The Multiple Trajectories of the Allergic March

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Abstract

The allergic march comprises the sequential appearance of a series of allergic comorbidities. However, variability in the onset and progression of allergic diseases generates a heterogeneous scenario that does not follow a linear and single trajectory.
Almost half of the pediatric population presents at least 1 allergy symptom. However, only 4%-6% present multimorbidity, with several allergic diseases co-occurring. It has recently been shown that although they share etiological mechanisms and risk factors, allergic diseases arise independently. In most cases, progression is not consecutive, or at least not the same in all patients.
T_H2-mediated inflammation, epithelial barrier dysfunction, and genetic predisposition play a fundamental role in the etiology of allergic diseases, on which the interaction with the exposome acts decisively.
Therefore, studying diseases from an omics point of view is essential when attempting to describe the various trajectories of allergic progression and to propose effective interventions to prevent multimorbidity.
In this narrative review, we provide an overview of the current perception of the allergic march, including clinical observations, omics data, risk factors, and measures aimed at modifying its course or even preventing its onset.

Key words: Allergic march. Atopic dermatitis. Asthma. Allergic rhinitis. Food allergy. Eosinophilic esophagitis. Omics. Epithelial barrier dysfunction. T2 inflammation.

Resumen

La marcha alérgica ha dado respuesta durante mucho tiempo a un escenario de aparición secuencial de diferentes comorbilidades alérgicas. Sin embargo, la variabilidad en la aparición y progresión de las diferentes enfermedades alérgicas dibuja un escenario heterogéneo que no responde a una trayectoria lineal y única.
Aunque en la actualidad casi la mitad de la población infantil presenta al menos un síntoma de alergia, tan solo un 4-6% presenta multimorbilidad, coexistiendo varias entidades alérgicas. Recientemente se ha demostrado que, aunque compartiendo mecanismos etiológicos y factores de riesgo, estas enfermedades alérgicas surgen de manera independiente y que, en la mayoría de los casos, no se observa una progresión consecutiva, o al menos, no la misma en todos los pacientes.
La inflamación mediada por células T helper de tipo 2 (Th2), la disfunción de la barrera epitelial y la predisposición genética juegan un papel fundamental en la etiología de estas enfermedades, sobre los que actúan de manera determinante la interacción con el exposoma. Por ello, el estudio de las enfermedades, desde un punto de vista de las ómicas, es fundamental para describir las diferentes trayectorias de la marcha alérgica y proponer intervenciones eficaces para evitar escenarios de multimorbilidad.
En esta revisión narrativa se incluye una descripción general de la percepción actual de la marcha alérgica, incluidas observaciones clínicas, datos ómicos, factores de riesgo y medidas preventivas propuestas para modificar su curso o incluso prevenir su aparición.

Palabras clave: Marcha alérgica. Dermatitis atópica. Asma. Rinitis alérgica. Alergia alimentaria. Esofagitis eosinofílica. Ómicas. Disfunción de la barrera epitelial. Inflamación T2.

Introduction

According to the World Health Organization (WHO), allergy is the fourth most relevant disease in the world, and it is estimated that, by 2050, more than half of the population will have one [1].

The allergic march (also known as the atopic march) refers to the natural course of onset of allergic conditions, based on the concept of a single trajectory of allergic disease progression, namely, a linear sequence beginning with atopic dermatitis (AD) and food allergy (FA) in infancy and the subsequent development during childhood and adulthood of respiratory allergies, including allergic asthma (AA) and allergic rhinitis (AR) [2]. Eosinophilic esophagitis (EoE) was subsequently included in the pathway and considered an element of the allergic march [3]. Nowadays, the most accepted timeline of onset begins with AD followed by immunoglobulin (Ig) E–mediated FA, AA, and AR [2,4]. However, recent cohort studies in pediatric populations have shown that only 7% of allergic children follow the classic allergic march [5], and some patients may skip some of the diseases in this trajectory [6].

The allergic march is proposed to be a result of type 2 helper T cell (T_H2) inflammation initiated by an impaired skin barrier exposed to various allergens, primarily food and inhaled allergens. Damage to the epithelial barrier triggers the release of alarmins (epithelial cell–derived thymic stromal lymphopoietin [TSLP], interleukin [IL] 25, and IL-33), which activate immature dendritic cells (DCs) and group 2 innate lymphoid cells (ILC2). T_H2 cells are generated in response to allergen presentation by DCs, with subsequent release of IL-4 and IL-13. In parallel, a change in B-cell isotype to specific IgE cells is initiated. Upon exposure to an allergen, IgE and allergen-specific memory T_H2 cells can penetrate the skin and circulate to distant organs, resulting in systemic involvement and progression of allergic disease [2].

The underlying pathophysiological features, including T_H2 inflammation, epithelial barrier impairment, and oxidative stress, together with genetic predisposition and the exposome (eg, pollution, rural environment, food introduction, and aeroallergens), interact and are reflected in various atopy-related disorders [7].

