The multiple trajectories of the allergic march

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Abstract

The allergic march has long responded to a scenario of the sequential appearance of different allergic comorbidities. However, the variability in the appearance and progression of different allergic diseases draws a heterogeneous scenario that does not respond to a linear and unique trajectory.

Although currently almost half of the child population presents at least one allergy symptom, only 4-6% present multimorbidity, with several allergic entities coexisting. It has recently been shown that although they share etiological mechanisms and risk factors, these allergic diseases arise independently. In most cases a consecutive progression is not observed, or at least not the same in all patients.

Inflammation mediated by T helper 2 (Th2) cells, epithelial barrier dysfunction and genetic predisposition plays a fundamental role in the etiology of these diseases, on which the interaction with the exposome acts decisively.

Therefore, the study of diseases from an omics point of view is essential to describe the different trajectories of allergic progression and propose effective interventions to avoid multimorbidity scenarios.

In this narrative review, we provide an overview of the current perception of allergic march, including clinical observations, omics data, risk factors, and preventative measures proposed for modifying its course or even preventing its onset.


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 linear 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.

Introduction

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

The Allergic March (also called “Atopic March”) refers to the natural course of onset of allergic conditions, based on the concept of a unique trajectory of allergic disease progression. 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]. Later, eosinophilic esophagitis (EoE) was introduced into the path and considered an allergic march element[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]. It points out the fact that some patients can skip some of the diseases of this trajectory[6].

The allergic march is proposed to be a result of T helper 2 (Th2) inflammation initiated by an impaired skin barrier exposed to different 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). In response to allergen presentation by DCs, Th2 cells are generated, with a 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 memory allergen specific Th2 cells may penetrate the skin and circulate until distant organs, resulting in systemic involvement and progression of allergic diseases[2].

The underlying pathophysiological features including Th2 inflammation, epithelial barrier impairment and oxidative stress, together with a genetic predisposition and the exposome (pollution, rural environment, food introduction, aeroallergens, etc), interact and are reflected in the different atopic-related disorders[7].

Recently, a multiomics study in children was conducted analyzing relevant transcriptomic components, proteins, and metabolites to describe the different endotypes of allergic diseases from a biological point of view[8]. They identified three allergic march endotypes according to omics, with a clear differentiation among them. The “classic” allergic march phenotype presented an upregulation of the genes related to eosinophilic disorders, while airway epithelial barrier repairment genes were silenced. In the asthma phenotype, Ros (response to oxidative stress)-generation genes were upregulated (a pro-asthmatic signal) and in the atopic dermatitis phenotype, genes attributed to the extracellular matrix proteins, key in maintaining skin integrity, were downregulated with circulating phosphatidylcholine levels increased[8].

A broader view of the allergic march, not only as an organized and exclusive sequence of the onset of allergic diseases, and a deeper understanding of the underlying immunological mechanisms, as well as the associated risk factors, will allow the application of precision medicine to prevent and/or modify the different allergic march trajectories[4].

This narrative review provides a state of the art on the current knowledge on the trajectories of allergic march including clinical observations, omics data, the 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 Figure 1.

1. Trajectories of the Allergic march: a heterogeneous landscape

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

There are approximately 50% of children with at least one allergy symptom, but only 4–6% have multimorbidity that arises independently and not in all cases the sequential progression of the allergic march is observed[20].

Classic allergic march trajectory: from AD to other allergic conditions

AD has been described as the first manifestation of the allergic march[4], influenced by a genetic predisposition (such as the loss of function in the filaggrin (FLG) gene) and environmental exposures. The clustering of the AD phenotypes has been 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 establish the risk of developing the rest of the allergic comorbidities[7].

The impairment of the skin barrier is considered the “entry point” of allergens, activating the Th2 inflammatory pathway and inducing epicutaneous sensitization. The generation of Th2 memory cells perpetuates the skin barrier impairment and impacts the exacerbation of the disease. Classically, the next allergic feature is the development of allergic sensitization with subsequent transition to asthma, AR and FA, mediated by the Th2 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 diseases, making some symptoms more prominent over time, while others subside[2].

However, not all conditions are present in every patient. Most of them only present eczema during childhood, with a resolution during adolescence[5]. In a pediatric cohort that included 9,801 children, followed from 1 to 11 years old (yo), it was shown that only 7% of them presented trajectory profiles from skin to respiratory symptoms[5]. Almost all cohort studies that analyze the establishment of the allergic march begin with the evaluation of the onset and evolution of AD, showing the impact of this disease on the rest of the conditions. Mainly, the onset of AD is divided into early and late onset, persistent and transient, and mild to severe[2,5,7].

