-14), and it is found to be beneficial in reducing exacerbations (4, 13), systemic steroid need, asthma symptoms, and respiratory parameters (4, 14). Omalizumab treatment is given at high doses in patients with ABPA due to high total IgE levels (10, 15, 16). In our first study, based on data in the literature, in 14 patients with ABPA, the dose of omalizumab was given at the highest recommended dose (375 mg every 2 weeks) and not based on the patient's weight and total IgE level (6). No dosing adjustments were made during the treatment period for this group. However, with the update of the recommended dosage table in omalizumab treatment, we changed treatment doses in new patients with ABPA accordingly. Our patients were given omalizumab treatment initially median total monthly dose of 750 mg (min 300, max 900), their mean total IgE level was 821.9 ± 494.8 IU/mL (min 356, max 2,030).

The resources needed for adding biological treatment to ABPA standard therapy are mainly driven by the cost of the drug. The other issue, which remains unresolved, is the duration of biological treatment in these patients as it is in asthma patients (2, 3, 17). In four patients (patients 4, 7, 9, 10), omalizumab was stopped before the fifth year. Three of them had to restart the treatment. In two patients, omalizumab treatment was given for longer than five years due to the loss of asthma control after treatment cessation. In these patients, omalizumab was again restarted and the patients responded well.

A few attempts have been done in patients with severe asthma and chronic urticaria, whether omalizumab can be withdrawn, or its dose be reduced in case of clinical improvement (18, 19). A recent paper evaluated the effects of extended intervals and dose reduction of omalizumab on asthma control in 37 patients with severe asthma in a real-life setting. The time intervals until loss of asthma control was compared and the authors reported that extension of omalizumab dose was a better approach than dose reduction after achieving asthma control (20). Similarly, in other study with 35 severe allergic asthma who are at least one and a half year of omalizumab treatment, omalizumab dose was reduced by half and if patients were clinically stable after 6 months, the dose was halved again. The study found that in more than 50% of asthma patients omalizumab dose can be safely reduced or withdrawn based on a progressive dose reduction protocol (18). However, there are no data in the literature regarding whether the reduction of the omalizumab dose or injection frequency leads to loss of control in patients with ABPA who receive high dose omalizumab (10) therefore we could not discuss our data comparing these studies but based on our results and results reported in severe allergic asthma patients the dose reduction seems to be possible.

Frequent (in every two weeks) omalizumab injections may affect personal and business life; it may also be associated with indirect expenses, such as travel expenses or loss of labor to go to the clinic for injections. Where it is possible to reduce the frequency of omalizumab injection every 4 weeks instead of every 2 weeks, patient burden and costs can be reduced (21). Lowe *et al.* (21) evaluated previous data of different omalizumab studies in asthma with a mathematical model because of the need for the evaluation of safety and efficacy of some doses of omalizumab given every 4 weeks at double doses instead of every 2 weeks according to the dosing table. They calculated that it would be hypothetically appropriate to reduce the recommended omalizumab dose frequency for some body weight and baseline IgE values. They found that free IgE suppression slightly increased in the initial phase, and slightly reduced at the trough of the dosing cycle, but the average suppression remained similar for both regimens. The safety profile of omalizumab was similar for patients receiving higher or lower doses. Therefore, they reported doubling the dose of omalizumab every 4 weeks instead of every 2 weeks, in a subset of patients (receiving 225-300 mg of omalizumab every two weeks), could efficiently suppress free IgE without compromising safety or efficacy (21). In literature, in a 63-year-old patient with house dust mite allergy and severe asthma, the omalizumab dose was reduced by half (375 mg/month instead of 750 mg/month) following long-term (3 years) use of omalizumab (22). In that report, serum free IgE level measurements were suggested to appropriately identify patients in whom the dose could be reduced, and to carefully monitor the clinical course (22). It was suggested that after months of omalizumab treatment, the IgE production rate might decrease, and the treatment could be discontinued by monitoring the total IgE level (23).

In our study, 13 patients with ABPA were evaluated, with a median duration of omalizumab use of 63 (min 38, max 99) months. To our best knowledge, this is the longest period among patients using omalizumab treatment with the diagnosis of ABPA. In the literature, patients with non-cystic fibrosis (CF) ABPA have been followed up until three years (24). Upon discontinuation of the omalizumab treatment, the disease was stable in some cases but worsened in others. In some patients with non-CF ABPA who are systemic steroid-dependent, discontinuation of omalizumab treatment could cause deterioration in asthma control (10). The results of our patients after discontinuation of treatment are concordant with these data. In six patients, after 3-5 years of omalizumab treatment, omalizumab was stopped. However, we had to restart omalizumab due to loss of asthma control within 2-19 months. Fortunately, these patients responded well to omalizumab, and asthma control was again achieved.

There are several limitations in our study. First, this is a small study with a limited number of patients. The second is the presence of two approaches instead of a standardized single approach to reach omalizumab dose reduction. Nevertheless, as a

real-life experience, our report proposes an innovative approach to omalizumab therapy in patients with ABPA. We believe that these data may have important clinical implications for the sustainability of this therapy in daily practice.

In conclusion, our real-life experience may suggest attempting to reduce monthly omalizumab dose in patients with ABPA after the disease has been controlled. However, there is clearly a need for controlled clinical trials with large number of patients to define in which ABPA patient is candidate for dose reduction and which approach can be more efficient to reduce omalizumab doses. If these reports support our experience, the possibility of lower cost and decreased hospital visits will encourage practicing physicians using omalizumab.

Fundings

None.

Contributions

ETK: data curation, writing - original draft, writing - review & editing. ÖA: conceptualization, study design, data curation, writing - original draft, writing - review & editing. DM, BAS, YSD: study design, writing - original draft, writing - review & editing. SB: conceptualization, study design, writing - original draft, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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COVID-19 infection and vaccination in patients with hereditary angioedema: a multicentric study

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Key words

COVID-19; hereditary angioedema; prophylaxis SARS-CoV-2; vaccination.

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Impact statement

Patients with HAE can safely receive COVID-19 vaccination. The severity of COVID-19 infection does not appear to be increased in HAE patients.