A recent multiomics study in children analyzed relevant transcriptomic components, proteins, and metabolites to describe the endotypes of allergic diseases from a biological perspective [8]. Based on omics, the authors identified 3 clearly differentiated allergic march endotypes. In the classic allergic march dominant type, genes related to eosinophilic disorders were upregulated, while airway epithelial barrier repair genes were silenced. In the group with a higher rate of asthma patients, genes related to reactive oxygen species were upregulated (a proasthmatic signal). And in the group in which atopic dermatitis predominated, genes related to extracellular matrix proteins, which are key to maintaining skin integrity, were downregulated with increased circulating phosphatidylcholine levels [8].

A broader view of the allergic march as an organized and exclusive sequence of onset of allergic diseases and a deeper understanding of the underlying immunological mechanisms and associated risk factors will enable the application of precision medicine to prevent and/or modify the various trajectories in the allergic march [4].

This narrative review provides the state of the art on the trajectories of the allergic march, including clinical observations, omics data, associated risk factors, and the preventive measures proposed to modify its course and even prevent its onset. A graphical summary of this review is presented in the Figure.

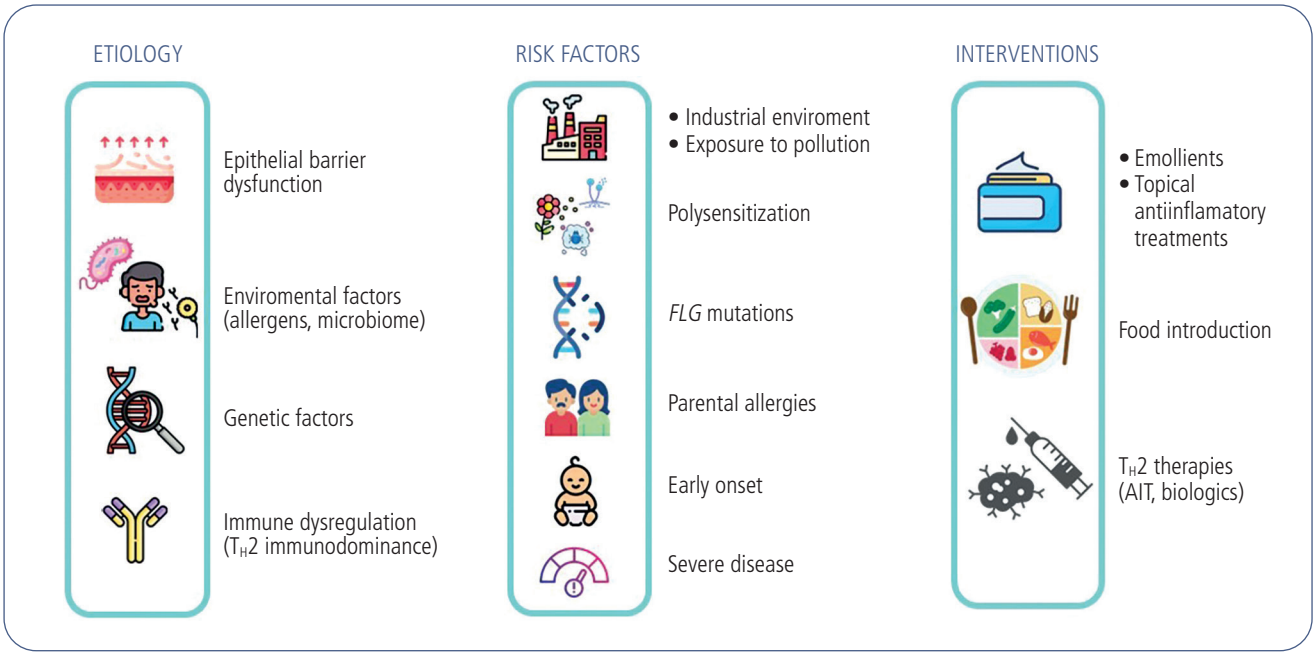

Figure. Etiologic features and risk factors related to the development of the allergic march and preventive interventions to impact its course. T_H2 indicates type 2 helper T cell; AIT, allergen immunotherapy.

Trajectories of the Allergic March: A Heterogeneous Landscape

Type 2 inflammation is a common characteristic in diseases that affect several organs and are mediated by both innate and adaptive immune responses [9-12]. It is the main mechanism underlying diseases involved in the allergic march [13-18]. Allergic conditions also share several risk factors, such as genetic traits and environmental exposures [19].

Approximately 50% of children have at least 1 allergy symptom. However, only 4%-6% have multimorbidity that arises independently, and the sequential progression of the allergic march is not observed in all cases [20].

