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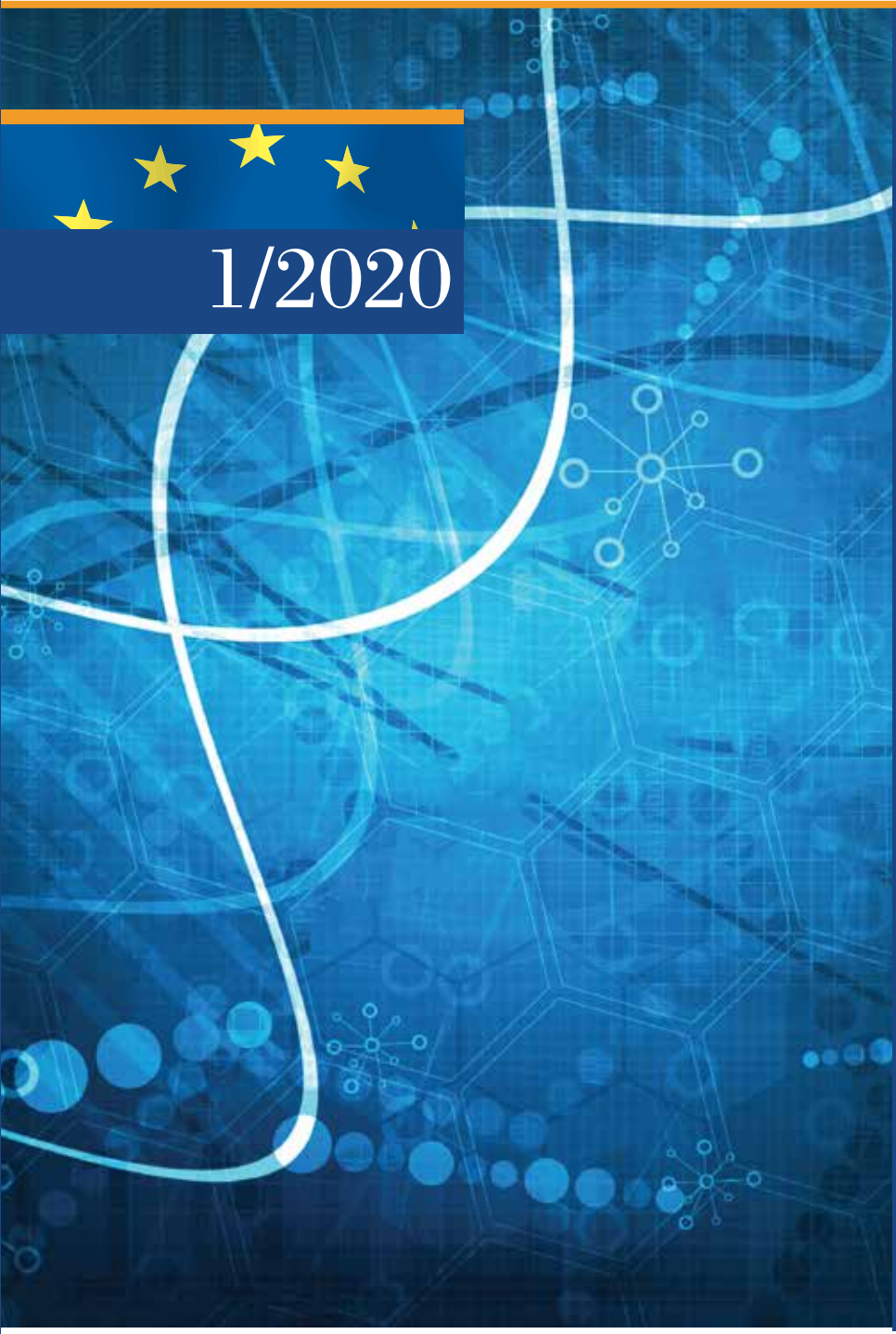

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Atopic Dermatitis Host and Environment Model: Revisiting Therapeutic Options

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Summary
Atopic Dermatitis affects both children and adults and is a serious health concern in many countries. AD is a complex disease with host and environmental factors underlying its pathology. Its treatment is multidimensional reflecting the diverse nature of its triggers and includes emollients, topical steroids and calcineurin inhibitors among others. Immunological dysfunction can be addressed broadly with systemic immunosupressors and specifically with monoclonal antibodies. Dupilumab, which targets IL-4 and IL-13 was granted approval for treatment of moderate-to-severe AD. Biologics targeting IgE/Th2 pathways may have its role in patients with overlapping AD and asthma.
Psychological distress can exacerbate symptoms and is associated with increased severity of AD. Environmental triggers, such as, allergens can be addressed in selected cases with allergic immunotherapy.
In this paper, we discuss AD treatment and propose a new step-by-step approach aiming at maintaining disease control and improving quality of life.

Introduction

Atopic disorders represent a global health problem with a number of studies demonstrating an increase in the prevalence of asthma, allergic rhinitis (AR) and atopic dermatitis (AD) over the last four decades (1). Although current estimates point to AD cases leveling off or even decreasing in some countries, such as, the United Kingdom and New Zealand, AD remains a serious health concern in many countries, particularly in the developing world where the disease is still very much on the rise (2). The sharp increase in allergic diseases between the early 60s and the late 80s is perceived to be a consequence of an intense migration from rural to urban regions, and from poor, developing countries to more affluent, heavily industrialized regions of Europe, Asia and the Americas. The recent biodiversity hypothesis on allergic diseases (3) claims that not only the loss of macrodiversity determined by climate change and pollution is associated with adverse health effects, but also that the loss of microdiversity is associated with various inflammatory conditions, including asthma and allergic diseases. As such, a fundamental role for microorganisms in human health, whether indigenous or environmental, is becoming increasingly evident.
Besides the importance of the environment in the development of allergic diseases, an increased familiar predisposition for the development of these conditions may exist. This observation led researchers to hypothesize that host genetic factors could be involved in the pathogenesis of AD. The description, back in 2006, that loss-of-function mutations in the filaggrin (FLG) gene were a strong genetic risk factor for AD, became a significant breakthrough regarding prognosis and treatment. FLG monomers aggregate keratin filaments into tight bundles, resulting in the collapse and flattening of corneocytes that maintain both skin barrier integrity and normal stratum corneum (SC) lipids. Therefore, mutations in the FLG gene may increase skin permeability, predisposing individuals to skin allergen penetration and subsequent infection. These mutations have also

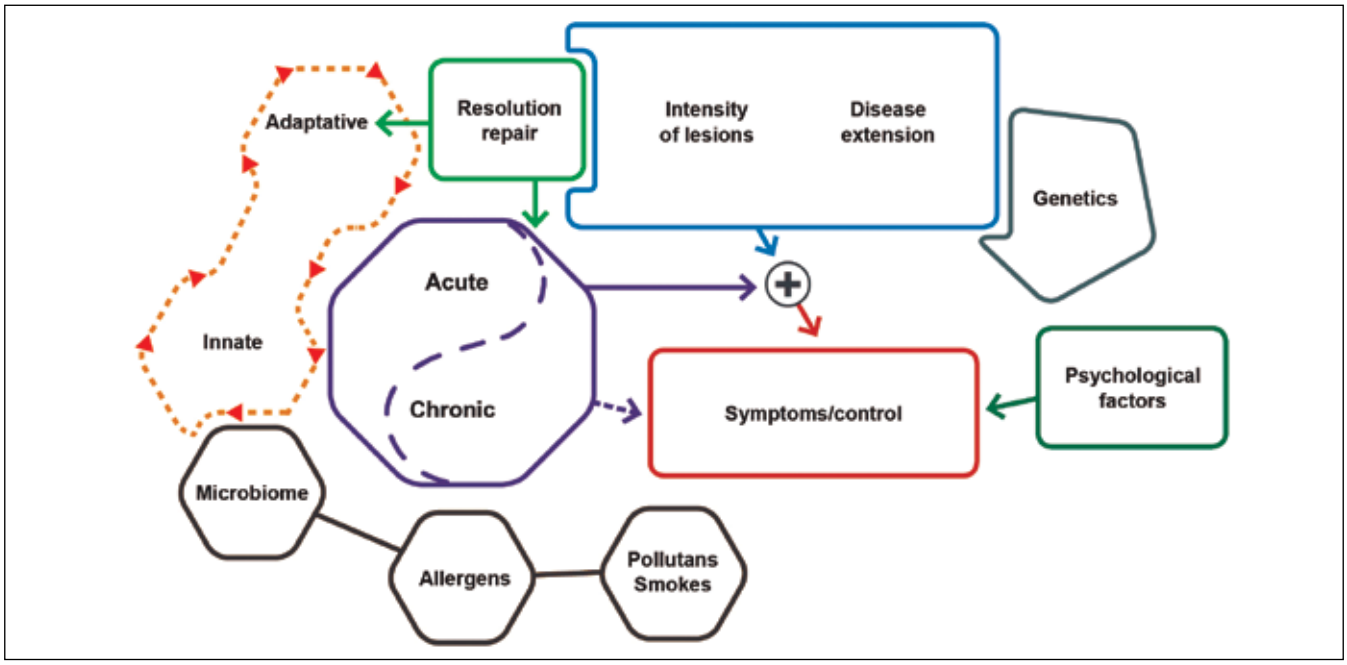
been correlated with other atopic disorders such as atopic asthma, although with conflicting and less clear results (4).
Dysfunction of innate and adaptive immune responses are typical features of AD. Atopic skin exhibits decreased levels of antimicrobial peptides and a decreased number of dendritic cells when compared with the skin of patients with other inflammatory skin diseases. AD patients have increased risk of developing rhinitis and asthma, which suggests a systemic Th2 allergic predisposition in this population (5).
We can consider that host and environmental factors contribute to AD pathogenesis and manifestations. The former includes genetic background, namely filaggrin gene mutations, innate and adaptive immunological dysfunction and psychological aspects that interfere with patient's quality of life. Environmental factors include allergens and skin microbiome that can modulate expression and severity of AD (**figure 1**).
The treatment of patients with AD is therefore multidimensional aiming at restoring skin hydration and lipid defects, down-regulation of allergen-driven skin inflammation, elimination of skin pathological inhabitants, and addressing the pruritus that perpetuates the vicious cycle of scratching. Recently, new immunomodulators have emerged as complementary treatment strategies to conventional AD therapies, because these molecules not only diminish symptoms but also address immunological dysfunction (6).
Our aim is to provide an updated revision on the treatment options for AD that target both the host (skin barrier, immunological deviation) and the environmental factors (allergens and skin microbiome) underlying this pathology, with special emphasis given to new immunomodulatory drugs.

Host factors

Skin barrier

The first approach to symptoms management is therapy directed at skin barrier impairment (7). The aim should be to maintain skin care, improve skin repair, and keep a healthy skin barrier, in order to suppress the inflammatory response and keep itching under control (7).

Figure 1 *- Atopic Dermatitis multicomponents model. AD has a complex pathogenesis with multiple players. Innate and adaptive immune dysfunction promote Th2 and Th1 driven inflammation and changes in the normal skin microbiome. The microbiome dysbiosis potentiate the irritating action of allergens, air pollutants and smoke. Immunological factors also act on resolution and skin repair leading to chronic lesions characterized by lichenification and fibrosis. The genetic background can, in some subjects, be responsible for the skin barrier impairment leading to a more severe disease. Intensity and extension of lesions are the main determinants of symptoms (pruritus, pain, skin discomfort). Psychological factors such as anxiety can potentiate symptoms and symptoms can lead to psychological distress such as depression and quality of life impairment. Adapted from Anderson (58).*



Emollients are the first step in the treatment regimen of AD because they promote skin care and repair, restore epidermal function, suppress inflammation and maintain itch control (8, 9). Emollients are topical preparations and can be delivered via a variety of formulations, including creams, ointments, oils, gels, and lotions. Emollients are normally used in a liberal way, aiming at maintaining minimal xerosis (8). Their use may be especially relevant in patients with FLG deficiency since this leads to defects in the formation of the stratum corneum (SC), decreases the ability to maintain its hydration, and induces a parallel elevation in pH, lipid bilayer disorganization, percutaneous allergen exposure and xerosis (10).

Emollients are designed to maintain the skin's softness and hydration and can be occlusive, humetant or lipidic. Occlusive emollients maintain the external hydrophobic layer of the skin surface reducing transepidermal water loss levels (TEWL); humetant emollients have hydrophilic hydroxil groups and are capable of retaining water within the skin, either by attracting water from the dermis or from the external environment (when relative ambient humidity is greater than 70%); lipidic emollients, such as ceramides, replenish the lipid component of the SC, which is decreased in AD, and by doing so, they improve transepidermal water content in children (11).

Emollients have numerous beneficial effects for AD patients including decreasing the number and increasing the time to flares and reducing the amount of topical corticosteroids needed (12) Randomized controlled trials have demonstrated the benefits of long-term use of emollients in xerosis control, which translates into better quality of life (QoL) of patients (13). When the regular use of emollients fails to achieve satisfactory skin care and reduced symptoms, other topical therapies are required(8).

Topical corticosteroids (TCS) are the core of anti-inflammatory therapy, being used in children and in adult patients when the lesions fail to respond to good skin care and regular use of moisturizers alone (9). They act on a multitude of immune cell populations, namely T lymphocytes, monocytes, macrophages, and dendritic cells, decreasing the release of pro-inflammatory cytokines (8). TCS also reduce *Staphylococcus aureus* bacterial load, likely via decreasing the inflammatory cytokines that inhibit antimicrobial peptide production.

TCS are utilized for active inflammatory flares of disease and for prevention of relapses, decreasing both acute and chronic signs of AD, as well as pruritus (8). A meta-analysis of randomized controlled trials has advocated a proactive approach of maintenance therapy for those patients with repeated outbreaks at the same body sites. When used once to twice weekly at these particular body locations, TCS reduced the rates of relapse and increased time to first flare relative to the use of moisturizers only. TCS are grouped into classes according to anti-inflammatory potency, and selection of steroid should be guided by location, extent and acute or chronic nature of skin lesions, patients' age, and disease severity. Low-potency TCS are indicated for mild disease, flexural and facial skin lesions, young children and pregnant women. High potency TCS are preferred for older patients, lichenified and chronic prurigo-like lesions and palms (14).

It has been shown that TCS have a greater absorption rate and systemic uptake in patients with clinically severe disease, when compared to patients with mild or moderate disease, suggesting caution in their use in more advanced stages of the disease and in infants (15). The incidence of reported side effects from TCS use is low; however, most studies fail to follow patients long-term for potential complications. Cutaneous side effects include purpura, telangiectasias, striae, focal hypertrichosis, and acneiform or rosacea-like eruptions. Of greatest concern is skin atrophy, which can be induced by any TCS, though higher potency agents, occlusion, use on thinner skin, and older patient age increase this risk. Continuous application of TCS for long periods of time should be avoided, to limit the occurrence of negative changes. Proactive, once to twice weekly application of mid-potency TCS for up to 40 weeks has not demonstrated these adverse events in clinical trials (8).

Topical calcineurin inhibitors (TCIs) are a class of anti-inflammatory topical therapy that inhibits calcineurin-dependent T-cell activation, decreasing the production of inflammatory cytokines (8). Pimecrolimus and tacrolimus are approved in the EU from 2 years of age and above. TCIs can be used in patients who fail to respond to other topical therapeutics such as TCS or as a complementary approach (8, 9). The long-term use of TCIs is supported by robust data, documenting safety and efficacy, while data supporting long-term TCS use are limited to low- to mid-potency products (8). Despite this, a meta-analysis by Broeders et al demonstrated that TCIs and TCS led to a similar percentage of patients presenting improvements in dermatitis and of treatment success rates both in children and adults (16).

Pruritus in AD is multifactorial depending on other mediators than histamine like nerve growth factor, substance P, protease, and cytokines/chemokines (thymic stromal lymphopoietin (TSLP), IL-2, IL-4, IL-13, and IL-31) (17) explaining with anti-histamines have demonstrated little utility despite their frequent use topical anti-histamines, because of risk of sensitization, are contra-indicated (8). Oral sedative H1 antihistamines are not recommended because of the risk of adverse reactions such as increased somnolence or restlessness, confusion, etc. A summary of the main conclusions regarding skin barrier is presented on **box 1**.

Immune deviation

Systemic immunomodulatory therapy is reserved for patients with poor response to non-pharmacological or topical treatment, with persistence of symptoms and impairment of QoL (18). All

Box 1 *Summary of the main conclusions regarding skin barrier.*

- The use of emollients prevents exacerbations
- Flares should be treated with topical corticosteroids
- Topical calcineurin inhibitors should be used as a complementary approach, especially in sensitive skin areas

immunomodulatory agents should be adjusted to the minimal effective dose once response is achieved, and topical treatments should also be maintained in order to allow the lowest dose and duration of systemic agents. Both non-specific and specific immune systemic therapies are available for these patients.

Non-biologic systemic drugs used for adult AD include cyclosporine, corticosteroids, azathioprine, methotrexate (MTX) and mycophenolate mofetil (MMF), which exert their immunosuppressive effects by reducing inflammatory cell numbers and pro-inflammatory cytokines expression (19). Phototherapy is also frequently used as a second-line treatment for moderate-to-severe AD in adults (20).

Cyclosporine is an immunomodulatory drug that inhibits interleukin IL-2 and T-lymphocytes. According to Consensus-based European guidelines for treatment of atopic dermatitis it is the first choice for systemic treatment of severe adult AD patients who are unresponsive to topical therapy and require systemic immunosuppressive treatment (21). An initial daily dose of 2.5–3.5 mg/kg/day and a maximal daily dose of 5 mg/kg/day, divided upon two single doses, is recommended. A dose reduction of 0.5–1.0 mg/kg/day every 2 weeks is desirable as indicated by clinical efficacy. It can be used as a continuous therapy, but a maximum duration of 1–2 years has been suggested to avoid adverse events such as nephrotoxicity, hypertension, tremors, headaches, paresthesia, nausea, diarrhea, myalgias, electrolyte imbalance, hyperlipidemia, hypertrichosis and gingival hyperplasia. Patients receiving cyclosporine should be monitored for blood pressure and renal parameters, as cyclosporine is known to induce structural and organic kidney damage. Nephrotoxic effects are more likely to occur if the daily dose exceeds 5 mg/kg body weight, serum creatinin values are elevated or elderly patients are treated (22). Cyclosporine may be used 'off label' in children and adolescent patients showing a refractory or severe course of disease (23).

Systemic corticosteroids decrease the transcription of several mediators involved in the pathogenesis of AD, including cytokines, chemokines and adhesion molecules, by binding to regulatory elements on many genes, thus leading to resolution of inflammation (19, 24). Despite rapidly improving disease activity, systemic corticosteroids (oral or parenteral) have a largely unfavorable risk/benefit ratio for adult AD treatment (19, 24) and long-term use is not recommended (18, 19, 24). Also, a rebound flare and increased disease severity is frequently seen after discontinuation of systemic steroids. Short-term (up to 1 week) treatment may be an option to treat acute flares in exceptional and severe cases of AD (19, 21, 24).