A birth cohort of patients with AD analyzed 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 in preadolescence that 39.8% of AD patients had asthma or AR with a higher prevalence in the group of moderate to severe eczema compared to the mild group (18.3% vs. 9.0%, P = 0.016)[22]. The development of FA followed by wheeze and AR, has been also linked with a parental history of allergy, allergic sensitizations and persistence of the skin disorder[5,22,23].
Furthermore, the poor prognosis of AD has been associated with an early onset of the disease and the early onset of wheezing[24].

It is important to consider that AD is not driven solely by Th2 inflammation and that not all patients suffer from the same clinical presentation, which is due to the different endophenotypes of this disease and may affect the allergic march trajectory[25].

**Atopic dermatitis, food allergy and eosinophilic esophagitis**

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

In most cases, AD precedes food sensitization and FA, however, it has been shown that it is not the only trajectory in FA. FLG mutations, linked to AD, have been associated independently 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, allowing food allergic reactions during the perinatal period without prior contact with the allergen[31]. These scenarios diverge from the classical allergic march, supporting that FA may have a different trajectory than the classic one preceded by AD.

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

There is epidemiologic evidence that EoE is also part of the allergic march conditions[32]. Two facts link this disease with the allergic march: the worsening of EoE symptoms due to exposure to aeroallergens in allergic patients, together with 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 positively associated[33,34], the rest of the allergic conditions appear to be independently and cumulative associated with a subsequent EoE diagnosis. This is especially associated with the presence of FA (HR 9.1)[33], and also with specific allergens’ sensitizations such as egg, milk and shellfish allergies[3]. Regarding EoE “position” in the sequence of the allergic march, the maximum incidence of this disease occurs coincident with 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 in murine models a few decades ago by inducing bronchial inflammation through epicutaneous sensitization[35]. However, the risk of developing both conditions, skin and airway diseases, differs between the different AD phenotypes, mainly due to the age of onset and its severity. A recent meta-analysis shows in patients with AD a RR=2.16 of developing AA, with a higher risk in those with an early-onset, persistent and severe AD phenotype[36]. In adults with AD, the risk of developing AA increased 1.6 fold-times[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 population, considering the presence of wheeze induced by viral infections, the main respiratory trait. The majority of these patients present a transient phenotype that does not end in AA, being considered the persistence of wheeze-AA a specific trajectory/endophenotype[38]. Furthermore, the concept of “one airway, one disease” related to the frequent coincidence of AR and AA in the same patients has recently been reviewed, considering that AR alone and AR + AA may represent two different diseases[34]. This is a more practical and real-life clinical approach since most patients present AR before AA. In terms of 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 multimorbidity airway phenotype. Furthermore, polysensitization to allergens is relevant in the “classic” allergic march phenotype, with an upregulation of IL-33 in children with early-onset AD[34]. However, IgE sensitization is not considered the dominant causal mechanism of multimorbidity because only 38% of patients presented allergic skin and respiratory diseases[34].

The different trajectories of respiratory allergies from childhood to adulthood have been described clinically in several cohort studies. In a German cohort (participants of the International Study of Asthma and Allergies in Childhood, ISAAC) five different trajectories for wheezing, rhinoconjunctivitis, and eczema were identified[38]. Three of them suffered from a single disease (eczema and wheezing) and two had 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, partly associated with environmental exposures (active smoking, dog ownership, mold, and occupational exposures), supporting that the development of the allergic march continues at this stage and does not end in childhood[38].

In the study by Belgrave et al.[5] there were also clusters with temporal fluctuations in the appearance of the different atopic conditions, demonstrating that the trajectory of the allergic march has several variations. There were three 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, the “classic” allergic march evolution, the development of persistent wheezing 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.

In a Canadian population that includes patients from birth up to 5 years of age, allergen sensitization has been shown to increase the incidence of AA[29]. Overall, an increased risk of asthma at 3 yo 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].
When analyzing the risk of AA or AR in patients with persistent AD phenotypes, the 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) were 8.5% and 7.9%, respectively[28].