Classic Allergic March Trajectory: From Atopic Dermatitis to Other Allergic Conditions

AD is the first manifestation of the classic allergic march [4]. It is influenced by genetic predisposition (eg, loss of function in the filaggrin [*FLG*] gene) and environmental exposures. The clustering of the AD phenotypes was initially proposed based on the time of onset (early vs late onset) and persistence (transient vs persistent) [7]. These characteristics, together with their severity, can be applied to establish the risk of developing the other allergic comorbidities [7].

Impairment of the skin barrier is considered the "entry point" of allergens, activating the T_H2 inflammatory pathway and inducing epicutaneous sensitization. The generation of memory T_H2 cells perpetuates skin barrier impairment and impacts exacerbation of the disease. Classically, the next allergic feature is the development of allergic sensitization with subsequent transition to asthma and AR and FA, which are mediated by the T_H2 cells distributed in the respiratory tract and intestinal mucosa, respectively. During this process, the exposome (interaction with allergens, dysbiosis) can modify the course of the disease, making some symptoms more prominent over time and leading others to subside [2].

However, not all conditions are present in every patient. Most only present eczema during childhood, with resolution during adolescence [5]. In a pediatric cohort that included 9801 children followed from 1 to 11 years, only 7% presented trajectory profiles running from skin to respiratory symptoms [5]. Almost all cohort studies that analyze the appearance of the allergic march begin by evaluating the onset and progress of AD, thus illustrating the impact of this disease on the other conditions. Onset of AD is classed as early and late, persistent and transient, and mild to severe [2,5,7].

Analysis of a birth cohort of patients with AD revealed the different phenotypes of the disease from birth to 36 months, showing that the risk of developing respiratory allergies or FA was lower if the skin condition resolved before 18 months of life [21]. Another birth cohort study observed that, in preadolescence, 39.8% of AD patients had asthma or AR, with a higher prevalence in the group of moderate-to-severe eczema than the group with mild disease (18.3% vs 9.0%, P=.016) [22]. The development of AD followed by wheeze and AR has also been associated with a parental history of allergy, allergic sensitization, and persistence of the skin disorder [5,22,23]. Furthermore, the poor prognosis of AD has been associated with early onset of the disease and early onset of wheezing [24].

Of note, AD is not driven solely by T_H2 inflammation, and not all patients have the same clinical presentation; therefore, the different endophenotypes of this disease may affect the trajectory of the allergic march [25].

Atopic Dermatitis, Food Allergy, and Eosinophilic Esophagitis

There is strong evidence of an association between AD, food sensitization, and FA [26]. FA is present in around one third of patients with AD, especially in those with the early-onset, severe, and persistent phenotype [2,27,28]. Allergen sensitization in AD patients has also been shown to increase the risk of developing FA [29].

In most cases, AD precedes food sensitization and FA, although it is not the only trajectory in FA. *FLG* mutations, which are associated with AD, have been independently associated with the development of FA and the persistence of allergy [30]. It has also been suggested that atopic mothers may passively sensitize their children in utero, enabling allergic reactions to food during the perinatal period despite no prior contact with the allergen [31]. These scenarios diverge from the classic allergic march, supporting the hypothesis that the trajectory of FA differs from the classic trajectory preceded by AD.

Concerning respiratory allergy, a European birth cohort study that analyzed the impact of pregnancy in rural and industrial settings showed that children with early-onset AD (first 2 years of life) had a higher risk of airway allergic symptoms, especially in those who already had FA [28].

There is epidemiologic evidence that EoE is also part of the allergic march [32], as a result of the worsening of EoE symptoms due to exposure to aeroallergens in allergic patients and the associated risk posed by the presence of the other components of the allergic march [3]. While the presence of EoE and AR are reciprocally and positively associated [33,34], the remaining allergic conditions appear to be independently and cumulatively associated with a subsequent diagnosis of EoE, which is in turn specifically associated with the presence of FA (HR, 9.1) [33] and with sensitization to specific allergens, such as egg, milk, and shellfish [3]. Regarding the position of EoE in the sequence of the allergic march, the maximum incidence of this disease is observed alongside that of AR and after the peak of AD, FA, and asthma [33].

Atopic Dermatitis With Allergic Asthma and Allergic Rhinitis

The risk of AA and AR is associated with the presence of AD, suggesting shared mechanisms. This relationship was also demonstrated a few decades ago in murine models, where bronchial inflammation was induced through epicutaneous sensitization [35]. However, the risk of developing both conditions, skin disease and airway disease, differs between the various AD phenotypes, mainly owing to the age at onset and severity. A recent meta-analysis showed an RR of 2.16 for developing AA in patients with AD, with a higher risk in those with early-onset disease and the persistent and severe AD phenotype [36]. In adults with AD, the risk of developing AA increased 1.6-fold [37].

