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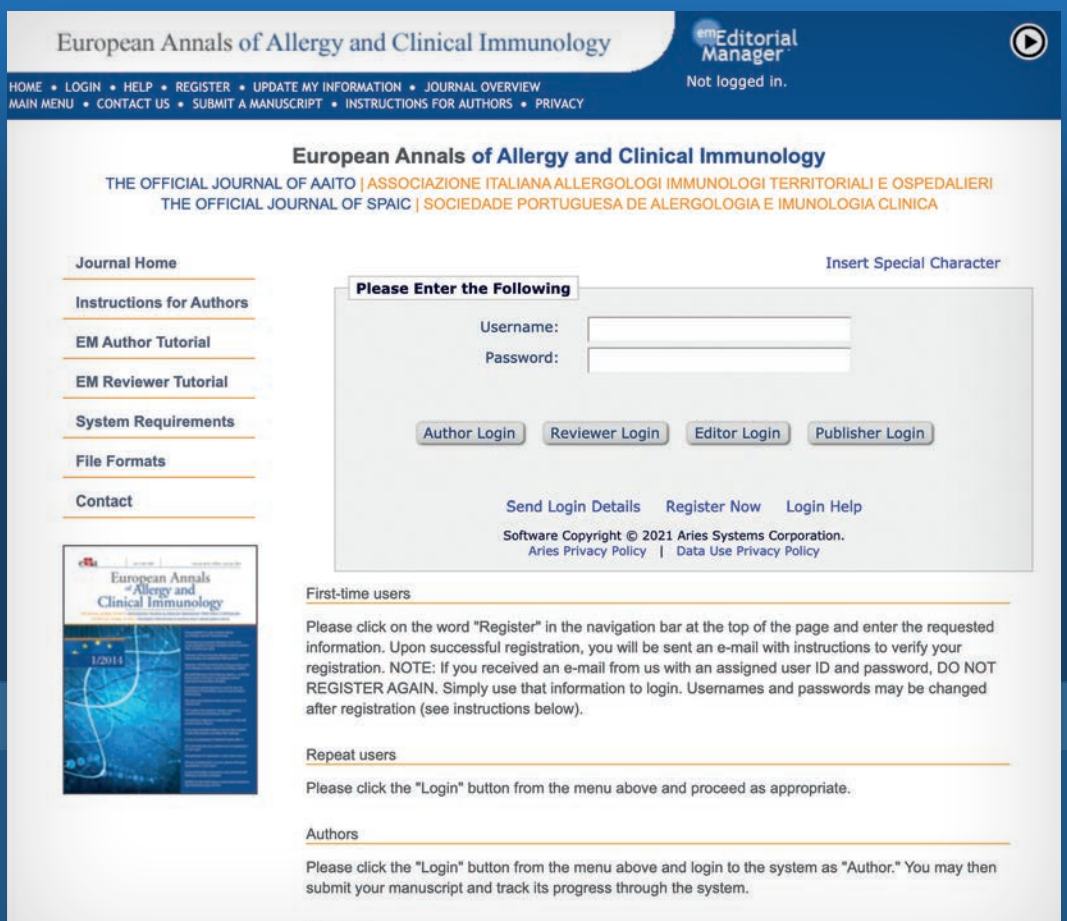

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Iodinated contrast media hypersensitivity reactions: is it time to re-evaluate risk factors?

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Hypersensitity reactions (HSRs) to iodinated contrast media (ICM) are classified into immediate reactions (IHRs) and non-immediate reactions (NIHRs) according to the time interval between ICM administration and appearance of symptoms, the first occurring within 1 (to 6) hours and the latter appearing more than 1 hour after the exposure, respectively. IHR may be of different severity, from urticaria and angioedema to reactions affecting the gastrointestinal, respiratory and cardiovascular systems and cardiovascular systems, sometimes with loss of consciousness (anaphylactic shock) (1, 2).
Maculopapular exanthema is the most frequent manifestation of NIHRs. More severe reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug eruption, drug reaction with eosinophilia and systemic symptoms, or acute generalized exanthematous pustulosis are less frequently observed. HSRs to ICMs have traditionally been considered as non-allergic, but growing evidence based on *in vivo* and in *vitro* tests points to immune mechanisms. According to a French study, the frequency of IgE-mediated allergy increases when three or four different organs are affected simultaneously, especially when cardiovascular symptoms appear in combination with respiratory or cutaneous reactions (3). Immediate, anaphylaxis-like reactions may be caused by an effect of the ICM on the mast cell membrane leading to mediator release (maybe through Mas-related G protein-coupled receptor member X2 (MRGPRX2)) or, possibly, by direct complement activation.
NIHR to ICM are characterized by a T-cell mediated mechanism, appearing from hours to days after administration of the ICM. Delayed appearing non-allergic urticaria and/or angioedema occurring > 6 hours after ICM administration seem to be caused by a different, poorly understood mechanism. In the past ionic ICM were used, with a prevalence of hypersensitivity reactions between 3.8% and 12.7% (4). With the introduction of nonionic ICM the prevalence has significantly decreased; however, over the last decade it has risen in parallel with their increased usage, ranging between 0.7% and 3% (5, 6). Severe IHRs as anaphylactic shock may also occur with nonionic ICM, even though with a frequency of 0.02%-0.04% and an estimated mortality rate of 1 in 100 000 examinations (5). However, no recent data are available on severe IHRs.
In this issue of *European Annals of Allergy and Clinical Immunology*, Cruz *et al*. (7) described three cases of anaphylactic shock following the use of ICM, putting the spotlight on the fact that severe, potentially fatal IHRs continue to occur, despite the use of low-osmolar ICM. As recently pointed out by the EAACI Position Paper (1) radiologists have to know they can experience this type of reaction, they should improve emergency awareness and training on emergency treatment of ICM IHR, and take a blood sample for the measurement of tryptase level. Moreover, they should contact the allergist for future patient management.
The main risk factor for IHR and NIHR seems to be a previous severe reaction to ICM. A previous IHR does not increase the risk for an NIHR and vice versa. Other presumed predisposing factors (like female gender, renal insufficiency, a history of doctor-diagnosed asthma, drug allergy, food allergy, contact allergy for NIHRs, and interleukin-2 treatment for NIHRs) as well as repeated exposures to ICM (**table I**) have not been confirmed in all studies, which are often dated, and therefore cannot be used as pre-requisite for performing ICM allergy work-up (1). Nevertheless, a better identification of the patients at risk could be of great utility to improve the safety of the procedures, and the articles of Voltolini (8) and Dellis (9) published in this issue of *European Annals of Allergy and Clinical Immunology* analyze this matter. Although both retrospective, these articles draw attention to the need to perform multicenter studies in order to confirm and/or identify new risk factors for severe ICM reactions and thus obtain a more precise risk stratification. In Voltolini's study, a large population (407) of Italian patients collected by 9 Allergy Units experiencing hypersensitivity reactions to ICM was compared with a control group of 152 subjects who tolerated one or more ICM-enhanced examinations. In line with other studies, a greater risk of HRSs in females and in patients under 65 years of age was observed (8). Moreover, it is of great interest that 35% of patients were on their first exposure, exactly in the

same percentage as in Dellis' study (9). In this study only 16% of the reactive group reported one or more previous ICM adverse reactions. Cardio-vascular disease, adverse drug reactions and respiratory allergy (but not asthma) were identified as risk factors for ICM reactions (8). Indeed, in the literature as well as in this study the term "atopy" is misused, mainly being an anamnestic data, without confirmation by diagnostic tests.

Dellis' study analyzed the characteristics of 80 patients experiencing HS reactions to ICM with a focus on oncological status. Half of patients had a history of cancer; cancer was active in 80% of cases, among them 31% were under treatment at the time of the reaction. There were no statistically significant differences between oncological patients and non-oncological patients with HSR in relation to gender, age, cardiovascular disease or asthma, history of previous reactions to ICM, and, interestingly, number of previous exposures. However, they were characterized by a low incidence of personal atopy (9).

The following question comes up: could the oncological diseases and/or their specific treatments be a risk factor for reaction to ICM? There are currently insufficient data in the literature to answer this question. More than cancer itself, repeated exposure could increase the risk of adverse reactions in patients with cancer (10, 11) or perhaps the combination of both factors. In contrast, in Voltolini's study, a high number of oncologic patients were part of the control group without HSRs and were significantly more exposed to ICM-enhanced examinations in the last year. Moreover, antineoplastic treatments as potential risk factors of HSRs have been only hypothesized.

Finally, it is noteworthy that the suspected culprit agent is often unknown in clinical practice (about 40% of cases in Voltolini's study). It depends on the fact that documentation in radiology and cardiology departments does not report the ICM name in most cases. Interestingly, a significant difference in reporting the name of the culprit ICM was observed between university centers in the same country (9). Accurate documentation of the contrast agent that induced the response/reaction should be mandatory to allow a more precise allergological work-up and therefore a more effective management of the patient choosing a different agent or premedication (12). Another important action to reduce the incidence of ICM-hypersensitivity reactions include the use of low-dose ICM and injection speed rate (13). In conclusion, at the moment we do not have certainties on the risk factors of HSRs. We cannot exclude that these reactions may be due to the concomitant presence of multiple and specific factors in predisposed subjects. Therefore, larger multicentric prospective studies are needed to explore different risk factors, to stratify the risk of the individual patient and adopt the best possible prevention strategies to avoid future HSR.

Table I *- Some potential risk factors for hypersensitivity reactions to ICM.*

Patient risk factors	**Procedure risk factors**
Previous reaction to ICM	First administration
Female gender	Repeated administration
Age < 65	Previous exposure via intra-arterial route for intra-arterial ICM
Atopy	Higher dose
Asthma	Injection speed
Drug allergy	
Oncological disease	
Severe cardiovascular disease	

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Allergic rhinitis and COVID-19: friends or foes?

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Key words

Allergic rhinitis; Coronavirus 2019; COVID-19; pandemic; SARS-Cov-2; allergy.

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Impact statement

Allergic rhinitis symptoms can be distinguished from those of COVID-19, and patients with allergic rhinitis do not carry a higher risk of worst COVID-19 outcome.

Summary

Allergic rhinitis (AR) is a common disease affecting up to 40% of the general population worldwide. In the Coronavirus 2019 (COVID-19) pandemic era, many observational studies analysing the effect of asthma and chronic obstructive pulmonary disease on the risk of developing COVID-19 were conducted, while data on AR are limited.

In this paper, we review the risk of developing SARS-Cov-2 infection carried by AR patients, the outcomes of those with COVID-19 disease, and the COVID-19 influence on the allergic and nasal symptoms and the psychological status of AR patients, in both adult and paediatric populations.

AR patients seem to be protected from COVID 19 infection. Even if data about the influence of AR on the severity of COVID-19 disease are still not conclusive, it seems that being an AR patient does not increase the risk of poor COVID-19 prognoses. The clinical manifestation of AR can be distinguished by COVID-19 symptoms. Treating AR adequately is also strongly recommended, especially during pandemic.

Introduction

The COVID-19 pandemic caused by SARS-Cov-2 infection raised important questions as to whether some chronic comorbidities could favour the infectiveness or the prognosis of the disease. Concerning respiratory diseases, many studies were conducted analysing the effect of asthma and chronic obstructive pulmonary disease (COPD) on the risk of COVID-19 but data on allergic rhinitis (AR) are scarce, even if AR is a common disease affecting up to 40% of the general population (1). In this review, we evaluate whether AR patients are at higher risk for SARS-Cov-2 infection or COVID-19 outcomes and whether COVID-19 can influence AR symptoms and the psychological status of AR patients, both in the adult and in the paediatric population.

Methods

This work was not intended to be a systematic literature review but a comprehensive narrative review. The literature search has been conducted consulting the most relevant scientific databases: PubMed/MEDLINE, Scopus, Web of Science. Controlled vocabulary supplemented with keywords was used to search for all type of articles on allergic rhinitis and COVID-19. The search strategy included different terms, *i.e.*, allergic rhinitis, rhinitis, allergy, atopy, COVID-19 and SARS-CoV-2, and was restricted to English language articles.

Allergic Rhinitis and risk of non-SARS-CoV-2 viral infections

A high proportion of patients with AR and other atopic diseases have a predisposition to produce lower levels of type I interferon (INF) upon viral respiratory infections (2, 3). Through different mechanisms, Type 2 inflammation may have an inhibitory effect on the induction of type I interferon (4). Intriguingly, defective production of IFNs by plasmacytoid dendritic cells (pDCs) and epithelial cells have been described in severe atopic patients (5) with a consequent delayed and inefficient antiviral defense. In this context, a cross-regulation mechanism between FceRI and TLRs in certain cell types such as pDCs has been described, which may explain why the crosslinking of IgE bound to FceRI by allergens may result in a reduced TLR expression and ultimately in a decreased capacity to secrete type I interferons for viral defense (4, 6). Furthermore, IL-5-induced airway eosinophilia appears to be a negative regulator of TLR7 expression and antiviral responses (7). Such impairment of antiviral responses suggests that patients with asthma might be at high risk of COVID-19 morbidity and mortality.

Allergic Rhinitis and risk of SARS-CoV-2 infection

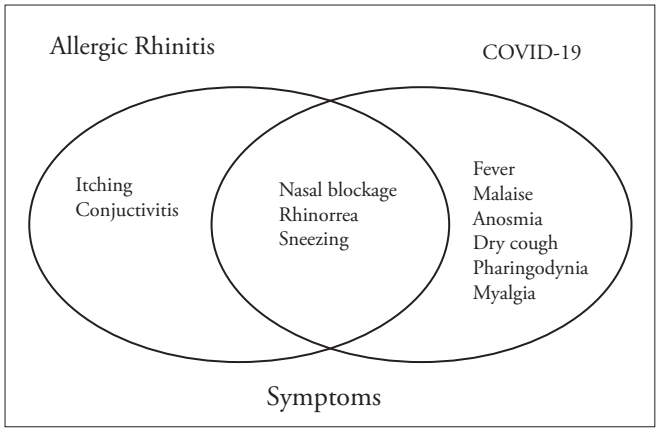
The prevalence of AR in the world is ranging from 10 to 40% varying according to different geographic areas (1). The spread of COVID-19 worldwide could have posed a significant psychological burden to patients suffering from AR, because some nasal and ocular manifestations of AR are also possible presenting symptoms of COVID-19 illness (**figure 1**), therefore potentially leading to misinterpretation and anxiety.

Nevertheless, available evidence shows that is not difficult to recognize and discriminate between these two different conditions. Bruno *et al.* (8) compared 40 patients suffering from AR with a similar group of 43 subjects affected by mild-moderate COVID-19 disease using the Sino-nasal Outcome Test 22 (SNOT 22). The mean overall score was higher in patients with COVID-19 compared to AR ones (39.9 *vs* 27.2). There was a significant difference in sneezing and blow nose between AR and COVID-19 patients ($p < 0.016$ and $p < 0.001$, respectively), while the COVID-19 group most frequently reported cough, loss of smell, fatigue during the day, reduced productivity and concentration, sadness and feeling of shame compared to AR group ($p < 0.001$). In a retrospective study, patients hospitalized with COVID-19 were interviewed via telephone by using the mini-Rhino-conjunctivitis Quality of Life Questionnaire (9). Among these patients, for those who were also affected by allergic rhino-conjunctivitis (10.8%), clinical manifestations of COVID-19 were regarded as completely different from AR in 62.8% of cases, and similar only in 18.2% of cases. No differences were found between sino-nasal symptoms in COVID-19 allergic *vs* non-allergic patients ($p = 0.288$), particularly for the prevalence of smell disfunction. The authors concluded that patients with AR are very familiar with their symptoms, can distinguish AR from COVID-19 rhino conjunctival manifestations, and have the same upper airway COVID-19 manifestations of non-AR patients (9). Finally, the EUFOREA expert team statement evidenced that cough and fever were the most prominent symptoms of COVID-19, whereas conjunctivitis and itching were typical of AR (**figure 1**) (10).

A multicentre questionnaire study conducted on 301 nurses with AR characterized the impact of face masks on AR symptoms (11). They used both surgical and N95 masks. Nurses with intermittent AR symptoms showed a significant improvement in overall symptoms after wearing the mask, regardless of the type, but no change in specific ocular symptoms. The mechanism of protection could be a physical filtration of face masks and the potential physiological response to allergens by breathing humid and hot air (11).

The mandatory lockdown established by governmental authorities during the first wave of COVID-19 forced people to stay home for several months and this could have influenced the AR course in patients with house dust mite (HDM) allergy. Gelardi *et al.* (12) compared the results of SNOT-22 of years 2019 (pre-lockdown) and 2020 collected from 42 patients with AR to HDM (28% with asthma comorbidity). These authors showed that all SNOT-22 scores were higher in the lockdown period than the year before. However, only the scores relative to runny nose, need to blow nose, nasal obstruction were statistically

Figure 1 *- Similarities and differences between allergic rhinitis and COVID-19 symptoms (adapted from (10)).*



different from 2019 to 2020 ($p < 0.05$). Other non-specific parameters, such as difficulty falling asleep, waking up at night, be frustrated/restless/irritable, and sad were statistically significant ($p < 0.05$). Of note, there was a significant increase in the use of systemic antihistamine, and nasal decongestants ($p < 0.05$) to reduce nasal congestion but not in accordance with ARIA guidelines recommendations.

These findings may suggest that being quarantined at home for a long time may increase the exposure to HDM and focus on the importance of treating patients according to ARIA guidelines to control AR symptoms (13). Avoiding contact with allergens (indoor or outdoor) is the primary preventive measure in patients with respiratory allergies and a strategy with pharmacotherapy associated with allergen immunotherapy (AIT), when indicated, must be considered (12). Regarding pharmacologic therapy of AR, it is recommended to start early and use it regularly throughout the pollen season. None of the recommended therapy for seasonal AR is contraindicated in COVID-19 patients. In particular, it is not advised to suspend intranasal steroids as this therapy does not reduce immunity, is effective in normalizing the structure and function of the nasal mucosa, and reduces sneezing, one of the means for spreading the coronavirus (14). There are also preliminary data indicating that some corticosteroids as mometasone may suppress coronavirus replication (15). Systemic steroids, however, should be avoided, if possible, as they may suppress the immune system (14).