Summary

Background. *Due to similarities between the pathophysiological mechanisms of hereditary angioedema and COVID-19, it has been hypothesized that SARS-CoV-2 infection may trigger HAE attacks or, alternatively, that HAE patients may experience different of COVID-19 disease severity. Furthermore, the potential for COVID-19 vaccination to trigger angioedema attacks in patients with HAE is still not completely defined.* ***Methods.*** *Retrospective observational, descriptive, non-interventional, multicenter study conducted in four Allergy Units and Departments in Central Portugal between March 2020 and July 2022. HAE patient data were obtained from electronic medical records.* ***Results.*** *The study included 34 patients (67.6% female): 26 with HAE type 1, 5 with HAE type 2, and 3 with HAE with normal C1 inhibitor. Most patients with HAE type 1 and 2 were receiving long-term prophylaxis. Among the 32 patients who received COVID-19 vaccination, 86 doses, were administered with one angioedema attack (1.2%) associated with vaccination. A small increase in the average number of attacks was observed in the year following COVID vaccination (7.1 versus 6.2 in the previous year, p = 0.029), however, this difference is unlikely to be clinically significant, as the context of the COVID-19 pandemic likely introduced numerous confounders. During the study period, 16 HAE patients had COVID-19, all presenting with mild disease. Four out of 16 patients (25%) reported angioedema attacks during COVID-19, and 43.8% during the convalescence period (3 months after infection).* ***Conclusions.*** *Patients with HAE can safely receive COVID-19 vaccination. The severity of COVID-19 infection does not appear to be increased in HAE patients.*

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Introduction

Hereditary angioedema (HAE) is a rare genetic disease characterized by recurrent, disabling and potentially fatal episodes of mucocutaneous swelling as a consequence of a transient increase in vascular permeability mediated by bradykinin (1, 2). Angioedema episodes are largely unpredictable and generally affect well-defined cutaneous-mucosal areas, predominantly the face, lips, tongue, larynx, abdomen, extremities, and genital areas, but may involve any part of the body. Angioedema attacks are usually self-limited, lasting 1 to 5 days with a very variable duration of inter-critical periods. However, potentially life-threatening attacks may occur. HAE is associated with professional incapacity, decreased quality of life, and with significant physical and emotional burdens for patients and families (1). HAE accounts for only about 2% of all cases of recurrent angioedema. In most cases there are other affected relatives with HAE, but the absence of a family history does not exclude the diagnosis, as about 25 to 30% of the cases are caused by *de novo* mutations (1, 2). Therefore, all patients with recurrent angioedema or unexplained abdominal pain in the absence of urticaria must be assessed for C1 inhibitor deficiency, as mutations of this protease inhibitor account for more than 95% of the HAE cases.

The differential diagnosis of HAE includes other types of angioedema, such as, acquired angioedema, drug-induced angioedema, allergic reactions, chronic urticaria, idiopathic histaminergic angioedema, superior vena cava syndrome or myxedema.

An early diagnosis is fundamental to prevent fatal outcomes. The diagnosis of HAE is typically made by measuring serum levels of C4 complement, C1 inhibitor, and functional C1 inhibitor (1, 2). HAE is classified into three types based on the results of serum complement fraction assays: type I or quantitative HAE, type II or qualitative HAE, and HAE with normal complement. Studies report widely varying prevalence rates of type I and II HAE, ranging from 1:50,000 to 1:100,000 (3). The prevalence of HAE with normal complement is unknown, but it is presumed to be much lower (3). In Portugal, there are an estimated 200 to 300 people with HAE (1). Among a cohort of 138 Portuguese patients with HAE, 94 single mutations were observed, corresponding to 22 different pathogenic mutations, of which 64% were not yet described in the HAE database (4).

Angioedema flares may occur spontaneously, but they are often triggered by various factors, including emotional stress, medical or surgical procedures, infections, pain, physical trauma or certain drugs (such as oral contraceptives, hormone replacement therapy and angiotensin-converting enzyme inhibitors) (2). In some cases, flares may be preceded by prodromal signs or symptoms, such as extreme fatigue, mood swings, pain, and *erythema marginatum*, among others.

The management of HAE involves regular reassessments and individualization of therapy based on the frequency, severity and location of attacks, as well as the patient's clinical profile (*e.g.*, age, sex, comorbidities and preferences). Treatment should include: 1) general measures to minimize trigger, 2) on-demand treatment, 3) short-term prophylactic therapy, and 4) long-term prophylactic therapy, when needed to control symptoms, reduce risk of future attacks and minimize adverse drug effects (1, 2).

According to existing consensus, HAE patients must receive short-term prophylaxis before dental, surgical, endoscopic and other minimally invasive procedures involving the head and/or neck (1, 2). This has been shown to effectively prevent HAE exacerbations and related complications. However, current guidelines do not provide guidance on some other potential situations for prophylaxis, *e.g.*, prior to administration of COVID-19 vaccines (5).

Coronavirus disease (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), which was declared a global pandemic on 11 March 2020 (6). While most infected individuals exhibit mild to moderate symptoms, a subset of patients develop severe symptoms that require medical assistance. The discovery that SARS-CoV-2 interacts with the angiotensin-converting enzyme 2 receptor in the context of the COVID-19 has led to the hypothesis that this infection may provoke angioedema attacks or result in more severe symptoms in HAE patients (6-8).

There are only some studies examining the frequency of angioedema attacks in HAE patients during COVID-19. Most published literature contradicts the hypothesis that HAE patients experience more severe clinical symptoms of COVID-19 or have worse outcomes than the general population without HAE (7, 9). Vaccination has emerged as a crucial strategy in the fight against COVID-19, with several vaccines approved by the European Medicines Agency (EMA) and administered to the general population in Portugal and globally. INFARMED, the Portuguese regulatory agency, has approved five vaccines to date for COVID-19: two modified nucleoside mRNA vaccines (Comirnaty/Pfizer and Spikevax/Moderna); one recombinant Chimpanzee adenovirus vector vaccine (Vaxzevria/AstraZeneca); one with recombinant adenovirus vector type 26 (Johnson & Johnson/Janssen); and, more recently, a vaccine with a laboratory-created version of the SARS-CoV-2 spike protein and adjuvant (Nuvaxovid/Novavax) (10).