It is difficult to have a real vision of the relationship between skin and airway diseases in the allergic march, since most of the studies that analyze the trajectory from AD to respiratory allergic conditions involve children, with the main respiratory trait considered to be the presence of wheeze induced by viral infections. Most patients present a transient phenotype that does not end in AA, with the persistence of wheeze-AA considered a specific trajectory/endophenotype [38]. Furthermore, the concept of one airway, one disease, which is related to the frequent co-occurrence of AR and AA in the same patient has recently been reviewed, and AR alone and AR and AA are now considered 2 different diseases [34]. This is a more practical and real-life clinical approach, since most patients present AR before AA. In terms of underlying mechanisms, toll-like receptor and IL-17 signaling pathways are predominant in AR alone, while IL-33 and IL-5 are more prevalent in the airway phenotype characterized by multimorbidity. Furthermore, polysensitization to allergens is relevant in the classic allergic march phenotype, with upregulation of IL-33 in children affected by early-onset AD [34]. However, IgE-mediated sensitization is not considered the dominant causal mechanism of multimorbidity, because only 38% of patients present allergic skin and respiratory diseases [34].

The symptoms of the different trajectories of respiratory allergies from childhood to adulthood have been described in several cohort studies. In a German cohort (participants of the International Study of Asthma and Allergies in Childhood [ISAAC]), 5 trajectories for wheezing, rhinoconjunctivitis, and eczema were identified [38]. Three of them involved a single disease (eczema and wheezing), and 2 involved a combination of symptoms. Those patients who only had eczema improved after adolescence. Those with only rhinoconjunctivitis had an increased risk of persistence, especially when they presented with parental allergies and sensitization to seasonal allergens. Patients with wheeze-related symptoms (late-onset wheeze, rhinoconjunctivitis+wheeze, and eczema+rhinoconjunctivitis +wheeze) were more affected by environmental exposures. In this sense, the study showed that the allergic trajectory in adulthood was conditioned by characteristics of both childhood and adolescence, mainly related to the persistence of airway symptoms. This indicates that adolescence is a critical phase for the development of allergic respiratory diseases and is partly associated with environmental exposures (active smoking, dog ownership, exposure to molds, and occupational exposures), thus supporting the hypothesis that the development of the allergic march continues at this stage and does not end in childhood [38].

Belgrave et al [5] found clusters with temporal fluctuations in the appearance of atopic conditions, demonstrating that the trajectory of the allergic march has several variations. There were 3 initial clusters: early-onset AD, early-onset wheeze, and early-onset AD+wheeze. AR appeared in a late-onset phenotype. The final scenarios contemplate the resolution of AD and wheeze and the classic trajectory of the allergic march, as well as the development of persistent wheeze and AR, persistent AD and wheeze, persistent AD and AR, and persistent AD alone. Allergen sensitization was associated with a higher prevalence of all allergic conditions.

Allergen sensitization was shown to increase the incidence of AA in a Canadian population including patients from birth up to 5 years of age [29]. Overall, an increased risk of asthma at age 3 years was related to AD (RR, 2.23), allergen sensitization (RR, 4.37), or both (RR, 7.04). For AR, a higher risk was shown in patients with AD (RR, 4.44) and allergic sensitized patients (RR, 4.85) [29].

Analysis of the risk of AA or AR in patients with persistent AD phenotypes showed that prevalence increases to 17.5% and 21%, respectively, in a cohort in which the overall rate of AA and AR in patients with AD (including all phenotypes) was 8.5% and 7.9%, respectively [28].

Compared with late-onset phenotypes, early-onset AD with concomitant wheeze has been associated with persistent wheeze at the age of 7 years. Furthermore, presenting with AD in the first 3 years of life seems to predict AR at age 20 years (HR, 1.83) [24]. In the same study, 28% of patients presented AD prior to wheeze. The authors conclude that the data do not suggest that AD preferentially precedes wheeze [24].

Risk Factors for Onset and Severity

The diseases involved in the allergic march share a common genetic predisposition and risk factors for environmental exposure. The factors associated with multimorbidity in children with AD include the severity and persistence of the skin disease, onset before 2 years of age, parental allergies, a polysensitization profile, and exposure to contaminants related to industrial environments [5,7,21,36,39]. The impact of climate (in reference to the months of the year in which the patient was born) on the trajectory, starting with AD, has also been analyzed, although results are contradictory [21,40].

The clinical phenotypes of AD vary widely between patients of different ages, ethnicities, and levels of disease severity [41,42]. A combination of genetic, environmental, and immunological factors is responsible for the abnormal skin barrier seen in AD, resulting in a heterogeneous presentation of the disease [43]. Patients with severe and early-onset AD are more likely to develop allergic airway diseases as well as FA, as described in the previous section. Furthermore, the phenotype of early-onset persistent AD is positively correlated with greater severity from the initial stages of the disease [28].