AIT should be continued in non-infected individuals and in those who completely recovered from COVID-19, whereas it should be interrupted in patients diagnosed with COVID-19 or suspected of having SARS-Cov-2 infection (16). Subcutaneous immunotherapy can be continued under strict safety protocols considering injection intervals expansion. AIT start in eligible patients is preferred to be in the sublingual route of administration to minimize in-person encounters for subcutaneous injections. Sublingual immunotherapy offers the possibility of taking it at home, thus avoiding the need to travel to or stay in an allergy clinic or doctor's office, which would increase the risk of infection (16).

Individuals with AR commonly report a higher proportion of anxiety, depression, and psychological disturbance than healthy people. In a cross-sectional study, 222 adults with AR and 133 healthy controls were asked to complete the Self-rating Anxiety Scale (SAS) and Self-rating Depression Scale (SDS) questionnaires. The SAS and SDS scores were significantly higher in AR patients than control, with a prevalence of anxiety and depression of 25% and 19%, respectively, in the AR group (17). Interestingly, the same data obtained one week after the period of lockdown were lower than before the COVID-19 pandemic and correlate with AR symptoms. The authors conclude that the COVID-19 pandemic had no significant influence on the psychological status of patients suffering from AR and confirmed that symptom severity is an important factor affecting the anxiety and depression of AR patients (17).

On the contrary, a cross-sectional survey-based study, designed to assess the degree of depression and the risk of post-traumatic stress disorder using the patient's health questionnaires and the impact of Event Scale-Revised, evidenced that, during the period of quarantine due to COVID-19, the psychological impact in patients with allergic diseases (n = 1,650) was greater than in non-allergic controls (n = 2,450). There was no difference between allergic respiratory and non-respiratory groups but in the hyperarousal scale, respiratory patients had higher scores (mean 1.15 *vs* 0.99 p = 0.013). Unfortunately, the authors didn't distinguish between patients with allergic asthma from patients with AR (18). Even if at the beginning of the COVID-19 pandemic asthma and allergy were considered as possible risk factors for COVID-19, subsequent statements from international societies and expert scientific bodies concluded that allergic respiratory diseases do not constitute risk factors for severe COVID-19 (10, 14). Accordingly, in a study from China, Shi *et al.* found that the rate of combined allergy was low in COVID-19 patients. The ratio of combined asthma and AR were far lower than those of domestic morbidity, which might suggest that asthma and AR may not be a susceptibility factor for SARS-CoV-2 (19).

Can Allergic Rhinitis influence the outcomes of COVID-19?

COVID-19 pandemic has caused many hospitalizations and intensive care unit admission with a high burden on health care resources. For this reason, many studies were conducted to identify risk factors for severe COVID-19 outcomes. Elderly age, cardiovascular diseases, obesity, and diabetes have been associated with more severe disease (20). Available evidences about asth-

ma are not conclusive and it seems that only non-atopic asthma might be a risk factor for the severity of COVID-19 (21).
Currently, there are only a few data about the risk of COVID-19 in patients with AR, and these are mostly indirect evidence from studies analysing the effect of atopy or asthma on COVID-19. In a retrospective study on 531 patients with SARS-Cov-2 induced pneumonia, Scala *et al.* (22) found that atopic subjects (n = 57; 10.7%) had a significantly lower prevalence of severe COVID-19 pneumonia than non-atopic patients (33.3% *vs* 67.7%; $p < 0.0001$). These authors concluded that atopic status may confer protection against COVID-19 infection, although but they didn't address what type of allergic disease participants suffered from (22). A recent American cohort study involving 1,043 COVID-19 patients was designed to understand the association between atopic conditions and COVID- 19 severity. 257 (24.6%) had atopy and this condition was associated with a significantly lower odds of hospitalization for COVID-19 ($p < 0.004$) and length of hospitalization ($p < 0.008$). Patients suffering from AR (n = 171; 16.4%) had a lower rate of hospitalization ($p < 0.02$), length of hospitalization ($p < 0.001$), and lower duration of intubation ($p < 0.039$). Also, eczema was associated with a significantly reduced risk of hospitalization (23).
Chhiba *et al.* (24) conducted a study to investigate if asthma could be a risk factor for the severity of COVID-19. Among 1,526 patients with COVID-19, 220 (14.4%) had asthma. The prevalence of AR was 35.9% in the asthmatics and 7.7% in the non-asthmatic groups ($p < 0.0001$), whereas rhinosinusitis was comorbidity in 35.9% of asthmatic patients *vs* 9.6% in non-asthmatic ones ($p < 0.0001$). Asthma was not associated with an increased risk of hospitalization, particularly in patients with AR and rhinosinusitis. The authors outlined the potential protective effect of Type-2 inflammation and perhaps of using inhaled corticosteroids, although the latter conclusion needs further investigation (24). Another study retrospectively analysed the comorbidity of 1172 hospitalized COVID-19 patients in Wuhan. 115 (9.8%) reported AR and tended to have higher asthma comorbidities. There was no difference in the frequencies of severe cases, need of mechanical ventilation or other treatment or complications (including severe acute respiratory syndrome) between patients with and without AR. The authors conclude that there is not any association between AR comorbidity and COVID-19 severity (25). On the contrary, Yang *et al.* (26) conducted a nationwide cohort study in South Korea involving 291,959 adult patients who were tested for SARS-Cov2 to determine the association of allergic disorders with the likelihood of a positive SARS-Cov-2 tests result and with clinical outcomes of the disease. The number of patients with positivity to SARS-Cov-2 was 7,340. The SARS-Cov-2 test positivity rate was 3,3% in individuals with AR compared to 2.8% in those without AR. Severe clinical outcomes from COVID-19 were observed in 4.7% and 3.7% of patients with and without AR, respectively. Also, patients with asthma had a significantly higher risk of severe COVID-19, but this data was particularly evident for non-allergic asthma, whereas atopic dermatitis didn't show an association with severe clinical outcomes. They concluded that patients with respiratory allergic diseases are at higher risk of worse clinical outcome and that AR is associated with an increased likelihood of SARS-Cov-2 test positivity and worse clinical outcomes as death, intensive care admission, non-invasive ventilation, and longer hospital stay.
The local immunologic environment in the respiratory system (impaired secretion of innate IFN) seems to be more important for SARS-Cov-2 infection than the systemic immunologic effects characteristic of atopic dermatitis (26). In a single-centre retrospective study with a small sample size (110 COVID-19 patients) in China, Shi *et al.* (19) observed a lower rate of comorbid allergy in patients with COVID-19 in comparison with the prevalence of allergic diseases in the general population. When excluding patients with other underlying diseases and stratifying COVID-19 patients into those with (n = 21) and without allergy history (n = 44), they found that patients with allergy demonstrated lower proportions of bilateral lung lesions on chest computed tomography scanning and severe illness and higher circulating total T-cell counts than those without allergy. Another study conducted in 949 COVID-19 patients showed that smell loss was associated with less severe COVID-19 and that a history of smell dysfunction ($p < 0.001$), AR ($p < 0.02$), rhinosinusitis ($p < 0.02$) was associated with a greater risk of acute smell loss in patients with COVID-19. So indirectly AR and rhinosinusitis could be related to a better course of COVID-19 disease (27).
The host immune response is integral to determining susceptibility to SARS-CoV-2 infection and the severity of consequent COVID-19 (28). Recently, Larsson *et al.* (29) provide evidence to support that the genetic factors underlying predisposition to allergic disease are protective against COVID-19. They considered 136 uncorrelated ($r^2 < 0.02$) single nucleotide polymorphisms associated with a broad allergic disease phenotype (presence of at least one allergic disease, including AR, atopic dermatitis and asthma) at $p < 3 \times 10^{-8}$ in a meta-analysis of 13 genome-wide association studies with a total of 180129 cases and 180709 controls (without the three allergic diseases), all of European descent. Genetic predisposition to any allergic disease was associated with reduced susceptibility to COVID-19 but not clearly with the risk of being hospitalized with COVID-19. Secondary analyses based on genetic variants associated with different allergic diseases did not reveal associations with any particular allergic disease specifically, although the magnitude of the inverse association was most pronounced for AR albeit with broad confidence intervals (29).

Can Allergic Rhinitis be protective against poor outcomes of COVID-19?

As previously stated, some studies have suggested possible non-harmful or protective effects of AR on the clinical outcomes of COVID-19. Allergy is an immune response to allergen stimulation that is charac-

terized by elevated Type-2 cytokines and eosinophilic inflammation. The above findings raise the possibility that allergy might be a protective factor for COVID-19. AR might protect against poor outcomes in COVID-19 due to several possible mechanisms, including altered viral entry receptor expression, chronic type-2 inflammation, younger age and/or absence of comorbidities, increased adherence to therapy and intranasal corticosteroids use (30).

ACE2 receptor

The lack of susceptibility to COVID-19 in patients with pre-existing allergic asthma seems to be in contrast with the established link between these chronic respiratory conditions and susceptibility to common respiratory viruses, particularly rhinoviruses (31). However, rhinovirus uses the intercellular adhesion molecule 1 (ICAM-1) molecule as an entrance into respiratory epithelial cells, which is overexpressed in allergic airways as a marker of allergic inflammation (32). In contrast, COVID-19 uses another host cell receptor abundantly present in the oral mucosa and within the (healthy) airways, (*i.e.*, the angiotensin-converting enzyme-2 (ACE2) (33)), which plays a crucial role in the disease development and associated lung injury (34). Cofactors facilitating SARS-CoV-2 infectivity are transmembrane peptidase serine 2 (TMPRSS2), which cleaves the SARS-CoV-2 spike protein, and possibly protease furin (35). A lower expression of ACE2 has been described in airway cells of patients with AR and/or asthma. Jackson *et al.* found that nasal cat allergen led to a significant reduction in ACE2 mRNA expression in nasal brush samples in adult AR patients allergic to cats (36). Furthermore, Kimura *et al*. reported that IL-13 exposure reduced ACE2 expression in airway epithelial cells from patients with asthma and atopy (37). These findings suggest that patients with AR and allergic asthma might be protected from COVID-19 because of the low expression of ACE2 in their epithelial cells (38).

Inflammatory endotypes and COVID-19

Certain aspects of type 2 immune response, including type 2 cytokines (IL-4, IL-13, *etc*.), could therefore provide potential protective effects against COVID-19. In a retrospective study on patients with SARS-CoV-2-induced pneumonia, hospitalized in several Italian hospitals, atopic subjects showed a much lower occurrence of severe or very severe COVID-19 pneumonia (33.3% *vs* 67.7%, $p < 0.0001$) (22).

Eosinophilic inflammation

Further, the role of eosinophils, foes in asthma but possibly friends in COVID-19 infected lungs, needs to be established (39). Previous experimental studies indicated a potential role of eosinophils in promoting viral clearance and antiviral host defense (40). The capacity of eosinophils to protect against viral infection might therefore account for a low prevalence of asthmatic individuals among patients with COVID-19. Eosinophils are reduced in peripheral blood of SARS-CoV-2-infected patients, (41) therefore, it is tempting to speculate that increased numbers of eosinophils in the airways of asthmatic patients might be protective against the exaggerated inflammatory responses of the severe COVID-19 phenotype (39). The severity of AR is typically classified into a mild and a moderate-severe form based on symptom severity according to the ARIA guidelines (13). The clinical severity of AR correlates with the levels of eosinophils in the blood and nose. Recently, Chen *et al.* found that the eosinophil levels in the blood were significantly higher in mild and moderate-severe AR compared to healthy controls (42). Severe COVID-19 occurring in susceptible individuals may be associated with cytokine-mediated hyper-inflammation and associated coagulopathy with multisystem involvement and death (43). Markers of worsening disease include hypoxemia, lymphopenia, thrombocytopenia, and raised levels of IL-6, C reactive protein, ferritin, lactate dehydrogenase, and D-dimers. Eosinopenia may also be part of the overall cytopenic process in the early phase of severe COVID-19, with the later resolution of eosinophil counts being associated with clinical recovery (44). Peripheral blood eosinophil counts may, therefore, be an effective and efficient indicator in the diagnosis, evaluation, monitoring, and prognosis of COVID-19 patients (45).

Younger age and/or absence of comorbidities

Susceptibility and severity of COVID-19 infection increase with age (46); therefore, age is an important confounder in the assessment of the risk of contracting severe COVID-19. Expression of ACE2, the co-receptor for SARS-CoV-2, varies with age (47). Because Type-2 asthma sufferers tend to be younger than those with other comorbidities, the age factor probably explains why patients with asthma may not be at greater risk. However, to better address this question, age-adjusted models need to be formulated.

Paediatric Allergic Rhinitis and COVID-19

Beken *et al*. conducted a study in 107 pediatric patients after hospitalization for COVID-19 (48). Questionnaires investigating environmental factors and an allergic evaluation, including allergy testing and spirometry, were conducted. The authors concluded that asthma and AR were not risk factors for hospitalization in children due to COVID-19. The presence of a pet in the environment might have a protective effect. Dul and colleagues (49) evaluated the data extracted from electronic medical records of 182 children hospitalized for COVID-19 and showed that allergic diseases do not increase the susceptibility to SARS-Cov-2 infection and hardly influenced the course of COVID-19 in children. Finally, Jackson *et al*. (36) reported that high levels of allergic sensitization are associated with a reduction in the expression of the ACE-2 receptor which is the gateway to the virus. Regarding inhaled corticosteroid therapy, Bousquet *et al*. (14) report that out of 40 children with AR admitted to the Wuhan chil-

dren's hospital for Covid 19, about one third regularly used intranasal steroids as before, the other two-thirds did not: in these two groups of patients there was no difference in severity and prognosis COVID-19, and everyone has recovered well (unpublished data). Also, Cardinale *et al.* (50) stress the importance of continuing treatment with intranasal steroids and antihistamines both to control the symptoms and to avoid superinfections potentially dangerous for the lower respiratory tract. Furthermore, these authors also underline how the failure to control rhinitis with the classic symptoms, in particular sneezing, can favor the transmission of the virus. Some authors also suggested that montelukast could be also considered in pediatric age to treat AR during the COVID-19 pandemic, considering the potential anti-inflammatory action of this medication (51). Recommendations for AIT during the COVID-19 pandemic for adults with AR also apply to children (16, 50).

In the period of lockdown, allergic patients inevitably remained more confined to the home environment. Yucel *et al.* (52) raised the question of relapses in patients allergic to HDM. This study carried out during 75 days of lockdown on 81 children showed an improvement in lung function and consequently in asthma symptoms, probably due to the reduction of respiratory tract infections and exposure to outdoor pollution. On the contrary, the nasal symptoms were significantly worsened in subjects with allergic rhinitis, underlining the importance of environmental remediation measures indoors. In conclusion, it seems that COVID-19 affects childhood and adolescence, fortunately in a modest way (53, 54). However, for this very reason, allergic children must continue the therapies for their allergies and scheduled visits as must be the case for all chronic diseases.

Conclusions

AR patients seem to be protected from COVID 19 infection. Even if data about the influence of AR on the severity of COVID-19 disease are still not conclusive, it seems that being an AR patient does not increase the risk of poor COVID-19 prognoses. The clinical manifestation of AR can be distinguished by COVID-19 symptoms. Treating AR adequately is also strongly recommended in the COVID-19 pandemic era.

Conflict of interests

The authors declare that they have no conflict of interests.

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Hypersensitivity reactions to iodinated contrast media in Italy: a retrospective study. Characteristics of patients and risk factors

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Key words

Iodinated contrast media; risk factors; drug hypersensitivity; drug immediate reactions; drug delayed reactions.

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Impact statement

Characteristics of patients with hypersensitivity reactions to iodinated contrast media are described and compared with subject tolerating the same contrast media allowing to identify some possible risk factors.

Summary

Objective. *The purpose of the study was to describe the characteristics of patients experiencing hypersensitivity reactions (HRs) to iodinated contrast media (ICM) in a large Italian population and to investigate potential risks factors in order to obtain a risk stratification, helpful in the management of these patients.* ***Methods****. Data of 407 patients investigated in 9 Italian Allergy Centers for suspected HRs to ICM were analyzed and compared with a control group of 152 subjects that tolerated one or more ICM-enhanced examinations. The univariate and multivariate logistic regression model was used to evaluate associated factors.* ***Results.*** *The mean age of reactive patients was 61 years and 60% were female; 67% of patients reported immediate reactions and 35% experienced the reaction, more frequently with immediate onset, at the first examination in life. Iomeprol, iopromide and iodixanol were the most frequent culprit agents and 20% of patients showed a positive skin test result. Previous adverse reactions to ICM were reported by 15.6% of patients. The multivariate analysis showed that male gender and age > 65 were associated with ICM reactions as protective factors [OR_{adja} = 0.51; 95% CI 0.33-0.77 and OR_{adja} = 0.60; 95% CI 0.39-0.92 respectively]. Cardio-vascular disease [OR_{adja} = 2.06; 95% CI 1.22-3.50)], respiratory allergy [OR_{adja} = 2.30; 95% CI 1.09-4.83)] and adverse drug reactions [OR_{adja} = 1.99; 95% CI 1.05-3.77)] were identified as risk factors for ICM reactions. Food allergy was not significantly associated with reactions [OR_{adja} = 1.51; 5% CI 0.41-5.56].* ***Conclusions.*** *This is the largest study on Italian patients experiencing hypersensitivity reactions to ICM. Most results are in line with other studies, showing some association with factors that could influence the incidence of hypersensitivity reactions but not allowing an easy risk stratification.*

Introduction

The introduction and increasing use of nonionic low-molecular-weight (LMW) iodinated contrast media (ICM) have significantly reduced the risk of adverse reactions related to contrast-enhanced radiologic imaging. Hypersensitivity reactions (HRs) to ICM are rare, but their potential severity represents a cause of concern both for radiologists and for people who need contrast-enhanced radiologic examinations.

This could explain the growing interest in the topic in the last 15 years, not only by radiologists but also by allergists who can give a contribution to knowledge, comprehension and consequently a more correct approach to these reactions (1-4). For this purpose, the European Network of Drug Allergy (ENDA) published in 2009 the results of a prospective multicenter study aimed to investigate clinical aspects and a potential allergy work-up in this field (5). Although some areas still remain controversial, as outlined in a recent international consensus, this new perspective has stimulated the interest to deepen various aspects of the problem (6). Among them, the identification of patients at risk of reaction and the real utility of the pharmacological premedication are particularly intriguing. The consensus well resumes the hypothetical risk factors based on the existing studies: while a previous reaction to contrast media is generally accepted as the main risk factor, the current role of other conditions, such as atopy, asthma, cardiovascular diseases, drug allergy, female gender, mastocytosis, repeated administrations of ICM, *etc*., is still uncertain. Nevertheless, these conditions are often considered in clinical practice, arising fear both in patients and operators. One of the practical consequences is the abuse of pharmacological premedication by antihistamines and steroids, without standardized regimes and with differences not only between allergists and radiologists, but also between the North American and European recommendations (7, 8).