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

2. Risk factors for onset and severity

The allergic march diseases share a common genetic predisposition and environmental exposure risk factors. Regarding the increased probability of presenting several allergic comorbidities in children with AD, the severity and persistence of the skin disease, its early onset before 2 years of age, parental allergies, a polysensitization profile, and exposure to contaminants related to industrial environments are identified factors that promote multimorbidity[5,7,21,36,39]. The impact of the 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 but currently yields contradictory results[21,40].

The clinical phenotypes of AD vary widely among 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]. It has been shown that 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].

In regards to genomic profiles, gene-disease associations have been identified in genome-wide association studies (GWAS). Some loci have been associated with an increased risk directly correlated with an AD severe phenotype, a persistent course, and the risk of developing other allergic conditions (multimorbidity phenotype). One of the most studied variants is those related to the FLG loss-of-function[44,45]. Their presence augments 1.5-3.3-fold times the risk of AA in AD patients and in those sensitized to allergens an increased risk of almost 5-fold times[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 if there is also the presence of allergen sensitization, regardless of the presence of AD (RR 1.34)[5]. Despite this strong correlation, in a Swedish study in a preadolescent cohort, FLG mutations did not impact eczema severity[22]. In another study, they did not show to be associated with the persistence of eczema/wheeze as single conditions either, but an increased risk of multimorbidity was found (FLG by 2- to 3-fold, rs7216389 risk variant by 1.4- to 1.7-fold)[20].

Other susceptible genes associated with an increased risk of allergic diseases have also been identified. Those genes play an important role in immune cell signaling and epidermal differentiation (such as IL2RA (interleukin 2 receptor alpha), GSDMB (Gasdermin B), 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 AD and AR

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phenotype and some that only affect the development of AA have also been described. Relative to subjects with AD and FA, the strongest association occurred for a KIF3A/IL13 variant (kinesin family member 3A related to IL-13), and for the phenotype including EoE (in addition to AD, FA, asthma, AR), variants of STAT6 (signal transducer and activator of transcription 6) and TSLP have been identified[4].

Along with genetic variants, other biomarkers have been identified using skin tape strips in patients with AD and FA that allow the identification of specific cytokine profiles. In this sense, although only a minority of children with FA had FLG mutations, the cytokine profile (elevated levels of IL-8 and IL-18 and decreased levels of NMF (natural moisturizing factor)) was similar among children with FLG mutations and children with FA, with significant differences with those patients without the mutation[44]. Concerning AD, when comparing data from skin biopsies and tape strip samples, the most characteristic observation in the biopsies was a Th2 inflammation. However, innate inflammation markers (interleukin (IL)-1α, IL-1β, IL-8, IL-18) along with TARC (thymus and activation-regulated chemokine) and CTACK (cutaneous T cell-attracting chemokine) were the most frequent finding in tape strip samples in correlation with AD severity in both lesional and non-lesional skin, while no significant correlations were observed in skin biopsy data[44]. Recently, in AD phenotypes that exhibit FA at early ages and progress to asthma later, a regulation by Wnt (Wingless and Int-1) signaling has been suggested[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 suffer from allergies, which increases the risk of a multimorbidity phenotype six-fold times[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 development of further airway symptoms[29,39], probably related to an 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 to those who were not sensitized[29]. The development of allergic contact dermatitis can also have a negative impact on the AD evolution, too[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 a reduced microbial diversity and vitamin D deficiency interfere with tolerance mechanisms and epidermal barrier function, promoting AD and FA[49,50]. The reduction in gut microbiome diversity associated with urbanization in Western countries has been linked to an 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, associated with multimorbidity, suggesting that the microbiome may play a relevant role in the allergic march trends[34]. Exposure to atmospheric irritants/pollutants/allergens or certain microbes, such as by caesarian 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, which may be related to a change in the microbiome[21]. Esophageal and pharyngeal microbiomes have been also shown to impact the development of EoE (related to the presence of Haemophilus species) and early onset of AA (when colonization
by Streptococcus pneumoniae, Haemophilus influenzae or Moraxella catarrhalis), respectively[4].

Regarding the pathophysiology of FA, the dual allergen exposure hypothesis suggests that allergen tolerance occurs as a result of oral exposure, since allergic sensitization results from skin contact, increasing the relevance of food introduction in early childhood to prevent or modify the allergic march trajectory linked to AD and FA[49].

These factors should be used as an opportunity to treat appropriately and try to prevent or minimize the progression of the allergic march.