Azathioprine is a purine analog that inhibits DNA production and reduces leukocyte proliferation thus decreasing inflammation (18). It is used off-label for the treatment of severe AD in adults, in particular in the UK and USA (18, 19, 24). It may be used off-label when cyclosporine is either not effective or contraindicated (21). Although several studies have demonstrated QoL improvement and symptomatic control with azathioprine usage in AD(18), data on efficacy and safety are still sparse. Adverse events of azathioprine include gastrointestinal disturbances, liver dysfunction and leukopenia (19, 24).

Methotrexate (MTX) is an antimetabolite that regulates the immune system and inflammatory processes, by interfering with folic acid metabolism through blocking of RNA, DNA and purines' synthesis (18). Several studies suggested that MTX is well-tolerated and effective in the treatment of moderate-to-severe forms of AD(19) even if its use is off-label. Nonetheless, liver and bone marrow toxicity have to be monitored before and during MTX therapy. The adverse events most commonly causing discontinuation of MTX treatment include nausea, fatigue, hepatotoxicity, hematological abnormalities, pulmonary toxicity and drug interaction. Folic acid supplementation is recommended during treatment with MTX to reduce the likelihood of hematologic and gastrointestinal toxicity.

Mycophenolate mofetil (MMF) is also an antimetabolite that blocks the purine biosynthesis pathway selectively inhibiting B- and T-cell proliferation. Several case reports and small studies showed its efficacy when used off-label in adult patients with AD who were unresponsive to cyclosporine therapy (19, 21). The main adverse events reported during MMF therapy were nausea, fatigue, flu-like syndrome and liver enzyme alteration.

Phototherapy with artificial UV radiation is frequently used as a second-line treatment for moderate-to-severe AD in adults (20). Narrowband UVB is preferred over broadband UVB for AD treatment if available (9). UV irradiation is able to modulate the immune response of AD patients through upregulation of FoxP3-positive regulatory T cells, whose number is directly correlated with the degree of AD severity score. Phototherapy can be used as short- and/or long-term treatment. TCS and emollients can be associated with phototherapy to reduce flare-ups, whereas TCIs should be avoided to limit the risk of carcinogenesis (9, 20). Phototherapy must be performed conscientiously, especially in children, and must take into account the patient's features and overall condition (20).

Severe refractory AD patients that fail to improve with systemic immunosuppressive therapy, or those who experienced import-

ant side effects, may benefit from biologic therapy. Biological therapies for AD include several monoclonal antibodies, of which omalizumab and dupilumab are the best studied. Currently, dupilumab is the only biological therapy approved for treatment of moderate-to-severe AD by the Food and Drug Administration (FDA) and European Medicines Agency (EMA).

Omalizumab is a humanized monoclonal antibody that binds to the high-affinity IgE receptor, preventing IgE from binding to the surface of several cell types including mast cells, basophils, dendritic cells and eosinophils, and so blocking mast-cell degranulation and decreasing the release of cytokines and recruitment of other inflammatory cells (25). Treatment with Omalizumab is currently indicated in adults, adolescents and children (> 6 years of age) with severe persistent allergic asthma and in refractory chronic spontaneous urticaria (26). Although data from case series and case reports documented clinical benefit of AD, some studies showed no improvement of disease with Omalizumab *both in adults and children* (27, 28). Nevertheless, a recent randomized clinical trial found that Omalizumab significantly reduced atopic dermatitis severity and improved quality of life in a pediatric population (4-19 years old) with atopy and severe AD despite highly elevated total IgE levels at baseline (29). Due to AD heterogeneity, it seems that some patients are most likely to respond to anti-IgE therapy: lack of filaggrin mutations and lower elevations of total serum IgE are factors associated with a likely favorable response to Omalizumab (30, 31). Based on case reports and case series, targeting IgE seems to be an option in patients who have overlapping allergic diseases such as asthma (32). However at this time, available scientific evidence does not support its use for the treatment of AD (21) and larger RCTs are needed.

Dupilumab is a fully human monoclonal antibody that targets IL-4Rα and inhibits signaling of IL-4 and IL-13, both of which are key Th2 cytokines that play an important role in AD.(33) The data supporting its efficacy and safety came from two randomized, placebo-controlled, phase 3 trials, SOLO 1 and SOLO 2, involving 671 and 708 adult patients, respectively, > 18 years of age with moderate-to-severe AD (34). Dupilumab has a favorable safety profile with no dose-limiting toxicity and few adverse events, including nasopharyngitis, upper respiratory tract infections, conjunctivitis, headache, injection-site reaction and back pain (33, 34). Dupilumab, is indicated for the treatment of moderate-to-severe AD in adolescent and adult patients who are candidates for systemic therapy (35, 36). European Guidelines for the treatment of AD recommend dupilumab as a disease-modifying drug for patients with moderate-to-severe AD, combined with daily emollients (21). Dupilumab has also recently been approved for treatment of severe asthma (37) and severe chronic rhinosinusitis with nasal polyps (38). **Box 2** summarizes the main conclusions regarding non-specific and specific immune systemic therapies.

Box 2 *Main conclusions regarding non-specific and specific immune systemic therapies.*

- Systemic therapy should only be used if topical therapy fails
- Cyclosporine is the first-line option for patients who require systemic immunosuppressive treatment
- Systemic corticosteroids should only be used in exacerbations and for short periods of time
  - *Dupilumab, which targets IL-4 and IL-13 is approved for treatment of moderate-to-severe AD.*
  - *Biologics targeting IgE/Th2 pathways may have its role in patients with overlapping AD and asthma.*

Psychotherapy

AD is associated with other allergic conditions and psychosocial disorders. Specifically, the prevalence of depression, anxiety and other psychiatric disorders are higher in AD patients than in the general population, due to social isolation, sleep deprivation and persistency of symptoms (39).

Psychotherapy through cognitive behavioral stress management has a positive impact in the burden of disease, namely on the improvement of endocrine and psychological stress responses (39). Some studies demonstrated an effective decrease of anxiety in adults, as well as in children (39). Moreover, psychological interventions are associated with better managing of symptoms and a decrease in itching intensity (39). A summary of the main conclusions regarding psychotherapy is presented on **box 3**.

Environmental factors

Allergens

Historically, the relationship between exposure to allergens, specifically inhaled allergens (horse dander, ragweed pollen, timothy grass) and AD was demonstrated in 1918 (40). Currently, it is known that in some phenotypes of AD there is an immune response to allergens, mediated by IgE and T cells (41). The skin barrier function and innate immunity are involved in this pathology due to the properties of some allergens (41) that facilitate barrier disruption and cutaneous sensitization. It has been shown that exogenous protease activity of house dust

Box 3 Main conclusions regarding psychotherapy.

- Psychological distress can be an exacerbating factor of AD
- Psychological interventions may benefit AD patients

mite, insects, fungi, and pollen disrupts inter-corneocyte connections and Der f 1 allergen disrupts epidermal tight junctions and induces inflammatory mediator release, such as IL-6, IL-8 and GM-CSF, by keratinocytes (42). Itching and delayed skin barrier recovery from mite and cockroach allergen exposure is mediated by activation of protease-activated receptor-2 (PAR-2) expressed by keratinocytes and dermal unmyelinated nerve fibers (41). It is also known that PAR-2 binding capacity is enhanced by exposure to UV, with PAR-2 expression increasing in the superficial epidermis after UV exposure. Therefore, the proteolytic properties of allergens, together with UV exposure, may be a possible link behind the seasonal trend of AD.

Despite the biological plausibility of avoidance measures, studies conducted so far provide conflicting results regarding reduced indoor contact with mite allergens (43). A recent Cochrane Review concluded that very low quality evidence was currently available regarding house dust mite reduction or avoidance measures for treating eczema (44). Several possible reasons for the failure of indoor avoidance measures exist: the effectiveness of avoidance measures is difficult to ascertain (e.g., are vacuum steam cleaning and air-filters effective?); adherence to avoidance measures is not measurable nor is the exposure to allergens outside home; and finally long-term established disease is less likely to respond to avoidance measures (43). When addressing specific immunotherapy (SIT) with aeroallergens in AD, there is conflicting evidence, with more recent literature being more in favor of it (45). SIT may have positive effects in selected, highly sensitized patients with AD and the best evidence so far is available for SIT with house dust mite allergens (45). There is no contraindication for performing SIT in patients with respiratory allergic diseases (allergic rhinoconjunctivitis, mild allergic bronchial asthma) and concomitant AD (22).

Regarding food allergens, the diagnosis of eczematous reactions to food requires a careful diagnostic procedure, taking into account the patient's history and sensitization patterns. The clinical relevance of sensitization often has to be proven by an oral food challenge, with the rating of the skin condition being performed by validated scores after 24h and the evaluation of the eczematous reaction at a later point in time (46). Moreover, a large recent study investigating food allergy and AD exacerbations concluded that children with AD exacerbations in the absence of other allergic symptoms are unlikely to be food allergic (46). **Box 4** summarizes the main conclusions regarding allergens.

Box 4 *Main conclusions regarding allergens.*

- An immunological rationale for aeroallergen eviction exists although scientific evidence for this measure to be undertaken lacks
- Physicians should be cautious when considering food allergen eviction and only propose it after evidence of clinical relevance
- Specific allergen immunotherapy to house dust mites has shown efficacy in some studies
- Exposure to irritant environmental factors such as tobacco should be avoided

Skin microbiome in AD patients

Metagenomic studies have revealed that diverse and complex microbial ecosystems inhabit the skin and are collectively known as the skin microbiome. The skin microbiome is composed mainly of members of the same four phyla that comprise the gut microbiome, although with dissimilar relative abundances. In all individuals, *Propionibacterium* species dominates in sebaceous areas such as the forehead, retroauricular crease, and back, whereas *Staphylococcus* and *Corynebacterium* species dominate in moist areas, such as the axillae. Abundant Gram-negative organisms, previously thought to colonize the skin rarely as gastrointestinal contaminants, were found in the microbiomes of dry skin habitats, such as the forearm or leg (47).

Interest in the relationship between AD and metagenomics is increasing. Studies show that *S. aureus* increased from 35% to 90% of the microbiome during flare-ups, with concomitant increase of *S. epidermidis* (48). It is still unclear if *S. aureus* and *S. epidermidis* mutually enhance each other's colonization or if *S. epidermidis* increase reflects an antagonistic response to an increasing *S. aureus* population. *S. aureus* produce superantigens (*S. enterotoxin A*, *B* and *C*, and toxic shock syndrome toxin-1), which are important effectors in AD. They cause *S. aureus*-specific IgE production and this correlates with disease severity. Superantigens also cause nonspecific IgE production, activate T cells, B cells and macrophages, and stimulate their proliferation (49). Superantigens also induce chemokines such as CCL1 and CCL18, which bind to CLA-positive T cells in peripheral blood and thus are likely to play a role in T cell homing to the skin. The superantigens seem to reduce the immunosuppressive activity of certain immunosuppressive regulatory T cells, which may, in turn, increase inflammatory T cell activation (49). They are also known to induce corticosteroid resistance, thus hampering the treatment of atopic diseases.

Although infected AD exacerbations require specific treatment of microorganisms in combination with AD treatment, no evidence supports the assumption that antimicrobial treatment of colonized skin will benefit patients in the long-term (49). Moreover, combining topical antibiotic agents with corticosteroid treatment has led to no further decrease in *S. aureus* colonization compared with corticosteroid alone (50). Therefore, antibiotic treatment should be used with caution.

With the development of nanotechnology, intelligent or functional textiles with antiseptic properties are available. Such

textiles have been used as adjuvants and antiseptic dressings in burns and wound healing with promising results. In immunologically mediated skin diseases, and AD in particular, the focus has been to improve itch, severity of lesions, and skin colonization by *S. aureus*. Most of the studies of functional textiles in AD have investigated the use of specially treated long-sleeved shirts and pants in close contact with the skin. Cotton textiles can be functionalized with antiseptic silver salts or borage oil, which supplies unsaturated fatty acids to the skin barrier (51). Silk coated with specific antimicrobial chemical compounds and smooth ethylene vinyl alcohol (EVOH) fibers are also used to diminish physical stimuli applied to the skin (51). A systematic review provided a weak recommendation for the use of these textiles in AD based on low quality of evidence supporting the effectiveness of these functional textiles in alleviating symptoms and reducing disease severity (51). Nevertheless, recent studies with new biocompounds showed that chitosan-coated textiles may impact disease severity, by modulating the staphylococcal profile in the skin, and have a potential effect on QoL (52). However, further studies are needed to confirm these data, to identify which mechanisms are targeted, and to determine how functional textiles contribute to symptom improvement.

Besides pathogenic bacteria, other causes of infections in AD patients are virus and fungi. Herpes simplex virus (HSV) can lead to the disseminated HSV infection eczema herpeticatum, probably the most feared complication of AD (53). In addition, *Malassezia* yeast species colonize the skin of 90% of AD patients compared with 35% of healthy controls, especially the sebaceous areas of the face, scalp and upper body. Species associated with AD include *Malassezia globosa, sympodialis, restricta,* and *furfur* (54). Their role in AD exacerbations is controversial despite the fact that specific IgE antibodies towards *Malassezia* species can be found in AD patients but not in healthy controls (55). No evidence supports that antifungal treatments reducing *Malassezia* colonization would relieve AD in the long-term, although treatment periods with an antifungal agent have had some effect, especially on eczema in the sebaceous areas. **Box 5** summarizes the main conclusions concerning the skin microbiome.

Box 5 Main conclusions concerning the skin microbiome.

- AD is associated with loss of diversity of the skin microbiome
- *Staphylococcus aureus* colonization is associated with increased disease severity
- When overt clinical infection, antibiotic treatment should be considered

Treatment algorithm proposal

Considering all the different treatment approaches in AD, we aimed to develop a rationale and step by step approach according to its degree of severity and control– **figures 2 and 3**.

Assessing disease severity

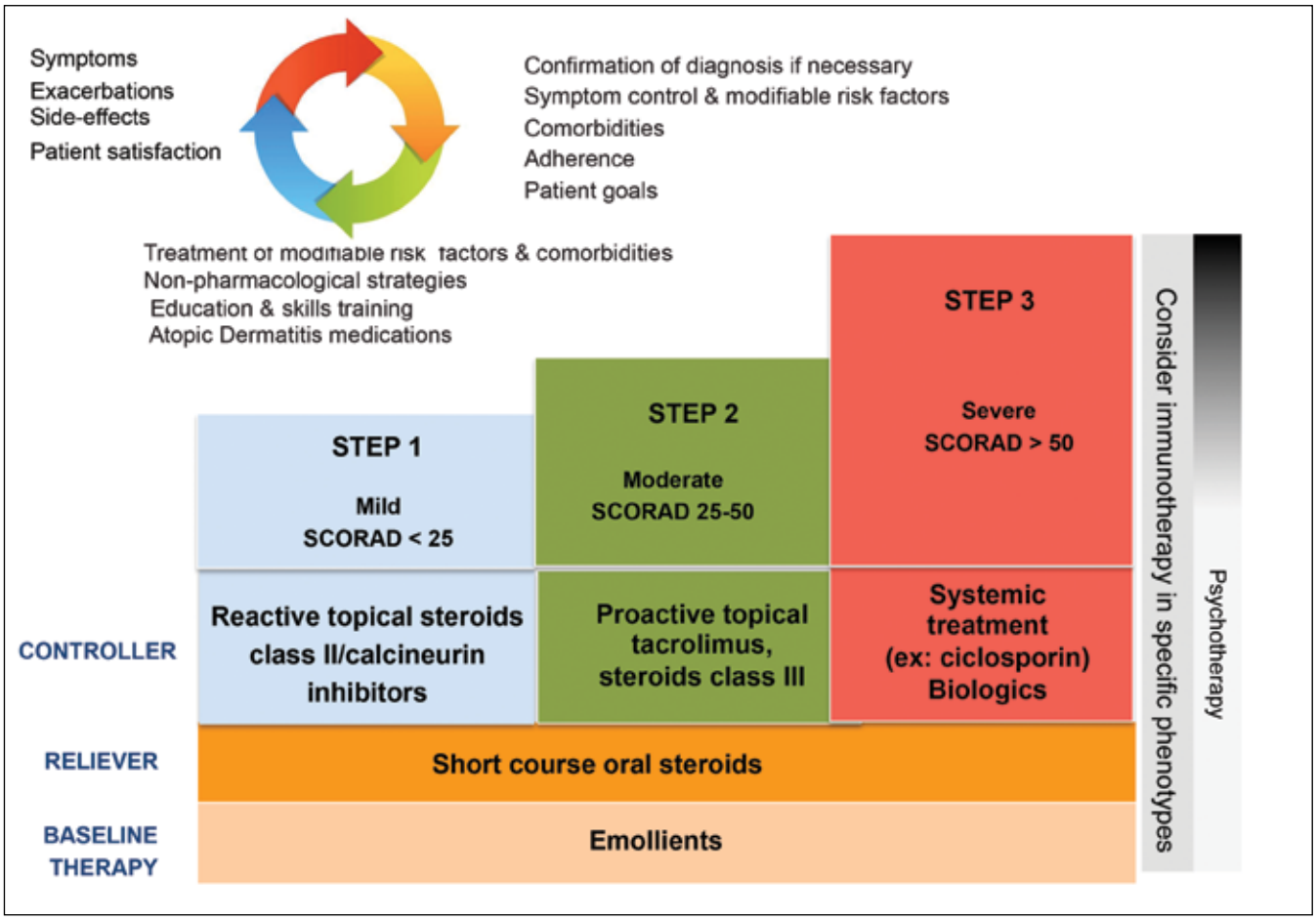
Regarding disease severity, it must be determined by evaluating both objective signs (physician assessments of disease severity) and subjective symptoms (patient-reported symptoms and Quality of life outcomes). One of the most commonly used tools for assessing AD severity is SCORing Atopic Dermatitis (SCORAD); SCORAD attributes around 60% of the total score to the intensity of lesions, 20% to spread and 20% to subjective signs scored by the patient(56). A SCORAD > 50 is regarded as severe, while SCORAD scores < 25 are considered mild. Considering Quality of life, Dermatology Quality of life questionnaires (DLQI) and the Infants' Dermatology Quality of Life Index (IDQOL) are the QoL instruments most commonly used in AD, taking into account the different disease domains, in particular signs and symptoms; sleep quality; work performance and social and emotional well-being; to quantify the different aspects of the individual burden of AD in a real-world setting.