To the best of our knowledge, there is no Italian national multicenter study on hypersensitivity reactions to ICM. Therefore, the main purpose of this study was to investigate the characteristics of patients referred to allergy evaluation for suspected hypersensitivity reactions to ICM in different Allergy Centers in Italy. The secondary aim was to analyze possible association between some factors and hypersensitivity reactions to ICM, with the purpose to identify the possibility of a risk stratification, a particularly useful tool in adverse drug reactions (ADRs) evaluation (9).

Methods

This is a retrospective multicenter study approved by the Ethics Committee of the coordinating Center (L'Aquila and Teramo provinces, Avezzano Hospital - 1/CE/17).

Patients

From 2013 to 2016, in nine Italian Allergy Centers with expertise in drug allergy management, 407 consecutive patients with hypersensitivity reactions to ICM were analyzed as "reactive group". Data of 152 consecutive patients from three Italian Radiologic Centers were collected as "control group" because they tolerated one or more contrast-enhanced examinations.

The following demographic and clinical data were recorded: age, sex, radiological examination, administered ICM, history of previous exposures, number of examinations in the last year, use of premedication, history of allergy (inhalant or food allergy) and/or ADRs other than ICM, concomitant cardiovascular diseases, usual anti-hypertensive medications (*i.e*., angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers). In the reactive group, the characteristics of the last ad-

verse reaction and the history of previous ICM reactions, bronchial asthma, angioedema or mastocytosis were also considered.

Clinical symptoms

In the reactive group, clinical symptom onset was classified in immediate (< 1 hour) and non-immediate (> 1 hour). Moreover, the reaction delay was further specified, in order to differentiate very rapid (< 10 minutes) and very delayed (> 48 hours) reactions. These data were correlated with the severity of the reaction. Immediate hypersensitivity reactions (IHRs) were classified according to the Ring and Messmer severity scale: grade I indicating only cutaneous and/or mucosal symptoms, grade II indicating moderate multiorgan involvement with cutaneous and respiratory or gastrointestinal and/or cardiovascular symptoms, grade III including severe life-threatening multiorgan involvement such as cardiovascular collapse, arrhythmias and bronchospasm, grade IV with the cardiac and/or respiratory arrest (10). The non-immediate hypersensitivity reactions (NIHRs) were classified according to the ENDA study in mild, moderate, and severe (5).

Skin tests

As a part of the routine allergy workup, skin tests for the culprit ICM (when known) and for others ICMs commonly used in Italy were performed in 400 patients. In accordance with the ENDA criteria (5), patients with history of IHR were analyzed with skin prick test (SPT) and, if negative, with intradermal test (IDT). Patients with clinical history of NIHR underwent patch test (PT) with reading until 96 hours and, if negative, SPT and IDT. Reactivity to IDT was evaluated after 20 minutes and during the following 48 hours to detect delayed reactions.

Statistical analysis

Continuous variables were expressed as mean and standard deviation, and categorical variables as numbers and percentages. Data were compared using Student's t- or chi-square tests depending on scale level and distribution.

To evaluate factors related to hypersensitivity reactions to ICM, subjects in the reactive group were compared with subjects in the control group. A logistic regression model was used for univariate analysis with reaction to ICM (yes/no) as dependent variable and the following factors as independent factors: gender, age in years (≤ 65; > 65), first exposure to ICM (yes/no), number of examinations in the last year, premedication (yes/no), cardiovascular disease (yes/no), number of concomitant pathologies (classes: 0; 1-2; ≥ 3), respiratory allergy (yes/no), food allergy (yes/no), adverse drug reactions (yes/no) and anti-hypertensive medications such as ACE-inhibitors (yes/no), and angiotensin receptors blockers (yes/no).

All factors statistically significant by univariate model were included in a multivariate logistic regression analysis (MLRA). Unadjusted odds ratios (ORs) and adjusted odds ratios (OR_{adj}) with 95% CIs were reported. Significance was assumed for $p < 0.05$. All analysis was performed using STATA 14 software.

Results

Characteristics of patients in the reactive group (see **table I**)

A total of 274 patients reported IHR (67%: 95% CI 63%-72%), whereas 133 patients reported NIHR (33%: 95% CI 28%-37%), 164 patients were males (40%) and the mean age was 61 (± 14.5) years. Eighty-five percent of them were diagnosed with ICM reactions after a computed tomography (CT) scanning.

Premedication had been administered before the radiological examination in 78 patients (19% out of 407) who showed significantly more frequently a non-immediate rather than an immediate reaction. Among 54 patients with previous adverse reactions, 42 were premedicated.

One hundred twenty-four patients (35% of 351 − because of missing data) experienced the reaction during the first ICM-enhanced examination in their life and significantly more frequently with an immediate rather than delayed onset.

Previous reactions to ICM were reported by 54 patients out of 351 (15.4%), without any difference between IHR and NIHR. Although the suspected culprit agent was known only in about 60% of cases, among the various ICM, iomeprol and iopromide were involved in over 50% of the known cases without significant difference between IHR and NIHR. Moreover, iomeprol was frequently the culprit agent of severe immediate reactions (degree 3 and 4), whereas iodixanol was responsible significantly more frequently in nonimmediate reactions (16% NIHR *vs* 3% IHR; $p < 0.001$). In the reactive group, 81 patients reported a history of respiratory and/or food allergy and 86 patients presented previous ADR to drugs other than ICM. Among patients with respiratory allergy only 26 (36.6%) reported bronchial asthma.

A history of angioedema was present in 2 patients, no cases of mastocytosis were registered.

Severity and time to onset of reaction

The grade of severity of immediate reactions was classified as follows: grade I in 142 (52%) patients, grade II in 80 (29%) patients, grade III in 41 (15%) patients and grade IV in 11 (4%) patients. NIHR were mostly mild (61%) and only one patient reported a severe nonimmediate reaction diagnosed as DRESS syndrome.

Forty-six per cent of immediate reactions (126/271) occurred within ten minutes, and the same rate within 30 minutes. Among the non-immediate reactive group, the reactions were mostly registered within 24 hours (97/130). Only 8.5% of patients reported reactions over 48 hours after the examination.

Figure 1 shows the relation between time of reactions and severity. More than half of immediate severe reactions happened within 10 minutes from the ICM injection.

Table I *- Characteristics of patients in the reactive group (n = 407).*

	IHR n = 274 [67%: 95% CI 63%-72%]	**NIHR n = 133 [33%: 95% CI 28%-37%]**	
	n (%)	n (%)	p**
Gender			
Female	156 (57)	87 (65)	0.102
Age (years)	60.7 (± 14.4)	62.5 (± 14.9)	0.245
Pre-medication (yes)	44 (16.3)	34 (26.15)	0.020
First examination (yes)	91 (39)	33 (28)	0.052
Previous reactions	34 (14.2)	20 (18.9)	
Exam type			
C.T. scan	233 (85.04)	113 (84.96)	0.563
Coronarography	17 (6.20)	13 (9.77)	0.196
Urography/cholangiography	18 (6.57)	1 (0.75)	0.010
Other	5 (1.82)	6 (4.51)	0.400
Implicated contrast medium			
Iomeprol	53 (19.34)	21 (15.79)	0.383
Iopromide	34 (12.41)	26 (19.55)	0.057
Iobitridol	23 (8.39)	7 (5.26)	0.315
Iopamidol	18 (6.57)	4 (3.01)	0.165
Iodixanol	9 (3.28)	21 (15.79)	< 0.001
Iohexol	5 (1.82)	3 (2.26)	0.720
Ioversol	14 (5.11)	9 (6.77)	0.497
Unknown	118 (43.07)	42 (31.58)	0.026
History of allergy	96 (35.04)	54 (40.60)	0.275
Respiratory	49 (18.08)	22 (17.05)	0.802
Food	18 (6.64)	7 (5.43)	0.639
Adverse drug reactions	52 (19.19)	34 (26.56)	0.188

**Chi Square/Fisher exact test.

Skin tests

Allergy workup demonstrated at least one positive skin test in 81 patients (20.25% of total enrolled patients): 42 patients were in the IHR group, representing the 15.7% of them, and 39 patients were in the NIHR group, accounting for the 29.3%. Among patients with history of reaction at their first exposure, 21% showed a positive test.

A more detailed description of the results will be the subject of a subsequent paper.

Factors related to ICM reactions (see **table II**)

In order to evaluate potential risk factors related to ICM hypersensitivity reactions, data of 152 subjects that underwent an ICM − enhanced CT − scan without any adverse reaction were collected as control group and analyzed.

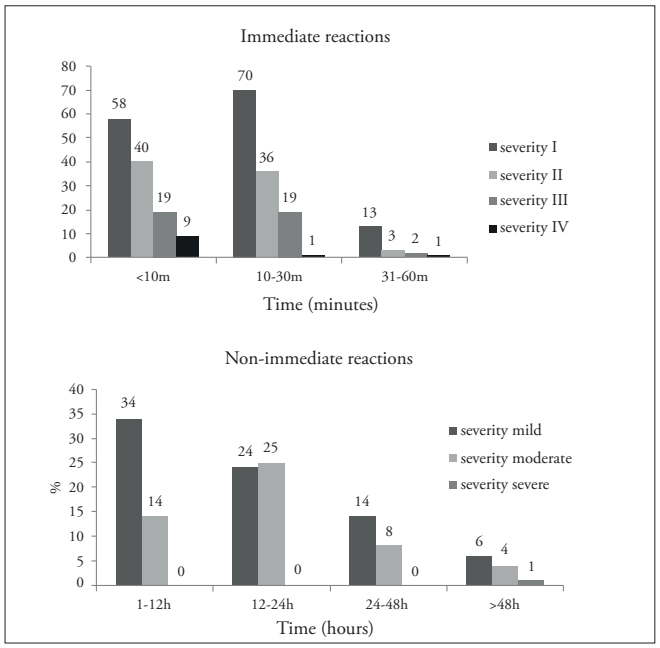
The ICMs used in the control group were the same as in the reactive group (iopamidol in 40%, iomeprol in 32%, iobitridol in 15%, iohexol in 9%, iodixanol in 4%) with the exception of iopromide and ioversol, never used in the control group.

Collectively, 176 patients reported history of at least one allergy (food allergy, respiratory allergy) and/or ADRs; 150 patients were in the reactive group (37%: 95% CI 32%-42%) whereas only 26 patients were in the control group (18%: 95% CI 12%-26%).

Univariate analysis between reactive and control group showed a significant association with the following factors: first exposure (OR = 2.2), cardio-vascular diseases (OR = 2.1), history of allergy (respiratory: OR = 3.0; food: OR =3 .3) or ADR (OR = 2.5). Male gender and age > 65 years were protective factors against reactions.

The multivariate analysis showed that food allergy was not a significant risk factor associated with reactions: OR_{adj}= 1.47 (95% CI 0.40-5.41), while female gender, age ≤ 65 years, first ICM exposure, associated cardio-vascular disease, a history of respiratory allergy and adverse drug reactions were significant risk factors for ICM hypersensitivity reactions (**table III**).

Figure 1 *- Time to onset of immediate and non-immediate reactions by severity.*



Not 407 because of missing data.

Discussion

This is the first Italian multicenter study aimed to analyze characteristics and risk factors of patients evaluated for suspected hypersensitivity reactions to ICM. Demographic characteristics were similar to those of the European multicenter study (5), with a larger sample size (407 *vs* 240) and to those of 98 patients in a recent Italian study (11).

Thirty-five percent of patients were on their first exposure, showing more frequently an immediate reaction. The possibility of hypersensitivity reactions to ICM, both immediate and non-immediate, in patients previously unexposed was already observed, ranging from 13.4% to 50% (5, 11-15). It is usually attributed to a non-immunological mechanism of action, but some cases show positive skin test with a variable prevalence (35% in ENDA study and 21% in our study). This seems to suggest a possible previous sensitization through unknown environmental molecules, or molecules containing carbamoyl side chains (14), or ICM-contaminated drinking water (16).

The use of pharmacological premedication was less frequent than expected: specifically, premedication treatment with either steroids and/or anti-histamines was administered in the majority of cases with a history of previous reactions but not in the totality of them. The reason why these patients showed more frequently non-immediate reactions is not clear. One hypotesis is that premedication could be not adequate to prevent late reactions.

In our study, the rate of patients with at least one positive skin test (20.25%) is lower than that reported in some studies (5, 12, 14) but higher in comparison with others (11, 13), confirming the role of allergy workup in diagnosing and discriminating between cases with immunological and non-immunological pathogenesis. The time interval between reaction and evaluation is an important factor influencing the results and could be the reason for the significant more frequent positivity of test in patients with non-immediate hypersensitivity reactions, less influenced by this factor.

Of note, only 16% of our reactive group reported one or more previous ICM adverse reactions. This is described as the most important risk factor for ICM hypersensitivity reactions, with a variable frequency from 13 to 26 % (5, 12). In a recent study the incidence of HRs was about 20 times higher in patients with a previous history of ICM reactions than in those without (17).

The secondary aim of our study was to evaluate also the role of other potential risk factors related to ICM hypersensitivity, in order to obtain a risk stratification that may enable a "delabelling" of low-risk subjects, focusing attention on high-risk subjects. Literature is rich but inconclusive and sometimes contradictory on this topic (15-19). Our analysis confirmed the results of other studies about higher risk in female sex (20, 21), age < 65 years and a more frequent association with cardiovascular diseases (22, 23) in the reactive group.

Regardless of his endotype, bronchial asthma is often included in the list of risk factors for ICM HRs with an important difference in the strength of association (OR 2.0-OR 8.74) (18, 19, 21). In our study population, the small number of patients with bronchial asthma did not allow us to correctly analyze this topic. Probably, only uncontrolled asthma has to be considered a risk factor because it may increase the severity of HR. Such patients are often poor candidates for receiving contrast, and it is usually avoided by the treating radiologist (24).

In line with other studies reporting a prevalence of atopy ranging from 29 up to 50% (5, 11-13), in our reactive group history of allergy and/or ADRs was present in 37% [95% CI: 32%-42%]. Inhalant allergy (but not asthma) and ADRs resulted significantly associated with ICM HRs, whereas food allergy was not significantly associated. In literature, history of concomitant allergy or atopy, with or without a specific disease, is often mentioned as a risk factor, even in recent studies, reviews, and guidelines (6, 9, 18, 25). The importance of this association should be reduced considering that this concept seems passively transferred from one review to another, while observational studies usually report only anamnestic data, not confirmed by diagnostic tests. This is also true for our study where the level of statistical significance of these results is very low. At the end, this

Table II *- Factors related to ICM reactions.*

		Reactive group N = 407	**Control group N = 152**			
		n (%)	n (%)	p*	OR**	95% CI
Gender	Female	243 (60%)	67 (44%)	< 0.01	Rif	
	Male	164 (40%)	85 (56%)		0.5	0.4-0.8
Age (years)	< 65	208 (51%)	58 (39%)	< 0.01	Rif	
	≥ 65	198 (49%)	89 (61%)		0.6	0.4-0.9
First exposure				< 0.01	Rif	
	Yes	124 (35%)	29 (20%)		2.2	1.4-3.5
Pre-medication	Yes	78 (20%)	20 (14%)	0.141	Rif	0.9-2.5
					1.5	
Number of examinations in the last year	0	193 (60%)	21 (31%)	< 0.01	Rif	
	1-2	112 (35%)	15 (22%)		0.8	0.4-1.6
	≥ 3	17 (5%)	32 (47%)		0.0	0.0-0.1
Cardio-vascular disease				< 0.01	Rif	
	Yes	120 (29%)	25 (16%)		2.1	1.3-3.4
Respiratory allergy				< 0.01	Rif	
	Yes	71 (18%)	10 (7%)		3.0	1.5-6.0
Food allergy				0.049	Rif	
	Yes	25 (6 %)	3 (2 %)		3.3	1.0-0.9
Adverse Drug reactions				< .001	Rif	
	Yes	86 (22%)	15 (10 %)		2.5	1.4-2.6
ACE-inhibitors				0.249	Rif	
	Yes	54 (15%)	15 (11 %)		1.4	0.8-2.6
Angiothensin receptor blockers				0.352	Rif	
	Yes	35 (10%)	4 (7 %)		1.4	0.5-4.2

*Chi Square test; **univariate logistic model. The numbers within the categories do not have the total of 559 due to missing data.

Table III *- Factors associated to reactions (multivariate analysis).*

		OR	**p**	**95% CI**
Gender	Female	Rif		
	Male	0.51	0.002	0.33-0.77
Age (years)	< 65	Rif		
	≥ 65	0.60	0.020	0.39-0.92
First exposure	No	Rif		
	Yes	2.84	0.005	1.24-3.30
Cardio-vascular disease	No	Rif		
	Yes	2.06	0.007	1.22-3.50
Respiratory allergy	No	Rif		
	Yes	2.30	0.027	1.09-4.83
Food allergy	No	Rif		
	Yes	1.47	0.560	0.40-5.42
Adverse drug reactions	No	Rif		
	Yes	1.99	0.034	1.05-3.77

could suggest only a generic predisposing role of other allergic conditions towards hypersensitivity reactions to ICM.
We did not find a significant difference about some factors often reported as a cause of increased risk or increased severity of anaphylactic reactions such as use of some antihypertensive drugs (21, 26) and history of angioedema or mastocytosis (18), due to the rarity of cases in our study population.
Considering the variables related to the examination, in our study a significant difference between reactor and control subjects seems to indicate that the first exposure of life may represent a risk of reaction. Hypothesis confirmed in the multivariate analysis and discussed above. Conversely, the number of previous ICM examinations or their frequency is sometimes indicated among risk factors (18, 25). Of note, in our study the number of examinations in the last year before the reaction was significantly greater in the control group compared to the reactive one, probably due to the high number of oncologic patients, more frequently exposed to ICM-enhanced examinations. This result seems to confirm the hypothesis of a lower risk in subjects not susceptible who did not react at the first examination (27).
A recent Italian document about the management of patients at risk of HRs to contrast media proposes a classification in which only patients with associated active pathologies such as urticaria-angioedema, mastocytosis, uncontrolled asthma, history of idiopathic anaphylaxis, and patients with previous reactions to ICMs regardless of their severity, are considered at increased risk (28). All the other discussed risk factors are considered irrelevant. The future practical use of these guidelines is needed to confirm whether this is the right way to manage these patients.