The necessity for short-term prophylaxis before administering COVID-19 vaccines to patients with hereditary angioedema (HAE) has been debated. Some of these vaccines have been associated with a higher frequency of adverse effects than other vaccines (5). Additionally, mRNA vaccines might have an associated risk of HAE attacks as RNA is known to serve as a potent stimulator of the contact activation system (5).

The objective of this study was twofold: 1) to investigate the clinical features associated with COVID-19 in HAE patients under the care of Allergy and Clinical Immunology Depart-

ments and Units in the Central region of Portugal, and 2) describe the adverse effects of COVID-19 vaccination in these patients, such as the potential onset of angioedema attacks.

Materials and methods

Study type and study population

This was a multicenter, observational, retrospective, descriptive, and non-intervention study conducted in four Allergy and Clinical Immunology Departments and Units of four Hospital Centers in the Central region of Portugal.

Data were retrieved from electronic medical records of patients diagnosed with hereditary angioedema, based on the latest guidelines of the World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI) (2). The patients were under follow-up in the Immunoallergology (Allergy and Clinical Immunology) consultations between March 2020 and July 2022. Patients with differential diagnoses of hereditary angioedema were excluded.

This study protocol was reviewed and approved by the competent Ethical Committees and was conducted in accordance with the ethical standards established in the Declaration of Helsinki of 1946.

Study variables

The study analyzed the following variables based on the patients' clinical records: gender, current age, angioedema classification, as per international and national consensus (1, 2), age of symptom onset, age at diagnosis, location of angioedema attacks and their frequency (number of episodes per year based on medical records of each appointment and episodes of Emergency Department), laboratory data (C4 and C1 inhibitor dosing, C1 inhibitor function), comorbidities, long-term and short-term pre-COVID-19 vaccination prophylactic treatment, doses and which vaccine was administered, attacks in the context of vaccination (considered if occurred in 2 days after vaccination), their severity (mild, moderate or severe according interference with daily activities) and therapy, hypersensitivity reaction to vaccine, adverse effects to vaccine, frequency of attacks in the year before the 1st dose of vaccine and in the year after (number of episodes based in medical records of each appointment and episodes of emergency department), occurrence of SARS-CoV-2 infection (based in a positive viral test either a reverse-transcription polymerase chain reaction (RT-PCR) assay or an antigen test), its severity and symptomatology (based in classification in Coronavirus Disease 2019 (COVID-19) Treatment Guidelines (11)), attacks during and after infection, and need for treatment.

The severity of disease was classified using the criteria published by Agostoni *et al.* and translated by Cadinha *et al*. (12), based on a score defined by the duration of angioedema attacks and their severity (mild − discomfort, no interference with daily activities; moderate − sufficient discomfort to limit daily activities; severe − inability to work or carry out daily activities), need for conservative emergency or replacement treatment, need for invasive emergency treatment such as intubation or tracheostomy, long-term prophylaxis for more than 6 months or for a period of 3 to 6 months. The total score allows classified patients from class 5 (asymptomatic) to class 1 (severe).

Statistical analysis

The statistical analysis was carried out using IBM SPSS Statistics®, version 27.0. All data were analyzed in an anonymized form. The frequencies of nominal variables were calculated, while medians and ranges were determined for continuous variables. Normality of continuous variables' distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables were compared using the non-parametric Wilcoxon test. Statistical significance was defined as $p < 0.05$.

Results

Thirty-four patients were enrolled in the study (67.6% female). The median current age of the patients was 40 years (IQR 26-51 years), and the median age at diagnosis was 26 years (IQR 15-32). On average, there was a 10-year delay between the onset of symptoms and the time of diagnosis. **Table I** provides a summary of the demographic, clinical characteristics and therapeutic approach of HAE patients.

The study population comprised 26 patients with HAE type I, 5 patients with HAE type II, and 3 patients with HAE with normal complement, one of whom with a pathogenic mutation of *SERPING1* gene.

Among patients with HAE type I and II, the majority (n = 19, 61.3%) were receiving long-term prophylaxis with attenuated androgens (danazol), while 5 were treated tranexamic acid. Seven patients were not receiving any long-term prophylactic therapy.

Regarding the severity of the disease, three patients presented with class 5 criteria (asymptomatic), four with class 4 (minimal), one with class 3 (mild), twenty-three with class 2 (moderate) and three with class 1 (severe). Twelve patients reported at least one episode of laryngeal edema during their lifetime. Nineteen patients had comorbidities, including twelve with rhinitis/rhinosinusitis, five with autoimmune disease, three with cardiovascular disease, two with asthma, one with obesity, and one with psychiatric disease.

As rare cardiovascular events have been reported as an adverse effect of androgen therapy, it is noteworthy that in our sample, several patients had significant cardiovascular past history: one patient had cerebrovascular thrombosis and myocardial infarction, another patient had myocardial infarction, and a third

Table I *- Demographic and clinical characteristics and therapeutic approach of HAE patients.*

Characteristics	
Total, n (%)	34 (100)
Female, n (%)	23 (67.6)
Age (years), median (IQR)	40 (26-51)
Comorbidities, n (%)	19 (55.9)
Classification	-
Type I, n (%)	26 (76.5)
Type II, n (%)	5 (14.7)
Type III, n (%)	3 (8.8)
Age at onset of symptoms (years), median (IQR)	14 (9-19)
Age at diagnosis (years), median (IQR)	26 (15-32)
Time between symptom onset and diagnosis (years), median (IQR)	5 (1-17)
Preferred locations of angioedema attacks	-
Face, n (%)	11 (32.4)
Extremities, n (%)	23 (67.6)
Abdomen, n (%)	15 (44.1)
At least one episode of laryngeal edema, n (%)	12 (35.3)
Severity of disease	-
Class 1 (severe), n (%)	3 (8.8)
Class 2 (moderate), n (%)	23 (67.6)
Class 3 (mild), n (%)	1 (2.9)
Class 4 (minimal), n (%)	4 (11.8)
Class 5 (asymptomatic), n (%)	3 (8.8)
Long-term prophylactic therapy, n (%)	27 (79.4)
Danazol, n (%)	20 (58.8)
Tranexamic Acid, n (%)	5 (14.7)
C1 inhibitor concentrate, n (%)	2 (5.9)

n: number of cases; IQR: Interquartil range.

required pacemaker implantation due to arrhythmia. However, it is difficult to establish a causal relationship between androgen therapy and these events.