Assessing control

In contrast with other allergic diseases such as asthma, no clear and globally accepted definition of control exists for AD. Langan et al (57) recently described a totally controlled week as one in which symptoms are well controlled every day. A well-controlled week was one in which increased symptoms have occurred or treatment has been applied for a period of 2 days or less and symptoms are controlled most of the time. In every clinical evaluation AD control should be addressed evaluating daytime and nocturnal symptoms, limitation of activities, need of rescue treatment and occurrence of flares (**figure 2**).

AD treatment should be based on a personalized cycle of assessment, adjustment of treatment, and review of the response. For each patient in addition to treatment of modifiable risk factors such as stress, controller medication can be adjusted up and down in a stepwise approach to achieve good symptom control and minimize risk of future exacerbations. The number of well controlled weeks will give the clinician a measure of disease control in a determined period of time. Once AD control has been maintained for 2-3 months treatment may be stepped down in order to find the patient minimum effective treatment. If a patient has persisting uncontrolled symptoms and/or exacerbations despite 2-3 months of controller treatment, the clinician should assess and correct some problems before considering any step up in treatment: poor adherence,

Figure 2 – *Algorithm proposal for Atopic Dermatitis management. Consider stepping up treatment, with or without overlapping, to attain total control. Adapted from Global Initiative for asthma available at https://ginasthma.org.*



persistent exposure to home/work agents such as allergens, comorbidities that may contribute to poor quality of life and incorrect diagnosis.

Key points regarding stepwise approach of AD treatment:

Mild Atopic dermatitis

- When used on a daily basis, moisturizers with non-aqueous emollients, occlusive agents and humectants improve barrier function; reduce AD signs and symptoms, and the need for topical corticosteroids.
- Topical corticosteroids remain the first line treatment, reducing disease recurrence when used intermittently in patients with established disease.

Stepping up if AD remains uncontrolled despite good adherence:
- for patients with persistent symptoms and /or flares consider proactive therapy with topical tacrolimus or glucocorticosteroids class III;
- if disease control cannot be achieved with topical measures, when topical therapies fail or become unacceptable or impractical, systemic therapy is indicated.

Stepping down to find the minimum effective dose:
- consider step-down once AD control has been achieved and maintained for about 3 months, to find the lowest treatment that controls both symptoms and exacerbations;
- provide the patient with a written AD action plan, monitor closely and schedule a follow up visit in a 3-4 month period.

For all patients with AD:
- encourage adherence to emollients use, even when symptoms are infrequent;
- provide training in AD self-management to control symptoms and minimize risk of exacerbations.

Figure 3 - *Definition of Atopic Dermatitis total, well and uncontrolled weeks. A totally controlled week as one in which symptoms are well controlled every day. A well-controlled week was one in which increased symptoms have occurred or treatment has been applied for a period of 2 days or less and symptoms are controlled most of the time.*

Characteristics	Total Controlled week (All of the following)	Well controlled week (All of the following)	Uncontrolled week (Any present)
Daytime symptoms	None	≤ 4 times	Most of the days
Limitations of activities	None	≤ 4 times	Most of the days
Nocturnal symptoms / awakening	None	≤ 4 times	Most of the days
Need for rescue / "reliever" treatment	None	≤ 2 days	≥ 3 days
Flare*	None	None	One in any week

A "flare" of AD is defined as an episode resulting in behavior such as requiring an escalation of treatment (independently of the baseline grade of severity); or seeking additional medical advice

Conclusions

AD is a complex disease with host and environmental factors underlying its pathology. There are several different treatment approaches in AD, such as emollients, topical steroids, calcineurin inhibitors, systemic general immunosupressors and monoclonal antibodies. Dupilumab is the only biologic currently approved for adolescents and adult patients with moderate-to-severe AD. Biologics targeting IgE/Th2 pathways may have its role in patients with overlapping AD and asthma.
We propose a new step by step approach aiming at maintaining disease control and improving quality of life.

Conflict of interests

Author Anabela Lopes declares collaborating and receiving fees from Novartis, Menarini and SANOFI through either participation in advisory boards or consultancy meetings or congress symposia. Author Anna Sokolova declares collaborating and receiving fees from Novartis, Astra Zeneca and Vitoria through either participation in advisory boards or consultancy meetings or congress symposia. Author Carmo Abreu declares collaborating and receiving fees from Novartis through either participation in advisory boards or consultancy meetings or congress symposia. Author Cristina Lopes declares collaborating and receiving fees from Astra-Zeneca, Novartis, Menarini, TEVA and SANOFI, through either participation in advisory boards or consultancy meetings or congress symposia.

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Severe CSU and Activation of the Coagulation/ Fibrinolysis System: Clinical Aspects

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Key words

chronic urticaria; D-dimer; coagulation biomarkers; inflammation

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Summary

Background. *About 50% of patients with severe chronic spontaneous urticaria (CSU) show signs of activation of the coagulation/fibrinolysis system, but the clinical significance of this phenomenon is unclear.* **Objective.** *The present study compared patients with severe CSU showing and not showing elevated D-dimer plasma levels.* **Methods.** *132 adult patients (m/f 44/88; mean age 51, 5 years; range 14 - 89 years) with severe CSU (UAS-7 > 30) were included in a cross-sectional, real life study. The study group was divided based on baseline D-dimer plasma levels, and compared for age, sex, disease duration, disease activity, CRP, thyroid autoimmunity, total IgE, and atopic status.* **Results.** *Identical numbers of patients showed elevated and normal D-dimer plasma levels (50% and 50%, respectively). Patients showing elevated D-dimer levels were slightly older ($p < 0.05$), were more frequently females ($p < 0.05$), had a longer disease duration ($p < 0.01$), and had a significantly higher prevalence of elevated PCR (26/66 vs 4/66; $p < 0.001$).* **Conclusions.** *Only 50% of patients with severe CSU show elevated D-dimer plasma levels. The activation of the coagulation/fibrinolysis system is associated with a systemic inflammatory milieu, suggesting the existence of a specific phenotype. Whether this reflects the existence of different endotypes in patients showing and not showing the activation of the coagulation cascade has still to be established.*

Introduction

The frequent occurrence of intense thrombin generation in patients with chronic spontaneous urticaria (CSU) was first described about 12 years ago (1). Such phenomenon, which is clearly associated with disease severity (2), seems to occur via the activation of the extrinsic pathway of the coagulation cascade (1). This finding was confirmed over time by several research groups (3-6), one of whom also showed that the activation of the extrinsic pathway of the coagulation might in turn activate the intrinsic pathway also, eventually producing a hyper-coagulable pattern (7). The activation of the coagulation / fibrinolysis system is possibly a consequence of the hyper-expression of tissue factor by activated eosinophils (8), although also endothelial cells seem able to play a role in this sense (9). The activation of the coagulation system in CSU occurs irrespectively of the presence or absence of autoreactivity (5,10), and has been shown to be negatively associated with patients' response to second-generation antihistamines (11). Although increased plasma levels of D-dimer are not predictive of CSU patients' response to the humanized anti-IgE mAb, omalizumab (12), it nonetheless parallels the clinical response to this drug (13). Patients with severe CSU show a detectable activation of the coagulation cascade in about 50% of cases (12). What differentiates patients with severe CSU showing and not showing the activation of the coagulation / fibrinolysis system has not been established so far. The present study compared the clinical features in these two subsets of patients with CSU.

Patients and methods

Patients

This cross-sectional, real life study included 132 patients (m/f 44/88; mean age 51, 5 years; range 14-89 years) with severe CSU (UAS-7 > 30) unresponsive to antihistamine treatment. The study group was divided based on baseline D-dimer plasma levels, which were measured by ELISA and expressed as ng/

ml; values exceeding 500 ng/ml were considered elevated. The following parameters were investigated: age, sex, disease duration (in months), disease activity (expressed as UAS-7 value), CRP, thyroid autoimmunity (defined as the presence of circulating IgG autoantibodies specific for thyroperoxidase and/or thyroglobulin), total IgE, and atopic status (defined as a positive history of respiratory and/or food allergy confirmed by positive SPT with commercial allergen extracts). Patients gave an informed written consent to the use of their data in anonymous form. Since the study was retrospective and based on routine diagnostic tests, a formal approval by an external ethical committee was not required.

Statistics

Means and proportions were compared by two-tailed Student's t-test and by chi-square test with Yates' correction, respectively. Probability values less than 5% were considered statistically significant.

Results

Results are summarized in **table I**. D-dimer plasma levels were elevated in 66 (50%) patients and normal in 66 (50%) patients, respectively. The two groups did not differ in terms of UAS-7 score, but patients showing elevated D-dimer levels showed a slight, albeit statistically significant difference in mean age (54.3 years vs 48.7 years; $p < 0.05$), and a higher prevalence of female patients (m/f 16/50 vs 28/38; $p < 0.05$). Further, this subgroup showed a significantly longer disease duration than patients showing normal D-dimer levels (mean 64.6 months [range 2-600 month; median 21 months] vs mean 28.6 months [range 2-500 months; median 6 months] $p < 0.01$). Atopic status (19/66 [29%] vs 15/66 [23%], in patients with elevated or normal D-dimer, respectively; p = ns), elevated total IgE (51% vs 52%, respectively; p = ns), and thyroid autoimmunity (14/66 [21%] vs 19/66 [29%], respectively; p = ns) were similarly distributed in the two groups. In contrast, the activation of the coagulation / fibrinolysis system was associated with a significantly higher prevalence of elevated PCR (26/66 vs 4/66; $p < 0.001$).

Discussion

Although the coagulation / fibrinolysis cascade can be activated in patients with CSU, and this event is unquestionably associated with a severe disease (2), not all patients with severe CSU do show elevated D-dimer plasma levels. This study, which was focused specifically on subjects with severe CSU (UAS-7 > 30) refractory to antihistamine treatment, confirmed that elevated D-dimer plasma levels are found only in 50%. The reasons for this are not yet clear. Patients showing signs of activation of the coagulation / fibrinolysis system were frequently older females with a longer disease duration showing a systemic inflammatory milieu, as suggested by the higher frequency of elevated CRP, a non-specific marker of inflammation. In a recent study, about one third of CSU patients showed elevated CRP levels, often in association with a positive autologous serum skin test, a marker of autoreactivity (14). The association between coagulation / fibrinolysis and inflammation markers has been observed about 9 years ago (15) and confirmed more recently (16,17). Altogether, these findings seem to suggest the existence of a phenotype of CSU characterized by more intense, clinically detectable inflammatory events, as also shown by studies that investigated different inflammation markers (18,19), that would involve the coagulation system. On the other hand, this study suggests that severe CSU may occur in the absence of any clinically detectable inflammation. Whether this reflects the existence of different endotypes in patients showing and not showing the activation of the coagulation cascade has still to be established.

Table I *- Clinical features of patients with severe CSU with or without signs of fibrinolysis.*

	elevated D-dimer	**normal D-dimer**	**p**
no.	66	66	
mean age (years)	54.3	48.7	< 0.05
females	50 (76%)	38 (56%)	< 0.05
disease duration (months) [median]	64.6 [21]	28.6 [6]	< 0.01
elevated CRP	26 (39%)	4 (6%)	< 0.001
atopic status	19 (29%)	15 (23%)	ns
thyroid autoimmunity	19 (29%)	14 (21%)	ns
elevated total IgE	19/37 (51%)	22/42 (52%)	ns

ns, not significant.

The inflammatory milieu involving the activation of coagulation / fibrinolysis system does not seem to interfere with the clinical response to omalizumab (12), suggesting that the activated coagulation cascade probably acts as a secondary amplification mechanism rather than the leading actor in this disease. The inflammatory milieu suddenly normalizes in CSU patients responding to omalizumab (13), suggesting that the interaction between autoreactive IgE (20) and their ligands is a likely starting point of the inflammation process, and that their neutralization by anti-IgE leads to the "shutdown" of the whole mechanism. Patients showing elevated D-dimer levels are often unresponsive to antihistamines (11,16), but this seems the case also in patients lacking signs of systemic inflammation, as shown by the present study.

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Risk Factors of Zinc Deficiency in Children with Atopic Dermatitis

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Summary
Background and objectives. *Zinc deficiency increases risk of infections, allergies and autoimmunity. We wished to determine risk factors in severe atopic dermatitis (AD) and identify of hypozincemia rate.* **Materials and methods.** *Retrospective study done on AD children (≤ 14 years) with serum zinc test. Data included demographic and laboratory tests (serum zinc level, IgE, food-specific IgE), and skin tests.* **Results.** *168 AD children, aged 38.9 months with concomitant allergies in 47 (28%), family history of allergies in 131 (80%), and parental consanguinity in 134 (79.9%). AD was mild in 12 (7.2%, SCORAD 15.8) children, moderate in 41 (24.5%, SCORAD 30.4), and severe in 115 (68.3%, SCORAD 69.4). Hypozincemia was observed in 42 (25%, zinc 8.6 ± 1.1 μmoI/L) children and associated only with severe AD (p = 0.0418) and elevated IgE (p = 0.001).* **Conclusions.** *Hypozincemia is rather prevalent in AD, and severe AD and high IgE increase its risk. An adjunct oral zinc may help reducing severe poorly responsive AD.*

Introduction

Zinc is a crucial trace element for biological processes of the cells. Zinc plays an important key role in a large number of enzymes and is involved in cell activities including cell-cell interactions, proliferation, and differentiation. It exerts a regulatory role on the immune system, with evidence indicating that zinc deficiency propagates inflammation in autoimmune and allergic diseases (1). A recent, large systematic review and meta-analysis on zinc status and autoimmunity indicated that zinc levels were consistently lower in autoimmune patients than controls (2). This study included various types of autoimmune diseases, such as alopecia areata, Hashimoto's thyroiditis, juvenile idiopathic arthritis, multiple sclerosis, pemphigus vulgaris, rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, and type 1 diabetes (2).
Whereas mild AD represents more than 70-80% of patients, moderate-to-severe AD comprises 20% of cases (3). Severe AD is associated with uncommon but significant complications such as infections (4), poor weight gain, marked malnutrition, or trace elements deficiency (5). Published literature on zinc deficiency and its association with AD is increasing. The significance of hypozincemia in AD seems to be poorly understood. There are no studies on how common zinc deficiency is in moderate-to-severe AD among children and on the risk factors. The aims of this study were to determine how common zinc deficiency is among children with AD, and to determine any risk factors for zinc deficiency in these children.

Materials and methods

In this retrospective study, we reviewed records of all children, 14 years or less, seen at our Pediatric Allergy-Immunology Clinics at Hamad General Hospital with severe AD and serum zinc level tested. Serum zinc level was considered low in AD chil-

dren if less than 9.8 umol/L (64 ug/L) (6). We excluded children with chronic GI disorders (e.g. malabsorptive syndromes, pancreatic disease, cirrhosis, and blind-loop syndrome), dietary problems or restrictions (e.g. total parenteral nutrition, severely restrictive diets, anorexia, and bulimia), trauma (e.g. burns, post-surgery), malignancy, blood transfusions in the preceding 3 months, renal disorders (e.g. tubular disease, nephrotic syndrome, dialysis), severe chronic infections, certain medications (e.g. anti-metabolites, chelators), diabetes mellitus, hemolytic anemia, collagen vascular disease, acrodermatitis enteropathica, or being on zinc supplements.

Each patient's record was reviewed and data, collected on a standard form, included patient's age, sex, clinical presentation, the presence of other allergies, and family history of allergic diseases. SCORing Atopic Dermatitis (SCORAD) was collected. Each patient's weight and height were collected, from which we calculated body mass index (BMI). We also collected results of CBC, white blood cell count (WBC) with differential counts, total serum IgE. Status of food allergy, whenever available, was reviewed and recorded as per food allergens tests such as skin prick tests or specific-IgE to a panel of 8 common food allergens, including cow's milk, egg, wheat, tree nuts, peanut, soy, fish, and seafood. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board (IRB) at Hamad Medical Corporation (RMC No. 14193/14).

Results

A total of 168 children with moderate-to-severe AD had zinc level measured. There were 89 (53%) males and 79 (47%) females, with a males-to-female ratio of 1.1:1. Mean age (± SD) was 38.9 ± 38.6 months. Simultaneous other allergic diseases were observed in 47 children (28%), mainly asthma and urticaria. Family history of allergic diseases was positive in 131 (80%) children, with 66 (39.2%) positive for AD, 35 (21%) for asthma, and the rest positive for various combinations of asthma, AD, allergic rhinitis, urticaria, and anaphylaxis. Parental consanguinity was noticed in 134 (79.9%) children. Regarding AD severity, 12 (7.2%) children had mild AD with SCORAD 15.8 ± 3.2 (95% CI 13.3-18.8), 41 (24.5%) moderate, SCORAD 30.4 ± 6.7 (95% CI 28.2-32.5), and 115 (68.3%) severe with SCORAD 69.4 ± 17.0, (95% CI 62-77).

Serum zinc was low in 42 patients (25%), with level of 8.6 ± 1.1 µmoI/L (95% CI 8.1-9.0). **Table I** shows that there is no significant difference between the low-zinc group compared to the normal-zinc group in term of age, sex, the presence of other allergies or family history of allergic diseases.

AD severity scores, WBC, peripheral eosinophil counts, total IgE levels, number of positive food allergens, and serum zinc levels for both groups are shown in **table II**.

Table I *- Demographic and clinical characteristics of AD children.*

Clinical variable		low zinc group (LZG)	normal zinc group (NZG)	p-value
children number (patients)		42	126	
age (months ± SD)		45.5 ± 36	37.1 ± 38.9	ns (0.2809)
gender				
males		18 (42.9 %)	71 (42.3%)	ns (0.154)
females		24 (57.1%)	55 (32.7%)	
male/female ratio		0.75/1.0	1.3/1.0	
other allergies:				
	present	11 (26.2%)	41 (32.5%)	ns (0.564)
	absent	31 (73.8%)	85 (67.5%)	
family history of allergies				
	present	36 (85.7%)	95 (75.4%)	ns (0.2000)
	absent	6 (14.3%)	31 (24.6%)	
consanguinity				
	present	10 (23.8%)	24 (19%)	ns (0.5115)
	absent	32 (76.2%)	102 (81%)	

There is a significant difference between the proportion of children with severe AD in the low-zinc group compared to the normal-zinc group, as depicted in **figure 1**.

Discussion

The present study demonstrates that zinc deficiency is present in 25% of children with severe AD. They were older than children with normal serum zinc levels, and family history of allergic diseases. We observed that severe AD and high serum IgE are associated with zinc deficiency. The proportion of patients with severe (SCORAD index > 40) AD was significantly higher in the low-zinc group compared to normal-zinc group. We did not find an association between low zinc in AD and co-existence of other allergic diseases, parental consanguinity, number of food allergens, WBC, and or peripheral blood eosinophilia.