Conclusions

This is a multicenter retrospective study on 407 patients evaluated for suspected hypersensitivity reactions to iodinated contrast media. Characteristics of patients and reactions are in line with other studies coming from different countries. One of the aims of the study was the evaluation of possible risk factors associated with HRs to ICM in order to obtain a risk stratification of patients. In summary, our data seem to suggest that these reactions could be the result of multiple factors acting together with different association in predisposed subjects: age, sex, allergic diseases, cardiovascular diseases, previous reactions to these agents and features of the contrast examination. This may be the reason for contradictory results in the literature and for the difficulty in obtaining a valid risk stratification. Among these factors, our study confirms the risk of reaction, mostly immediate and also with the possibility of severe anaphylaxis, in patients at their first contrast examination (35% of patients in this study): it deserves great attention among radiologists and others who administer these drugs. Future research will better clarify the mechanisms and may suggest some corrective action, for example, to reduce the ICM environmental contamination and consequent sensitization of general population (29). This study, of course, presents some limitations. First of all, the retrospective design limiting the interpretation of the results. In fact, the study may be affected by selection and detection bias and the lack of possible investigations about some concerns. The lack of some data represents a further limitation. Nevertheless, until now, it represents the largest study on patients with ICM hypersensitivity reactions in Italy. A prospective observational study would better assess various investigated or not investigated aspects of the topic.

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Conflict of interests

The authors declare that they have no conflict of interests.

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Isn't it time to consider oncological status as a new risk factor of iodinated contrast media hypersensitivity?

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Impact statement

This study finds an equivalent proportion of oncological and non-oncological patients in a population of patients with hypersensitivity to ICM. Oncological patients did not have other known risk factors, and they were less atopic suggesting a new risk factor.

Summary

Background. *The literature describes several risk factors for hypersensitivity (HS) reactions to iodinated contrast media (ICM).* ***Objective.*** *To analyze the characteristics of patients experiencing HS reactions to ICM with a focus on oncological status.* ***Methods.*** *All patients (n = 80) with suspected HS to ICM who underwent an allergy evaluation in a Belgian University Hospital over a 5-year period were retrospectively included.* ***Results.*** *Overall, forty patients (50%) had a history of neoplasia, and this group was characterized by less atopy (p < 0.004). No significant difference was observed between oncological and non-oncological patients in terms of gender, age, cardiovascular diseases, medical treatment, and number of previous exposures or reactions to ICM.* ***Conclusions.*** *A high proportion of oncological patients was observed in our population with HS to ICM. They did not have other known risk factors, and they were less atopic. Larger multicentric studies should explore cancer as a potential new risk factor.*

Introduction

Adverse reactions following the administration of iodinated contrast media (ICM) are a major concern for allergists and have been reported to occur in up to 3% of patients receiving nonionic ICM (1, 2). These events associated with ICM can lead to toxic reactions and immediate or delayed hypersensitivity (HS) reactions (2). The involvement of immune mechanisms was demonstrated over the past few decades in some of these HS reactions (3-5). In our daily practice, we have observed that oncological patients were frequently concerned by ICM HS reactions. Repeated exposures to ICM, which were previously described as risk factors, are particularly common in the oncological population (6, 7). Moreover, antineoplastic treatments as potential risk factors of these HS reactions have been the topic of some studies, although clear conclusions have yet to be drawn (8-11). The aim of our study was to analyze the characteristics

of patients evaluated for suspected ICM HS in our allergy unit while focusing on oncological status as a possible risk factor.

Materials and methods

This retrospective study included all patients who underwent an allergy assessment for a suspected ICM HS reaction (immediate or delayed) with the same specialist between January 2015 and December 2019 in the Department of Pneumology/Allergology of Cliniques Universitaires Saint-Luc (Brussels, Belgium). The evaluation was not limited to patients who experienced the reaction at our institution. The study was approved by the Commission d'Ethique Biomédicale Hospitalo-Facultaire UCL (2019/17JUL/325). Demographic and clinical data in addition to the findings of the allergy investigations were collected from medical records. Clinical symptom onset was classified as immediate (≤ 1 hour after administration) or delayed if occurring > 1 hour until 7 days later (12).
In the case of anaphylaxis (13), the severity level was defined by the Ring and Messmer classification (14). Immediate minor cutaneous manifestations (*e.g.*, isolated pruritus, localized urticaria), isolated malaise, or respiratory symptoms (*e.g.*, sneezing, nasal congestion, dyspnea, bronchospasm, cough) were considered to be non-anaphylactic isolated reactions. The severity of delayed reactions was classified according to Brockow *et al.* (2, 15).
Skin tests (ST) were performed in conformity with the European Academy of Allergy and Clinical Immunology (EAACI) recommendations (16, 17). Patients were initially tested with the suspected ICM. In the case of a positive ST, other available ICM were tested (ioxitalamate, ioxaglate, iopromide, iomeprol, iohexol, iobitridol, iodixanol) to document cross-sensitivity. If the nature of the suspected ICM was unknown while the observed reaction was highly suggestive of a true HS reaction, patients were tested with all the available ICM. Skin prick tests (SPT) were performed on the forearm with pure ICM commercial solutions combined with positive (histamine 10 mg/ml) and negative control tests (glycerinated solution). Intradermal tests (IDT) were then performed on the arm using 0.02 ml of 10-fold diluted solutions from 10^{-3} to 10^{-1} and a negative control IDT. To evaluate non-immediate hypersensitivity (NIHS) reactions in patients without delayed severe manifestations, IDT were performed with a reading from the 48th to 120th hours. Patients without well-documented atopy (n = 35) were also tested for common aeroallergens using standardized extracts (Stallergènes®, Antony, France). Latex sensitization was evaluated by SPT (Latex© ALK-Abelló solution, Almere, Netherlands). Chlorhexidine digluconate sensitization was screened by SPT and IDT (18). Both were also evaluated by specific IgE.
The level of total serum tryptase was measured by ImmunoCAP™ Tryptase (Thermofisher Scientific) in the acute phase and/or at the time of the allergy evaluation for the basal value (19).
Investigations were followed by a drug provocation test (DPT) for a subset of patients with manifestations suggestive of HS but with negative ST. ICM was administered intravenously every 30 minutes with increasing doses from a 10^{-2} diluted solution until reaching a tenth of the normal dose, adjusted for weight and renal function (20).
At the end of the allergy evaluation, patients were divided into different groups based on their clinical features and test results: 1) IgE-mediated immediate hypersensitivity (IHS) reactions proven by ST; 2) non-IgE-mediated immediate reactions with negative ST (pseudo-allergic group as suggested by Pichler (21)); 3) absence of hypersensitivity to ICM, including immediate reactions due to other mechanisms (type A reaction, panic attack, reaction due to another agent); 4) delayed reactions with immunological mechanisms proven by ST; and 5) delayed reactions with negative ST.

Statistical analysis

The normality of the distribution of the quantitative variables was tested the Shapiro-Wilks test. The parametric Student t test and non-parametric Mann-Whitney U test/Wilcoxon test were used to compare the means of independent serial data. The comparison of the distribution of qualitative criteria in two or more populations was performed using Fisher's exact test/Pearson's Chi-squared test. The limit of significance was set at $p = 0.05$. All statistical analyses were performed with the StatEL© software, version 2.17 (Ad Science Paris, France) and JMP pro software version 14 3.0 (jmp. Statistical Discovery™ from SAS, Cary USA).

Results

Eighty patients were evaluated for suspected HS following the administration of ICM. Their demographic data are shown in **table I**.
Overall, 31% of patients (n = 25) were referred by another institution: the median time interval before the allergy assessment was longer for these patients ($p < 0.01$) than for patients coming from our institution.
The culprit ICM was identified in 66 patients (82.5%): iobitridol (n = 39), iomeprol (n = 16), ioxitalamate (n = 8), iopromide (n = 4), iodixanol (n = 4), and ioxaglate (n = 2), while 7 patients received ioxitalamate concomitantly with another non-ionic ICM. The ICM was unknown for 14 patients (17.5%), 12 of whom came from other institutions ($p < 0.00001$).
At the time of the allergy workup, 36 patients (35%) were evaluated after a reaction on the first exposure, while the remaining 44 (55%) had been previously exposed to an ICM on at least one occasion. Among the 44 patients, 8 had already reported manifestations on the first exposure and 4 on another exposure (but without an allergy evaluation).
A total of 58 patients reported an immediate reaction (72.5%), while 21 had a non-immediate reaction (26.3%); for one patient, the chronology was imprecise.

Table I *- Demographic data of the population (n = 80).*

		P-value
Gender ratio, male/female, n (%)	29 (36.2)/51 (63.8)	
Patients referred from other institutions, n (%)	25 (31.2)	
Mean age at the time of the event, years ± SD	51.1 ± 17.2	
In our institution	55 ± 16.7	< 0.01 (Student test)
From other institutions	44 ± 15.5	
Median time between reaction and allergy assessment, months [min-max]	6 [0.75-396]	
In our institution	4 [0.75-185]	< 0.01 (Mann-Whitney)
From other institutions	36 [1-396]	
Cardiovascular disease, n (%)	39 (48,8)	
Personal atopya, n (%)	26 (32.5)	
Asthma	7 (26.9)	
Allergic rhinitis	12 (46.1)	
Known latex allergy prior the reaction	0 (0)	
Latex sensitization identified in ICM allergy assessment	4 (5)	
Neoplasia (active or past), n (%)	40 (50)	
Active neoplasia at the time of the incident	32 (80)	
Oncological treatment at the time of the incident	10 (25)	
Ongoing medical treatment, n (%)		
None	17 (21.25)	
ACE inhibitors or ARB	26 (32.5)	
Beta-blockers	22 (27.5)	
PPI	24 (30)	
Indication for ICM administration, n (%)		
Contrast-enhanced CT scan	64 (80)	
Coronary and peripheral angiography	8 (10)	
Intra-cavity opacification (arthrography, gynecological, digestive)	5 (6.2)	
Intravenous urography	2 (2.5)	
Unknown	1 (1.2)	
Previous exposure to ICM, n (%)	44 (55)	
Reaction on previous exposure	12 (27.2)	

[a]Documented previous allergy and asymptomatic patients with positive SPT; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; CT: computed tomography; ICM: iodinated contrast media; PPI: proton pump inhibitors.

Half of patients (n = 40) had a history of cancer. Cancer was active in 80% of cases (n = 32), and 10 patients were under treatment at the time of the reaction (5 on chemotherapy, 4 on targeted therapy, and 1 on immunotherapy). Their characteristics are described in **table II**. Oncological and non-oncological populations did not statistically differ in terms of age at the time of the incident, time interval to the allergy assessment, gender, previous exposure or history of a previous reaction with an ICM, as well as a reaction on the first exposure ($p > 0.05$). Personal atopy was more statistically frequent in the non-oncological group ($p < 0.004$).

In the immediate reaction group (n = 58) (**figure 1**), 24 patients (41.4%) reported manifestations consistent with anaphylaxis: 7 (12%) for grade 1, 10 (17%) for grade 2, 5 (9%) for grade 3, and 2 (3%) for grade 4. Furthermore, 34 patients (58.6%) described

Table II *- Characteristics of patients with and without a history of cancer.*

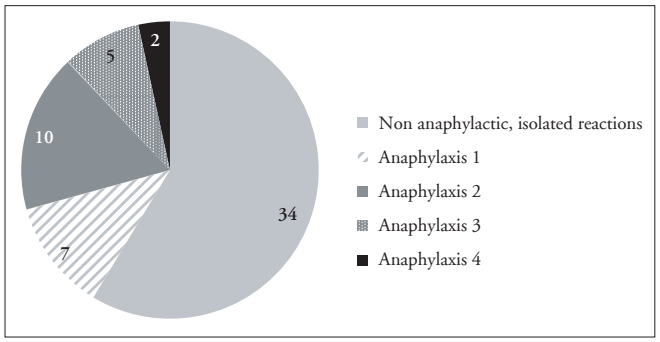
	Neoplasia (active or past) (n = 40)[a]	**No neoplasia (n = 40)**
Gender ratio, male/female, n (%)[b]	13 (32.5)/27 (67.5)	16 (40)/24 (60)
Median age at the time of the incident, years [min-max][b]	52 [18-85]	53 [9-80]
Median time until allergy assessment, months [min-max][b]	5 [1-180]	7.5 [0.75-396]
Cardiovascular disease, n (%)	18 (45)	21 (52.5)
Personal atopy, n (%)[c]	7 (17.5)	19 (47.5)
Rhinitis	3 (7.5)	9 (22.5)
Asthma	2 (5)	5 (12.5)
Latex sensitization	1 (2.5)	3 (7.5)
Previous exposure to ICM, n (%)[b]	25 (62.5)	19 (45.5)
Reaction on previous exposure	8 (20)	4 (10)
Current treatment, n (%)[b]		
ACE inhibitors or ARB	10 (25)	14 (35)
Beta-blockers	9 (45)	12 (30)
Chronology of reaction, n (%)[b]		
Immediate	30 (75)	28 (70)
Delayed	10 (25)	11 (27.5)
Unknown	0 (0)	1 (2.5)
Severity of immediate reaction, n (%)[b]		
Anaphylaxis grades 1-2	10 (25)	7 (17.5)
Anaphylaxis grades 3-4	5 (12.5)	2 (5)
Non-anaphylactic isolated reactions	15 (37.5)	19 (47.5)
Severity of delayed reaction, n (%)[b]		
Mild	3 (7.5)	7 (17.5)
Moderate	7 (17.5)	4 (10)
Positive ST to ICM, n (%)[b]	10 (25)	5 (12.5)
Immediate ST	6 (15)	3 (7.5)
Delayed ST	4 (10)	2 (5)

ACE: angiotensin-converting enzyme; ARBs: angiotensin II receptor blockers; ICM: iodinated contrast media; ST: skin test; [a]types of neoplasia were as follows: 11 digestive (27.5%), 8 urologic or gynecologic (20%), 7 hematologic (17.5%), 7 breast (17.5%), 5 lung (12.5%) and 5 (12.5%) other types of cancer. Three patients had multiple cancers; [b]between-group differences for the different criteria are not statistically significant (Mann-Whitney and Fisher exact tests, $p > 0.05$); [c]between-group difference is statistically significant ($p < 0.004$, Chi^2 test).

non-anaphylactic isolated reactions: 9 with isolated respiratory symptoms, 13 with local cutaneous manifestations, 3 with malaises, and 9 with other/unknown reactions). Non-immediate manifestations (n = 21) were mostly cutaneous (95%) of mild to moderate severity.

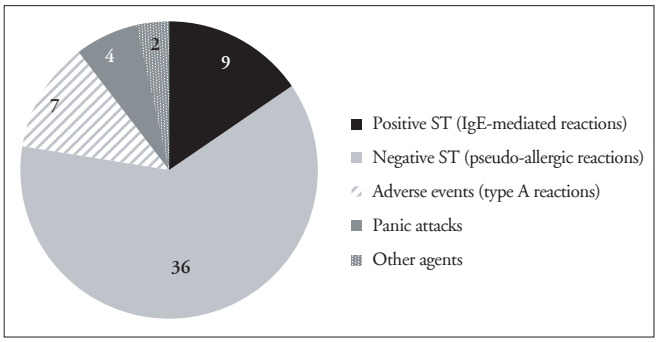
A total of 15 patients (18.75%) had a positive ST to at least one ICM associated with their culprit: 9 with immediate ST (60%) and 6 (40%) with delayed ST. ST with the suspected ICM were positive in 12 patients (80%) with iobitridol (7 immediate, 5 delayed), in 2 patients (13.3%) with iomeprol (1 immediate, 1 delayed), and in 1 patient (6.7%) with iopromide (immediate). For 2 patients, a responsible agent other than ICM was identified with ST and specific IgE (1 anaphylaxis of grade II to latex, 1 anaphylaxis of grade III to gelatin) (**figure 2**). A DPT also confirmed ICM HS in 2 patients (1 IHS, 1 NIHS).

Figure 1 *- Distribution of the clinical manifestations in immediate reactions (n = 58).*



The severity of anaphylactic reactions is graded according to the Ring and Messmer scale (14). Non-anaphylactic isolated reactions include local or mono-systemic symptoms such as isolated respiratory symptoms, local cutaneous manifestations, malaises, and other reactions/undetermined.

Figure 2 *- Classification of immediate reactions based on skin test results and symptoms (n = 58).*



Reactions to other agents refer to hypersensitivity to latex (n = 1) and gelatin (n = 1).

Personal atopy was found in 26 patients (32.5%) with at least one positive SPT for common aeroallergens (excluding latex). Latex sensitization, which was assessed by SPT (n = 30) and specific IgE (n = 12), was positive for 4 patients, who had a concomitant sensitization to at least one other aeroallergen. Sensitization to chlorhexidine was evaluated in 32 patients and was negative. No case of mastocytosis was suspected after the allergy evaluation.
In the immediate manifestation group, 14 patients who reported symptoms suggestive of grade 1 to 3 anaphylaxis had negative ST and were finally classified in the pseudo-allergic group (**figure 3**). Although the vast majority (95.6%) of patients with non-anaphylactic isolated symptoms (not attributed to panic attacks or adverse events) had negative ST, one patient nevertheless had positive ST. Both patients with grade 4 anaphylaxis had positive ST. For patients with non-immediate manifestations (n = 21), 28.6% had positive delayed ST, suggestive of a T-cell-mediated allergic mechanism.

Cross-sensitization

In patients with immediate positive ST (**table III a,** n = 9), 4 were mono-sensitized and 5 (55%) had at least one cross-sensitization documented by ST. All patients with positive delayed ST (**table III b**, n = 6), had at least one cross-sensitization. These allergic patients were advised to receive an ICM for which the ST were negative.

Re-exposure

Re-exposure to ICM occurred in 55% of patients (32 with immediate and 12 with delayed initial reactions) and was well tolerated for 97.7% of them: 31.8% were re-exposed to their culprit ICM with negative ST, 13.6% received an ICM tolerated during DPT, and 13.6% with positive ST received an alternative ICM for which they tested negative.