As for genomic profiles, gene–disease associations have been identified in genome-wide association studies. Some loci have been associated with an increased risk that is directly correlated with a severe AD phenotype, a persistent course, and the risk of developing other allergic conditions (multimorbidity phenotype). The most studied variants are related to loss of function in the *FLG* gene [44,45], and their presence augments the risk of AA 1.5- to 3.3-fold in AD patients and almost 5-fold in those sensitized to allergens [39]. Patients already diagnosed with FA who presented *FLG* mutations also have a higher risk of developing AA (RR, 4.93), and some *FLG* variants are associated with AR in the presence of allergen sensitization, regardless of the presence of AD (RR, 1.34) [5]. Despite this strong correlation, a Swedish study in a preadolescent cohort found that *FLG* mutations did not impact the severity of eczema [22]. Similarly, in another study, they were not associated with the persistence of eczema/wheeze as single conditions, although an increased risk of multimorbidity was

found (2- to 3-fold for FLG, 1.4- to 1.7-fold for the rs7216389 risk variant) [20].

Other susceptible genes associated with an increased risk of allergic diseases play an important role in immune cell signaling and epidermal differentiation (such as *IL2RA*, *GSDMB*, and several intergenic regions). Many loci have been linked to the classic allergic march phenotype including AD, AA, and AR. Furthermore, loci with strong effects on the AD and AR phenotype and some that only affect the development of AA have also been described. The strongest association in patients with AD and FA was observed for a *KIF3A/IL13* variant, and variants of *STAT6*, and *TSLP* have been identified for the phenotype including EoE (in addition to AD, FA, asthma, and AR) [4].

Biomarkers other than genetic variants have been identified in patients with AD and FA using skin tape strips, which can reveal specific cytokine profiles. In this sense, although only a minority of children with FA carried *FLG* mutations, the cytokine profile (elevated levels of IL-8 and IL-18 and decreased levels of natural moisturizing factor) was similar among children with *FLG* mutations and children with FA, and significant differences were observed with patients who did not carry the mutation [44]. Concerning AD, when data from skin biopsies and tape strip samples were compared, the most characteristic observation in the biopsies was T_H2 inflammation. However, innate inflammation markers (IL-1α, IL-1β, IL-8, and IL-18), along with thymus and activation-regulated chemokine and cutaneous T cell–attracting chemokine, were the most frequent finding in tape strip samples, correlating with severity of AD in both lesional and nonlesional skin, while no significant correlations were observed in skin biopsy data [44]. Regulation by Wnt signaling was recently suggested in AD phenotypes that exhibit FA at early ages and subsequently progress to asthma [46].

A family history of atopy has been strongly associated with the risk of developing not only AD, but also other allergic conditions, particularly if both parents have allergy, which increases the risk of a multimorbidity phenotype 6-fold [28]. It is also related to the development of more severe and early persistent phenotypes [28,47]. Polysensitization and a worse prognosis have also been related to parental allergies [39].

Being sensitized to multiple allergens in early childhood increases the risk of more severe AD and the further development of airway symptoms [29,39], probably because of upregulation of IL-33 in children with early-onset AD [34]. The risk of developing AA and FA at 3 years of age increased 7-fold when the patient presented AD with allergic sensitization at 1 year of age, compared with those who were not sensitized [29]. The development of allergic contact dermatitis can also have a negative impact on the course of AD [48].

The microbiome, as well as its interaction with the exposome, also appears to play a crucial role in the onset and progression of allergic diseases and multimorbidity. It has been hypothesized that both reduced microbial diversity and vitamin D deficiency interfere with tolerance mechanisms and epidermal barrier function, thus promoting AD and FA [49,50]. The reduction in gut microbiome diversity associated with urbanization in Western countries has been linked to inhibition of the protective role of IL-17 in the microbiome. Dysbiosis improves its production to restore balance. If altered, it results in an IL-33–driven pathway, which is associated with multimorbidity, suggesting that the microbiome may play a relevant role in the allergic march [34]. Exposure to atmospheric irritants/pollutants/allergens or specific microbes, eg, through cesarian vs vaginal delivery or skewing of the microbiome toward *Staphylococcus aureus*, may affect the development of allergic sensitization [7]. The use of antibiotics during the first 4 months of life has also been associated with an early-onset and persistent AD phenotype, possibly in association with a change in the microbiome [21]. Esophageal and pharyngeal microbiomes, respectively, have also been shown to impact the development of EoE (related to the presence of *Haemophilus* species) and early onset of AA (in colonization by *Streptococcus pneumoniae, Haemophilus influenzae*, or *Moraxella catarrhalis*) [4].

Regarding the pathophysiology of FA, the dual allergen exposure hypothesis suggests that allergen tolerance arises from oral exposure, since allergic sensitization results from skin contact, thus increasing the relevance of introducing food during early childhood to prevent or modify the allergic march trajectory linked to AD and FA [49].

These factors should be taken into account in order to treat appropriately and prevent or minimize the progression of the allergic march.