The role of zinc as a micronutrient in AD has been investigated in a limited number of studies, with contradictory results, some investigators reported lower levels (5-7) whereas others found no differences (8-10). However, a recent systematic and meta-analysis on and atopic dermatitis conclude that low zinc is associated with AD (11). In 1984, a case-controlled study on 144 children (65 AD, 79 controls) showed that the mean serum zinc of the AD patients was significantly lower ($p < 0.0001$) than

Figure 1 *- Distribution of patients according to AD severity in low-zinc (LZG) compared to normal zinc group (NZG).*

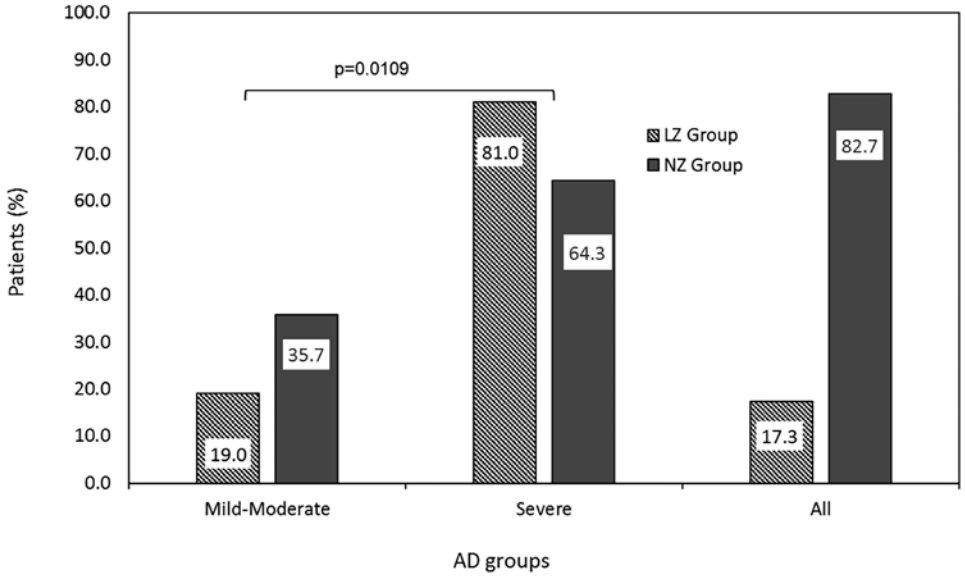

Table II *- Disease severity index and laboratory variables of children with severe AD.*

laboratory variable	low zinc group	normal zinc group	p-value
total SCORAD (number)	63.9 ± 23.3	53.9 ± 25.0	0.0418
no. of positive food allergens	2.1 ± 1.6	1.9 ± 1.7	ns (0.7492)
WBC (cells/ul)	11,855.6 ± 4,140.4	11,521.8 ± 3,968.1	ns (0.6476)
AEC (cells/ul)[1]	963.2 ± 860.8	981.9 ± 964.9	ns (0.8256)
serum IgE (KU/l)	6,818.7 ± 8,357.2	2,161.7 ± 4,841.1	0.001
vitamin D (ng/ml)	19.2 ± 8.8	8.9 ± 12.9	ns (0.381)
serum zinc (µmol/L)	8.6 ± 1.1	12.4 ± 1.9	< 0.001

[1]AEC, absolute eosinophil count.

that of the controls (12). Endre et al. study on 134 children who were admitted to hospital with AD, found 41 (29.1%) with low serum zinc levels (13). El-Kholy et al. demonstrated that in 18 AD children and 20 controls, serum and hair zinc levels were significantly lower ($p < 0.0001$) in AD children in comparison to the control subjects (14). In contrast in 1990, David et al. study on 134 children with atopic eczema and 112 controls failed to prove the hypothesis that atopic eczema is associated with a non-specific decrease in the serum concentration of trace metals, including zinc (8). *This study supports previous* findings of Endre et al. that serum zinc was low in 29.1% of 134 children who were admitted to hospital with AD (8).

Our results revealed that AD severity is associated with low zinc in AD. *These findings are* compatible *with previous* studies (11,15). Karabacak et al. demonstrated in a recent, controlled study on AD patients (n = 67 study patients and 49 controls; mean age 17.9 years) that serum erythrocyte zinc level, but not the serum level, had a significant negative correlation with SCORAD index (15). Although some people take erythrocyte zinc level as the most sensitive clinical marker of zinc level in AD (8), in our study we found that serum zinc was low.

This is the first study to assess the association between serum IgE levels and zinc levels in children with AD. Our study shows that study subjects with increased total serum IgE levels had significantly lower zinc levels. Recent data on the participants in the 5th Korean National Health and Nutrition Examination Survey 2010 (n = 8,958), and on 1,867 adults, confirmed an association between serum zinc status and allergic sensitization in adults (16). There was a negative correlation between serum zinc levels and total IgE and allergen-specific IgE levels. A controlled study on children with food allergy (IgE- and non-IgE mediated), revealed that they had low serum levels of zinc (a cofactor of superoxide dismutase) and selenium (a cofactor of glutathione peroxidase), and low concentrations of superoxide dismutase and glutathione peroxidase (17). These enzymes increased after elimination diet. Agin's study on a total of 48 subjects with allergic (skin prick tested) asthma, of mean age 32.8 ± 9.9 years (range 15-48 years), showed that hypozincemic group (23%) had a markedly higher mean of total IgE level than normozincemic controls (18). Using HR-1 hairless mice, mice fed a diet with low magnesium and zinc developed AD-like (skin dryness, wrinkle-like changes, scratching, reduced skin water content, high transepidermal water loss), and a significantly ($p < 0.001$) elevated serum IgE compared with control mice fed standard diet (19). Although the exact role of zinc in AD immunopathology is not well determined, it seems to work through immune regulation. Zinc deficiency was associated with immune dysregulation. Regulatory T (Treg) cells play a key role in immune suppression, promoting tolerance to allergens, and preventing allergic responses including the chronic skin inflammation in AD.

They regulate allergen-specific Th2 immune responses and B cell IgE production, block of naïve CD4+ Tconv cells conversion into allergen-specific Th2 T cells, control B cells, and block their IgE production (20).

The percentage of Tregs in allergic patients (2.3%) was significantly lower in AD patients in comparison to healthy controls (4.6%, $p = 0.003$), even in the asymptomatic AD or food allergy subjects (21). Atopic food-allergic children also had decreased percentages of Treg cells compared with healthy age-matched healthy controls (22). In a recent mouse model study, allergen-specific immunotherapy revealed local suppression of Th2 and infiltration of Treg cells into the skin, and induced local and systemic Treg cells and regulatory NK cells (23). In addition to the results that Treg cells percentage and TGF-β level were decreased in AD lesions, Treg cells percentage negatively correlated with AD severity score (24).

Conversely, zinc supplementation was demonstrated to restore immune regulatory mechanism. In vitro, zinc supplementation significantly diminished the differentiation of Th9 cells, key players promoting immune-mediated diseases, including allergic inflammation (25), and was capable, by modulating molecular targets Foxp3, KLF-10, and IRF-1, to ameliorate the immune reaction by enhancement of antigen-specific iTreg cells (26). Zinc was also able to induce dendritic cell tolerogenic phenotype and enhanced regulatory T cell-Th17 balance (27). A study on peripheral blood mononuclear cells (PBMCs) from non-atopic and atopic subjects treated with timothy grass allergen pre-incubated with or without zinc, revealed that zinc enhanced regulatory T cell numbers and suppressed their proliferation through a significant shift from IL-10 to the Th1 cytokine IFN-γ (28).

The strength of this study is that it includes a large sample of AD children, and that all were evaluated by the same physician (ME) thus eliminating any inter-rater difference during AD SCORAD assessment. It may appear that zinc testing in AD children is a possible bias. In fact, it is not. We were prompted to study zinc level as part of workup of poor weight and linear growth in these severe AD children (29). The main limitations of this study include its retrospective design. The rate of zinc deficiency might be overrepresented among AD children as these cases are referred to a tertiary care center, but the study concentrates on those with severe form of AD. It may appear that serum zinc level is a limitation; however, there are numerous studies that used serum samples, not hair samples, as a valid test for determining zinc levels in allergic diseases, including AD.

Conclusions

Zinc deficiency is quite common among AD children. Severe AD and high total IgE are risk factors associated with zinc deficiency. In severe AD poorly responsive standard therapy, an ad-

junct oral zinc supplementation might be warranted to reduce disease severity.

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Conflict of interest

The authors declare they have no conflict of interest.

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Anaphylaxis in an Emergency Department: a Retrospective 10-year Study in a Tertiary Hospital

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Summary

Background. *Anaphylaxis is a potentially fatal medical emergency. The frequency of hospital admissions for anaphylaxis seems to be increasing in the recent decades.* **Objective.** *Characterize the patients admitted for anaphylaxis to the adult emergency department (ED) of a tertiary care hospital over a 10-year period, discriminating aetiologies, clinical features and therapy administered.* **Methods.** *Retrospective, descriptive and inferential study, evaluating age, sex, Manchester triage system, suspected allergen, site of allergen exposure, comorbidities, cofactors, clinical findings and symptoms, treatment and management. Patients admitted between January 2007 and December 2016 were included.* **Results.** *Forty-three patients were enrolled: 23 males, mean age 54.3 ± 16.2 years, n = 22 had history of allergic disease. Two patients were triaged as non-urgent. The most frequently suspected causes of anaphylaxis were: drugs (33%, n = 14), Hymenoptera venoms (23%, n = 10), foods (21%, n = 9) and iodinated contrast products (12%, n = 5). Adrenaline was used in 88% of the episodes (n = 38), 55% of which (n = 21) intramuscularly. Mortality was registered in one case. At discharge, adrenaline auto-injector was prescribed in 7% (n = 3) of the patients, and Allergy and Clinical Immunology consultation (ACIC) was requested in 65% of the episodes (n = 28). Statistically significant associations ($p < 0.05$) were established: a, anaphylaxis to drugs associated with a low intramuscular adrenaline use and with frequent oxygen therapy; b, anaphylaxis to food associated with intramuscular adrenaline administration; c, anaphylaxis to Hymenoptera venom associated with male sex; and d, anaphylaxis to iodinated contrasts associated with referral to ACIC and with shock. All obese patients developed shock.* **Conclusions.** *Anaphylaxis is a life-threatening condition that requires early recognition. Although most patients received adrenaline, administration was not always performed by the recommended route and only a few patients were prescribed adrenaline auto-injector.*

Introduction

Anaphylaxis was first described by Charles Richet and Paul Portier in the 20th century and it is considered the maximal variant of immediate type systemic hypersensitivity (1-3). Severe anaphylactic reactions are potentially life-threatening, and their symptoms can vary depending on the organic systems affected (4). Anaphylaxis manifestations usually affect skin and mucosas, but may also involve airway, respiratory, gastrointestinal and/or circulatory disfunction (4-6).

Patients may report to the emergency department (ED) at various stages of the anaphylaxis reaction, with symptoms ranging from urticaria to cardiorespiratory failure (7). Severe reactions may require evaluation in the emergency department, management in intensive care units or hospitalization (8).

Despite published criteria and guidelines, diagnostic or coding errors are common, as stated in the World Health Organization (WHO) International Classification of Diseases (ICD) (9). Consequently, the underuse or late administration of adrenaline as first-line treatment remains an issue (10,11).
The prevalence and incidence of hospital admissions for anaphylaxis varies widely between studies (13). The incidence of anaphylaxis in the United States of America is 10 to 21 per 100 000 person-years, and the estimated prevalence is 1.6% (12-14). In Europe, reported incidence rates vary from 1.5 to 32 per 100 000 person-years and, according to a study of primary healthcare data from the United Kingdom, the annual incidence of anaphylaxis is 8.4 cases per 100 000 individuals in the general population (15,16). Many studies have shown that the prevalence of anaphylaxis is increasing, particularly in developed countries (16).
The most frequent aetiologies in adults are drugs and *Hymenoptera* venom (2). However, the correct identification of the causes is not always easy, and often requires referral to specialized consultation for diagnosis and follow-up.

Objective of the study

The objective of this study was to characterize the aetiologies, the clinical features and the administered treatment in adult patients presenting with anaphylaxis to the ED of the Centro Hospitalar e Universitário de Coimbra (CHUC), Portugal.

Methods

Type of study

Retrospective, descriptive and inferential study conducted at the Centro Hospitalar e Universitário de Coimbra (CHUC), Portugal, between January 2007 and December 2016 (10 years).

Patient selection

Patients were selected using the electronic medical codifications on ED-CHUC software (ALERT®) to include the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9 CM) codes: 995.0 (other anaphylactic shock) and 995.6 (anaphylactic shock due to adverse food reaction) (17).
Patient files were reviewed, and the criteria for inclusion in the study were adults patients admitted to ED-CHUC with a diagnosis of anaphylaxis as defined by Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology (4) (see below). A total of 45 cases were identified, two of which were excluded after clinical file revision for not fulfilling anaphylaxis criteria.
The following variables were evaluated: sex, age, year of the episode, site of allergen exposure, site of reaction (out-of-hospital or in-hospital), suspected aetiology, time interval between exposure and allergic reaction, profession, history, comorbidities, cofactors, Manchester triage, clinical manifestations, therapy, need for surveillance, need of intensive care, hospitalization, subsequent referral to Allergy and Clinical Immunology consultation (ACIC), and prescription of adrenaline auto-injector at discharge. Data was collected from the ED records of the anaphylaxis episode. The "suspected allergens" are those so considered by the ED doctors at the anaphylaxis episode report.

Definitions

The European Academy of Allergy and Clinical Immunology defines anaphylaxis as "a severe, life-threatening generalized or systemic hypersensitivity reaction, which is characterized by being rapid in onset with life-threatening airway, breathing or circulatory problems, and is usually associated with skin and mucosal changes" (4). The presence of shock is defined as systolic blood pressure of < 90 mmHg or > 30% decrease of the baseline blood pressure (4).
History of allergic disease was collected from the patients' medical records. We considered the World Allergy Organization definition of atopy, a genetic tendency to develop allergic diseases, such as allergic rhinitis, asthma and atopic dermatitis (18). We also considered history of chronic spontaneous urticarial and history of probable allergic reactions to drugs, foods, *Hymenoptera*, or others.

Statistical analysis

Statistics were performed using SPSS Statistics version 20.0®.
Descriptive statistics were analysed as mean and standard deviation for the variables with normal distribution, and median and interquartile range for the variables without normal distribution. The variables were described in absolute number (n).
The nominal variables were compared using Pearson's chi square test or Fisher's exact test according to Cochran's rules. The normal distribution of the ordinal variables was evaluated using the Kolmogorov-Smirnov test (considering a population sample of more than 30 individuals in both groups). The comparison of these variables was tested using Student's t tests (parametric test, applied after verifying the homogeneity of variances by the Levene test) or Mann-Whitney test (non-parametric test). A type I error of 0.05 was considered.

Results

Clinical presentation

Epidemiology, triage and site of allergen exposure (out-of-hospital/in-hospital)

In the 2007-2016 period, 43 cases of anaphylaxis were identified and codified in ED-CHUC, 53% (n = 23) were male and 47% (n = 20) female, with a mean age of 54.3 ± 16.2 years, and ranging from 23 to 84 years-old. The years of 2014, 2015 and

2016 had the highest number of registries, n = 18, accounting for 42% of the total population (**figure 1**).
Considering the Manchester triage criteria, n = 10 were classified "red / immediate evaluation", and n = 22 were classified "orange / very urgent", these two levels accounting for almost 3/4 of the cases. The remaining patients were classified "yellow / urgent" (n = 9) or "green / standard evaluation" (n = 2). Most of the anaphylaxis episodes occurred out-of-hospital (n = 31), while the remaining occurred inside the hospital, for example during the administration of iodinated contrast for computed tomography scan.
A history of probable allergic disease was found in n = 22 (comorbid allergic pathologies are described on **table I**).

Aetiologies, clinical manifestations and occupational risk
The suspected causes of anaphylaxis are shown in **figure 2**. Most anaphylactic reactions (n = 32) were described as immediate (defined as onset of symptoms less than 1 hour after exposure to the suspected allergen) and the time interval recorded was < 15 minutes in the majority of these cases (n = 30). In 6 patients the time interval for symptom onset was not recorded. The remaining 5 patients showed intervals between exposure and reaction between 90 to 120 minutes, most of them (n = 4) corresponding to cases of suspected food aetiology and 1 to suspected *Hymenoptera* venom allergy.
One case of biphasic anaphylaxis caused by drugs (tramadol) was registered, with a second peak occurring 12 hours after the first symptoms. In this patient, the late reaction was more severe than the initial reaction: 30 minutes after drug administration the patient developed urticarial rash and dyspnoea, with no therapy or health care assistance in the first phase of the reaction, whereas the late reaction was more severe and included dyspnoea, oropharyngeal tightening, urticarial rash and syncope.
Anaphylaxis was identified due to combinations of dermatological, respiratory and cardiovascular symptoms in n = 17 patients; dermatological and respiratory symptoms in n = 6 patients; respiratory and cardiovascular symptoms in n = 4 patients; respiratory, cardiovascular and neurological symptoms in n = 4 patients and a combination of dermatological, respiratory, cardiovascular and gastrointestinal in n = 4 patients. Anaphylactic shock occurred in 70% (n = 30) (**figure 3**).
One case of occupational risk was reported in a forest ranger that suffered anaphylaxis after *Hymenoptera* stinging.

***Figure 1** - Number of hospital admissions to ED-CHUC for anaphylaxis per year.*

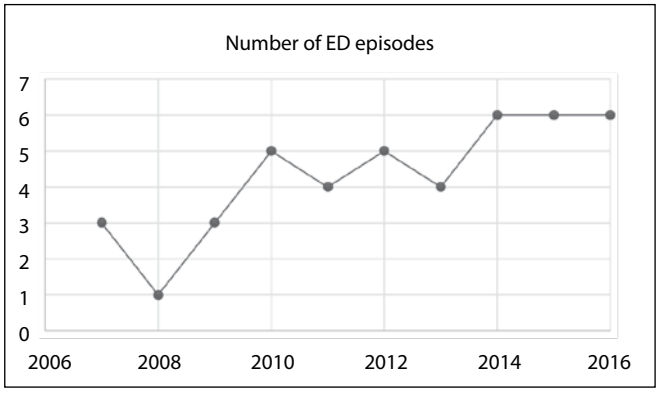

***Table I** - Comorbid allergic diseases in patients with anaphylaxis admitted to ED-CHUC.*

Comorbid allergic diseases	n = 22
allergic asthma	n = 7
allergy to beta-lactams	n = 6
allergic rhinitis	n = 5
chronic spontaneous urticaria	n = 5
allergy to non-steroidal anti-inflammatory drugs	n = 3
allergy to cow's milk proteins	n = 3
anaphylaxis to *Hymenoptera* sting	n = 2
anaphylaxis	n = 2
allergy to corticosteroids	n = 1

Comorbidities, cofactors and mortality
Comorbidities are presented in **table II**. Possible anaphylaxis co-factors were observed in some patients, namely: medication with angiotensin-converting enzyme inhibitors (ACEI), n = 19, with beta-blockers, n = 5, and with non-steroidal anti-inflammatory drugs (NSAIDs), n = 2; alcohol was a possible cofactor (intake before the anaphylactic episode) in two cases, and one patient had a suspected case of food-dependent exercise-induced anaphylaxis (FDEIA) to wheat.
Intensive care / rapid-response emergency-team was called in n = 18 episodes, n = 7 required orotracheal intubation, and n = 5 had cardiorespiratory arrest. One patient died from anaphylaxis to *Hymenoptera* venom after multiple stings.