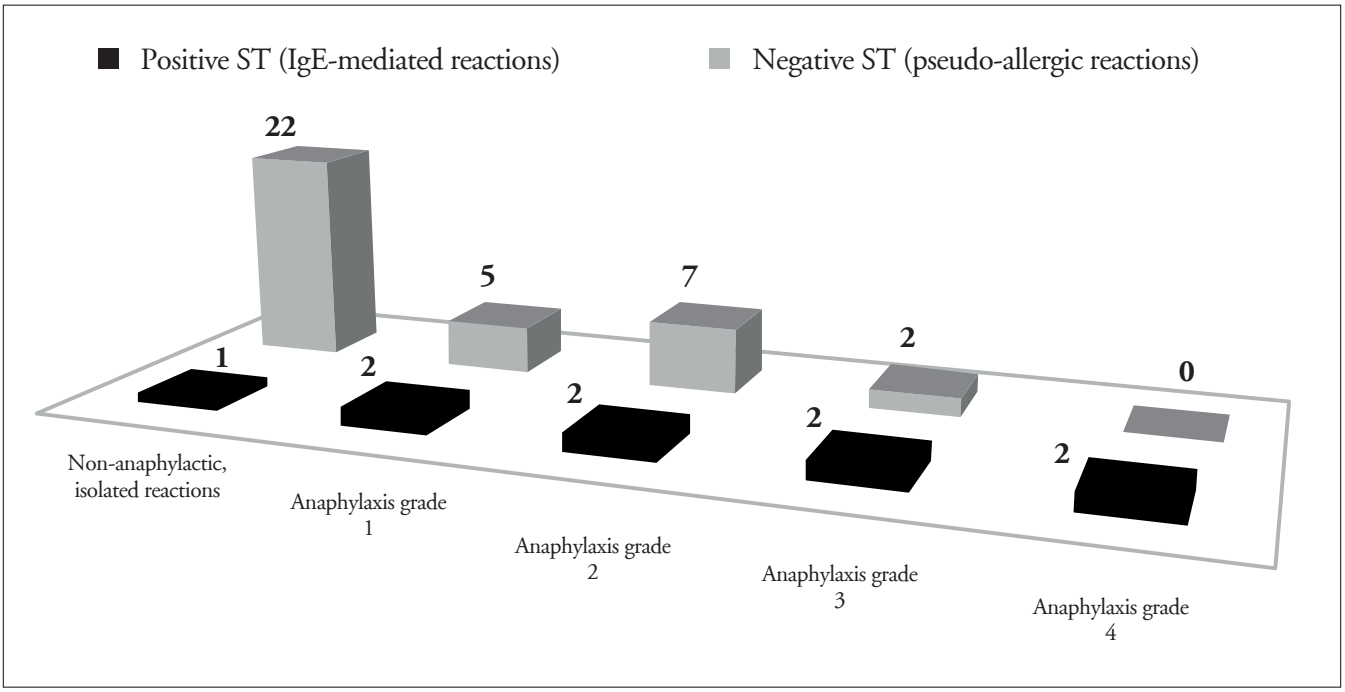
Subgroup analyses

Univariate analyses were conducted on the 45 patients from two sub-groups experiencing immediate reactions (group 1: IgE-mediated; group 2: IHS with negative ST "pseudo-allergic"), including several co-factors (gender, cardiovascular disease, age, history of active or past neoplasia, personal atopy, ongoing medical treatment, number of previous exposures and previous reactions to ICM). Patients with cardiovascular diseases (hypertension, ischemia, or valve disease) were significantly older at the time of the reaction than those without ($p < 0.02$). Nevertheless, none of the criteria were associated with a higher incidence of IHS reaction to ICM. Although drugs like ACE inhibitors, ARBs ($p < 0.0001$), statins ($p < 0.001$), and proton pump inhibitors (PPI) ($p < 0.05$) were more often prescribed to patients with cardiovascular diseases, cardiovascular risk was not identified as a risk factor of ICM IHS reaction in our study. Oncological patients (past and/or active cancer) with IHS (n = 21) did not differ statistically from non-oncological patients concerning gender, age, cardiovascular disease, number of previous exposures, history of previous reactions to ICM, or asthma. However, they were characterized by less allergic rhinitis ($p < 0.05$) and tendency toward less personal atopy ($p = 0.05$).

Discussion

Our study included 80 patients, including 58 with an immediate clinical reaction of HS to ICM, 21 with a delayed reaction, and 1 unclassifiable patient. An immunological HS to ICM was documented for 17 patients (21.3%): 15 patients by ST (18.75%) including 9 with an IHS and 6 with a NIHS, and 2 patients (2.5%) by DPT (1 IHS, 1 NIHS).
A high proportion of oncological patients was observed in our study. Indeed, 40 patients (50%) had a history of cancer at the time of the

Figure 3 *- Distribution of patients according to the severity of their immediate clinical reactions and the mechanism involved (n = 45).*



Reactions due to agents other than iodinated contrast media, panic attacks, and adverse events are excluded.

reaction. To our knowledge, in previous studies, oncological status was rarely mentioned in the population characteristics. Moreover, our oncological group did not have more known risk factors.

Risk factors for HS reactions to ICM are not fully established and are still matter of debate. In line with other authors, a recent multicentric Italian study comparing reactive and control groups reported female gender, age ≤ 65 years, first ICM exposure, cardiovascular diseases, and respiratory allergy to be significant risk factors for ICM HS in multivariate analysis (22). Previous studies also mention asthma, treatment with ACE inhibitors, beta-blockers, or proton pump inhibitors, previous or repeated ICM administrations, and mastocytosis to be risk factors (6, 23-27). The main risk factor seems to be a previous reaction, even if a significant number of subjects experienced HS to ICM on the first exposure (4, 22). In our study, no significant difference was observed in terms of gender, age, ongoing medical treatment, previous exposure, previous reaction, and reaction on the first exposure for oncological patients, although these results could be biased by our small population size. However, the oncological population was characterized by a lower incidence of personal atopy ($p < 0.004$). This suggests that oncological diseases and/or their specific treatment could be a risk factor for reaction to ICM.

In the literature, cancer and/or its treatment have not yet been clearly identified as risk factors, as these topics have been poorly studied to date. The incidence of IHS reactions to ICM was higher in patients with cancer (2.1% *vs* 1.1% for patients without cancer, $p < 0.001$) in a cohort of 86,328 patients (23) who underwent an enhanced computed tomography (CT) scan, but evidence is lacking regarding the association between oncological status and HS reactions to ICM. Repeated administrations of ICM are common in the oncological population and may lead to a higher risk of adverse reactions. Fujiwara *et al.* (7) retrospectively reviewed 1,861 patients with hepatocellular carcinoma and showed an increased risk of adverse reactions with repeated exposures. In our study, even though oncological patients were exposed to ICM more frequently but not significantly compared to non-oncological patients (62.5% *vs* 45.5%, $p > 0.05$), previous reactions were not reported more often (20% *vs* 10%, $p > 0.05$). In our recent survey, 10 patients (8%) who experienced HS reactions to ICM were receiving oncological treatment at the time of the event, with half of them under immunotherapy or targeted therapy. The association between oncological treatments and the risk of adverse reactions to ICM has been the topic of very few studies. Farolfi *et al.* (8) reviewed 1,878 cancer subjects who underwent a contrast-enhanced CT scan within 30 days of their last chemotherapy and did not find any correlation between time to CT and the risk of acute ICM adverse reactions. Concomitant treatment with taxane-based chemotherapy was reported as a risk factor for acute adverse reactions to ICM compared to the non-treatment group in a cohort of 3,804 oncological patients (9). Few cases of anaphylaxis in oncological patients

Table III *- Cross-sensitivity patterns for patients with immediate* ***(a)*** *and delayed* ***(b)*** *hypersensitivity (HS) reactions to iodinated contrast media (ICM).*

a (n = 9)	**Immediate HS**							
	Cross-sensitivity							
Culprit ICM	Ioxitalamate	Ioxaglate	Iopromide	Iomeprol	Iohexol	Ioversol	Iobitridol	Iodixanol
Iopromide (n = 1)								
Iomeprol (n = 1)					A1			A1
Iobitridol (n = 7)			A3, A6, A8	A7				A6
b (n = 6)	**Non-immediate HS**							
	Cross-sensitivity							
Culprit ICM	Ioxitalamate	Ioxaglate	Iopromide	Iomeprol	Iohexol	Ioversol	Iobitridol	Iodixanol
Iomeprol (n = 2)			B4		B4		B1	B4
Iobitridol (n = 4)			B2, B3, B5	B2, B3	B5			B2, B3, B5, B6

treated with immunotherapy following a contrast-enhanced CT scan have also been described (10, 11), particularly ipilimumab and nivolumab. As these therapeutic options are relatively recent, it could be a new risk factor to monitor. Interestingly, personal atopy was observed significantly less in our oncological group ($p < 0.004$). Moreover, this was confirmed for oncological patients with IHS in whom allergic rhinitis was less frequent ($p < 0.05$). Previous studies (28-32) obtained mixed results about the association between atopic diseases and the risk of cancer.

For example, asthmatic patients had a greater risk of cancer, including lung cancer (33), although the phenotype seemed to play a major role as the incidence of cancer was higher in non-atopic than in atopic asthma (34). Nevertheless, the dominant picture emerging from the majority of epidemiological data (28, 32, 35, 36) indicates that several atopic diseases (asthma, atopic dermatitis, and allergic rhinitis) were associated with a lower incidence of cancer, which supports our results.

The sensitivity of ST varies widely among studies, ranging from 4.2% to 73% (4, 5, 22, 37-44) depending on the clinical severity and the time interval between the reaction and ST. A meta-analysis of 21 studies (45) showed positive ST rates of 17% in patients with IHS reactions and up to 52% when limited to severe IHS reactions. In a prospective multicentric study (4), ST were positive for 50% of IHS and 47% of NIHS reactions when performed within 6 months after the reaction, dropping to 18% for IHS and 22% for NIHS reactions investigated after 6 months. Our rate of positive ST could be explained by the large proportion of patients (87.9%) with light and mild immediate symptoms (non-anaphylactic with isolated reactions and grades 1-2 of anaphylaxis). Nevertheless, it was interesting to note that these symptoms could rarely be induced by immunological mechanisms (8.6%). This was previously reported by Clement *et al.* (44) and could probably be an argument to perform an allergy evaluation even if the symptoms are minor. As in previous studies (37, 39, 42-44), several cases of severe anaphylaxis (≥ grade 3) following ICM administration had negative ST. New concepts to explain non-IgE-mediated anaphylactic reactions to ICM are emerging such as the Mas-related G protein-coupled receptor X2 (MRGPRX2) (21, 46).

Our rate of positive ST was also influenced by the time until allergy workup, as nearly half of patients (48.75%) were evaluated within 6 months of the event, and ST were positive in 30.8% of cases, falling to 7.3% after this time. This interval was significantly longer for patients who developed their reaction in another institution, which was further characterized by a higher proportion of unknown administered ICM (48% *vs* 3.6% in our institution). DPT was useful to highlight a possible immunological mechanism for a subset of patients (2.5%) with negative ST. Nevertheless, this procedure was not systematically

performed, and there is still no consensus regarding its role in the diagnostic algorithm of ICM HS (47, 48).
Several examples of cross-sensitivity have been described in the literature (4, 5, 37, 38, 40-43, 49, 50) with various patterns and may be observed in up to 69% of NIHS reactions, less commonly in the case of IHS. It has been reported that iobitridol showed less cross-sensitivity than other ICM in the case of NIHS (51). We found cross-sensitivity in 11 patients (73.3%), 5 with IHS and 6 with NIHS. Iobitridol was the most reported culprit ICM in our study and frequently involved in cross-sensitivity reactions (81.2%), contrary to previous studies where it was also administrated less often. In fact, it is the most commonly used ICM in our institution, representing almost 60% of ICM administrations.

Conclusions

In conclusion, our study was characterized by a particularly large oncological population of patients with HS reactions to ICM. It is difficult to confirm whether cancer and its treatment are risk factors of these events, as we were limited by the small population size. In the future, greater attention should be given to emerging oncological therapies, which could be new potential risk factors. These topics should be investigated in larger multicentric studies with cohorts of both oncological and non-oncological patients. We need evidence to prove that the risk is not only due to the number of previous exposures or previous reactions to ICM in the oncological group. The role of atopy should also be evaluated in this particular population.

Contributors

PD: collection, analysis and interpretation of data, redaction of the manuscript. FP: acquisition, statistical analysis of data, supervision and critical revision of the manuscript.

Conflict of interests

The authors declare that they have no conflict of interests.

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Subcutaneous immunotherapy with aeroallergens: safety profile assessment

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Key words

Allergy; subcutaneous immunotherapy; safety; local reaction; systemic reaction.

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Summary

Introduction*. Severe systemic reactions (SR) to allergen subcutaneous immunotherapy (SCIT) are rare but local reactions (LR) are common. We aimed to characterize the type of reactions and safety profile.* ***Methods****. Retrospective analysis of medical record from patients under SCIT between 2013-2016.* ***Results.*** *Total of 7372 SCIT injections in 323 patients: 52% female; mean age 30 years (SD 13); mean treatment time 19 months (SD 13). There were 57 patients (17.6% of population, 70% female) with at least one adverse reaction, for 93 reactions described (1.3% injections). There were 79 LR (1.1% injections) in 46 (14.2%) patients: 36 in build-up, 43 in maintenance. There were 14 SR (0.19% injections) in 12 (3.7%) patients: 12 in build-up, 2 in maintenance. All SR were grade 1. The majority of reactions were caused by mite SCIT (69.9%).* ***Conclusions.*** *SCIT is safe and well tolerated, with no report of SR grade > 1.*

Impact statement

Local and systemic reactions after subcutaneous immunotherapy with aeroallergens were analyzed. It was shown that this treatment was well tolerated and had a good safety profile, with no report of severe systemic reactions.

Introduction

Respiratory allergy (allergic rhinitis and asthma) is caused by airborne allergens (dust mite, pollen, fungi, cat and dog epithelium) that when inhaled can trigger airway inflammation in susceptible individuals. Management of respiratory allergy includes allergen avoidance and pharmacotherapy (1). There are some patients who remain symptomatic besides being under treatment. In these cases, allergen immunotherapy (AIT) should be considered (2). Strong evidence suggests that subcutaneous immunotherapy (SCIT) improves symptoms, medication use, and quality of life in these patients (3). AIT is the only treatment that modify the natural history of allergic disease by reducing symptoms upon exposure to aeroallergens (4). During immunotherapy, there is an initial increase of specific IgE (sIgE) levels followed by a progressive decrease. It is also verified an increase in $CD4^+CD25^+$ regulatory T lymphocytes, secreting IL-10 and TGF-ß, which are associated with immunologic tolerance. During treatment, IgG antibodies subtypes, IgG_4 and IgG_1, increase about 10 to 100 times. These subtypes are non-inflammatory with inhibitory activity: they can prevent allergic reaction by conjugating with the allergen, before its binding with IgE, avoiding mastocyte and basophil activation with release of inflammatory mediators. Progressively, immunotherapy acts on T cells to modify peripheral and mucosal Th2 (responsible for allergic reaction) reactions to allergen promoting a Th1 cytokine profile (5, 6). The two major modalities for AIT are subcutaneous and sublingual. SCIT, was introduced more than 100 years ago (7). Immune tolerance is obtained through the administration of increasing amounts

of the same allergen responsible for the allergic symptoms in sensitized individuals.

Adverse reactions may occur, ranging from mild symptoms at the site of injection to anaphylactic reactions (8). They can be classified as either local or systemic reactions and the majority of systemic reactions (SR) occur within 30 minutes of injection, according to European Academy of Allergy and Clinical Immunology (EAACI) guidelines (9, 10). Local reactions (LR) are fairly common, affecting 26% to 82% of the patients and 0.7% to 4% of injections (11-13). They can occur as redness, itching or swelling at the site of injection. They are considered to be large when erythema or swelling diameter is greater than the size of patients' palm (average adult, 8-10 cm) (14). SR are characterized by the occurrence of systemic symptoms, with different severity grades, from mild (Grade 1) to severe systemic reactions, potentially fatal (Grade 5), according to World Allergy Organization (WAO) Subcutaneous Immunotherapy Systemic Reaction Grading System (15). They are less common, affecting 2% to 5% of the patients and 0.1% to 0.2% of injections (15, 16).

The frequency of SR induced by SCIT varies widely according to the allergen extract used, the administration buildup protocol (conventional, cluster or rush), the maintenance dose administered and the severity and type of disease (17-19). The first fatal reaction was described by Lamson RW in 1924 (20). History of uncontrolled or severe asthma is the most important contributing factor for the occurrence of fatal reactions. Other recognized risk factors include dosing errors, a delay in the/no administration of epinephrine during anaphylaxis or concomitant treatment with ß-blockers, a prior history of injection-related SR and administration of SCIT during peak pollen season or an inadequate surveillance period after injection (3, 4, 8, 16, 21). The risk of SR was found to be lower in dust-mite sensitized patients compared with pollen-allergic patients (22). The objectives of this retrospective database review were to characterize the type of reactions after SCIT administration: LR or SR, late or immediate reactions and analyze the safety profile of SCIT in patients.

Methods

Population and study design

Retrospective review of the medical records from patients submitted to SCIT from January 2013 to December 2016, in our Immunotherapy Center (Immunoallergology Outpatient Clinic of Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte). Demographic data (age and gender), diagnosis of allergic diseases (rhinitis, asthma, atopic dermatitis, conjunctivitis or food allergy), aeroallergen sensitization, SCIT composition, date of initiation, duration and SCIT administration schedule were registered. The occurrence of local and systemic reactions was verified by analyzing clinical and nursing records of each patient. There were excluded patients receiving injections at another facility or missing information in patient's medical records concerning SCIT administration. A written informed consent was obtained from all patients and/or their legal representatives before initiating SCIT. The diagnosis, severity and treatment of allergic rhinitis and asthma were established according to the current guidelines − Allergic Rhinitis and its Impact on Asthma (ARIA) (23) and Global Initiative for Asthma (24) −, respectively.

Skin tests and specific IgE

Roxall's® (Hamburg, Deutschland) allergen extracts were used for skin prick tests and serum specific IgE (sIgE) tests were from ImmunoCAP system® (Thermo Fisher Scientific, Uppsala, Sweden). Regarding skin prick tests, all patients were tested with the following allergens: house dust mites, storage mites, pollens (grass, parietaria, olive tree and artemisia), cat and dog epithelium. All patients had positive skin prick tests and/or sIgE tests ≥ 0.70 kU/L, to at least one aeroallergen.

Subcutaneous immunotherapy

SCIT was initiated in patients with allergic symptoms despite being under medical treatment and allergen avoidance. It was chosen considering the results of skin prick tests and/or sIgE tests and by correlating them with patients' symptoms, according to EAACI Guidelines on Allergen Immunotherapy (10) and GA²LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma (25). The route of therapy (subcutaneous) was prescribed taking into consideration the patient's preference, allergic symptoms and personal concerns. All used extracts were polymerized, chemically and physically modified (allergoids), conditioning less allergenicity and increasing efficiency and safety.