Interventions to Prevent, Delay Onset of, or Modify the Allergic March

The allergic march is the result of the combination of defects in the epithelial barrier and immune dysfunction based on an imbalance toward the T_H2 pathway. It is influenced by genetic predisposition and interaction with the exposome (environment, allergens, microbiome). This scenario comprises several treatable factors that may impact the allergic march.

Proposed interventions that can hinder the "allergic march" include prophylactic/preventive strategies, such as those targeting the epidermal barrier defect (emollients), active treatment for the skin inflammation (topical corticosteroids and calcineurin inhibitors), and interventions to treat allergic comorbidities [51,52]. The most widely investigated interventions include assessment of impact of measures during pregnancy, early use of probiotics, not delaying the introduction of foods, early exposure to pets, modification of the microbiome, care of the skin barrier, anti-inflammatory treatment for AD, and biologics targeting the T_H2 pathway [53,54].

Allergens have been found in amniotic fluid [55]. Mononuclear cells respond by secreting T_H2 cytokines such as IL-13 into umbilical cord blood [56]. Pregnancy is also characterized by placental translocation of maternal IgE through the neonatal Fc receptor, with subsequent sensitization of fetal mast cells. This in turn provides temporary protection not only against bacterial toxins and venoms, but also against sensitized mast cells in the fetus. Nevertheless, the offspring of atopic mothers might become passively sensitized. Despite not having been previously exposed to the culprit allergen, newborns can experience allergic reactions. All these factors influence the risk of developing allergic multimorbidity; however, direct interventions have not yet been established [31]. Women at

high risk are unlikely to benefit substantially from antigen avoidance diets during pregnancy to prevent allergic diseases in their children, and such diets may affect maternal and fetal nutrition [55].

Exclusive breastfeeding for the first 4-6 months after birth has been recommended to prevent allergy [57]. Furthermore, breastfeeding mothers with infants affected by atopic eczema seem to be able to reduce the severity of the skin disease by avoiding dietary antigens, although larger trials are needed [55].

Diversity of microbiota and exposure to oral allergens have been identified as promoters of tolerance, while nondiverse microbiota and exposure of the skin to allergens have been associated with allergic sensitization [49,50]. Furthermore, the timing of food introduction during early childhood has been shown to affect future tolerance or development of FA by increasing multimorbidity. In general, the early introduction of peanuts and boiled eggs at 4 to 12 months of age in high-risk patients has been shown to be effective in preventing sensitization to food [2,53]. However, this approach is aimed only at allergen-specific prevention, with no impact on development of AD [58]. Further research is needed to identify and characterize the high-risk population and the most appropriate introduction timelines. Measures related to dietary avoidance during pregnancy and breastfeeding, hydrolyzed formulas, and cow's milk–based infant feeding have not been shown to have a positive or any impact on the development/improvement/avoidance of allergic diseases, mainly AD and FA [53,57]. In patients diagnosed with cow's milk allergy, the use of extensively hydrolyzed casein formula containing probiotics recently proved more effective in the prevention of the allergic march than amino acid–based formula or rice-/soy-/whey-based hydrolyzed formulas [59].

Results are inconclusive for vitamin supplements and fish oil [49,50,60]. Additionally, findings for the use of probiotics during pregnancy or in early childhood are conflicting. One meta-analysis found that the prevalence of FA decreased (RR, 0.77; 95%CI, 0.61-0.98), although the results could not be generalized owing to variability in the characteristics of the population and the probiotics used [61].

Exposure to pets during the first year of life seems to help prevent sensitization to a specific allergen [62], although, once again, the results are inconclusive [63]. Furthermore, prenatal contact with a greater number of farm animal and pet species has been shown to have a protective effect on developing AD [28]. Irritant occupational exposures, smoking, and environmental exposure to molds have been associated with a higher risk for developing late-onset skin symptoms (eczema) and airway symptoms [38].

The use of emollients during the first weeks of life and its impact on the appearance of AD and FA have been analyzed, albeit with controversial results [53]. A recent meta-analysis concludes that in high-risk patients, the continuous use of emollients from the first weeks of life could delay rather than prevent onset of AD, with an uncertain impact on the development of FA [64]. Moreover, a study of high-risk children [65] demonstrated no reduction in FA at 2 years, and other studies have shown that the preventive effect may differ depending on the type of emollient (eg, food-derived oils, ceramides) [66,67].

The treatment of AD is based on topical anti-inflammatory agents such as corticosteroids and calcineurin inhibitors [52]. If therapy is continued, topical corticosteroids (betamethasone valerate) are effective in reducing the duration of eczema in pediatric patients with AD and may also reduce the subsequent development of FA at 2 years of age [68]. A study of the long-term use of topical tacrolimus in patients with AD showed that in responding patients with a ≥60% decrease in affected body surface, the drug had a beneficial effect on airway symptoms (including AA and AR) and decreased total serum IgE levels, skin prick test reactivity, and bronchial hyperreactivity [69].