Treatment
We here analyse together the pre-hospital and the in-hospital therapy registered in patients' medical records. Adrenaline was administered in n = 38 cases. The route of administration was intramuscular in n = 21, subcutaneous in n = 13, intravenous in n = 5 and inhaled in n = 1. All patients that received intravenous adrenaline had developed anaphylactic shock, including a fatal case of *Hymenoptera* venom allergy. The single patient that received inhaled adrenaline was an obese and hypertensive patient, that developed anaphylactic shock with severe bron-

Figure 2 - *The most frequent causes of anaphylaxis admitted to ED-CHUC.*

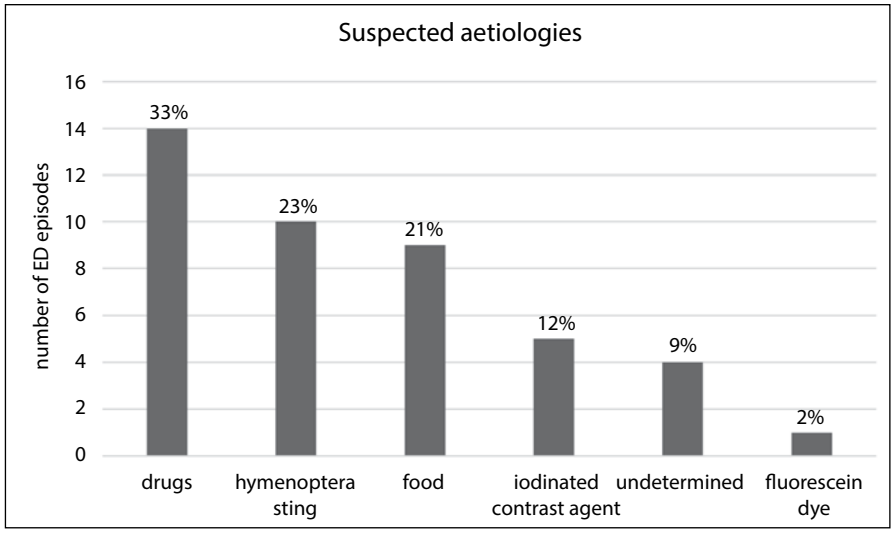

Figure 3 - *Signs and symptoms of anaphylaxis in the studied population.*

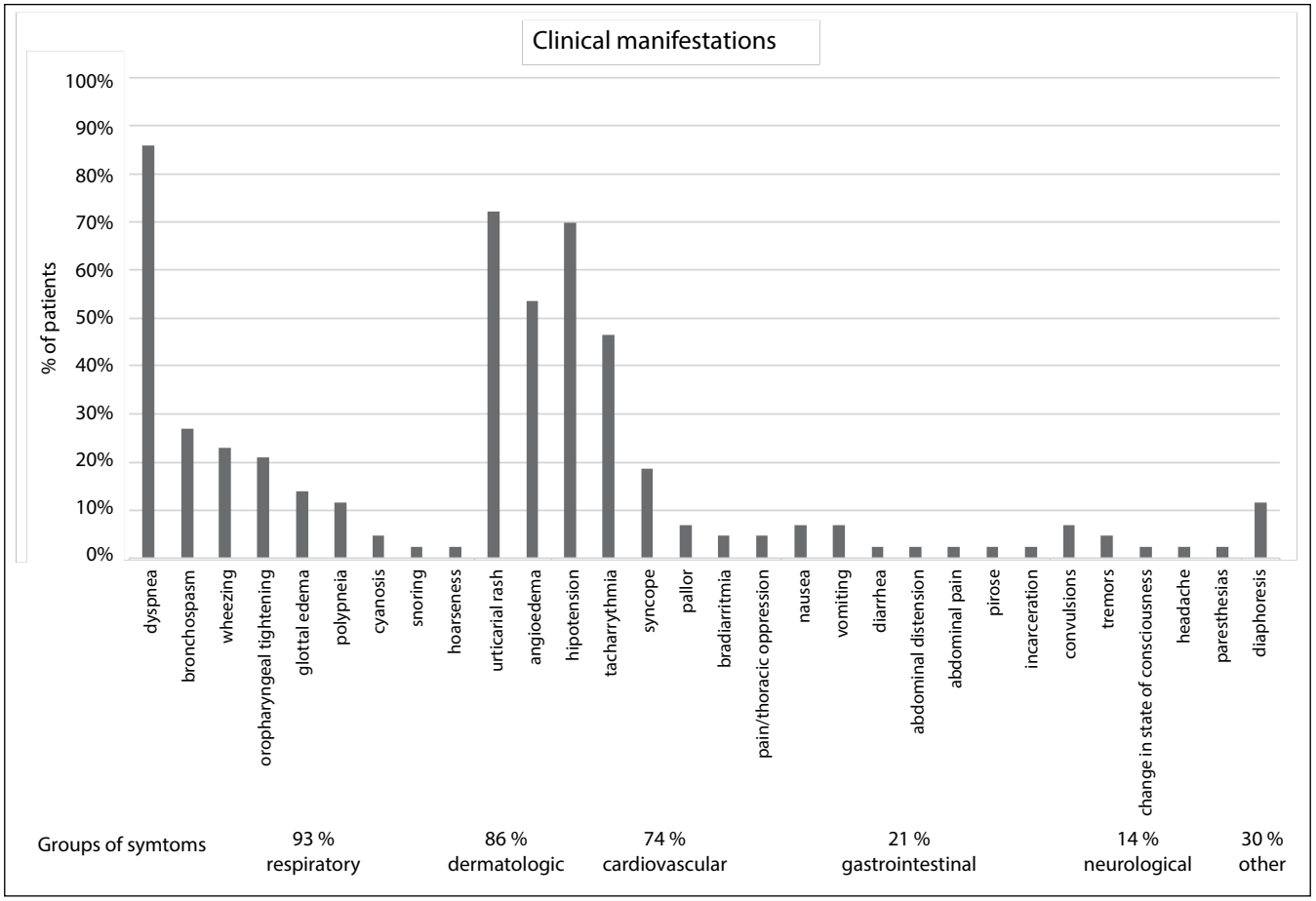

Table II *- Comorbidities in the studied population.*

Comorbidities	n = 35
arterial hypertension	n = 22
obesity	n = 11
oncological disease	n = 10
alcohol, drug or tobacco abuse	n = 9
depression	n = 8
non-insulin treated diabetes	n = 8
dyslipidaemia	n = 8
thromboembolic disease	n = 5
cardiac arrhythmias	n = 3
sarcoidosis	n = 3
chronic obstructive pulmonary disease	n = 3
thyroid diseases	n = 2
infectious diseases (acquired immunodeficiency syndrome, tuberculosis and hepatitis c)	n = 1

chospasm attributed to diclofenac, suggesting the hypothesis of anaphylaxis associated with a history of respiratory disease exacerbated by anti-inflammatory drugs (AERD). Among the patients that received adrenaline treatment, n = 30 received only one dose (0.5 mg), n = 5 two doses, and n = 3 three doses.

Regarding other concurrent therapies: n = 42 patients were treated with systemic glucocorticoids (median 250.0 mg of methylprednisolone conversion), n = 32 received antihistamine H1 therapy (clemastine was the most frequently used); n = 5 antihistamine H2 therapy (ranitidine); n = 27 received oxygen therapy (median 2.0 L/min; IR 10.0 L/min); n = 35 received fluid therapy (n = 25 crystalloids, n = 7 combination of crystalloids and colloids, and n = 3 colloids); and n = 2 were given dopamine.

Serum tryptase during the anaphylaxis episode (minimum 1 h - maximum 6 h after symptom onset) was evaluated in n = 4 cases, with values ranging from 32 to 169 mcg/mL (normal range < 11.4 mcg/mL).

The mean time of permanence in the ED was 7.0 ± 4.0 hours. Most of the patients were referred for follow-up consultations: allergy and clinical immunology consultation in n = 28. Hospitalization was decided in n = 23 patients (n = 19 in the short-stay hospital unit, n = 2 in the allergy and clinical immunology department, n = 1 in the intensive care unit, n = 1 in the internal medicine department).

CHUC uses an electronic prescription system that allows prescription alerts / limitations. Among the patients with suspected drug allergy (here including drugs, iodinated contrast and fluorescein dye), the hospital prescription of the suspected drug was blocked in n = 9/20 of the anaphylaxis episodes.

Adrenaline auto-injector was prescribed at ED discharge in n = 3 of patients.

Table III *- Description of the suspected drugs and foods involved in anaphylactic reaction.*

Food	n = 9
hellfish and molluscs	n = 4
shrimp	n = 3
shrimp and squid	n = 1
dry fruits	n = 2
nut	n = 1
hazelnut	n = 1
fish	n = 1
codfish, hake and tuna	n = 1
fresh fruits	n = 1
peach	n = 1
legumes	n = 1
white bean and cabbage	n = 1
Drugs	n = 14
antibiotics	n = 4
amoxicillin-clavulanic acid	n = 1
cefazolin	n = 1
cefuroxime	n = 1
penicillin	n = 1
analgesics	n = 3
tramadol	n = 1
paracetamol	n = 1
magnesium metamizole	n = 1
non-steroidal anti-inflammatory drugs	n = 3
ibuprofen	n = 1
diclofenac	n = 1
etoricoxib	n = 1
anesthetics	n = 2
lidocaine	n = 2
benzodiazepines	n = 1
diazepam	n = 1
chemotherapeutic agents	n = 1
paclitaxel and carboplatin	n = 1

Characteristics of anaphylaxis and relevant clinical associations

Location

Regarding the location where anaphylaxis occurred, all suspected food allergies occurred out-of-hospital ($p < 0.05$, Fisher's exact test). Conversely, in suspected drug allergy, half of the cases of anaphylaxis occurred inside the hospital, and drug allergy corresponded to 58% (n = 7/12) of all in-hospital episodes ($p < 0.05$, Fisher's exact test), with the remaining attributable to CT contrasts and fluorescein dye.

Professional occupation

Professions with performance in external environments, such as farmer, mason, forest ranger and fireman were exclusively reported in the group of suspected *Hymenoptera* venom anaphylaxis.

Suspected causes

Possible epidemiological differences were found between suspected etiologic groups: all patients with suspected *Hymenoptera* venom anaphylaxis were male ($p < 0.05$, Fisher's exact test) whereas all patients with suspected iodinated contrast agent anaphylaxis were female ($p < 0.05$, Fisher's exact test). One of the patients with drug anaphylaxis, intravenous magnesium metamizole, had a history of previous metamizole anaphylaxis described in the record of the clinical history of the emergency episode. One patient had a likely diagnosis of food dependent exercise induced anaphylaxis with wheat ingestion, tolerating the ingestion of wheat in the absence of the cofactor. Regarding the Manchester triage, unlike other aetiologies, patients with suspected food allergy anaphylaxis were all classified as severe ($p < 0.05$, Fisher's exact test).

Shock

The percentage of patients who developed anaphylactic shock was 70% (n = 30). The totality of cases with anaphylaxis to iodinated contrast presented with anaphylactic shock were referenced to ACIC ($p < 0.05$, Fisher's exact test). All obese patients developed shock ($p < 0.05$, Fisher's exact test). All patients with shock had immediate anaphylaxis, and 87.5% of them initiated symptoms less than 15 minutes after allergen exposure (21 out of the 24 patients with shock and reported time of symptom onset). Patients who developed shock had arterial hypertension in 57% (n = 17), and were medicated with angiotensin converting enzyme inhibitor in 40% (n = 12). The presence of tachyarrhythmia occurred in 60%, n = 18 ($p < 0.05$, Pearson's chi square) and fluid therapy was required in 90%, n = 27 ($p < 0.05$, Fisher's exact test). Half the patients with shock presented comorbid allergic diseases. Almost all patients with shock, n = 29, were treated with the first-line therapy adrenaline ($p < 0.05$, Fisher's exact test), by the intramuscular route, n = 14, and intravenously, n = 5. The only patient treated with inhaled adrenaline was included in this group. Rapid-response emergency-team was called in n = 16 of anaphylactic shock cases ($p < 0.05$, Pearson's chi square). All patients who presented anaphylaxis due to iodinated contrast agent developed shock.

Treatment

The suspected causes of the two patients that required dopaminergic support were ibuprofen and cefazolin, and one of them received also intravenous adrenaline. Eleven out of 14 patients with suspected drug related anaphylaxis were treated with oxygen and this group showed significant differences in oxygen flow, with higher flow records.

All patients with suspected food-related anaphylaxis were treated with adrenaline by the recommended IM route ($p < 0.05$ Fisher's exact test), compared with n = 11/14 that received adrenaline in suspected drug allergy, out of which only 3/11 was intramuscularly ($p < 0.05$, Pearson chi square).

Mortality

The only fatal case was a patient that developed anaphylactic shock with cardiorespiratory arrest due to multiple *Hymenoptera* stings (three, one of them in the cervical region). This patient had a previous episode of anaphylaxis due to *Hymenoptera* venom, about 2 years before the fatal episode and no specialty consultation was performed after the initial episode. This patient had arterial hypertension treated with ACEI. Clinical manifestations were urticaria, angioedema, glottal edema and dyspnoea, about 10-15 minutes after *Hymenoptera* stingings. In ED, the patient presented with hypotension refractory to fluid therapy and was administered 3 doses of 0.5 mg adrenaline IV, with time intervals of 5 minutes, oxygen and corticosteroid therapy. The patient did not respond to resuscitation and died about one hour after admission (approximately two and a half hours after exposure to venom).

Discussion

In this study we characterized the clinical manifestations and treatment of patients admitted for anaphylaxis in the ED of a tertiary hospital. Several clinical associations between anaphylaxis manifestations and patients' characteristics were observed.

The male preponderance (54%) in cases of anaphylaxis noted in this study is not consistent with other published studies that cited a slightly higher incidence in females (19-22). We also observed differences in the gender predisposition of different groups of this study, such as, *Hymenoptera* venom allergy was present only in males, whereas allergy to iodinated contrast agents occurred exclusively in females.

The presence of comorbidities had a clear association with the severity of anaphylaxis in our study. Obesity was strongly associated with severe clinical manifestations and it was present

in all patients that developed shock. This is concordant with several studies that showed an association between obesity and fatal outcomes (23,24).

The attributable causes of anaphylaxis reported in our study were similar to those reported in the literature for this age group (4): drugs were the main cause, in particular beta-lactam antibiotics. Regarding food allergy, shellfish, in particular shrimp, was the most frequently suspected trigger, contrarily to what was found in other Portuguese studies, in which nuts were the most frequently cited food (25).

Our study included 5 cases of anaphylaxis with onset > 1 hour after allergen contact. In this group of patients, four had suspected food allergies, in agreement with previous observations that type I hypersensitivity reactions to food may take longer to develop, but usually within 2 hours after ingestion (26).

The treatment discrepancies between suspected food anaphylaxis and suspected drug anaphylaxis is possibly related with the non-recognition of the allergic reaction in drug related cases, as some cases may be interpreted as a non-immunological adverse reaction. The high number of patients with suspected drug related anaphylaxis treated with high oxygen flow therapy may be justified by the fact that most of the reactions occurred inside the hospital.

Regarding anaphylaxis due to *Hymenoptera* venom allergy, two patients had a previous history of anaphylactic reaction to the same trigger, none of them had previous follow-up in allergy and clinical immunology consultation (and therefore no previous *Hymenoptera* venom immunotherapy).

An accurate diagnosis of anaphylaxis may be difficult in the emergency department, due to the wide spectrum of clinical presentations and the absence of optimal clinical or laboratorial markers (27). Late diagnosis of anaphylaxis may delay adrenaline administration and result in worse outcomes. Serum tryptase is considered a specific marker of mast cell degranulation, but it is not always elevated during anaphylaxis and laboratorial processing is usually deferred in time (28,29). However, it is the only available marker that supports the diagnosis of anaphylaxis, especially when compared with patient's baseline values (4). In this study, serum tryptase during the anaphylaxis episode was collected only in 4 patients, probably because the clinical presentation was easily recognized on the initial approach, or due to the inability of some ED doctors to add this specific analysis on our ALERT® system.

Intramuscular adrenaline is considered the treatment of choice for anaphylaxis in most anaphylaxis consensus and guidelines (10,21,30,31). However, as also observed in other studies (12,25), there is still a gap in the route of administration of first line therapy: only n = 21 patients received adrenaline intramuscularly and n = 5 received adrenaline IV (all of which in shock situations), whereas a high proportion of patients were administered subcutaneous adrenaline (n = 13).

Despite the long period studied (10 years), only 43 patients were included, at least in part due to the absence of a specific coding for anaphylaxis in ICD-9. ICD-9 has diagnostic codes only for "allergy" and "anaphylactic shock", leaving out the rest of the spectre of anaphylactic reactions (17). This issue is a major concern of allergy scientific societies and is currently being addressed in the forthcoming ICD-11 (31). In addition, it is sometimes difficult for physicians to codify during clinical practice. These reasons may help explain the low number of cases identified and the fact that a large proportion of patients included in our study presented with severe reactions, namely anaphylactic shock.

The limitations of our study include its retrospective nature, the possibility of under-reporting / lack of correct codification, and missing data from incomplete data records. The lack of anaphylaxis codification or incorrect ICD codification has likely limited the number of patients included in the study. Due to the patient selection method, the incidence of anaphylaxis could not be determined.

Conclusions

Anaphylaxis is a medical emergency and its early recognition and treatment is paramount to prevent fatal outcomes. In this study we evaluated clinical presentation of anaphylaxis, evaluation of its possible causes, treatment and adequate referral in a tertiary hospital centre. Incomplete medical records were frequent and an investment in their improvement would be necessary to obtain more accurate estimates of the burden of anaphylaxis. Obesity was highlighted as an important factor of poor prognosis, as all obese patients developed shock during the anaphylactic reaction.

Conflict of interests

The authors declare that they have no conflict of interest.