A total of 27 patients received at least one dose of mRNA vaccine, with 23 of them receiving Comirnaty/Pfizer vaccine and 4 patients receiving Spikevax/Moderna vaccine. Six patients received at least one dose of a vectored vaccine, with 3 patients receiving Vaxzevria/AstraZeneca vaccine and 3 patients receiving Johnson & Johnson/Janssen vaccine. Two patients refused COVID-19 vaccination. Data regarding the type of vaccine and number of doses administered are summarized in **table II**. None of the patients reported a prior SARS-CoV-2 infection before completing the primary vaccination.

Out the 32 patients who received COVID-19 vaccination, a total of 86 vaccine doses were administered. None of the patients reported suspected hypersensitivity reactions to the vaccine. However, twenty-one patients reported other mild adverse effects, such as pain at the administration site, myalgia, fatigue and fever.

None of the patients received pre-vaccination prophylaxis with C1 inhibitor concentrate. However, four patients were given short-term pre-vaccination prophylaxis with increased doses of danazol on the five days prior to the vaccination procedure and continued for three days after the procedure.

Among the study population, one case of angioedema attack was reported in association with COVID-19 vaccination (1 in 86 vaccine administrations, 1.2%). The affected patient was a 40-year-old woman with HAE with normal complement serum levels and C1 inhibitor function but with a pathogenic *SERPING1* mutation, and she was on long-term prophylaxis with twice weekly C1 inhibitor concentrate. The attack started 2 hours after the first dose of an mRNA vac-

Table II *- COVID-19 vaccination in HAE patients*.*

Characteristics	Total	mRNA vaccine	Vectored vaccine
Total doses, n (%)	86	76 (88.4)	10 (11.6)
1st dose	32	26	6
2nd dose	29	27	2
3rd dose	25	23	2
Previous SARS-CoV-2 infection	0	0	0
Vaccination adverse effects	21	17	4
Hypersensitivity reaction	0	0	0
Angioedema attacks	1	1	0
Long-term prophylaxis	27	22	5
Short-term prophylaxis	4	2	2

*Two patients decided not to be vaccinated against COVID-19.

cine (Comirnaty/Pfizer), with swelling localized to the abdominal region and rated as mild in severity. The patient did not require additional therapy or specialized medical care. Subsequently, the patient received the 2nd and 3rd doses of the same vaccine, without short-term prophylaxis, and there were no associated angioedema attacks.

The frequency of angioedema attacks per year showed significant variability among patients. Most patients (22 out of 32, two patients were excluded from this analysis due to missing data) experienced 0-3 attacks per year, whereas four patients experienced more than 20 attacks per year. We compared the number of angioedema attacks in the year before and after the first dose of vaccine. Eighteen patients experienced an identical number of episodes in both the year before and after vaccination, three patients had fewer episodes in the year following vaccination (two had one episode less, one had two), while 11 had more episodes (six had one episode more, one had two, one had three, one had six, one had seven, and one had eight). The average number of attacks in the year preceding vaccination was 6.2 (standard deviation 2.14, 95% confidence interval (CI) 1.82-10.55) with a median of 1.5. During the year after vaccination, the mean number of attacks was 7.1 (standard deviation 2.13, 95%CI 2.72-11.40) with an identical median of 1.5. Although a statistically significant difference was detected (p = 0.0278, Wilcoxon signed-rank test), the magnitude of the observed difference was unlikely to be clinically significant, as further discussed below.

Table III *- Clinical characteristics and management of HAE patients with SARS-CoV-2 infection.*

Id	Age/Sex	Comorbidities	Type AEH	Severity of AEH	Long term prophylaxis	COVID-19 infection		Attacks*	
						Main symptoms	Severity	During	After
1	38M	No	I	Moderate	Danazol	Fever, myalgia, rhinorrhea	Mild	No	Yes
2	61F	Asthma	III	Severe	C1 inhibitor	Dyspnea, myalgia	Mild	Yes	No
3	40F	No	II	Minimal	No	Odynophagia, fatigue	Mild	No	Yes
4	32M	No	III	Moderate	Danazol	Fever, rhinorrhea	Mild	Yes	Yes
5	48F	Rhinitis	I	Severe	Danazol	Myalgia	Mild	No	No
6	40F	Rhinitis	I	Minimal	No	Headache	Mild	No	No
7	48M	MI	I	Moderate	Danazol	Myalgia	Mild	No	No
8	23F	Rhinitis	I	Severe	Tranexamic A.	Headache, rhinorrhea	Mild	No	Yes
9	35F	Rhinitis	I	Moderate	Danazol	Rhinorrhea	Mild	No	Yes
10	24F	Rhinitis	I	Moderate	Danazol	Headache, myalgia, fatigue	Mild	No	Yes
11	32M	Rhinitis and asthma	I	Moderate	Danazol	Headache, myalgia	Mild	No	No
12	52F	No	I	Moderate	Danazol	Fever, cough, rhinorrhea	Mild	No	No
13	40F	AI	III	Moderate	C1 inhibitor	Fever, headache, myalgia	Mild	Yes	Yes
14	52F	No	I	Moderate	Danazol	Fever, myalgia	Mild	No	No
15	24F	No	I	Asymptomatic	No	Fever, headache, Odynophagia	Mild	No	No
16	45F	No	I	Moderate	Danazol	Cough, rhinorrhea, myalgia	Mild	Yes	No

F: female; M: male; MI: acute myocardial infarction; AI: autoimmune disease; *no patient received prophylactic therapy to prevent angioedema attacks during the infection.