Build-up phase was administered as conventional or rush protocols and the maintenance dose was administered at four-to-six-week intervals over a period of three to five years. All injections were given by trained nurses with supervision of the immunoallergologist in the Immunotherapy Center, equipped with material for the treatment of systemic reactions. All patients were monitored for 30 minutes after the SCIT administration.

Safety was studied by analyzing the occurrence of LR and SR, immediate and late reactions (according to the EAACI Immunotherapy Position Paper (26)) and correlating it with the SCIT composition, in order to determine safety profile. Local reactions were classified by measuring the largest reaction diameter. There is no consensus in relation to large local reactions diameter, so we considered local reactions to be large if redness or swelling had > 10 cm of diameter (10). Systemic reactions were classified in grades 1 to 5 (WAO Subcutaneous Systemic Reaction Grading System (15)). Immediate reactions were those which occurred in the first 30 minutes after injection.

Data were anonymized, and their confidentiality guaranteed, and this study protocol was approved by the Ethical Board of Centro Hospitalar Universitário de Lisboa Norte.

Statistical analysis

It was analyzed and compared the groups of patients with and without adverse reactions after SCIT (age, gender, clinical diagnosis, involved SCIT extract) and which factors were associated with its occurrence. Continuous variables were presented as means and standard deviations, or medians and interquartile ranges for variables with skewed distributions, and categorical variables as frequencies and percentages. Normal distribution was confirmed using Shapiro-Wilk test or skewness and kurtosis. For bivariate analysis, t-independent test and Mann-Whitney test were used to compare parametric and non-parametric independent samples, respectively. Categorical variables were compared using Fisher's exact test or the Chi-square test, as appropriate. P-values < 0.05 were considered statistically significant. Analyses were performed using version 27 of SPSS software for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

From a total of 631 patients under SCIT during the study period, 323 patients were included and 308 excluded due to data unavailability. According to the demographic data (**table I**), there was a predominance of female gender (n = 167; 52%), the mean age of the patients was 30 years (SD 13; range 7-73). The age group between 18 and 30 years was the most prevalent with 45% (n = 145), followed by the one between 31 and 50 years with 31.5% (n = 102), between 7 and 17 with 16.4% (n = 53) and the group over 50 years was the least prevalent (n = 23; 7.1%).

The average treatment time was 19.2 months (SD 13) and induction protocol was rush in 78.6% of the patients. Regarding the SCIT composition, there was a predominance of dust mite allergen (n = 220; 68.3%). More information about SCIT composition and patients' diagnosis is detailed in **table I**.

All patients had allergic respiratory disease, with rhinitis being the most frequent diagnosis (n = 313; 97%), followed by asthma (n = 145; 45%), about 40% of patients had concomitant asthma and rhinitis. There were also patients with conjunctivitis (n = 92; 28.5%), atopic dermatitis (n = 52; 16%) and less frequently food allergy (n = 30; 9%).

In the 323 patients included, 7372 SCIT injections (mean 22 injections/patient) were administered.

There were 57 patients (17.6% of the population) with, at least, one adverse reaction: 40 (70%) were female (comparing both genders, the number of adverse reactions was significantly higher in female (P-value = 0.002)), mean age 30.8 years (SD 11.4). The majority (n = 55; 96.5%) had rhinitis, 26 (45.6%) asthma, 16 (28.1%) conjunctivitis, 8 (14%) atopic dermatitis and 3 (5.3%) had food allergy. The age group 18-30 years was more affected, with 33 patients (57.9%) reporting a reaction.

Regarding SCIT composition of the 57 patients with adverse reactions, 65.0% were under mite allergen SCIT (the number of reactions was significantly higher with *Dermatophagoides pteronyssinus* and/or *farinae* (P-value 0.04) and with *Dermatophagoides* plus another mite (P-value 0.002)), followed by pollen (28.0%) and by mite and pollen (7.0%) SCIT. By analysing SCIT composition per reaction, the result is similar: mites were responsible for the majority (65 reactions; 69.9%), followed by pollen (26 reactions; 28.0%) and by mite and pollen (2 reactions; 2.1%). We also observed that from the patients under mite SCIT, 16.8% had an adverse reaction and from the patients under pollen SCIT and 18.0% had an adverse reaction. In a total of 93 adverse reactions described (1.3% of the SCIT injections), 48 (51.6%) were on the build-up and 45 (48.4%) on the maintenance phase (**table II**).

Local reactions

Regarding local reactions (LR), 46 patients (14.2%) had at least one LR, 32 (69.6%) female, mean age 32.3 years (SD 11.8, range 15-57), of a total of 79 (1.1% of the total injections) reactions described: 36 in the build-up phase (17 were immediate, all presented with local edema between 8 and 10 cm; 19 were late, only 5 with local edema > 10 cm) and 43 in the maintenance phase (18 immediate and 25 late reactions).

Only five of the build-up LR, were during a conventional protocol, while the others were during rush protocol.

From the 79 LR, two patients had six, three patients had five LR and the remaining had just one LR. The two patients who had six LR, both were female, under mite allergen SCIT; one of them quit SCIT because of frequent and severe local adverse reactions. The patients that had five LR each, all were female, two were under mite allergen SCIT and the other was under pollen SCIT. None of them quit SCIT during the studied period. No systemic reaction observed in these five patients (**table III**).

Systemic reactions

Regarding systemic reactions (SR), there were 14 (0.19% of the injections) in 12 (3.7%) patients: 66.7% female, mean age 25.9 years (SD 6.0, range 19-41). All were grade 1 (generalized pruritus). The majority (78.6%) were immediate, during build-up (85.7%) and more than a half (8; 57%) occurred in asthmatic patients: five were under mite SCIT, two pollen SCIT and one mite and pollen SCIT (**table IV**).

No fatal reactions were registered. All SR during build-up phase were in rush protocols. Oral antihistamines were given to each patient with SR; no patient received epinephrine and/or systemic corticosteroids.

Discussion

In our population, LR were very common (frequency of adverse drug reaction ≥ 10% (27)), once they occurred in 14.2% of the patients and 1.1% of the administered injections. Although the percentage of patients with LR is below of the values reported in other important

Table I - *Demographic and clinical data from patients under subcutaneous immunotherapy, total population and patients with adverse reactions.*

Variables	Patients			P-value
	Total (n = 323; 100%)	**Without Adverse Reactions (n = 266; 82.4%)**	**With Adverse Reactions (n = 57; 17.6%)**	
Age [mean (SD)] years	30 (SD 13.0)	29 (SD 13)	31 (SD 11.4)	0.227
Age groups				
[7 – 17] n (%)	53 (16.4)	50 (18.8)	3 (5.3)	
[18 – 30] n (%)	145 (45)	112 (42.1)	33 (57.9)	
[31 – 50] n (%)	102 (31.5)	87 (32.7)	15 (26.3)	
[51-65] n (%)	23 (7.1)	17 (6.4)	6 (10.5)	
Gender				0.002
Female n (%)	167 (52)	127 (48)	40 (70)	
Male n (%)	156 (48)	139 (52)	17 (30)	
Clinical diagnosis				
Rhinitis n (%)	313 (97)	258 (97)	55 (96.5)	0.692
Asthma n (%)	145 (45)	119 (44.7)	26 (45.6)	0.530
Rhinitis and Asthma n (%)	129 (40)	103 (38.7)	26 (45.6)	0.769
Conjunctivitis n (%)	92 (28.5)	76 (29)	16 (28.1)	0.540
Rhinitis and Conjunctivitis (%)	91 (28.2)	75 (28.2)	16 (28.1)	0.563
Atopic dermatitis n (%)	52 (16)	44 (16.5)	8 (14)	0.697
Food allergy n (%)	30 (9)	27 (10)	3 (5.3)	0.227
Allergen Immunotherapy extract				
Dermatophagoides (*pteronyssinus* and/or *farinae*) n (%)	172 (53.4)	149 (56)	23 (40.4)	0.04
Dermatophagoides + another mite n (%)	41 (12.7)	27 (10.2)	14 (24.6)	0.002
Storage mites n (%)	7 (2.2)	7 (2.6)	0	0.611
Dermatophagoides + pollen n (%)	13 (4)	9 (3.4)	4 (7.0)	0.590
Grass n (%)	66 (20.4)	54 (20.3)	12 (21.0)	0.488
Parietaria n (%)	10 (3.1)	9 (3.4)	1 (1.7)	0.448
Grass + olive tree n (%)	5 (1.5)	2 (0.8)	3 (5.3)	0.083
Grass + parietaria n (%)	4 (1.2)	4 (1.6)	0	0.458
Grass + artemisia n (%)	2 (0.6)	2 (0.8)	0	0.322
Olive tree n (%)	2 (0.6)	2 (0.8)	0	0.322
Cat epithelium n (%)	1 (0.3)	1 (0.4)	0	0.824

SD: standard deviation.

Table II - *Number of adverse reactions during Subcutaneous Immunotherapy (SCIT).*

Reactions	Build-up			Maintenance			
	Immediate	**Non-Immediate**	**Total**	**Immediate**	**Non-Immediate**	**Total**	
Local (n)	17	19	36	18	25	43	**79**
Systemic (n)	9	3	12	2	0	2	**14**
Total (n)	26	22	**48**	20	25	**45**	**93**

papers (26 to 82% of the patients (11-13)), our percentage of LR per injection, is in line with literature (0.7 to 4% of injections (11-13)). In relation to SR, our data relative to percentage of patients and injections (3.7% and 0.19%, respectively) is in accordance with literature (2 to 5% and 0.1 to 0.2% (15, 16), respectively).

Although some patients with a greater frequency of large LR might be at increased risk of SR (14, 28, 29), published studies suggest that individual LR are not predictive of future SR. In fact, our five patients with more LR did not have subsequent SR. They were instructed to maintain their medication with antihis-

Table III - *Patients with recurrent Local Reactions (LR).*

Patient	Gender	Age	SCIT Allergen	N. reactions	Quit SCIT	Adverse reactions	
						Build up	Maintenance
1	F	29	Mite	6	No	1 non-immediate LR > 10 cm	6 non-immediate LR
2	F	26	Mite	6	Yes	1 immediate LR 8-10 cm	5 non-immediate LR
3	F	51	Mite	5	No	1 non-immediate LR > 10 cm	4 non-immediate LR
4	F	41	Mite	5	No	1 immediate LR 8-10 cm	4 immediate LR
5	F	54	Pollen	5	No	1 immediate LR 8-10 cm	2 immediate LR 3 non-immediate LR

M: male; F: female; LR: local reactions; SCIT: subcutaneous immunotherapy.

Table IV - *Patients with Systemic Reactions.*

Patient	Gender	Age	Allergic disease	SCIT Allergen	Buildup	Maintenance
1	M	31	R, A	Pollen	Grade 1	Grade 1
2	M	30	R, A	Mite	Grade 1	-
3	F	29	R, A, FA	Pollen	Grade 1	Grade 1
4	M	19	R, A	Mite + Pollen	Grade 1	-
5	F	24	R, A, AD	Mite	Grade 1	-
6	F	22	R	Mite	Grade 1	-
7	F	28	R, A, AD	Mite	Grade 1	-
8	M	23	R	Mite	Grade 1	-
9	F	20	R	Mite	Grade 1	-
10	F	41	R, A	Mite	Grade 1	-
11	F	20	R, A	Mite	Grade 1	-
12	F	24	R	Pollen	Grade 1	-

M: male; F: female; R: rhinitis; A: asthma; FA: food allergy; AD: atopic dermatitis; SCIT: subcutaneous immunotherapy.

tamines, in order to minimize the occurrence of adverse reactions after SCIT. Only one of them had to quit SCIT because of frequent LR, as it was impossible to reach the maintenance dose.

As many studies suggest (28, 30, 31), SR are most frequently reported within the first 30 minutes after the administration (immediate reactions) and during the build-up phase, mainly in rush protocols. In our population, 85.7% of the SR were at build-up phase (all during rush protocols) and 78.6% were immediate. From this perspective and as it is recommended, SCIT was administered in the outpatient visit and all patients stay in surveillance for at least 30 minutes, so that severe reactions were promptly assisted.

Many studies do not report differences between male and female nor between adults and children in the occurrence of adverse reactions (32-34). We verified that female had much more reactions (n = 40; 70%) than male. Even in systemic reactions, the majority of the patients were female (n = 8; 67%). We have found three studies reporting a higher SR rate in female (35-37). Regarding age, we also did not find important differences between adults and children. We reported more reactions (n = 33) in the age group between 18 and 30 years, but it also had more patients in comparison with the other age groups.

Generally, reactions are more frequently induced by pollen extracts than by mites (19, 22). Regarding our population, the majority (68.3%) of the patients were only under mite SCIT. That could explain why most of the adverse reactions occurred with mite extract. By analysing the group of patients only under pollen SCIT or only under mite SCIT, it was verified that a higher percentage of patients under pollen SCIT had an adverse reaction: 18.0% *versus* 16.8% in the mite group. SCIT has revealed to be a safe treatment, based on the low frequency and severity of SR (4). However, there is still a small risk of fatal allergic reactions associated with subcutaneous administration of aeroallergens, occurring in one event in 2.5 million of injections (4, 8).

Table V *- Fatal reactions in Subcutaneous Immunotherapy studies.*

	Observation interval	(N)	Number of fatal reactions
Surveillance studies in the US		**Questionnaires**	
Lockey *et al.* (39)	1945-1984	60	24
Reid *et al.* (38)	1985-1989	NS	17
Bernstein *et al.* (3)	1990-2001	646	41
Bernstein *et al.* (40)	2001-2007	806	6
Epstein *et al.* (31)	2008-2011	806	0
Epstein *et al.* (41)	2011-2012	806	1
Other studies		**Population**	
Moreno *et al.* (21)	1996-1997	419	0
Schiappoli *et al.* (33)	2003-2006	1738	0
Cardona *et al.* (42)	2007-2011	575	0
Arêde *et al.* (43)	2007-2012	100	0

NS: not specified.

Since Lockey *et al.* (38) published the first retrospective survey on fatalities from SCIT and skin testing in the United States (US), other surveillance studies in SCIT safety were made in US and Europe (**table V**). By analysing **table V**, it is evident that the number of fatal reactions has significantly decreased passing the years. The first study reported 24 fatal reactions, while the most recent studies have no fatalities described. No fatalities were verified in our population. To minimize the occurrence of serious adverse systemic reactions, all of the studied patients were evaluated before starting SCIT, all of them had well-controlled, mild-to-moderate asthma. Initiation of pollen extract SCIT was administrated out of pollen season: from September to February. As it is a retrospective study from only one centre and there was an exclusion of almost half of the total population due to lack of clinical information about SCIT administration, the results may be limited. This study also does not specify the timing of reactions (how long were patients under SCIT) on maintenance phase.

Conclusions

SCIT has revealed to be safe and well tolerated in the majority of the patients. Only 17.6% of the studied patients and 1.3% of the SCIT administrations registered an adverse reaction.

The majority were LR – affecting 14.2% of our population – a value below of the reported in other studies, and 1.1% of the administered injections, as it is described in literature. SR were common (frequency of adverse drug reactions ≥ 1% and < 10% (27)), once they occurred in 3.7% of the patients and 0.19% of injections, which is in line with other studies (15, 16). We didn't report SR of grade > 1. No fatalities were found. So, SR were infrequent and not severe, occurring mainly during build-up phase. Adverse reactions were mostly caused by mite SCIT, the more frequent used composition in our population and SCIT with *Dermatophagoides pteronyssinus* and/or *farinae* and *Dermatophagoides* plus another mite may be associated with the occurrence of adverse reactions. More than a half of all reactions were non-immediate and occurred at build-up phase. Female had more adverse reactions. Patients who had a higher number of LR didn't have more SR.

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Conflict of interests

The authors declare that they have no conflict of interests.

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Predictive factors of non-adherence to asthma medication in pregnancy

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Key words

Asthma; pregnancy; medication adherence; non-adherence; risk factors.

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Impact statement

Mild asthma and marital status of single, separated or divorced were independent predictors of poor adherence to asthma medications in pregnant females.

Summary

Background. *Adherence to asthma medications is a significant problem among pregnant women.* ***Objective.*** *To evaluate asthma medication adherence in pregnant women and to determine the factors that may predict non-adherence in a real-life setting.* ***Methods.*** *A cross-sectional study was performed with pregnant women with asthma followed in a specialized asthma consultation at the Pulmonology Department, between 2014 and 2019. Sociodemographic and clinical variables were collected. Structured telephone interviews were conducted to determine regular medication use during pregnancy. Multiple logistic regression was used to identify predictive factors of asthma medication non-adherence (cessation or dose reduction).* ***Results.*** *A total of 82 pregnant women were included: mean age of 31.3 ± 6.5 years, non-adherence was detected in 29% (n = 24). Multivariable logistic regression analysis revealed that mild asthma during pregnancy (OR 4.8; 95% CI 1.4-17.1; p = 0.015) and single, separated or divorced mothers (OR 4.0; 95% CI 1.3-11.8; p = 0.014) were independent predictors of poor adherence to asthma medications.* ***Conclusions.*** *Asthma severity and marital status can strongly predict the asthma medication non-adherence in pregnant females. These findings may help improve asthma education strategies to promote medication adherence.*

Introduction

Asthma is one of the most common chronic medical conditions complicating pregnancy, affecting up to 13% of pregnant women worldwide (1-4). Maternal asthma, particularly poorly controlled asthma, has been associated with increased risk of perinatal complications, including pre-eclampsia, gestational diabetes, placental abruption, placenta praevia, low birthweight, small for gestational age, preterm delivery and increased risk of maternal and perinatal mortality (5-10). To maintain asthma control, guidelines recommend the continued use of prepregnancy medication throughout pregnancy and adjusted according to the current treatment steps if required. The maternal and fetal risks associated with uncontrolled asthma are greater than the risks from using asthma medications (10, 11). However, there are some concerns about complications of pregnancy resulting from asthma treatment. These concerns usually lead to a behavioral change in pregnant women with asthma against the medications that they had previously used. Some studies have demonstrated that women tend to decrease or cease their asthma medication during pregnancy. One study demonstrated that 40% of females with asthma reported non-adherence to inhaled corticosteroids (ICS) during pregnancy (12). Similarly, in another study, the authors reported a decrease of asthma medication use in early pregnancy (from 5 to 13 weeks). During the first trimester, there was a 23% decline in ICS prescriptions,

a 13% decline in short-acting β_2-agonist (SABA) prescriptions, and a 54% decline in rescue corticosteroid prescriptions (13).
However, factors that may influence this adherence change have not been well addressed.
The identification of these factors can help prevent this behaviour, increasing treatment compliance, and consequently improving asthma control, which might contribute to decrease maternal and perinatal complications.
Therefore, the aim of this study was to evaluate asthma medication adherence in pregnant women and to determine the factors that may predict non-adherence in a real-life setting in our population.