APPENDIX

Supplementary table I *- Patient characteristics.*

Patient	Age (years)	Gender	Shock	Etiology	Atopy	Comorbidities	Angiotensin Converting Enzyme Inhibitors
1	63	male	yes	drug	no	yes	no
2	64	female	no	drug	no	yes	yes
3	54	male	yes	drug	no	yes	no
4	56	male	yes	drug	no	yes	yes
5	61	male	yes	drug	no	yes	yes
6	71	female	yes	drug	no	yes	no
7	48	female	no	drug	no	yes	no
8	58	female	yes	drug	yes	yes	yes
9	24	female	yes	drug	yes	no	no
10	55	female	yes	drug	yes	yes	no
11	57	male	no	drug	yes	yes	yes
12	56	male	yes	drug	yes	yes	no
13	79	female	yes	drug	yes	yes	no
14	66	female	no	drug	yes	yes	no
15	73	male	yes	food	no	yes	yes
16	27	male	no	food	yes	no	no
17	82	female	yes	food	yes	yes	yes
18	78	male	no	food	yes	yes	no
19	27	male	no	food	no	no	no
20	43	female	yes	food	yes	no	no
21	84	female	yes	food	yes	yes	yes
22	60	female	yes	food	yes	yes	yes
23	59	female	no	food	no	yes	yes
24	65	male	yes	dyestuff	no	yes	yes
25	61	male	no	venon	yes	no	no
26	52	male	yes	venon	yes	yes	yes
27	44	male	no	venon	no	no	no
28	23	male	yes	venon	yes	no	no
29	42	male	yes	venon	yes	yes	no
30	28	male	yes	venon	no	no	no
31	52	male	no	venon	yes	yes	yes
32	38	male	yes	venon	no	yes	no
33	43	male	yes	venon	no	yes	no
34	55	male	yes	venon	no	yes	no
35	38	female	yes	iodinated contrast agent	no	yes	no
36	64	female	yes	iodinated contrast agent	no	yes	yes
37	62	female	yes	iodinated contrast agent	no	yes	yes
38	73	female	yes	iodinated contrast agent	no	yes	yes
39	68	female	yes	iodinated contrast agent	yes	yes	yes
40	49	male	no	undetermined	no	yes	no
41	23	female	yes	undetermined	yes	no	no
42	49	female	yes	undetermined	yes	yes	yes
43	61	male	no	undetermined	yes	yes	yes

Non-steroidal anti-inflammatory drugs	Beta-blockers	Physical exercise	Mortality	Intensive Care	Dermato-logical	Respiratory	Cardiovascular	Neurological
no	no	no	no	No	Yes	Yes	Yes	Yes
no	yes	no	no	No	Yes	Yes	No	No
no	no	no	no	No	Yes	Yes	Yes	No
no	no	no	no	Yes	Yes	Yes	Yes	Yes
no	no	no	no	No	No	Yes	Yes	No
no	no	no	no	Yes	Yes	Yes	Yes	No
no	no	no	no	No	Yes	No	No	No
no	no	no	no	No	Yes	Yes	Yes	No
no	no	no	no	Yes	Yes	Yes	Yes	No
no	no	no	no	Yes	No	Yes	Yes	No
no	no	no	no	No	Yes	Yes	No	Yes
no	no	no	no	No	Yes	Yes	Yes	Yes
no	no	no	no	Yes	Yes	Yes	Yes	No
no	no	no	no	Yes	Yes	Yes	No	No
no	yes	no	no	Yes	Yes	Yes	Yes	No
no	no	no	no	No	Yes	Yes	No	No
no	no	no	no	Yes	No	Yes	Yes	No
no	no	no	no	No	Yes	Yes	No	No
no	no	yes	no	No	Yes	Yes	Yes	No
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no	yes	no	no	No	Yes	No	No	Yes
no	no	no	no	No	Yes	Yes	Yes	No
no	no	no	no	Yes	Yes	Yes	Yes	No
no	no	no	no	No	No	Yes	Yes	No
no	no	no	no	Yes	Yes	Yes	Yes	No
no	no	no	no	Yes	Yes	Yes	Yes	No
yes	no	no	no	No	Yes	Yes	Yes	No
no	no	no	no	Yes	Yes	Yes	Yes	No
no	no	no	no	Yes	Yes	Yes	Yes	No
no	no	no	no	No	Yes	Yes	Yes	No
no	no	no	no	No	Yes	Yes	Yes	Yes
no	no	no	no	No	Yes	No	Yes	No
no	no	no	no	No	Yes	Yes	No	No

Patient	Oxygen therapy (L/min)	Orotracheal intubation	Cardiorespiratory arrest	Fluid Therapy	Anti-H1	Anti-H2	Salbutamol and/or Ipratropium bromide
1	no	no	no	yes	yes	no	no
2	10	no	no	yes	yes	no	yes
3	3	no	no	yes	no	no	no
4	4	no	no	yes	no	no	no
5	15	no	no	yes	yes	yes	yes
6	4	no	no	yes	no	no	yes
7	no	no	no	no	yes	no	no
8	2	no	no	yes	yes	no	no
9	15	yes	no	yes	no	no	no
10	2	no	yes	yes	no	no	no
11	12	no	no	no	yes	no	yes
12	3	no	no	yes	yes	no	yes
13	10	no	no	no	yes	yes	no
14	12	no	no	yes	yes	no	yes
15	2	no	no	yes	yes	no	no
16	no	no	no	no	yes	no	no
17	2	no	yes	yes	no	no	no
18	no	no	no	yes	yes	no	no
19	2	no	no	yes	yes	no	no
20	4	no	no	yes	yes	no	no
21	15	no	no	yes	yes	no	yes
22	6	no	no	yes	yes	yes	no
23	no	no	no	no	yes	no	yes
24	15	yes	yes	no	yes	no	no
25	no	no	no	no	yes	no	no
26	15	yes	yes	yes	no	no	no
27	2	no	no	yes	yes	no	no
28	3	no	no	yes	yes	no	no
29	no	no	no	yes	yes	no	no
30	no	no	no	yes	yes	yes	yes
31	no	no	no	yes	no	no	no
32	no	no	no	yes	yes	no	no
33	15	yes	no	yes	yes	no	no
34	2	no	no	yes	no	no	yes
35	no	no	no	yes	yes	no	no
36	3	no	no	yes	yes	no	no
37	no	no	no	yes	no	no	no
38	15	yes	yes	yes	no	no	yes
39	no	no	no	yes	yes	no	no
40	no	no	no	yes	yes	no	yes
41	no	no	no	no	yes	no	no
42	3	no	no	yes	yes	no	no
43	no	no	no	yes	yes	yes	no

Intravenous corticosteroid therapy	Dopaminergic support	ADR	ADR Inhalation	ADR Intravenous	ADR Intra muscular	ADR Sub cutaneous	Allergology and Clinical Immunology consultation
yes	no	no	no	no	no	no	no
yes	no	no	no	no	no	no	no
yes	no	yes	yes	no	no	no	no
yes	no	yes	no	yes	no	no	no
yes	no	yes	no	no	yes	no	no
yes	no	yes	no	no	no	yes	no
yes	no	no	no	no	no	no	yes
yes	yes	yes	no	yes	no	no	yes
yes	no	yes	no	no	yes	no	yes
yes	no	yes	no	no	no	yes	yes
yes	no	yes	no	no	no	yes	yes
yes	no	yes	no	no	no	yes	yes
yes	yes	yes	no	no	no	yes	yes
yes	no	yes	no	no	yes	yes	yes
yes	no	yes	no	no	yes	no	no
yes	no	no	no	no	no	no	yes
yes	no	yes	no	no	yes	no	yes
yes	no	yes	no	no	yes	no	yes
yes	no	yes	no	no	yes	no	yes
yes	no	yes	no	no	yes	no	yes
yes	no	yes	no	no	yes	no	yes
yes	no	yes	no	no	yes	no	yes
yes	no	yes	no	no	yes	no	yes
yes	no	no	no	no	no	no	no
yes	no	yes	no	yes	no	no	no
yes	no	yes	no	no	yes	no	no
yes	no	yes	no	yes	no	no	yes
yes	no	yes	no	no	yes	no	yes
yes	no	yes	no	no	yes	no	yes
yes	no	yes	no	no	no	yes	yes
yes	no	yes	no	no	no	yes	yes
yes	no	yes	no	no	no	yes	yes
yes	no	yes	no	no	no	yes	yes
yes	no	yes	no	no	yes	no	no
yes	no	yes	no	no	yes	no	no
yes	no	yes	no	no	no	yes	no
yes	no	yes	no	yes	no	yes	no
yes	no	yes	no	no	no	yes	yes
yes	no	yes	no	no	yes	no	no
no	no	yes	no	no	yes	no	yes
yes	no	yes	no	no	yes	no	yes
yes	no	yes	no	no	yes	no	yes

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Drug allergy is Associated with the Development of Extraintestinal Manifestations in Patients with Ulcerative Colitis

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Summary
Drug allergies are developed by antibody or cell-mediated reactions as immunologic mechanisms. It has been demonstrated that hypersensitivity reaction to certain allergens may play a role in the pathogenesis of inflammatory bowel disease (IBD) focused on food allergies.
A total of 256 patients with UC were divided in two groups: 203 patients with active UC and 53 in remission UC were included in the present study. In the present study we found that 11.7% had allergy to at least one drug distributed. The most frequent drug-allergies were sulfonamides in 2.8% and penicillin in 3.1%. Sulfonamide allergy was associated with several extraintestinal manifestations such as: peripheral arthritis / arthralgia (OR = 9.06, 95% CI 1.71 - 48.00, p = 0.002); pyoderma gangrenosum (OR = 24.10, 95% CI 3.55 - 163.48, p < 0.0001) and uveitis (OR = 15.93, 95% CI 2.55 - 99.23, p < 0.0001). The frequency of drug allergy was 11.7% in Mexican UC patients, most frequently to sulfonamides and penicillin drugs. The presence of sulfonamide allergy was associated with the presence of several extra-intestinal manifestations.

Introduction

Several gene mutations that control innate immune recognition, adaptive immunity, and epithelial permeability are associated with gut inflammation. These phenomena suggest that perturbations of homeostasis between gut antigens and host immunity represent a critical determinant in the development of gut inflammation and allergy (1). An abnormal intestinal permeability is one of the hallmarks of an inflamed gut that has been observed in around 42.9% of patients affected by Ulcerative Colitis (UC) (2).
Intestinal barrier defects have been associated with a broad range of diseases, including GI (celiac disease, inflammatory bowel disease and colon carcinoma) but also extra intestinal disorders (chronic liver disease, type 1 diabetes, obesity) (3).

A previous study reported that UC patients may have an allergic etiology in approximately 66%; several cases of UC have been associated with pollen allergy milk consumption and allergy to other specific foods (4,5). In previous studies where specific immunotherapy was administered, it was demonstrated that alterations in regulation of IgE, Il4, TNF-α and IgG4 had an important involvement in the pathogenesis of Inflammatory Bowel Disease (IBD) (6).
Drug allergies are developed by antibody or cell-mediated reactions as immunologic mechanisms (7). In several cases, the mechanism involved in the development of drug hypersensitivity is mediated by T-cells (Type IV hypersensitivity) and is associated with a wide range of clinical manifestations, ranging from affection of skin to anaphylaxis. Frequently drugs involved in this type of allergic mechanism are sulfa antibiotics and β-lac-

tams (8). A Th2 response is characteristic of the subject with allergy and it is also present in patients with UC (9).
Also, it has been demonstrated that hypersensitivity reaction to certain allergens may play a role in the pathogenesis of inflammatory bowel disease (IBD) focused on food allergies. Even specific immunotherapy has demonstrated improvement in the clinical course of patients with UC (10).
No previous studies have evaluated the role of drug allergy in patients with UC. The aim of the present study was to determine the most frequent drug allergies in Mexican patients with UC and its association with clinical outcomes.

Materials and methods

A total of 289 patients with histopathologic diagnosis of UC belonging to the Inflammatory Bowel Disease Clinic at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán were recruited in the period between 2016 and 2017.
Sociodemographic variables (current age, gender, occupation), clinical (age at diagnosis, smoking habit, appendectomy, clinical course of disease, extent according to Montreal's classification, extraintestinal manifestations, concomitant autoimmune diseases, number of previous hospitalizations, disease activity by endoscopic and histologic according to Mayo's and Riley's classification respectively, and current medical treatment. All previous or current medication allergy were documented by frequency such as penicillin, sulpha drugs, acetylsalicylic acid, metoclopramide, iodeine, ceftriaxone, metamizole, quinolones, pseudoephedrine, cefuroxime, acetaminophen, naproxen, ambroxol, opioids, infliximab, racecadotril, thiethylperazine.

Statistical analysis

The Kolmogorov-Smirnov test was used as normality test. Descriptive statistics as well as Chi squared and Fisher's exact test for categorical variables and U-Mann Whitney or t Student test for numerical variables. The strength of the association was determined by Odds Ratio (OR) and $p < 0.05$ was considered as statistically significant. All data was analyzed by SPSS v.24 statistical analysis program.

Results

A total of 256 patients with UC were divided in two groups: 203 patients with active UC and 53 in remission UC were included in the present study. A 51% (n = 130) were women and 49% (n = 126) men, with a median age of 41 years (range 18-89 years). The extent of UC was evaluated by colonoscopy in all patients and classified according to Montreal classification, which was distributed as follows: 18.5% distal colitis; 12.14% left-sided colitis and 69.36% extensive colitis. The clinical course of disease was: 46.1% had initially active and then inactive disease; 46.1% showed intermittent disease (< 2 relapses per year) and 7.8% continuous disease. In 28.9% had at least one extra-intestinal manifestation such as arthritis / arthralgia in 22.7%; spondylitis 1.2%; sacroiliitis 1.6%; primary sclerosing cholangitis 6.3%; pyoderma gangrenosum 2.3%, erythema nodosum 0.4% and uveitis in 3.1%. In only 3.5% had at least one concomitant autoimmune disease such as: ankylosing spondylitis 0.4%, autoimmune hepatitis 1.2%, systemic lupus erythematosus 0.4%, idiopathic thrombocytopenic purpura 0.4%, Hashimoto's thyroiditis 0.4%, multiple sclerosis 0.4% and vitiligo 1.2%.
In the present study, we found that 11.7% had allergy to at least one drug distributed as shown in **figure 1**. The most frequent drug-allergies were penicillin in 3.1%, sulfonamides in 2.8%, acetylsalicylic acid 1% and other drugs under 1%.

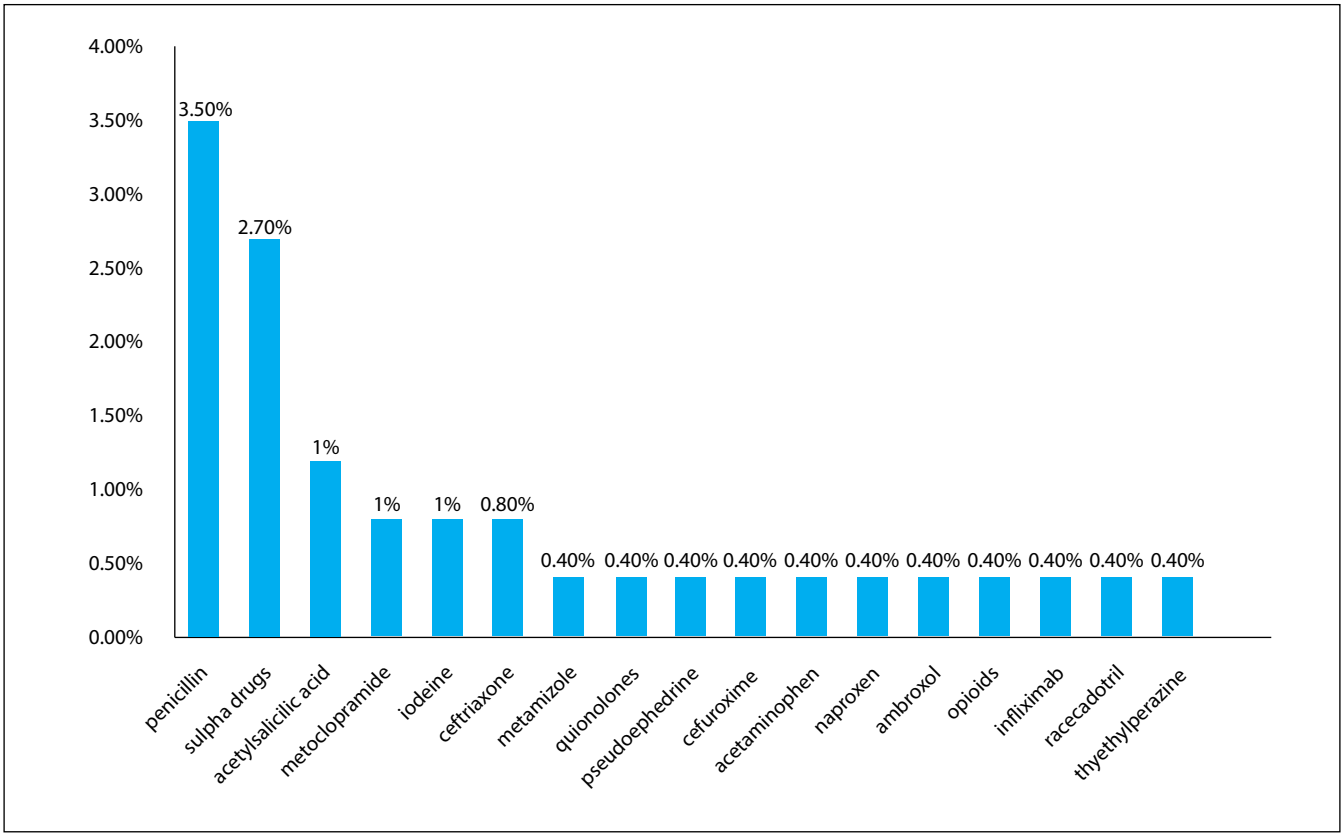
Association between drug allergy and clinical outcomes

Sulfonamide allergy was associated with several extraintestinal manifestations such as: peripheral arthritis / arthralgia (OR = 9.06, 95% CI 1.71 - 48.00, p = 0.002); pyoderma gangrenosum (OR = 24.10, 95% CI 3.55 - 163.48, $p < 0.0001$) and uveitis (OR = 15.93, 95% CI 2.55 - 99.23, $p < 0.0001$).