After comparing patients treated with pimecrolimus and patients who received vehicle with fluticasone rescue cream, Schneider et al [70] found no difference in the development of atopic conditions in high-risk children with recent-onset AD. However, the frequency of AA and AR decreased in the whole cohort at a mean of 2.8 years after initiation of treatment, suggesting that improvement of cutaneous symptoms may reduce the probability of other atopic diseases.

Allergen immunotherapy (AIT) is a disease-modifying therapeutic option for IgE-mediated diseases. Its mechanisms of action include desensitization of effector cells (which reduces the underlying allergic T_H2 inflammation in target tissues), the stimulation of regulatory T cells, and the production of blocking antibodies (IgG4 and IgA) [71]. Clinically, AIT has been shown to reduce the prevalence of AA in patients at risk of AR in the short term (ie, during the 2 years after completion of treatment), with inconclusive results in the long term [72]. Both subcutaneous and sublingual immunotherapy have also been shown to be effective in preventing short-term allergic sensitization. The effects of sublingual pollen immunotherapy on control of symptoms and/or medication use have been demonstrated in randomized, double-blind, placebo-controlled studies [73-76], namely, disease modification and long-term tolerance after 3 years of treatment [77].

Alternative and more recent immunotherapy approaches include new adjuvants, recombinant allergens (including hypoallergenic variants), and combinations of allergens with immune modifiers or monoclonal antibodies targeting the T_H2 cell pathway to improve safety, effectiveness, convenience, and long-term tolerance [71]. Whether biologics can interrupt the allergic march has also been explored [32]. Dupilumab, a monoclonal antibody that blocks IL-4R, has proven effective in treating moderate-to-severe AD, AA, chronic rhinosinusitis with nasal polyposis, and EoE, all of which are driven by T_H2 inflammation. A recent meta-analysis of clinical trials with adolescents and adult patients has shown that patients treated with dupilumab presented a 34%-37% lower risk of new-onset allergy and/or worsening of pre-existing allergy than the placebo groups. Moreover, in off-treatment follow-up, these benefits did not revert, suggesting an immunomodulatory disease-modifying effect that can attenuate the allergic march [78].

The combination of monoclonal antibody therapies with AIT has been proposed as a complementary strategy to treat T_H2-driven diseases [79]. The available data show that omalizumab could prove effective as an add-on to AIT for respiratory allergy and food desensitization, especially to prevent adverse events

during the build-up phases. A recent meta-analysis has shown that omalizumab+AIT can significantly enhance the efficacy and safety of AIT by increasing the target maintenance dose and sustained unresponsiveness to allergens while decreasing severe systemic adverse effects [80].

A phase 2a, multicenter, double-blind, placebo-controlled parallel-group study compared the efficacy and safety of subcutaneous AIT with dupilumab and that of subcutaneous AIT alone. The results showed that dupilumab as add-on therapy improved the tolerability of AIT, although, based on nasal symptoms, efficacy was not improved after a nasal challenge with allergens [81].

Tezepelumab has also been analyzed as an additional therapy in patients receiving SCIT, showing a positive impact on the efficacy of immunotherapy for improving nasal symptoms and on promoting tolerance over 1 year of treatment [82].

Recently, immune checkpoint molecules have been proposed as promising therapeutic targets for prevention and modification of T_H2 diseases [83].

Table. Concluding Remarks

There is a need to better phenotype/endotype AD and identify risk factors for the allergic march
The possibility of studying biomarkers and microbiome using "tape strips" should be investigated
Risk factors for progression include polysensitization, severity of AD, early onset, and parental atopy
Aggressive and proactive treatment of AD in children improves control of AD and may reduce allergic and nonallergic comorbidities
Treatment of AD, AR, and type 2 asthma with disease-modifying drugs (biologics, AIT) should be assessed
Control and clinical remission are plausible therapeutic goals, although there is no cure
Personalized medicine, new vaccines, and immunomodulation are options for future treatment

Abbreviations: AD, atopic dermatitis; AIT, allergen immunotherapy; AR, allergic rhinitis.

Remarks and Conclusions

AD is considered the initial stage of the allergic march. However, current evidence points to different trajectories in the acquisition of allergic diseases that are conditioned by environmental and patient-related factors [1-6].

Several hypotheses have been put forward to decipher the complexities of AD and the allergic march based on the order in which an event or disorder occurs, namely, whether the barrier dysfunction enables penetration of microbes and allergens with a subsequent immune interaction (outside-in hypothesis) or whether the polarized immune response increases the skin barrier defect (inside-out hypothesis) [43]. In terms of management and treatment, clinicians need to address both aspects. However, concerning prevention strategies, it may be necessary to compare primary defects with immune dysfunction.