We did not find a significant correlation between the severity classification of HAE disease and an increase in reported attacks during the year after the first dose of the vaccine ($r = -0.245$, $p = 0.177$).

During the study period, 16 HAE patients (75% female; median age of 40 years) were diagnosed with COVID-19. All of the patients had symptomatic mild disease (**table III**). The most frequent symptoms were myalgias (9 of 16 (56%)), fever, headache, odynophagia, nasal congestion/rhinorrhea (each 6 of 16 (38%)), and fatigue (2 of 16 (13%)). None of the patients required medical intervention for COVID-19. However, in our sample, 10 out of 16 (62.5%) patients who became infected were receiving prophylactic danazol therapy, and none experienced more severe infection or complications.

Four out of 16 patients (25%) reported angioedema attacks during the COVID-19, with 3 experiencing mild and 1 moderate attacks, none of them requiring hospitalization. Treatment was necessary in two patients (one patient increased the dose of attenuated androgens and another patient received C1 inhibitor concentrate replacement), while 2 did not require any specific treatment. The most common sites of angioedema among the patients who had flares were the face and extremities.

Seven out of 16 patients (43.8%) reported flares during the COVID-19 convalescence period (which was assessed 3 months after infection), and three of them required adjustments to their prophylactic therapy and on demand treatment. Most patients (5 out of 7) experienced 1-2 attacks, while two patients experienced 4-6 attacks. We compared the number of angioedema attacks in the 3 months before and after infection. Five patients experienced an identical number of episodes in both periods, seven patients had fewer episodes in the convalescence period, while four had more episodes. The average number of attacks was 1.6 *versus* 0.5 in the 3 months before and after infection, respectively.

Discussion

This is the first national study in Portugal to assess the impact of the COVID-19 pandemic on acute attacks in HAE patients, including the effects of SARS-CoV-2 infection and of COVID-19 vaccination.

In our study population (most of which was on long-term prophylactic therapy), both the mRNA and adenoviral vector-based COVID-19 vaccines were found to be safe and well tolerated in HAE patients, with only one patient (1.2% of administrations) reporting a mild angioedema flare, that did not require any treatment.

In our study population, we observed a very low number of attacks per year (69% reported 0 to 3 attacks per year, or less than one attack every 4 months) and only four patients experienced more than 20 attacks per year during the study period.

Most of the patients in our study reported a comparable number of angioedema attacks both before and after COVID-19 vaccination. Specifically, 56% of patients experienced the exact same number of episodes in both years in our study, while the remaining patients reported only minor variations in the number of episodes. Most published studies only analyze the number of angioedema attacks reported after administration of COVID-19 vaccines (13). One study compared the number of angioedema attacks a month before and after the first, second and third doses of COVID-19 vaccines, and concluded that COVID-19 vaccination did not increase the frequency of HAE attacks (14).

Although we did observe a small increase in the average number of angioedema attacks during the years before and after vaccination, this difference is unlikely to be clinically significant, as the context of the COVID-19 pandemic likely introduced numerous uncontrolled variables in our retrospective study. For example, the implementation of lockdowns and reduced mobility and professional exposures, and the well-known reduced number of infections, may have led to a lower incidence of angioedema attacks in the year before vaccination. Additionally, reduced access to medical care before mass vaccination may have influenced the reporting of episodes. It is also possible that increased awareness of health issues after vaccination may have contributed to a higher reporting of episodes. COVID-19 pandemic significantly limited the availability of HAE medical care worldwide (8). This was primarily due to the strain on healthcare resources caused by the pandemic, as well as the implementation of social distancing measures, which have prevented on-site clinical visits and treatments for HAE patients.

Regarding COVID-19 infection, all HAE patients in our study who contracted COVID-19 were symptomatic but experienced only mild symptoms. Importantly, our study sample consisted of predominantly female patients with a median age of 40 years, who had no additional risk factors for severe COVID-19 disease (15). Our findings support previous research indicating that HAE patients typically experience mild COVID-19 symptoms and infrequent angioedema attacks during infection, even in the absence of short-term prophylactic therapy (7-9, 16).

In our cohort, 75% (12/16) of the patients did not report angioedema flares during SARS-CoV-2 infection. This rate is not statistically different from those reported in previous studies by Can Bostan *et al*. (50%, 5/10) (7), Belbezier *et al*. (69%, 9/13) (17), and Grumach *et al*. (62%, 8/13) (9). It is noteworthy that 13 out of 16 patients were on long-term prophylactic treatment, which may have contributed to the low incidence of angioedema flares during the infection. Of the three patients without long-term prophylaxis who developed COVID-19, none experienced angioedema attacks during the infection, and only one patient reported an attack during the convalescence period.

During the COVID-19 pandemic, there were concerns about the use of danazol, an attenuated androgen, due to its potential to inhibit the antiviral immune response to SARS-CoV-2 or alter the expression of the TMPRSS2 receptor, which is used by the virus. Some experts recommended caution or discontinuation of danazol in HAE patients who become infected with SARS-CoV-2 (18), however, none of 62.5% patients on prophylactic danazol that were infected experienced more severe infection or complications.

Several studies suggest that HAE patients in the convalescent phase of COVID-19 are more susceptible to experiencing acute angioedema attacks (7, 17). Within our study population, 43.8% of patients reported angioedema attacks during the convalescence period of their COVID-19 disease. This rate is similar to that reported in a cohort of 13 patients, where four patients (30.8%) experienced HAE attacks during their COVID-19 convalescence, and the difference is not statistically significant (15). Most patients experienced an equal or smaller number of episodes during the convalescence period compared to the same time period before infection, indicating that convalescence does not appear to significantly increase the risk of attacks.

In conclusions, this study provides further evidence that HAE patients do not have an increased risk of acute attacks during COVID-19 vaccination and can safely receive the vaccine against COVID-19 without requiring short-term prophylaxis. Our findings also suggest that COVID-19 symptoms are not more severe in HAE patients, which is consistent with other international studies with small samples. We observed a small increase in the number of reported attacks in the year following vaccination that is unlikely to be clinically significant, as the context of the COVID-19 pandemic likely introduced numerous societal/professional/psychologic uncontrolled and possible confounders variables during the pandemic/lockdowns.