Discussion

In the present study, we found that the most common drug-allergies were penicillin in 3.1%, sulfonamides in 2.8%, acetylsalicylic acid 1%, and other drugs under 1%. Our results contrast from cross-sectional survey of a general adult population of Portugal, that found a 7.8% prevalence of self-reported drug allergy, of which 4.5% were to penicillins or other b-lactams, 1.9% to aspirin or other NSAIDs, and 1.5% to other drugs (11). Important to note in our study, the presence of allergy to sulfonamides was associated with extra-intestinal manifestations in Mexican UC patients.
Hypersensitivity reactions represent about one third of all adverse drug reactions. Adverse drug reactions affect 10-20% of hospitalized patients and more than 7% of the general population (12). A meta-analysis of prospective studies demonstrated an overall incidence of adverse drug reactions of 6.7% (95% CI 5.2 - 8.2%). However, it is important to mention that several bias factors might influenced by length of stay, gender and ward type (13).
On the other hand, the presence of food allergy in UC patients (30.17%) was higher than general population (2.34%) considering the treatment of food allergy treatment is the allergen specific immunotherapy (SIT) and *Clostridium butyricum* (CB) efficiently inhibited the clinical symptoms of IBD patients with food allergy (14).
Certain specific allergens have been associated with a higher risk of developing UC such as Cow's milk (15). Also, high titers of antibodies had been related with a more symptomatic

Figure 1 *- Frequency of drug allergies in UC patients.*



clinical course in the case of subclinical allergy to several foods, most commonly cow's milk (16). Although it has been postulated that allergy could be involved in the development of UC, however, there are no studies about the role of drug allergies in the development of extraintestinal manifestations in patients with UC.

We found an association between the existence of sulfonamide drug allergy and the presence of extraintestinal manifestations such as arthritis / arthralgia, pyoderma gangrenosum and uveitis. This could be explained by a hapten like mechanism, or overlapping antibody-binding sites that predisposes patients with UC to develop affection in sites like joints, skin and uvea (16-22).

Variations in T-cell receptor and both HLA types I and II are more frequent in this population, which could help to explain the propensity of these patients to develop specific extraintestinal manifestations (23,24). On the other hand, regulatory B-cells might have an important role in the development of the extraintestinal manifestations, as postulated in previous studies involving specific immunotherapy (25). Specific immunotherapy has been proposed as a useful alternative for treating the extraintestinal manifestations in patients with uveitis and UC (11,26).

Another hypothesis about the causal link between uveitis and sulfonamide consumption could be that these manifestations are due to a direct effect of such drugs and not to the systemic inflammatory response induced in patients with UC (27,28). Finally, for a better characterization of the systemic inflammatory response of UC patients, it could be useful to analyze which appear first, the reported extraintestinal manifestations or the intestinal disease. Further studies are needed to evaluate the implication of Th2 immunologic response in these patients.

Conclusions

The frequency of drug allergy was 11.7% in Mexican UC patients, most frequently to sulfonamides and penicillin drugs. The presence of sulfonamide allergy was associated with the presence of several extraintestinal manifestations such as arthritis / arthralgia, pyoderma gangrenosum and uveitis in Mexican patients with UC.

Conflicts of interests

The authors declare they have no conflict of interests.

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Familial Clustering of Hypereosinophilic Diseases Treated with Mepolizumab: a Case Report from Japan

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Key words

anti-IL-5 antibody; eosinophilic asthma; eosinophilic granulomatosis with polyangiitis; hypereosinophilic syndrome; mepolizumab

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Summary

We describe a female diagnosed with non-allergic asthma. On March 24, 2016, examination of the skin-biopsy specimen revealed dense eosinophilic infiltration, and the Fip-1-like 1-platelet-derived growth factor receptor α fusion gene in peripheral blood mononuclear cells was negative. She was diagnosed with idiopathic hypereosinophilic syndrome. She was treated with intravenous methylprednisolone (MPSL), and subsequent oral MPSL. Then, she started to receive a monthly mepolizumab in June 2016, and successfully withdrew from daily use of oral MPSL. The patient has a mother diagnosed with non-allergic asthma. In February 2005, she was diagnosed with eosinophilic granulomatosis with polyangiitis because of elevated antineutrophil myeloperoxidase antibodies, and the skin-biopsy specimen findings. She started to receive a monthly mepolizumab in June 2016. Corticosteroid therapy was successfully withdrawn. To our knowledge, this is the first case report suggesting mepolizumab may be a useful treatment for familial clustering of hypereosinophilic diseases.

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) (formerly known as Churg-Strauss syndrome) and idiopathic hypereosinophilic syndrome (HES) are rare eosinophilic disorders. Definitive diagnosis of EGPA relies on the demonstration of vasculitis in tissue-biopsy specimen (1). HES is defined by unexplained blood eosinophilia above 1500/μL on 2 separate occasions at least 1 month apart and evidence of end-organ involvement attributed to eosinophilia (2). Although it is quite rare that EGPA and/or HES are seen in several members of the same family, familial clustering of hypereosinophilic diseases has been reported in medical literature since the early 1900s (3,4). In these families, the distribution of eosinophilia was suggested to involve autosomal dominant inheritance (5). On the other hand, Ota et al. (6) reported 3 siblings who suffered from marked eosinophilia, 2 of them were diagnosed with EGPA and 1 was with HES, and suggested they may be affected by another type of familial eosinophilia distinguishable from those previously described.

We describe a case of familial clustering of hypereosinophilic diseases treated with mepolizumab, a humanized IgG_1 monoclonal antibody that prevents human interleukin 5 (IL-5) from binding to the IL-5 receptor (7), and suggest mepolizumab may be a useful treatment for familial clustering of hypereosinophilic diseases.

Materials and methods

Mepolizumab was administered subcutaneously every 4 weeks at a dose of 100 mg. Asthma Control Test (ACT) (8), peripheral blood eosinophils, forced expiratory volume in 1 second (FEV_1) and drug safety were assessed at each visit; fractional exhaled nitric oxide (FeNO) was not assessed, because no significant differences were found in the DREAM trial (9). FEV_1 values were reported as a percentage of predicted values, using a spirometer (FUKUDA-77, Fukuda Denshi, Tokyo, Japan), and the best of 3 expiratory maneuvers was recorded. The scores in the ACT range from 5 (absence of disease control) to 25 (total disease control). The cut off value for controlled asthma (ACT ≥ 20) was chosen according to previous studies cut off value (10). Peripheral blood eosinophils were counted automatically by the Beckman Coulter counter (Beckman Coulter, Fullerton,

CA, USA) and MAXM A/L system (Beckman Coulter). Serum levels of IgE were measured using the CAP system (Phadia, Uppsala, Sweden), and antineutrophil myeloperoxidase (MPO) antibodies were measured by an enzyme-linked immunosorbent assay (ELISA) analysis (Orgentec Diagnostika GmbH, Mainz, Germany), and the analyses and cut-off procedures were performed according to the manufacturer's instructions (reference < 3.5 U/mL). De Lavareille et al. (11) reported that serum levels of thymus and activation-regulated chemokine (TARC) may represent a precious and discriminative diagnostic tool for the patients with lymphocytic HES, and we measured TARC concentration by an ELISA kit (R&D Systems, Minneapolis, USA) as reported (12). The Fip-1-like 1-platelet-derived growth factor receptor α (FIP1L1-PDGFRA) fusion gene in peripheral blood mononuclear cells was analyzed by the fluorescence in situ hybridization method as reported (13).

This study was performed in accordance with the Good Clinical Practice guidelines, the ethics principles outlined in the Declaration of Helsinki 2008, in accordance with the Institutional Ethics Committee of Sutoh Hospital (IRB#20160050). Written informed consent was obtained from each individual before the study commenced.

Case report

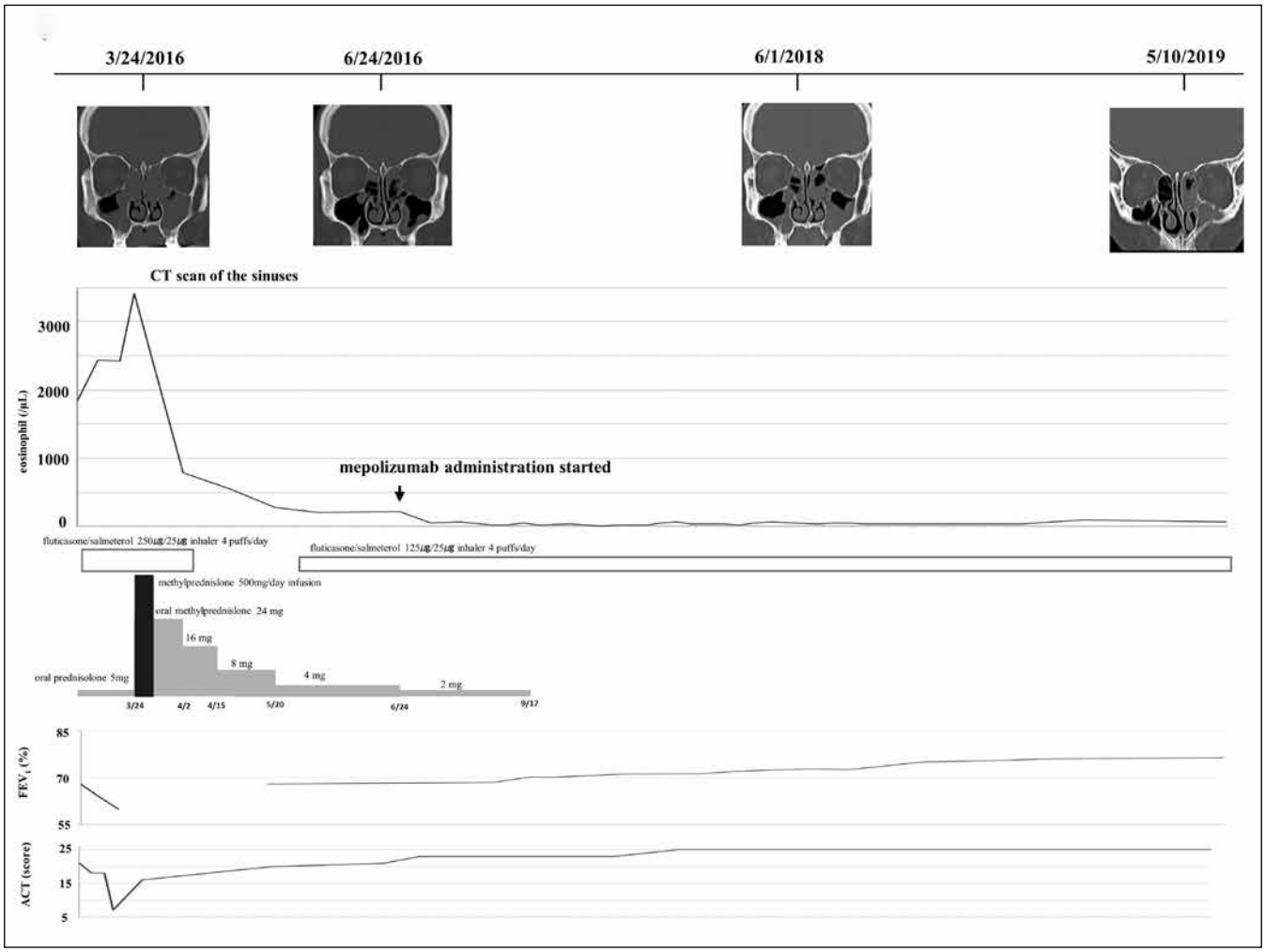
A 56-year-old female was diagnosed with bronchial asthma by the author in April 1994. She had non-allergic asthma phenotype, confirmed by low serum total IgE levels (71 IU/mL) and negative results of serum specific IgE for common inhaled allergens, including molds, and *Dermatophagoides farinae* and *petronyssinus*. The diagnosis was confirmed using the Global Initiative for Asthma (GINA) guidelines (14). Her asthma was corticosteroid-dependent and met the American Thoracic Society criteria for a diagnosis of refractory asthma (15). Her basal therapy regimen had included daily use of inhaled fluticasone 800 μg (maximum recommended dose in Japan) and inhaled salmeterol 100 μg, and near continuous (≥ 50% of year) 5 mg/day corticosteroids orally. She had experienced at least 2 or more asthma exacerbations each year that were treated with 300 mg hydrocortisone administered intravenously. Blood eosinophil count had been above 1500/μL from May to December 2014 with recurrent asthma exacerbations each month, which were treated with 30 mg prednisolone orally for 3 days or required a visit to the emergency department with 200 ~ 300 mg hydrocortisone intravenous administration. However, she didn't require hospitalizations. Blood eosinophil count decreased to 836/μL in January 2015, and asthma was well controlled with therapy consisting of fluticasone / salmeterol 125 μg / 25 μg inhaler 4 puffs/day and 5 mg prednisolone orally for a while. On September 4, 2015, she visited our clinic because of moderate asthma exacerbation. Blood eosinophil count was 1187/μL, and she was given 250 mg aminophylline and 300 mg hydrocortisone infusion. Since then, her asthma became unstable. On October 2, 2015, blood eosinophil count increased (1843/μL) with worsening of asthma requiring 300 mg hydrocortisone infusion, and since then, she was treated with fluticasone / salmeterol 250 μg / 25 μg inhaler 4 puffs/day and 5 mg prednisolone orally. Eosinophil count remained above 1500/μL without clinical manifestations of end-organ involvement except asthma. On March 24, 2016, she visited the emergency department with dyspnea. She also had low-grade-fever, general fatigue, anosmia, nasal congestion, and eczematous lesions of the skin, but not peripheral limb neuropathy. Blood eosinophil count was 3416/μL. Computed tomography (CT) scan of nasal sinuses showed bilateral opacities. She was thus hospitalized for a detailed work-up (**figure 1**).

Examination of the skin-biopsy specimen revealed dense eosinophilic infiltration of the dermis and subcutis. Stool microscopy did not identify any ova, cysts or parasites, and serum antibody tests for the parasites *Fasciola hepatica, Strongyloides* spp., *Trichinella* spp., *Taenia solium, Schistosoma mansoni* and *Toxocara canis* were negative. Specific IgE antibodies to *Aspergillus fumigatus* and *Candida albicans* were negative. Serum *Aspergillus* antigen was negative. Endoscopic examinations and whole-body CT scan examinations were normal, and blood tests for tumor markers were negative, ruling out secondary causes of eosinophilia. Serum levels of total IgE and C-reactive protein (CRP) were 102 IU/mL and 36.6 mg/L, respectively. Antineutrophil MPO antibodies were negative (< 0.5 U/mL). Serum TARC concentration was increased to 1270 pg/mL (range in healthy controls: 7 - 470 pg/mL). The patient was negative for the FIP1L1-PDGFRA fusion gene in peripheral blood mononuclear cells. However, flow cytometric analysis to look for IL-5 producing clonal lymphocyte subpopulations and bone marrow biopsy could not be performed. Given the above findings, she was diagnosed with idiopathic HES based on the criteria (2).

She was given methylprednisolone (MPSL) 500 mg/day infusion for 3 days and then oral MPSL 24 mg/day; skin lesions completely resolved, eosinophil count decreased (778/μL), serum CRP levels dropped to normal levels. MPSL dose was tapered gradually to 8 mg/day. On April 15, 2016, eosinophil count was 276/μL and she was discharged.

Her baseline medication included oral MPSL 4 mg/day and fluticasone / salmeterol 125 μg / 25 μg inhaler 4 puffs/day (maximum recommended inhaled dose in Japan). She came to our clinic on June 24, 2016 as a regular visit. Blood eosinophil count, FEV_1 (%) value, and the ACT score were 223/μL, 68.44%, and 21, respectively. She started to receive a monthly mepolizumab administration. Blood eosinophil count decreased to 44/μL on July 22, 2017. Oral MPSL was stopped, and FEV_1 (%) value and the ACT score gradually improved up to 76.45% and 25 on

Figure 1 *- Clinical course of a 56-year-old female diagnosed with idiopathic hypereosinophilic syndrome. After start of monthly mepolizumab administration, she withdrew from daily use of oral methylprednisolone in parallel with stable clinical symptoms.*



May 10, 2019. Her asthma control has been good, and no side effects of mepolizumab have been observed until May 2019.

The patient has an 81-year-old mother, diagnosed with bronchial asthma by the author in September 1994. She had non-allergic asthma with serum total IgE level 45 IU/mL, and negative results of serum specific IgE for common inhaled allergens. The diagnosis was confirmed using the GINA guidelines (14). In February 2005, she experienced fever and weight loss with palpable purpura of the skin, arthralgia, myalgia, tenderness of four limbs, and multiplex mononeuritis. Antineutrophil MPO antibodies were elevated (10 U/mL), and the skin-biopsy specimen revealed small-vessel vasculitis. Given these findings, she was diagnosed with EGPA based on the American College of Rheumatology criteria (1). As she had been treated for a very long time with corticosteroids, she had a very heavy burden of corticosteroids side effects, including hyperglycemia.