Precision medicine applied to the concept of the allergic march will enable better endophenotyping of allergic conditions and reveal risk factors for the acquisition of other disorders on the allergic spectrum. Recently, the allergic march paradigm has included T2-driven disorders beyond AD, asthma, and FA, such as EoE, and should be expanded in the near future to include other upper airway diseases, such as chronic rhinosinusitis with nasal polyps [84-86]. This results in the definition of various disease trajectories, considering all allergic conditions present in a patient as co-occurring features in a multimorbidity framework rather than as a linear sum of comorbidities. Such an approach would allow clinicians to monitor patients closely owing to an identified potential to develop comorbidities.

Early onset of initial allergic disease has been shown to increase the risk of persistent multimorbidity in the future. Current evidence demonstrates that allergic diseases are not independent and that multimorbidity does not have a specific or typical sequence of symptom onset [20,28,34].

Adequate control and effective treatment of allergic conditions can have a direct effect on the allergic march and may even prevent its progression. A therapeutic approach with upstream-acting therapies may potentially be able to alter the course of the allergic march [87]. The development of more effective early intervention strategies to alter the sequential onset of these allergic disorders requires urgent advances in research to target the correct populations and avoid unnecessary recommendations and late interventions.

Although there is currently no cure for atopic diseases, AIT and biologics can modify allergic pathways by acting as true disease-modifying therapies [73-82]. To effectively change the course of the allergic march, future research should resolve the major questions of how, when, and to whom specific treatment should be applied. To answer these questions, some of the unmet needs include accurate identification of allergic trajectories from childhood, as well as associated biomarkers to perform early and accurate endotyping, followed by early and aggressive treatment.

The application of systems medicine, including clinical data, omics, epidemiology, and mechanistic models to elucidate the pathophysiology underlying the different trajectories of the allergic march, will enable a disruptive approach to diagnosis and treatment and, more importantly, individual prognoses, thus preventing onset of allergic conditions.

Concluding remarks are presented in the Table.

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Conflicts of Interest

S. Quirce has received speaking and consulting honoraria from ALK, Allergy Therapeutics, AstraZeneca, Chiesi, GSK, Mundipharma, Novartis, Sanofi, and Teva.

L. de las Vecillas declares that she has no conflicts of interest.

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CME Items

1. Which of the following factors is relevant during the different trajectories of the allergic march?
   a. Exposome
   b. Genetic predisposition
   c. Epithelial barrier impairment
   d. All the above

2. Which of the following statements about the allergic march and multimorbidity is true?
   a. It always starts with the development of atopic dermatitis (AD) during childhood
   b. Around 7% of patients present multimorbidity
   c. The severity of AD is not associated with the development of other T2 diseases
   d. Early onset of AD is linked to a lower risk of developing multimorbidity

3. With respect to food allergy (FA) in the allergic march, which of the following statements is true?
   a. One-third of AD patients present FA
   b. Filaggrin mutations are associated with AD but not with FA
   c. Eosinophilic esophagitis is considered an allergic march disorder
   d. Both a and c are true

4. With respect to airway disorders in the allergic march, which of the following statements is true?
   a. Adults with AD have a 1.6-fold increased risk of developing allergic asthma (AA)
   b. Wheezing related to viral infection during childhood in patients without AD is associated with a higher risk of developing AA
   c. To present allergic rhinitis with or without AA is considered the same disease under the one airway, one disease concept.
   d. Sensitization to seasonal allergens may favor resolution of AD during adulthood

5. Which of the following risk factors is associated with multimorbidity?
   a. Loss of function variant in the filaggrin gene
   b. Both parents affected by allergy
   c. Detection of markers of inflammation (eg, IL-1α, TRAC, CTACK) in skin samples
   d. All the above

6. Which factor is associated with a lower risk of multimorbidity?
   a. High microbial diversity
   b. Late introduction of allergenic food
   c. Early antibiotic use (before 4 months of life)
   d. Exposure to a diverse, polluted atmosphere

7. Which of the following interventions has been shown to affect the allergic march?
   a. Exclusive breastfeeding until 4-6 months of life
   b. Contact with pets
   c. The avoidance of allergenic food until 12 months of life
   d. None of the above

8. Which of the following pharmacological interventions has been shown to impact the course of the allergic march?
   a. Early use of emollients in the general population
   b. Intermittent use of topical anti-inflammatory treatment (corticosteroids, calcineurin inhibitors)
   c. Use of allergen immunotherapy combined with biologics
   d. All the above

9. Which of the following treatments is considered disease-modifying?
   a. Allergen immunotherapy
   b. Biologics
   c. Corticosteroids (systemic treatment)
   d. a and b are true

10. Which of the following statements is not true?
   a. Tape strips are a promising tool for studying inflammatory biomarkers and the microbiome
   b. Severe and early-onset AD is a high-risk phenotype for the persistence and development of other T2 diseases
   c. Aggressive and proactive treatment of AD during childhood may reduce allergic and nonallergic comorbidities
   d. Current treatments for AD, AR, and T2 asthma are curative