This is the first study in Portugal to investigate the differences in the frequency of angioedema attacks in HAE patients related to COVID-19 infection and vaccination. Further studies will be required to assess the long-term impact of COVID-19 vaccination and SARS-CoV-2 infection on the frequency and severity of angioedema attacks in HAE patients.

Fundings

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Contributions

ICF: investigation, data curation, methodology, writing - original draft, conceptualization, visualization. BT: conceptualization, methodology, resources, writing - review & editing. NS, EA, CL: resources. FSR: resources, methodology, writing - review & editing. AT-B: supervision. EF: conceptualization, resources, writing - review & editing, supervision.

Conflict of interests

The authors declare that they have no conflict of interests.

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CASE REPORT | Eur Ann Allergy Clin Immunol | Vol 56, N.1, 42-44, 2024

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D-dimer levels decline after immunosuppressive treatment rather than anticoagulant treatment in severe autoimmune chronic spontaneous urticaria

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Key words

Chronic urticaria; coagulation; cyclosporine; disease activity; D-dimer.

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Summary

Chronic spontaneous urticaria (CSU) is a common dermatological condition presenting with wheals and/or angioedema for more than 6 weeks. The role of autoimmunity and inflammation in the pathogenesis of CSU have been studied, but the precise mechanism remains unknown. Association with coagulation cascade has been suggested based on the observations of increased coagulation indicators such as serum D-dimer levels. We report an omalizumab refractory case of severe CSU with high D-dimer levels that declined only after disease remission with cyclosporine treatment but not with anticoagulation. Activation of coagulation cascade occurs secondary to the pro-inflammatory state in CSU patients and the correlation between D-dimer levels and disease activity may indicate the need for more studies to better understand the relationship of D-dimer levels and omalizumab resistance. Clinicians should consider this relationship in CSU patients with significant D-dimer levels before considering treatment with anticoagulants.

Impact statement

D-dimer levels decline after immunosuppressive treatment with cyclosporine rather than anticoagulant treatment in patients with severe autoimmune CSU.

Introduction

Chronic spontaneous urticaria (CSU) is a condition characterized by the development of wheals and/or angioedema for longer than 6 weeks. Lesions can occur spontaneously or be induced by various stimuli and usually disappear in minutes to hours (1). It is a highly prevalent skin disorder with female predominance (2). It presents with a systemic inflammatory state and results from activation of mast cells with release of pro- inflammatory cytokines such as histamine and platelet-activating factors, leading to wheal formation (3). Although studies on the pathogenesis of CU have increased in recent years, the exact mechanism is still poorly understood. Until now, several studies have shown the effect of multiple mech-

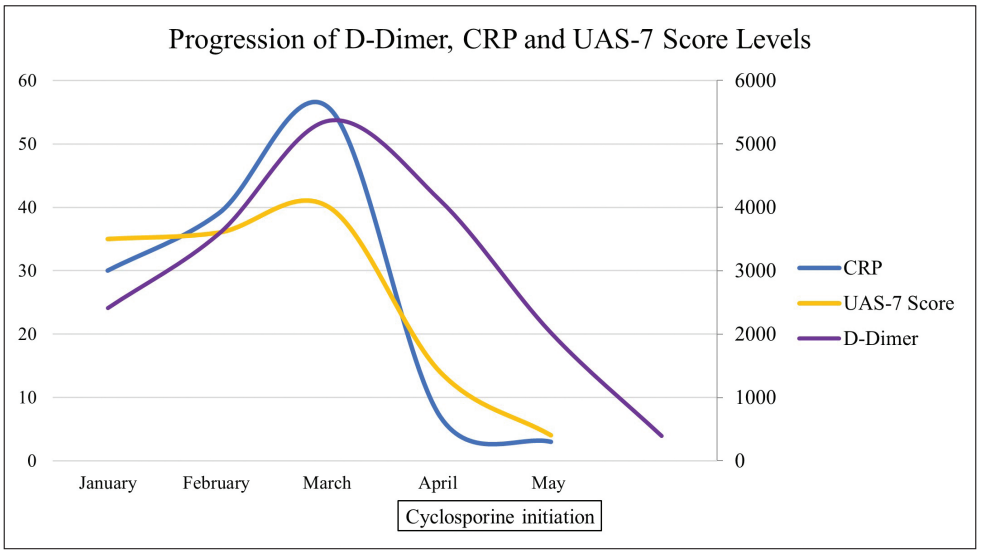
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anisms including autoimmunity, with some patients carrying IgE or IgG autoantibodies against a multitude of self-antigens, including those on mast cells and basophils (2), and some with recently discovered auto-reactive $CD4^+$ T cells (4). The role of coagulation cascade has been recently proposed as part of the pathogenesis and the activation of the extrinsic pathway of clotting cascade has been found to be associated with disease severity in CSU (5). Additionally, there have been reports of increased levels of D-dimer in patients with CSU paralleling disease activity (6) and even anticoagulant treatment has been proposed as a potential treatment option in CSU (5). However there have been discussions whether this coagulation pathway activation is the cause or a result of the inflammation in CSU. Here, we report a case of CSU with extremely high D-dimer levels that declined with remission of disease with cyclosporine treatment but did not change despite anticoagulant treatment.