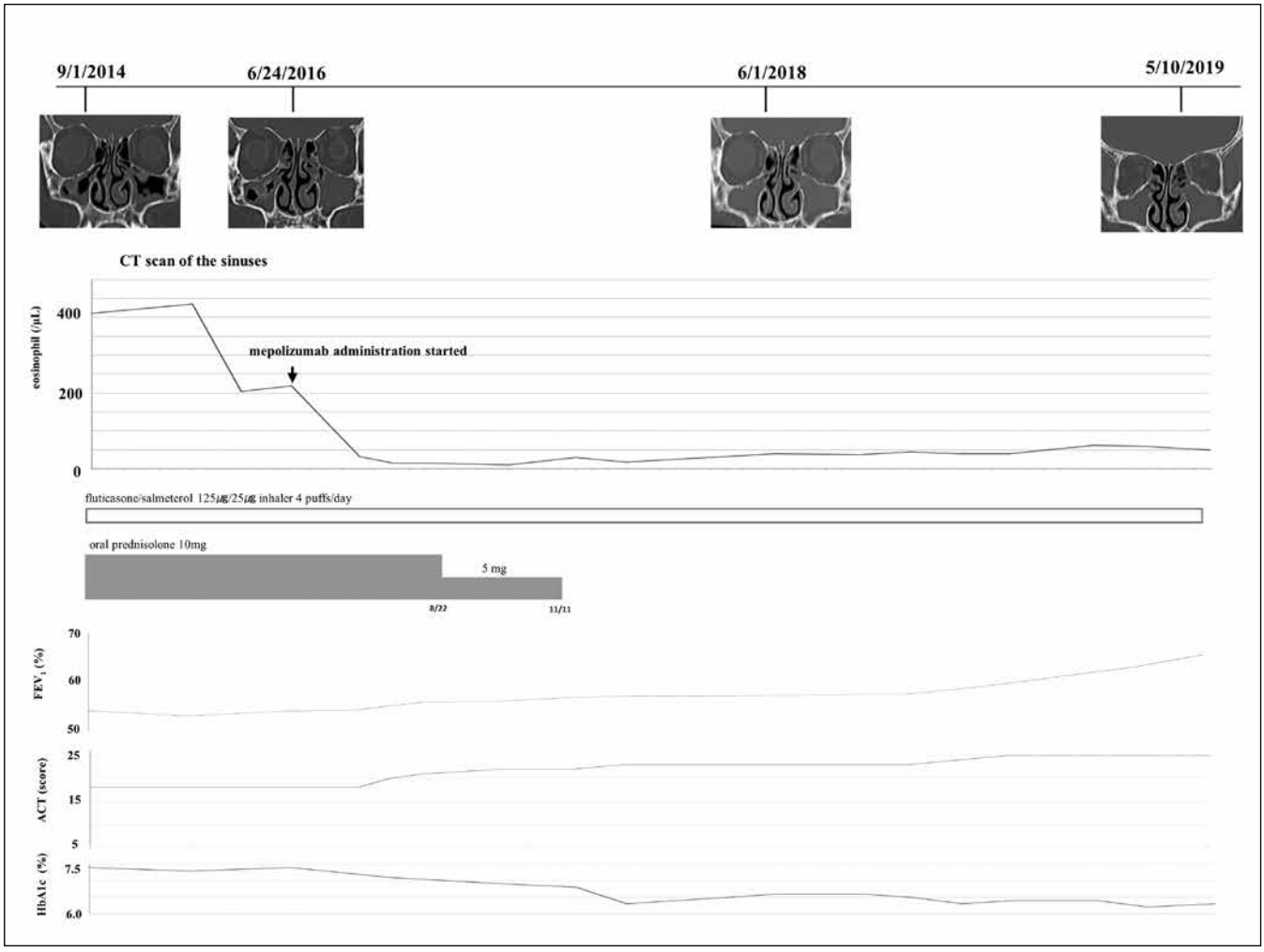
She visited our clinic on September 1, 2014 with recent worsening of asthma symptoms. Blood eosinophil count was 410/μL, and CT scan of the sinuses confirmed chronic sinusitis. Serum total IgE level was 80 IU/mL. She was treated with fluticasone / salmeterol 125 μg/25 μg inhaler 4 puffs/day and 10 mg prednisolone orally. She came to our clinic with her daughter on June 24, 2016 as a regular visit. Blood eosinophil count, glycated hemoglobin (HbA_{1C}) level, FEV_1 (%) value, and the ACT score were 220/μL, 7.4%, 53.96%, and 18, respectively. She started to receive a monthly mepolizumab administration because her asthma was corticosteroid-dependent. Then, corticosteroid therapy was successfully withdrawn in parallel with sustained

reduction in blood eosinophil count and HbA_{1C} level. FEV_1 (%) value and ACT score gradually improved up to 65.38% and 25 on May 10, 2019. However, the findings of CT scan of the sinuses remained unchanged (**figure 2**). She has been stable in asthma symptoms, and no side effects of mepolizumab have been observed until May 2019. Clinical symptoms of EGPA, such as palpable purpura of the skin, mononeuritis multiplex and chronic sinusitis did not change.

Discussion

Eosinophilia is caused by several diseases, including allergic reaction, parasitic and viral infections, malignancies. EGPA and HES are known to be associated with peripheral blood eosinophilia. However, they are clearly distinguished from allergic reactions because they have distinctive clinical features, namely organ damage due to eosinophilia (16,17). Although EGPA and/or HES are rarely observed in the same family, familial clustering of hypereosinophilic diseases has been reported in medical literature since 1909 (3-6). In this case report, we describe a case of familial clustering of hypereosinophilic diseases, EGPA and idiopathic HES, diagnosed according to current clinical criteria (1,2), and both of them were treated with mepolizumab. Currently available therapies for eosinophil-associated diseases including corticosteroids, and immunomodulatory and cytotoxic therapies have variable efficacy and significant toxicity,

Figure 2 *- Clinical course of an 81-year-old female, mother of the patient in figure 1, diagnosed with eosinophilic granulomatosis with polyangiitis. After start of monthly mepolizumab administration, she withdrew from daily use of prednisolone. In parallel with sustained reduction in blood eosinophil count and HbA1C level, FEV1 (%) values and ACT scores gradually improved with mepolizumab administration.*



and safe and effective therapies that target eosinophils are clearly needed (18).

IL-5 plays a key role on chemotaxis, differentiation, activation, and survival of eosinophils (19), and antagonism of IL-5 is considered a therapeutic target in patients with eosinophilic disorders. In November 2015, the US Food and Drug Administration (FDA) committee approved mepolizumab for use in patients older than 18 years with severe eosinophilic asthma at a dose of 100 mg administered once every 4 weeks (20), and in December 2015, the European Medicines Agency (EMA) approved a marketing authorization valid throughout the European Union as medicine under additional monitoring (21). In June 2016, mepolizumab was approved in Japan for use in patients with severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. In December 2017, the US FDA expanded the use to treat adult patients with EGPA, based on the results of the phase III trial report (22), with subsequent approval in May 2018 in Japan.

Advances in diagnostic approaches and therapeutic options for HES have prompted reevaluation of the definition and classification of HES. Some limitations of the diagnostic criteria established by Chusid et al. in 1975 (23) are present, and the revised-classification of HES into myeloproliferative, lymphocytic, and other forms is considered to be more useful in guiding clinical evaluation and therapeutic decisions (2). Tyrosine kinase inhibitor imatinib mesylate has been shown to be useful in myeloproliferative HES resulting from the fusion of the FIP1L1-PDGFRA and Fip1-like 1 genes (24,25). However, currently available therapies, including corticosteroids and imatinib, have variable efficacy and significant toxicity (26). On the other hand, mepolizumab has been suggested to be an effective and safety management of lymphocytic HES (27,28). Mepolizumab has a long-term safety for the treatment of lymphocytic HES (29,30).

We describe a case of familial clustering of hypereosinophilic diseases treated with mepolizumab for 3 years in the present study. A 56-year-old female diagnosed with idiopathic HES was treated with 3 day-intravenous administrations of MPSL, and subsequent oral MPSL. After starting mepolizumab administration, she was able to stop daily therapy with oral MPSL, which was consistent with the results of a previous report (31). FEV_1 (%) value and the ACT score gradually improved. The limitation of this study is lack of low cytometric and bone marrow evaluations to rule out some hematological diseases in the patient, however her clinical symptoms have been stable and no side effects have been observed during the 3 years of treatment. Her clinical response points to the diagnosis, and she will keep the therapy. The patient has an 81-year-old mother diagnosed with EGPA. After beginning mepolizumab administration, she was able to stop daily therapy with oral prednisolone, which was consistent with the results of a previous report (32). In parallel with sustained reduction in blood eosinophil count, FEV_1 (%) value and ACT score gradually improved as reported about asthmatic findings (33,34). Her asthma symptoms have been stable and no side effects have been observed during the 3 years of the treatment. However, clinical symptoms of EGPA, with the exception of asthmatic symptoms, remained unchanged, which was consistent with previous reports (32). The lack of efficacy of mepolizumab on the non-asthmatic symptoms may be due to the dose of mepolizumab. Namely, the patient started to receive a monthly mepolizumab administration at a dose of 100 mg in June 2016, and continued it for 3 years. On the other hand, the FDA approval of mepolizumab in adult patients affected by EGPA was at a dose of 300 mg administered subcutaneously every 4 weeks, and the same dose was approved for EGPA in Japan. Further studies are needed.

Needless to say, this case report has limitations. This study is an open-label, non-controlled trial, and definite proof that mepolizumab is responsible for these improvements cannot be ensured. However, to our best knowledge, this is the first report of familial clustering of hypereosinophilic diseases, idiopathic HES and EGPA, treated with mepolizumab for 3 years, suggesting mepolizumab may be a useful treatment for familial clustering of hypereosinophilic diseases.

Conclusions

This case report showed a favorable long-term safety and clinical efficacy of mepolizumab in familial clustering of hypereosinophilic diseases.

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Conflict of interests

The authors declare that they have no conflict of interest.

Ethical disclosures

Institutional ethics committee approved this study and written informed consent from each individual was obtained before the study.

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The Changing Landscape of Atopic Dermatitis - Focusing on JAK Inhibitors

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Key words

janus kinase inhibitors; atopic dermatitis; molecular targeted therapy; baricitinib; upadacitinib

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To the editor

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, with a lifetime prevalence of 15-20% in developed countries, with 20% of patients suffering from moderate-to-severe disease (1). According to the 2010 Global Burden of Disease Study, AD carries some of the highest disease burden worldwide, comparable to other chronic conditions like diabetes mellitus and cystic fibrosis (2). Described as the 'itching that erupts', clinically it is characterized by highly pruritic recurrent eczematous lesions with a negative impact in health-related quality of life (1), with a reported increased risk of developing depression and anxiety (1). AD is associated with several atopic and non-atopic comorbid conditions (3). The most common comorbidities are allergic rhinitis and asthma (present in up to one-quarter to one-third of patients) (4-6). Classically AD was regarded as a disease of early childhood (where the prevalence can reach 25%) but recent data shows prevalence in adults reaching 7 to 10% (7). This translates to a significant proportion of patients with persistent or adult-onset disease.

Phenotypically, it is an extremely heterogeneous disease, thought to be triggered by environmental factors in genetically susceptible individuals. It presumably encompasses a variety of subtypes with distinct and overlapping pathophysiological mechanisms with varying degrees of epidermal barrier disruption, activation of different T-cell subsets and dysbiosis of the commensal skin microbiota, which interact and contribute to cause the varying clinical presentations (1).

The molecular basis for AD has been increasingly understood as well as for pruritus. AD is characterized by skin epidermal barrier disruption which leads to chronic inflammation with epidermal hyperplasia and cellular infiltrates, including T-cells, dendritic cells, eosinophils, and type-2 T-helper cell (Th2) (8). Regarding inflammatory pathways, it is linked to increased T-helper (Th) immune response, elevated levels of inflammatory cytokines, including Th2-associated interleukin (IL)-4, -13, -31, Th22-associated IL-22, and Th1-associated interferon (IFN)-gamma, with downstream activation of the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathway (9). The cellular infiltrate of AD lesions mainly consists of CD4+ T cells, which are considered the key

drivers of inflammation (2). Although IgE has been considered a hallmark of atopic diseases, including AD, IgE itself is not a key mediator of AD pathogenesis (8).

The current management of AD includes a combination of emollients, antibiotics, anti-pruritic, and topical anti-inflammatory therapies. In the cases when this approach is insufficient, mainly the moderate-to-severe AD, the treatment remained challenging and limited. Systemic corticosteroids can only be used in short courses, and so, until recently, cyclosporine was the only systemic option approved in many European countries, unfortunately with limited efficacy and safety concerns with long-term therapy. Off-label options included methotrexate, azathioprine and mycophenolate-mofetil, with similar response rates, and also limited by their safety profile (10,11).

Despite an obvious unmet need regarding systemic treatment options, the cornerstone of AD treatment has remained relatively unchanged for over 15 years. But this is not the case anymore, as the field is currently evolving at a rapid pace. The growing understanding of the mechanism for AD, particularly focused on suppressing the skewed immune activation, is leading to an expanding pipeline of new and targeted topical and systemic therapies, similar to what happened in psoriasis (12).

Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have recently approved two targeted therapies for AD: crisaborole (a topical PDE4i) and dupilumab (an injectable monoclonal antibody against the IL-4 receptor A) (13,14).

Dupilumab, a human monoclonal antibody that blocks receptor binding of IL-4 and IL-13 (reducing Th2 response), approved for the treatment of adults with moderate-to-severe AD, was a natural approach to a targeted therapy (15). Clinical trials have demonstrated that it significantly improved clinical and patient-reported outcomes in the majority of patients. It also has a favorable safety profile. Frequent adverse events reported were mostly mild-to-moderate and included nasopharyngitis, upper respiratory tract infection, injection site reactions, and conjunctivitis (the only dupilumab-specific side effect). An added benefit is the effect on asthma. Dupilumab has recently received the approval from EMA as an add-on maintenance therapy for severe asthma with type 2 inflammation (16,17).

Despite dupilumab, the need for alternative treatments remains. Only 40% of patients on dupilumab with background topical corticosteroids (TCS) achieved clear or almost clear skin (18). Other biologic drugs currently being studied include pitrakinra (that specifically blocks IL-4), tralokinumab and lebrikizumab (that selectively target IL-13), and nemolizumab (an IL-31 receptor inhibitor, the first biologic specifically targeting IL-31, also known as the 'pruritus cytokine').

Pitrakinra is a recombinant human IL-4 protein that binds to IL-4Rα, therefore specifically blocking IL-4. The results from a 25-person phase II clinical trial from 2006 are still awaited (19).

Tralokinumab is an IgG4 humanized monoclonal antibody that acts by competitively blocking IL-13 attachment to its receptor subunits (IL-4Rα/IL-13Rα1 and IL-13Rα2 decoy receptor). In the phase IIb clinical trial, that included 204 patients, there was a statistically significant number of patients achieving EASI-75 and EASI-50, as well as an increased number of patients who achieved an IGA of 0 or 1. A phase III clinical trial was initiated in May 2017 and is expected to be completed in June 2020 (19).

Lebrikizumab alto targets IL-13. It acts by binding to IL-13 and preventing the epitope needed for IL-4R binding from attaching. Unlike tralokinumab, it does not affect binding to IL-13Rα2. A 12-week phase IIb trial showed that the group in the 125 mg of lebrikizumab once monthly achieved an EASI-50 that was statistically significant, despite all groups including the placebo receiving intensive topical corticosteroid regimens throughout the study.

IL-31, produced by Th2 cells and in lesser quantities by Th1 cells, appears to be involved in acute and chronic phases of AD and it seems to mediate transmission of itch sensation to the central nervous system. It also inhibits eosinophil apoptosis and is involved in disruption of skin barrier via downregulation of profilaggrin and filaggrin (19).

Nemolizumab is a monoclonal antibody that acts on the IL-31 receptor A. In a 12-week phase two clinical trial that enrolled 216 moderate-to-severe AD patients, monthly subcutaneous injections of nemolizumab showed a decrease in EASI, itch, improvement in Dermatology Quality of Life Index (DLQI), and improved sleep quality. Still, it is not clarified yet if nemolizumab controls AD or only AD-associated pruritus (19). But monoclonal antibodies are far from being the only area of excitement regarding new treatment options.

Another important area of focus in AD is the development of new oral agents with minimal side effect profiles, including the category of small molecules. Small molecules are non-biologic drugs that modulate inflammatory cytokines and affect signaling pathways in immune cells. Several oral small molecules with differing mechanisms of action are being investigated for AD, namely JAK inhibitors, phosphodiesterase inhibitors and histamine receptor antagonists (20). In this category, JAK inhibitors are a promising therapeutic class that so far is proving again and again to be a safe bet and maybe even a JAKpot for the treatment of AD.

JAK/STAT pathway is a master regulator of immune function, involved in the downstream signaling of inflammatory cytokines, including interleukins, interferons, and multiple growth factors. The mammalian JAK kinase family is composed by four different members (JAK1, JAK2, JAK3, and tyrosine kinase 2 - TYK2) (21). Many different proinflammatory cytokines (including IL-4, IL-5, IL-13, and IL-31) elicit their pathophysiologic functions through JAK-STAT pathway, inducing Th2

and eosinophil activation, B-cell maturation, up-regulation of epidermal chemokines, and down-regulation of anti-microbial peptides (22). This makes JAK inhibitors broad-acting small molecules for oral or topical administration, with anti-inflammatory and anti-proliferative activity.

Their success in rheumatoid arthritis and other inflammatory diseases made them an important focus of therapeutic research for AD. They inhibit the kinase component of JAKs, preventing them from phosphorylating and stopping the transduction of intracellular signaling. Unlike psoriasis or alopecia areata, in which only one JAK pathway is upregulated, atopic dermatitis is associated with increased signaling through all four JAKs (JAK1, JAK2, JAK3, and TYK2) (23). Due to their good oral bioavailability and lack of immunogenicity, oral JAK inhibitors address some of the limitations of biologics for the treatment of moderate-to-severe AD. Topical formulations are therapeutic options for mild-to-moderate AD (20,21).

The first published randomized clinical trial demonstrating a clinical benefit of a topical JAK inhibitor in atopic dermatitis appeared in September 2016 (24). Within 2 years, 7 different agents entered randomized trials targeting the pathway: oral upadacitinib, oral abrocitinib (PF-04965842), oral baricitinib, oral ASN002, oral tofacitinib, topical tofacitinib, topical ruxolitinib and topical delgocitinib.

Results thus far are encouraging, with the majority of the patients achieving the primary outcome of their trial as well as reporting improvement in pruritus and quality of life. Of note, both selective JAK1 inhibitors upadacitinib and abrocitinib (PF-04965842) received breakthrough therapy designation from the FDA for treatment of patients with moderate-to-severe atopic dermatitis. Based in preliminary phase II data, upadacitinib (a selective JAK1 inhibitor) seems to achieve even better outcomes than dupilumab (21). Also relevant is an improvement in pruritus as soon as week 1 and skin improvement as soon as week 2, positioning it as an excellent option for induction of remission (21). If the short time to response is a class feature is yet to be determined. Baricitinib (a non-selective JAK inhibitor) also reported improvement in pruritus as soon as week 1 (25).

The most extensive safety data for JAK inhibitors has come from tofacitinib, ruxolitinib and baricitinib for their use in rheumatoid arthritis and myelofibrosis. Overall, JAK inhibitors are well tolerated and have good safety profiles. There is a slight increased risk herpes zoster, but the most frequent adverse effects are nasopharyngitis and upper respiratory tract infections (26,27). There is a slight increase in CPK (asymptomatic) as well as slight changes in hemogram, the latter being dose dependent and transient. Importantly, there does not seem to be an increased risk of malignancy (20). Of note, EMA has recently issued restrictions in the use of tofacitinib, while it reviews the risk of pulmonary embolism in patients under 10 mg twice daily dose (the drug is approved for the treatment of rheumatoid arthritis, psoriatic arthritis and severe ulcerative colitis; it is not being pursued for atopic dermatitis treatment) (28).

Finally, burden of atopic dermatitis in the pediatric population will certainly not be overseen. In the coming years, the pediatric patients will certainly become an important investigational focus and the gap between the number of adult trials and pediatric trials in atopic dermatitis is expected to decrease, as there are already some ongoing trials enrolling pediatric patients.

Without a doubt, these are exciting times in AD. In the near future the physicians' ability to help improving the patients' lives will increase. However, despite overall confidence it will be important to be aware of unexpected risks. Although the side effect profile of these new drugs appears safe, long-term effects are still unclear. Going forward, it will be important to better define the different subtypes of AD, and to be able to early identify the patients who are in need of a maximum treatment. These new directed therapies will soon change current algorithms of care and its careful use will allow practitioners to provide optimal therapy while minimizing adverse impacts on safety and cost.

Conflict of interests

Maria Alexandra Rodrigues has no research contracts or conflicts of interest to declare.

Tiago Torres declares the following research contracts and conflicts of interest:

AbbVie, Celgene, Janssen-Cilag, Leo-Pharma, Eli-Lilly, Pfizer and Sanofi-Genzyme.

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