Methods

Study design

Cross-sectional, descriptive and inferential study conducted in a specialized asthma consultation at the Pulmonology Department from a terciary hospital in Northern Portugal. Patients followed up in the department at any time between January 2014 and December 2019 (6 years) were considered for inclusion.

Ethics

This study was approved by the Ethics Committee of the Centro Hospitalar Vila Nova de Gaia/Espinho (Registration No. 132/2020) and was conducted according to ethical standards established in the Declaration of Helsinki. Verbal informed consent was obtained from all participants before enrolment in the study.

Patient selection

Female patients referenced from the Gynecology and Obstetrics medical appointment or emergency department were included. Patient files were reviewed, and the criteria for inclusion in the study were pregnant women with a diagnosis of asthma. A total of 94 cases were identified, nine of which were excluded after clinical file review for not fulfilling asthma criteria, and three were excluded for not being pregnant.

Data collection and study variables

Data collection was performed in 2020 and reported to the time of pregnancy. All patients were included after delivery.
The following variables were evaluated: age, age of asthma onset, asthma treatment, control and severity, asthma medication adherence, asthma status during pregnancy, admission to emergency department or hospitalization due to asthma symptoms during pregnancy, worsened asthma in a previous pregnancy, smoking habits, presence of atopy and rhinitis, number of pregnancies and children, place of residence, economic status, educational status, employment, and marital status.
Structured telephone interviews were conducted by the lead author (allergist resident with 4 years of clinical experience) to determine asthma medication adherence, asthma status, educational status, employment and marital status during pregnancy. The remaining data were collected from hospital chart records.
Medication adherence during the 3 trimesters of pregnancy was assessed in a non-judgemental and nonthreatening manner by asking: "It can be difficult to remember all of your medicines when things get busy. How many times in a week have you missed a dose of your control medication in the first trimester?", "And in the second and third trimester?". The assessment of the therapeutic plan and adherence during pregnancy followed a review of the medication prescriptions and patient's medical records on medication adherence. All asthma medication classes were evaluated. Although there is no consensus regarding what an acceptable adherence rate is, most researchers consider an adherence rate greater than 80% to be adequate (14). Participants were considered to be adherent if they missed ≤ 20% of their prescribed medication doses. Following this evaluation, the patients were allocated into two groups; group I consisted of pregnant women with good adherence (if they took 80% of their prescribed doses) and group II was comprised of poor adherent pregnant (if they reduce or cease medication).
We also asked the patients to classify their asthma status during pregnancy into worse, improved or stable.
Educational status, employment and marital status were classified into the groups described below. Educational status was divided in 3 groups: basic education (less than 9 years of education), upper secondary education (between 10 and 12 years) and tertiary education (more than 12 years of education). Employment was divided in 2 groups: employed and unemployed. Marital status included 2 groups: single, separated or divorced group and married or in a cohabitating relationship group.
Economic status included 2 groups: the presence or absence of economic insufficiency that is defined by the Portuguese Tax and Customs Authority, according to the average monthly income.
The assessment of control and severity of asthma was performed according to GINA-guidelines (11).

Statistical analysis

All analyses were performed using Statistical Package for the Social Sciences, version 24.0 (SPSS Inc., Chicago, IL, USA). Nominal values are described as frequencies and percentages. Quantitative variables are expressed as mean ± standard deviation (SD). Two independent sample paired t-test or Mann–Whitney U test was used for comparison of the continuous variables. Differences in distributions for categorical variables were tested using chi-square test or Fisher's exact test. Univariate and multiple logistic regression models were developed using independent variables as risk factors for non-adherence to asthma medication; results were presented as odds ratio (OR) with 95% confidence interval (CI). Variables used in the model included age, age of asthma onset, asthma control and severity, asthma status during

pregnancy, worsened asthma in a previous pregnancy, smoking during pregnancy, atopy, rhinitis, number of pregnancies, number of children, place of residence, economic status, educational status, employment and marital status. The variables that had P-value < 0.25 in the univariate analysis were included in the multivariable model and a forward stepwise method was used to reach the final model. The goodness of fit of the logistic regression model was confirmed by the Hosmer-Lemeshow test. A P-value < 0.05 was considered statistically significant.

Results

Characteristics of patients

In 2014-2019 period, a total of 82 pregnant women with asthma were identified. The mean age was 31.3 ± 6.5 years (range 18-49 years), and the mean age of asthma onset was 16.8 ± 9.1 years (range 1-37 years). In our population, the minority of patients (17%) had mild asthma, 52% had moderate asthma and the remaining 31% had severe asthma, according to GINA guidelines. According to the patients' own evaluations, asthma status improved in 9% of pregnant patients, remained unchanged in 38%, and worsened in 50% of the subjects during pregnancy. Three patients (4%) only initiated their symptoms during pregnancy. Twenty-seven patients (33%) were classified as having well-controlled asthma, whereas 39 patients (48%) and 16 patients (20%), respectively, had partly controlled and uncontrolled asthma. Atopy was present in 61% and rhinitis in 77%. Most patients did not smoke during pregnancy (71%). Seventy patients (73%) were single, separated or divorced while pregnant and 22 females (27%) were married or cohabiting couples. Sixteen patients (20%) went to an emergency department for asthma acute exacerbation, and 3 (4%) had been hospitalized during pregnancy.

In general, self-reported adherence was consistent throughout the pregnancy period. Fifty-eight patients (71%) had good asthma medication adherence, and 24 patients (29%) had poor adherence. **Table I** shows the characteristics for subjects with good and poor adherence. The two groups were statistically different in terms of asthma severity, asthma status during pregnancy and marital status. Females with mild asthma used their asthma medication significantly less during pregnancy compared with pregnant women with moderate and severe asthma (p = 0.024). Pregnant patients with stable asthma had significant lower adherence to asthma medication than those with improved or worsened asthma (p = 0.014). In single, separated or divorced females, the rate of medication non-adherence was 71%, which was significantly higher compared with married or cohabiting couples (29%; p = 0.012) (**table I**).

No differences were found between the 2 groups regarding asthma control. Among pregnant women with asthma with poor adherence, 50% (n = 12) used ICS, 50% (n = 12) used SABA, and 42% (n = 10) used long-acting β_2-agonist (LABA) during pregnancy. The usage rates of asthma medications according to the medication class were not significantly different between the 2 groups. In this study the ICS and LABA medications used by patients were fluticasone or budesonide and formoterol or salmeterol, respectively.

There were no significant differences between the groups in terms of age, onset age of asthma, worsened asthma in a previous pregnancy, acute exacerbation of asthma requiring emergency service or hospitalization during pregnancy, smoking habits during pregnancy, atopy, rhinitis, number of pregnancies or children, place of residence, economic status, educational status, or employment (**table I**).

Multiple Logistic Regression

The effects of asthma severity, asthma status during pregnancy, worsened asthma in a previous pregnancy and marital status were tested in the multivariable logistic regression. Asthma severity and marital status remained in the final model; it had a good fit (P-value for Hosmer-Lemeshow test: 0.592). The model explained 34% (Nagelkerke R2) of the variance in the medication adherence and correctly classified 71% of cases. Mild asthma and marital status of single, separated or divorced were associated with medication poor adherence; asthma status during pregnancy and worsened asthma in a previous pregnancy were not associated with medication compliance. The subjects with mild asthma were 4.8 times more likely to exhibit poor adherence of asthma medication than the subjects with moderate or severe asthma (95% CI 1.4-17.1; p = 0.015). Single, separated or divorced mothers were 4.0 times more likely to exhibit poor adherence of asthma medication than the married or cohabiting couple (95% CI 1.3-11.8; p = 0.014) (**table II**).

Discussion

Our results revealed that almost 30% of the pregnant women with asthma did not use their controller medications regularly during pregnancy. Similarly, a survey of 501 females with asthma reported that 39% of women were reported to discontinue or reduce asthma medication use while pregnant, mostly without consultation with their physician, mainly because of concerns related to the safety of these medications on the foetus (15). Despite that, Yilmaz *et al.* in a study with 32 pregnant women with asthma, demonstrated that the regular use of asthma medications increased 12% during pregnancy when compared to the pre-pregnant period, but without statistical significance. The rate of irregular asthma medication use was 68% (n = 17) before pregnancy and 56% (n = 14) during pregnancy (p = 0.561) (16). In non-pregnant asthma population, adherence to inhaled corticosteroids might be as low as 20% (17).

Most pregnant women had moderate or severe asthma (83%), according to GINA guidelines. These data can be explained by the fact that the study was carried out with patients followed in

Table I *- Comparison of pregnant women with asthma according to asthma medication adherence (n = 82).*

Variable	Good adherence (n = 58)	Poor adherence (n = 24)	P-value
Age, years, mean ± SD (min-max)	31.3 ± 6.5 (19-49)	30.6 ± 7.0 (18-42)	0.407
Age of asthma onset, years, mean ± SD (min-max)	16.0 ± 9.0 (1-37)	18.0 ± 9.1 (6-37)	0.812
Asthma control			
Well-controlled	17 (29.3)	10 (41.7)	
Partly controlled	28 (48.3)	11 (45.8)	0.435
Uncontrolled	13 (22.4)	3 (12.5)	
Asthma severity			
Mild	6 (10.3)	8 (33.3)	0.024
Moderate or severe	52 (89.6)	16 (66.7)	
Asthma status during pregnancy			
Stayed stable	17 (29.3)	14 (58.3)	
Improved	7 (12.1)	0 (0)	0.014
Worsen	33 (56.9)	8 (33.3)	
Initiated during pregnancy	1 (1.7)	2 (8.3)	
Worsened asthma in a previous pregnancy	12 of 28 (42.9)	1 of 9 (11.1)	0.119
Smoked during pregnancy	15 (25.9)	7 (29.2)	0.725
Atopy	35 (60.3)	15 (62.5)	0.487
Rhinitis	44 (75.9)	19 (79.2)	0.423
Number of pregnancies, mean ± SD (min-max)	2.1 ± 1.1 (1-5)	2.1 ± 1.4 (1-6)	0.277
Number of children, mean ± SD (min-max)	1.7 ± 0.8 (0-5)	1.8 ± 1.0 (1-5)	0.262
Place of residence (Urban area)	22 (37.9)	9 (37.5)	0.971
Economic status (insufficiency)	21 (36.2)	9 (37.5)	0.912
Educational status			
Basic education	14 (24.1)	3 (12.5)	
Upper secondary education	15 (25.9)	10 (41.7)	0.278
Tertiary education	29 (50.0)	11 (45.8)	
Employment	35 (60.3)	13 (54.2)	0.899
Marital status			
Single, separated or divorced	5 (8.6)	17 (70.8)	0.012
Married or cohabiting couple	53 (91.4)	7 (29.2)	

Data are presented as n (%), except when indicated otherwise.

a specialized asthma consultation at the Pulmonology Department. The remaining with mild asthma (17%) had significantly worse asthma treatment compliance. Some studies corroborate this finding, Murphy *et al.* demonstrated that females with mild asthma used significantly less ICS in all trimesters and had inadequate inhaler technique compared with females with moderate and severe asthma (12).

Another finding of our study was that marital status significantly influenced the asthma medication adherence, with single, separated or divorced mothers being less adherent. To our knowledge, there is no published information regarding the relationship between asthma medication adherence during pregnancy and marital status. The authors hypothesize that family support and emotional stability is greater in married or cohabiting couples, and can contribute to therapy compliance during pregnancy. In fact, this finding is similar to studies on other health conditions. One study reported that married pregnant participants with HIV-infection have a better chance of anti-retroviral medication adherence than separated, single and widowed patients (18). In another study, single marital status was a factor for inadequate preconception use of folic acid, when compared to married or living together participants (19).

The clinical effect of pregnancy on asthma is variable, as demonstrated by Schatz *et al.* (20), in this prospective study 366 pregnancies were followed in women with asthma, of which 35% suffered worsening asthma, 28% improved and in 33% no changes were

Table II *- Multiple logistic regression using the forward stepwise method of the factors associated with non-compliance with asthma medication in pregnant women with asthma (n = 82).*

	Initial model			Final model		
Factor	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Asthma severity						
Mild	5.1	1.0-26.5	0.051	4.8	1.4-17.1	0.015
Moderate or severe	1.0					
Asthma status during pregnancy						
Improved	1.0					
Stayed stable	0.5	0.1-2.0	0.357	---	---	
Worsened	1.5	0.1-21.1	0.576	---	---	
Initiated during pregnancy	2.8	0.2-41.8	0.458	---	---	
Worsened asthma in a previous pregnancy	0.3	0.03-3.2	0.336	---	---	
Marital status						
Single, separated or divorced	3.3	1.0-10.9	0.052	4	1.3-11.8	0.014
Married or cohabiting couple	1.0					

OR: odds ratio; CI: confidence interval.

detected; in about 4%, it was not possible to classify the course of asthma during pregnancy. In contrast, in our study population we found that half of pregnant women reported worsened asthma symptoms during pregnancy, 38% remained unchanged, and the minority (9%) improved their asthma status. Only 3 patients (4%) initiated their symptoms during pregnancy. The group with stable asthma symptoms had significant lower adherence to asthma medication. Another Portuguese study, that included 26 pregnant women, found that only 4% improved, 54% remained stable and 42% worsened their asthma symptoms.

Asthma control seems to be poor in most pregnant women with asthma (48% partly controlled and 20% uncontrolled asthma), and with only 33% having well-controlled asthma. Consequently, they needed to use medications regularly to keep their asthma in a more stable state. Considering these evaluations, we can infer that poor asthma control during pregnancy may positively influence pregnant women to use their asthma medications.

Some clinical parameters, such as hospital and emergency room admissions, showed that asthma was not controlled well enough in some women with asthma during pregnancy, with percentages of 20% and 4%, respectively. Other studies reported that between 20 and 36% of females with asthma had exacerbations during pregnancy (20-22), especially in the second trimester (23). The suggested reason for this unequal distribution has been the possibility that several women may decrease or even discontinue preventive therapy shortly after pregnancy identification, especially with regard to ICS (23).

Using multivariable logistic regression analysis, we can demonstrate that marital status of single, separated or divorced mothers and mild asthma during pregnancy are independent predictors of poor adherence of asthma medications in pregnant women.

Asthma medication non-adherence is a particular problem in pregnancy, due to the potential for maternal and fetal complications. Females with asthma may benefit from closer monitoring of their asthma during pregnancy, in order to ensure optimum treatment and control during this period. Asthma self-management education programmes are an important component of asthma management and should include education, self-monitoring, regular review with optimisation of pharmacotherapy, inhaler technique training and a written plan for the management of unstable asthma. Our findings may help improve asthma education strategies, particularly in those who are single, separated or divorced mothers or have a mild asthma, in order to promote medication adherence. This may lead to improved outcomes for both mother and child.

There are many limitations of this study. Firstly, this is a cross sectional, single-centered, questionnaire-based study; some data used in this study (like regular medication usage, status of asthma during pregnancy compared to a previous period) depend on the patients' statements and recall capacity. Level of medication adherence may depende on the adherence cut-off used. An important factor for recording or recall bias is the time that elapsed between delivery and the study interview, especially those women who were pregnant in 2014, as the elapsed time is long this bias is expected to increase. To decrease the impact of this limitation, these data

were compared with clinical records and the medications prescriptions during pregnancy where evaluated. Another limitation of this study is the small number of cases. Finally, it was not possible to evaluate the different trimesters in a specific week of pregnancy; instead, the assessment was made globally over the trimesters.
Despite these limitations, this study can provide important information about factors that may predict the non-adherence to asthma medication in pregnant women.

Conclusions

Almost 30% of the included female had low asthma medication adherence during pregnancy. Single, separated or divorced females and mild asthma were independent factors that influence poor-adherence. These findings may help improve asthma education strategies, namely reinforcing the recommendations for continuing the appropriate use of medication, in order to allow good control of the disease and minimize complications inherent to exacerbations, in particular in women with these risk factors.

Conflict of interests

The authors declare that they have no conflict of interests.

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Successful desensitization with chemotherapeutic drugs: a tertiary care center experience

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Key words

Chemotherapy; desensitization; drug allergy; hypersensitivity; cancer.

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Impact statement

Desensitization is an effective and safe treatment approach for chemotherapeutic drug hypersensitivity by observing general precautions to anaphylaxis.

Summary

Introduction. *Hypersensitivity reactions to chemotherapeutic drugs are increasing all over the world, and desensitization to them has become the standard treatment approach. This study aimed to evaluate the characteristics of chemotherapeutic drug hypersensitivity reactions and the outcome of desensitization procedures.* ***Methods.*** *Between January 2017 and 2019, patients who have been desensitized to chemotherapeutic drugs were included retrospectively. Data were obtained from the medical records of the patients.* ***Results.*** *A total of 35 patients were evaluated, of whom 24 (68.5%) were female and 11 were male (31.5%). The mean age was 54.54 ± 13.39 (min-max: 41-69) years. Colorectal cancer was the most common malignancy (n = 14; 40%). Desensitization was performed with oxaliplatin in 17 (48.5%), carboplatin in nine (25.7%), paclitaxel in four (11.4%), cisplatin in two (5.7%), irinotecan in two (5.7%), rituximab in two (5.7%), and docetaxel in one (2.8%) patients. Thirty-four (97.1%) were successfully desensitized without any reactions. Anaphylaxis occurred during desensitization with rituximab and the procedure could not be completed. The reactions occurred during the first administration of the chemotherapeutic agent in five (14.2%) patients. Skin tests were performed on 26 (74.2%) patients. Skin prick and intradermal tests were positive in 7 (26.9%) and 12 (46.1%) patients, respectively.* ***Conclusions.*** *Desensitization is an effective and safe treatment approach for chemotherapeutic drug hypersensitivity and can be performed safely by observing general precautions to anaphylaxis.*

Introduction

Various chemotherapeutic drugs are used for cancer treatment nowadays. Hypersensitivity reactions to chemotherapeutic drugs are unexpected reactions, unlike the expected toxicities of these drugs. Hypersensitivity reactions are increasing and may occur with any chemotherapeutic drug. The severity of the reactions may vary from a mild skin rash to life-threatening anaphylactic shock (1).