Case presentation

A-45-year-old female patient has been on regular follow up for CSU and currently visited our institution for an ongoing urticaria attack for 5 months. She first noticed symptoms eight years ago, and attacks at that time had been under control with antihistamines and rare on-demand steroid treatments. Angioedema attacks occurred only in the first 6 weeks of symptom initiation and involved upper lips, cheeks, forehead, and periorbital area. No trigger has been reported for the initiation of CSU. The patient did not have any other systemic illnesses and was not on other systemic medications. She has been using various antihistamines without success and even though steroids provided temporary relief, they were ineffective in long term management of the lesions. Her current attack has continued for 5 months and there was no response to treatment with omalizumab 450 milligram/month. Biopsy was taken from the lesions, confirming the diagnosis of CSU with a mixed inflammatory cell infiltrate and negative direct immunofluorescence staining. Autologous serum skin test (ASST) was intensely positive. Blood investigations of the patient showed an eosinophil percentage of 0.2% (reference range 0.5-6.5%), basophil percentage of 0.1% (reference range 0.0-2.0) and an elevated CRP of 39 mg/L. Total IgE was 29 IU/mL (reference range < 100 IU/mL) and anti-thyroglobulin (anti-Tg) and anti-thyroid peroxidase (anti-TPO) IgG were negative at 13 IU/mL (reference range < 115 IU/mL) and 14 IU/mL (reference range < 35 IU/mL), respectively. Significantly elevated D-dimer levels of 5,370 µg/L (reference range < 500 µg/L) were detected when she was on omalizumab treatment. D-dimer levels have been increasing since the attack has started and has reached a peak level of 5,370 µg/L (reference range < 500 µg/L) (**figure 1**). She was not on steroid treatment at that time. An internalist started subcutaneous enoxaparin injections 8,000 IU (80 mg/0.8 mL) to the patient twice daily. However, D-dimer levels were still elevated even after using enoxaparin daily for two months and the patient had an urticaria activity score 7 (UAS7) of 36 after long term treatment with antihistamines, omalizumab and enoxaparin. After trying 450 mg/monthly omalizumab for 3 months with no meaningful response, treatment with cyclosporine 5 mg/kg was initiated. The patient responded very well to cyclosporine with apparent improvement visible even at the first week of treatment. With remission of the disease while on cyclosporine treatment after one month (UAS7 score: 4), D-dimer

Figure 1 *- Progression of D-dimer, CRP and UAS-7 score levels.*



levels have decreased substantially to 390 ng/mL as well as CRP level to 3 mg/L (**figure 1**).

Discussion

Our case reflects an example of severe autoimmune urticaria with a positive ASST, eosinopenia, low total IgE and elevated CRP levels which favorably responded to immunosuppressive treatment but not to omalizumab treatment; probably representing the type IIb autoimmune type of CSU (7). We believe this case supports the idea of activation of coagulation cascade in CSU patients most probably developing secondary to the systemic pro-inflammatory state, rather than as a primary pathogenetic mechanism in CSU because: 1) two months of anticoagulant treatment did not yield either a clinical remission or decline in D-dimer levels, 2) D-dimer levels dropped parallel to decrease in CRP levels and decrease in disease activity after immunosuppressive treatment (**figure 1**). Although the enoxaparin dose may have been insufficient in lowering the D-dimer levels, based on the effective response to cyclosporine, we believe that the elevation of D-dimer was a consequence of ongoing inflammation in CSU, rather than a coagulation process. The correlation of D-dimer with disease activity has been previously discussed (5) and elevated D-dimer as well as high CRP and high UAS-7 scores have been associated with antihistamine resistant CSU (9). Although elevated D-dimer levels has been associated with a favorable response to cyclosporine (3) and also a good response to omalizumab (8), in our case high D-dimer was associated with omalizumab resistance which was also reported (10). Since low IgE and high CRP levels has been suggested as a marker of type IIb autoimmune CSU (7), we suspected our patient might have type IIb autoimmune CSU. However, whether high D-dimer levels is a marker for type IIb autoimmune CSU needs to be further clarified in future studies. Elevated D-dimer levels in CSU patients, however, do not indicate an elevated risk of thromboembolic complications. Fujii *et al.* demonstrated that CSU patients with high D-dimer levels had intense deposits of fibrinogen in dermis, along with normal laboratory parameters of other coagulation indicators, suggesting that the activation of coagulation cascade occurs outside of the vessels, not intravascularly, providing an explanation as to why CSU patients do not show an increased rate of thrombosis (11).

As a conclusion, D-dimer may be found substantially elevated in severe autoimmune urticaria, but this does not necessarily prompt anti-coagulant treatment. Treating the patient properly to keep their symptoms under control leads to diminished D-dimer levels and lowers the proinflammatory state. Significantly elevated D-dimer levels and its relationship with type IIb autoimmune CSU and omalizumab resistance might be a subject for further studies which could aid recognizing poor response to omalizumab in advance to avoid patients' further devastation.

Fundings

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Contributions

EK, DB: conceptualization, data curation, methodology, writing – original draft. EK, DB, ES: investigation, resources. EK: project administration. EK, RA: supervision, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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Factors associated with asthma exacerbations in schoolchildren: an experience in clinical practice

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To the Editor,

chronic airway inflammation is the primary pathophysiological feature in patients with asthma (1). The type-2 phenotype is most common in childhood (2). Consistently, children with type-2 phenotype have frequently respiratory infections as type-2 immune response is characterized by a defective defense against pathogens (3). This aspect has a clinically relevant consequence as acute respiratory infections usually precede asthma exacerbations, mainly in children (4).

Asthma exacerbation is an acute or sub-acute episode of airflow obstruction occurring on a background of chronic airway inflammation and bronchial hyperresponsiveness (5). Bronchoconstriction and increased mucus production characterize asthma exacerbation. As a result, asthma symptoms, including wheeze, cough, dyspnea, and respiratory distress, worsen during asthma exacerbation (6). The exacerbation outcomes usually include the need for systemic corticosteroids, urgent unscheduled care, emergency department or urgent care visits, and hospitalizations for asthma (7). Asthma exacerbations, therefore, represent a demanding challenge in daily practice. As a result, a thorough workup should identify factors associated with asthma exacerbations.

Here, we would propose our experience conducted on a sample of schoolchildren with asthma and followed at the level of primary care pediatrics. The research aimed to investigate possible factors associated with asthma exacerbation in a defined narrow time frame, *i.e.*, the fall/winter season.

The inclusion criteria were: age between 6 to 14 years, and asthma diagnosis, according to GINA criteria (1). The exclusion criteria were: previous or current allergen immunotherapy, congenital or acquired immunodeficiency, cystic fibrosis, and chronic pulmonary diseases.

All the children with asthma exacerbation were evaluated by one of the participant investigators.

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Clinical characteristics included demographic data, family atopy, smoking habitude, history of asthma exacerbations, allergies (documented by sensitization), and current treatment.

Children were considered allergic if symptoms occurred after exposure to the sensitizing allergen (8). Sensitization was defined as presence of allergen-specific IgE, documented by skin prick test (a wheal 3 mm or larger than the negative control was considered positive; the extracts were manufactured by Lofarma, Milan, Italy). The list of tested allergen extracts included: grasses, pellitory wall, ragweed, birch, hazelnut tree, olive tree, cypress, house dust mites, dog, cat, *Aspergillus fumigatus,* and *Alternaria alternata.*

The Ethics Committee of the ASL Naples 2 approved the study. In addition, written informed consent was obtained from all parents.

The statistical analysis consisted of the independent samples t-test or non-parametric Mann-Whitney test to compare continuous variables between groups (no exacerbation episode *vs* at least one episode).

Table I *- Factors associated with the occurrence of at least one asthma exacerbation.*

	Total (n = 139)	**No asthma exacerbation (n = 107)**	**With asthma exacerbation (n = 32)**	**Univariate P-value**	**Multivariate OR (95%CI); P-value**
Age	8.4 ± 2.72	8.6 ± 2.79	7.5 ± 2.30	0.020*	
Sex					
Female	60 (43.2%)	50 (46.7%)	10 (31.3%)	0.12	
Male	79 (56.8%)	57 (53.3%)	22 (68.8%)		
Living					
City	94 (67.6%)	70 (65.4%)	24 (75.0%)	0.31	
Countryside	45 (32.4%)	37 (34.6%)	8 (25.0%)		
Passive smoking					
None	80 (57.6%)	61 (57.0%)	19 (59.4%)	0.81 (none *vs* any smoker)	
Father	25 (18.0%)	21 (19.6%)	4 (12.5%)		
Mother	9 (6.5%)	7 (6.5%)	2 (6.3%)		
Both parents	22 (15.8%)	16 (15.0%)	6 (18.8%)		
Other cohabitants	3 (2.2%)	2 (1.9%)	1 (3.1%)		
Family atopy					
No	40 (28.8%)	30 (28.0%)	10 (31.3%)	0.73	
Yes	99 (71.2%)	77 (72.0%)	22 (68.8%)		
Number of asthma exacerbations in the past	5.8 ± 4.32	5.3 ± 3.28	7.4 ± 6.5	0.044*	OR 1.11 (1.01-1.24); 0.048
Allergy					
No allergy	68 (48.9%)	51 (47.7%)	17 (53.1%)	0.86	
Mono-allergy	39 (28.1%)	31 (29.0%)	8 (25.0%)		
Poly-allergy	32 (23.0%)	25 (23.4%)	7 (21.9%)		
Pet allergy	5 (3.6%)	3 (2.8%)	2 (6.3%)	0.33	
HDM allergy	52 (38.8%)	42 (40.4%)	10 (33.3%)	0.49	
Pollen allergy	14 (10.1%)	11 (10.3%)	3 (9.4%)	0.88	
Background treatment					
No medication	52 (37.4%)	39 (36.4%)	13 (40.6%)	0.64	
SABA alone as needed	28 (20.1%)	22 (20.6%)	6 (18.8%)		
Low-dose ICS	23 (16.5%)	16 (15.0%)	7 (21.9%)		
Medium-dose ICS	36 (25.9%)	30 (28.0%)	6 (18.8%)		

In addition, the chi-square test or Fisher's exact test evaluated the association between categorical variables. Subsequent modeling (univariate and multivariate) was performed using stepwise selection with the significance level for retention in the model set at $\alpha \leq 0.10$.

Results were quantified by odds ratio (OR) and a 95% confidence level (95%CI). The significance level was set at 0.05. The analyses were computed using SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA).

The characteristics of the schoolchildren are reported in **table I**. Comprehensively, 139 children were evaluated. The mean age was 8.4 years; the male gender was prevalent (56.8%), and passive smoking was declared in 42.4% of families. Family atopy was common (71.2%). The mean number of asthma exacerbations in the past was 5.8. About half (51.1%) of children were allergic (mainly with a single allergy). House dust mite (HDM) allergy was prevalent. About one-third of children did not take any medication, about 40% took inhaled corticosteroids, and 20% bronchodilators alone.

The study analysis stratified children into two subgroups: children without asthma exacerbation during the observation period and children with at least one asthma exacerbation. Children with at least one asthma exacerbation were older than those without asthma. In addition, children with asthma exacerbation had more exacerbation episodes in the past than children without exacerbation. The multivariate analysis demonstrated that the number of previous asthma exacerbations was associated with current asthma exacerbation (OR 1.11).

However, second-hand smoke, allergy, and type of medications were not associated with asthma exacerbation occurrence.

Asthma exacerbations represent an important issue in pediatric clinical practice (9). In childhood, the acute upper airway infections, mainly of viral origin, represent the leading cause of asthma attacks requiring medical aid (10). Viral infections implicate bronchial inflammation that triggers airway hyperresponsiveness and further narrows the bronchial lumen (11). These phenomena depend on the overexpression of type-2 immune response usually involved in pediatric asthma.

In addition, asthma exacerbations, mainly if associated with hospitalization, create a burden for the healthcare system and negatively affect children and their families. Frequent exacerbations are also associated with asthma worsening, including function (12).

The present report had some limitations, including the short observation period, the lack of biomarkers assessment, and the documentation of infections origin. However, the clinical relevance resides in its being conducted in a real-life pediatric primary care setting.

It is clinically relevant to highlight the importance of an adequate and thorough workup in managing children with asthma exacerbation. In addition, this observation underlined the relevance of the number of previous exacerbations. Finally, it implies the need to consider adequate preventive measures to adopt, such as vaccinations, anti-inflammatory agents, allergen-specific immunotherapy, if indicated, and potentially, as recently reported, immunomodulation (13).

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Contributions

GC: conceptualization, writing - original draft. MG, IS: data curation. MMdG, MAT: writing - review editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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