The sensitivity of a tumor to certain chemotherapeutics and the necessity to choose the most effective treatment for survival, usually do not allow for selection of an alternative chemotherapeutic agents. When a hypersensitivity reaction to a chemotherapeutic drug develops, there may be no alternative medication regimens. In such cases, desensitization is the appropriate treatment approach. During desensitization, the drug is administered in small doses until the target dose is reached within a few hours. Using this procedure, temporary tolerance is achieved,

and the protocol should be repeated for each treatment cycle which should be performed in experienced centers in the intensive care unit (2). The aim of this study was to evaluate the characteristics of chemotherapeutic drug hypersensitivity reactions and the outcome of desensitization procedures.

Methods

Between January 2017 and 2019, patients who were admitted to a tertiary adult allergy outpatient clinic with hypersensitivity reactions to chemotherapeutic drugs and desensitized were included retrospectively. Data were obtained from the medical records of every patient. Patients who were younger than 18 years old and had a hypersensitivity reaction 24 hours after drug infusion were excluded from the study. In addition, desensitization was not performed to patients who developed type 2, type 3 or type 4 hypersensitivity reactions after chemotherapeutic infusion. Initial hypersensitivity reactions of patients were classified according to the National Cancer Institute (NCI) Common Toxicity Criteria (3). Skin prick tests and intradermal tests were performed on the volar side of the forearm with the culprit drug, with positive (histamine; 10 mg/ml) and negative (saline) controls. Skin tests were not performed on patients who had received antihistamines in the last seven days or who had dermographism and were evaluated after 20 minutes. Skin tests were performed at least 2 weeks after the initial hypersensitivity reaction to reduce false negative results. For both the skin-prick and intradermal tests, an induration diameter of 3 mm and over was considered positive, respectively. Drug concentrations for skin prick test and intradermal tests were performed based on other studies (4-9). **Table I** shows the concentration of drugs used in skin testing. Brigham and Women's Hospital (BWH) standard 12, 16, or 20 step desensitization protocol, developed by Castells *et al.* (2), was performed on the patients. The most commonly used desensitization protocol was based on 12 steps. Patients with severe hypersensitivity reactions and anaphylactic reactions were desensitized with 16 steps or 20 steps (10). Premedication was initiated before infusion. Dexamethasone 20 mg orally or intravenously (iv) before 6 and 12 hours, diphenhydramine 50 mg or pheniramine 45.5 mg iv before 30 minutes, ranitidine 50 mg iv or famotidine 20 mg iv before 30 minutes, and 50 mg of oral hydroxyzine before 30 minutes were given as premedication. Chemotherapeutic drugs were administered in 250 mL of 5% dextrose or saline at 1/10000, 1/1000, 1/100, 1/10, and 1/1 dilutions. The study protocol was approved by the Hacettepe University Faculty of Medicine Ethics Committee (no: 2020/03-33). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data were analyzed with the IBM SPSS Statistics 21 program. Descriptive statistics (mean, standard deviation, minimum and maximum value) were performed for numerical data, and frequency distributions were performed for categorical variables.

Table I *- The concentrations of drugs used in skin testing.*

Drug	Prick test (mg/mL)	Intradermal test (mg/mL)
Carboplatin	10	1, 10
Cisplatin	1	0.1, 1
Oxaliplatin	5	0.5, 5
Paclitaxel	1	0.001, 0.01
Docetaxel	0.4	0.004, 0.04
Rituximab	10	0.1, 1, 3
Irinotecan	20	2

Results

A total of 35 patients were evaluated, of whom 24 (68.5%) were female and 11 were male (31.5%). The mean age was 54.54 ± 13.39 (min-max: 41-69) years. Colorectal cancer was the most common tumor in patients (n = 14; 40%). Desensitization was performed with oxaliplatin in 17 (48.5%), carboplatin in nine (25.7%), paclitaxel in four (11.4%), cisplatin in two (5.7%), irinotecan in two (5.7%), rituximab in two (5.7%), and docetaxel in one (2.8%) patients. Gender distribution, the type of chemotherapeutic drugs, and malignancies are shown in **table II**.

Desensitization was successful in 34 (97.1%) of 35 patients. In one patient, desensitization with rituximab could not be completed due to anaphylaxis. Allergic reactions occurred during the first chemotherapeutic cycle of treatment in five (14.2%) patients. Skin tests were performed in a total of 26 (74.2%) patients. Skin prick and intradermal tests were positive in 7 (26.9%) and 12 (46.1%) patients, respectively. Reactions, skin test results, and desensitization characteristics of the patients are shown in **table III**.

Discussion

In this study, we successfully desensitized 34 of 35 (97.1%) patients who had chemotherapeutic-drug hypersensitivity. There are different desensitization protocols for various chemotherapeutic drugs in the literature. In recent years, the BWH standard desensitization protocol, developed by Castells *et al.* (2), has been used for all chemotherapeutic drugs. This protocol was used in the current study. A shorter protocol was developed by Madrigal-Burgaleta *et al.* (11) because of the long duration of the protocol developed by Castells *et al.* More than 2000 desensitizations were performed with various chemotherapeutic drugs by both protocols. Desensitization was successful in 99% of patients (12). Hypersensitivity reactions can be observed to any chemotherapeutic drugs. Reactions often occur against taxanes (paclitaxel, docitaxel), platinum-containing agents (cisplatin, carboplatin, oxaliplatin), and

Table II *- Gender, malignancies and chemotherapeutic drugs.*

Malignancy	Gender (m/f)	Oxaliplatin	Carboplatin	Cisplatin	Paclitaxel	Docetaxel	Irinotecan	Rituximab
Colorectal	6/8	12					2	
Ovarian	-/6		6		1			
Gastric	3/1	3				1		
Endometrial	-/3		1	1	2			
Lymphoma	-/2							2
Malignant melanoma	-/1				1			
Breast	-/1	1						
Larynx	1/-			1				
Lung	1/-		1					
Peritoneal	-/1		1					
Cholangio-cellular	-/1	1						
Total	11/24	17 (48.5%)	9 (25.7%)	2 (5.7%)	4 (11.4%)	1 (2.8%)	2 (5.7%)	2 (5.7%)

m: male; f: female.

epipodophyllotoxins (etaposide) (13). In this study, the most common hypersensitivity reactions observed were to platinum agents and taxanes. These chemotherapeutic drugs are frequently used in more common cancers such as colon, lung, breast, stomach, and ovarian cancers. Due to the frequent use of these drugs, hypersensitivity reactions may often be observed. Hypersensitivity reactions usually occur during or after infusion. Hypersensitivity reactions to taxanes usually occur within the first few minutes of infusion during the first or second chemotherapy cycle. Taxanes rarely cause IgE-mediated hypersensitivity reactions but lead to hypersensitivity reactions generally by directly releasing mediators, such as histamine, neutral proteases, proteoglycans, and cytokines from mast cells. Hypersensitivity reactions to platinum agents are usually observed after multiple chemotherapy cycles, which are often IgE-mediated (2, 14, 15). In the current study, desensitization to platinum agents and taxanes was successfully performed in 28 (80%) and five (14.2%) patients, respectively. Patients with platinum allergy had hypersensitivity reactions after multiple cycles of platinum-containing chemotherapy, usually for treatment of colon and ovarian cancer.

In our study, in a single patient desensitization with rituximab could not be completed due to anaphylaxis. A hypersensitivity reaction developed in the second chemotherapy cycle with rituximab in this patient. When this desensitization process was unsuccessful, we increased the number of the desensitization step. The 16-step desensitization procedure also proved unsuccessful. Thereafter, we planned a 20-step desensitization procedure, but the patient refused, due to the previous severe allergic reaction, and a different chemotherapy regimen was planned by the oncologist. Hypersensitivity to rituximab is often observed after the first chemotherapy cycle. Urticaria, hypotension, anaphylaxis, angioedema, bronchospasm, acute lung injury, cardiogenic shock, and, in some cases, death have been reported within two hours of infusion of rituximab (16). Desensitization with rituximab is usually successful according to literature (17, 18).

Desensitization with irinotecan was successful in two patients with colon cancer in the current study. Irinotecan is a chemotherapeutic agent commonly used in the treatment of gastrointestinal malignancies. Hypersensitivity reactions with irinotecan are less common than with other chemotherapeutics. Successful desensitization with irinotecan has been reported in a few case reports in the literature (19, 20). Although clinical history is important in the diagnosis of drug allergies, the diagnosis can be supported by skin tests. Allergic reactions to platinum agents are usually type I immunological reactions. Reactions to taxanes are usually mediated by mast cell degranulation or complement activation. Skin tests provide reliable results for platinum allergies. However, the role of skin tests in the diagnosis of taxane allergy is limited (13-15). In a multi-center study investigating the role of skin tests in the diagnosis of immediate hypersensitivity reactions to taxanes, prick test results were negative in all patients. Intradermal test results were positive in 14 patients (10 paclitaxel [15.9%] and 4 docetaxel [19%]). The authors stated that the skin test is useful in the diagnosis of taxan allergies (21). Positive skin tests were frequently observed to oxaliplatin in the current study. Positive intradermal tests were observed in eight (57.1%) of 14 patients with oxaliplatin and in one (20%) of 5 patients

Table III *- Desensitization results, skin tests and systemic symptoms of chemotherapeutic drugs before desensitization.*

No	Malignancy	Drug	Reaction	Reaction developing cycle	Skin Tests		Desensitization steps
					Prick	Intradermal	
1	Gastric	Docetaxel	Flushing, dyspnea	3	Negative	Positive	12
2	Malignant melanoma	Paclitaxel	Urticaria, dyspnea	1	Negative	Negative	12
3	Endometrial	Paclitaxel	Urticaria, dyspnea	1	Negative	Negative	12
4	Ovarian	Paclitaxel Carboplatin	Urticaria, dyspnea	14	Negative	Negative	12
5	Endometrial	Paclitaxel Carboplatin	Flushing, angioedema	7	Negative	Negative	12
6	Ovarian	Carboplatin	Urticaria, dyspnea	9	Not performed		12
7	Ovarian	Carboplatin	Urticaria, dyspnea	8	Negative	Negative	12
8	Lung	Carboplatin	Flushing, dyspnea	4	Negative	Negative	12
9	Ovarian	Carboplatin	Urticaria, dyspnea	15	Negative	Negative	12
10	Ovarian	Carboplatin	Nausea, vomiting, dyspnea	14	Not performed		12
11	Peritoneal	Carboplatin	Urticaria, dyspnea	6	Positive	Positive	20
12	Ovarian	Carboplatin	Urticaria, dyspnea, hypotension	8	Not performed		20
13	Gastric	Oxaliplatin	Nausea, vomiting, tachycardia	2	Negative	Positive	12
14	Colorectal	Oxaliplatin	Flushing, dyspnea, angioedema	13	Positive	Positive	12
15	Colorectal	Oxaliplatin	Urticaria, dyspnea	3	Negative	Negative	12
16	Colorectal	Oxaliplatin	Flushing, dyspnea	4	Not performed		12
17	Colorectal	Oxaliplatin	Flushing, hypotension	7	Negative	Negative	12
18	Cholangio-cellular	Oxaliplatin	Urticaria, tachycardia	3	Negative	Negative	12
19	Gastric	Oxaliplatin	Urticaria, dyspnea, hypotension	6	Negative	Negative	12
20	Colorectal	Oxaliplatin	Urticaria, dyspnea	10	Positive	Positive	12
21	Colorectal	Oxaliplatin	Urticaria, dyspnea	9	Negative	Positive	12
22	Gastric	Oxaliplatin	Angioedema, dyspnea	5	Negative	Negative	12
23	Colorectal	Oxaliplatin	Urticaria, abdominal pain	14	Positive	Positive	12
24	Colorectal	Oxaliplatin	Urticaria, dyspnea	10	Not performed		16
25	Colorectal	Oxaliplatin	Urticaria, dyspnea	16	Positive	Positive	16
26	Colorectal	Oxaliplatin	Flushing, dyspnea	8	Not performed		16
27	Colorectal	Oxaliplatin	Flushing, dyspnea	9	Negative	Positive	20
28	Colorectal	Oxaliplatin	Flushing, angioedema	5	Positive	Positive	20
29	Breast	Oxaliplatin	Dyspnea, hypotension	1	Negative	Negative	20
30	Larynx	Cisplatin	Dyspnea	2	Not performed		12
31	Endometrial	Cisplatin	Urticaria, dyspnea	6	Negative	Positive	16
32	Colorectal	Irinotecan	Nausea, vomiting	1	Not performed		12
33	Colorectal	Irinotecan	Nausea, vomiting, hypotension	2	Positive	Positive	16
34	Lymphoma	Rituximab*	Urticaria, flushing, dyspnea, angioedema	2	Negative	Negative	16
35	Lymphoma	Rituximab	Chest pain, dyspnea	1	Not performed		16

*Desensitization was not successful.

with taxanes. Skin tests for oxaliplatin allergy are highly sensitive. The sensitivity of the skin test was between 75% and 100% in several studies (6, 22, 23). In this study, we observed lower skin-test positivity with platinum agents compared to previous data in the literature. We could not perform skin tests on all of the patients for various reasons: dermographism, recent use of antihistamines, *etc*. In addition, these patients receive chemotherapy at frequent intervals; therefore, when they are admitted to our allergy clinic, it may not be the appropriate time to perform skin tests. Skin-test positivity may have been low due to this reason.

Conclusions

In conclusion, desensitization is an effective and safe treatment approach for chemotherapeutic drug hypersensitivity and can be performed safely by following general precautions to anaphylaxis.

Previous presentations

This study has been presented as oral presentation at the XXVI National Allergy and Clinical Immunology Congress between 9-13 November 2019 and presented as a poster EAACI Digital Congress 06-08 June 2020.

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Conflict of interests

The authors declare that they have no conflict of interests.

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Anaphylactic shock to iodinated contrast media: not so rare after all

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To the Editor,

immediate and non-immediate hypersensitivity reactions to iodinated contrast media (ICM) have been reported to occur in a frequency of about 0.5-3% of patients receiving non-ionic ICM (1). Severe reactions occur in 0.04% to 0.22% of intravenous administrations (2). Immediate reactions can be caused by IgE and non-IgE mechanisms. The presence of positive skin tests indicates an IgE-mediated mechanism. Tryptase serum levels increase with the severity of the reaction (1). A recent multicentric prospective study documented allergy in 52.9% of patients with anaphylaxis and in all patients with cardiac arrest (3). IgE-mediated allergic hypersensitivity reactions may have been underreported in the past due to the lack of allergy testing (4).

The main risk factor for developing an immediate hypersensitivity reaction to an ICM is a previous immediate reaction. Other presumed risk factors (asthma, atopy, drug allergy) (5) have shown inconsistent results and therefore cannot be used as a condition for performing ICM allergy work-up (1). In a 2 week period, we had in our hospital 3 anaphylactic shocks to ICM.

Case 1: female, 62 years old, no history of atopy. The patient had indication for ablation of atrial fibrillation and was proposed to have a coronary computed tomography (CT) angiogram (CCTA). During the exam the patient experienced a non-specific discomfort while administering Ultravist® 370 (iopromide), but the exam was completed. Shortly after, the patient became tachycardic, hypotensive and unresponsive to external stimuli, and with generalized erythema. She was treated with intramuscular (IM) adrenaline, hydrocortisone and clemastine, intubated and transferred to the Intensive Care Unit (ICU). Her condition progressively improved and she was discharged 48 hours later.

Case 2: female, 75 years old, history of asthma. The patient also had indication for ablation of atrial fibrillation and was proposed to have a CCTA. Immediately after the administration of iopromide, she became agitated and dyspneic, with central cyanosis and peripheral desaturation. Hydrocortisone and clemastine were administered. The condition evolved into cardiac arrest, and generalized urticaria and angioedema of the tongue, lips and eyelids were observed. Advanced life support was immediately initiated, and intravenous adrenaline was administered, with rapid recovery of spontaneous circulation. She was transferred to the ICU, and was discharged 3 days later.

After these episodes, and although the iopromide administered in these cases had different lot numbers, this ICM was discontinued in the whole hospital and was replaced by Visipaque® 320 (iodixanol).
Case 3: female, 21 years old, history of allergic rhinitis and mild asthma. The patient resorted to the Emergency Room for abdominal pain, and was prescribed an abdominal CT. After the administration of iodixanol, she developed angioedema of the lips and ear lobes, generalized pruritus and erythema, and went into anaphylactic shock. She was promptly treated with IM adrenaline, hydrocortisone and clemastine. The symptoms rapidly improved. She was admitted in the Observation Room for monitoring and discharged after 12 hours.
In the first two reactions tryptase serum levels were found to be extremely elevated. Skin tests with the ICM involved in the reaction were performed 2 months later as recommended by the recent EAACI practice parameters (1): undiluted at 320-370 mg/mL for skin prick tests (SPT) and diluted at 1:10 for intradermal tests (IDT). The SPTs were negative, so we continued with IDT, which were positive in all cases, confirming the IgE-mediated reaction.
All three patients had negative SPTs and IDT to an alternative ICM (iodixanol in the first two and iopromide in the latter). The first patient has already been submitted to a provocation test with iodixanol, which was negative. We performed a protocol that consisted of serial administrations in increasing doses (5 mL, 15 mL, 30 mL, 50 mL), with 45 minutes intervals.
The other two patients are scheduled to have a provocation test with the alternative ICM in the near future. They have a written medical report that states the diagnosis and the need for absolute avoidance of the implicated ICM until completion of the allergy study. The report also emphasizes the need to perform premedication if, in the mean time, an exam with ICM is absolutely required. The premedication protocol we recommend includes the administration of 40 mg prednisolone 12 and 2 hours before the exam and also 10 mg loratadine 2 hours before the exam.
The protocol for ICM administration was precisely the same in all cases and it is nowadays fully automated, so there is no room for human error.
Although the appearance of low-osmolar ICM allowed for a significant reduction in the number of adverse reactions (6) we highlight that severe hypersensitivity reactions continue to occur. These potentially fatal cases reinforce the importance of the awareness for these reactions among radiology and cardiology staff, as well as the existence of acute treatment protocols and even premedication protocols, in cases of increased risk of reaction, in close relation with allergists.

Conflict of interests

The authors declare that they have no conflict of interests.

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