3. Interventions to prevent, delay onset or impair/modify the allergic march

The allergic march is the result of the combination of defects in the epithelial barrier, an immune dysfunction based on an immunological imbalance towards the Th2 pathway, influenced by a genetic predisposition and its interaction with the exposome (environment, allergens, microbiome). This scenario offers several treatable factors that may impact the allergic march.

Proposed interventions that may 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 those interventions to treat allergic comorbidities[51,52]. The 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 skin barrier, anti-inflammatory treatment for AD and biologics targeting the Th2 cell pathway, are some of the most investigated interventions[53,54].

During pregnancy, allergens have been found in the amniotic fluid[55]. In response, mononuclear cells secrete Th2 cytokines such as IL-13 into the umbilical cord blood[56]. During this period, placental translocation of maternal IgE through the neonatal Fc receptor also occurs, with subsequent sensitization of fetal mast cells. This fact is related to a temporary protection against bacterial toxins and venoms, but also to sensitized mast cells in the offspring. Despite not having been previously exposed to the culprit allergen, these newborns can experience allergic reactions. All these factors influence the risk of developing allergic multimorbidity; however, direct interventions have not been established yet[31]. Women at high risk are unlikely to benefit substantially from antigen avoidance diets during pregnancy to avoid allergic diseases in their children, and such diets may harm maternal and fetal nutrition[55].

Exclusive breastfeeding has been recommended for the first 4 – 6 months after birth as a positive intervention to prevent allergy[57]. Also, breastfeeding mothers with infants suffering from atopic eczema seem to be able to reduce the severity of the skin disease by avoiding dietary antigens, but larger trials are needed[55].

The diversity of microbiota and exposure to oral allergens versus skin interaction have been identified as promoters of tolerance, while the opposite scenarios 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, promoting a
scenario of additional multimorbidity. In general, the early introduction of peanuts and boiled eggs in high-risk patients at 4 to 12 months of age has been shown to be effective in avoiding food sensitization[2,53]. However, it is only allergen-specific prevention with no impact on AD development[58]. Further research is needed to identify and characterize the high-risk population and the most appropriate introduction timelines. Those measures related to diet avoidance during pregnancy or breastfeeding, hydrolyzed formulas or 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 has recently been shown to impact effectively in the prevention of the allergic march compared to the use of amino acid–based formula or rice/soy/whey hydrolyzed formulas[59].

About vitamin supplements and fish oil, the results are inconclusive[49,50,60]. Additionally, the use of probiotics during pregnancy or in early childhood has shown conflicting results. In a meta-analysis evaluating its use, the prevalence of FA appeared to be reduced (risk ratio, 0.77; 95% CI, 0.61-0.98), with a limitation to generalizing the results due to the variability in the population characteristics and probiotics used[61].

Exposure to pets during the first year of life seems to have a favorable impact on preventing specific allergen sensitization[62], but there are also conflicting results[63]. Furthermore, prenatal contact with a greater number of different farm animal species and pets 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 factor for developing late-onset skin (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, 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 the onset of AD, with an uncertain impact on the development of FA[64]. Moreover, in a study that includes a high-risk children population[65], no reduction in FA at 2 years has been demonstrated, and other studies have shown that depending on the type of emollient (food-derived oils, ceramides...), the preventive effect may differ[66,67].

The treatment of AD is based on topical anti-inflammatory treatments such as corticosteroids and calcineurin inhibitors[52]. As long as therapy is continued, the use of topical corticosteroids (betamethasone valerate) is 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]. In a study that analyzed the long-term use of topical tacrolimus in patients with AD, it was shown that those responding patients with a ≥ 60% decrease in affected body surface, had a beneficial effect on airway symptoms (including AA and AR), and a decrease in the total serum IgE levels, skin prick test reactivity and bronchial hyperreactivity[69].

Schneider et al.[70] found no difference in the development of atopic conditions in high-risk children with recent-onset AD comparing those treated with pimecrolimus versus vehicle with fluticasone rescue cream. However, the entire included cohort had a reduced frequency of AA and AR at a mean of 2.8 years after the start of treatment, suggesting that skin improvement may decrease the development of other atopic diseases.
Allergen-specific immunotherapy (AIT) is a disease-modifying therapeutic option for IgE-mediated diseases. Its mechanisms of action include desensitization of effector cells that reduce the underlying allergic Th2 inflammation in target tissues, as well as, 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 AR risk patients in the short-term (<2 years of treatment completion) with inconclusive results in the long term[72]. Subcutaneous and sublingual immunotherapy has also been shown to be effective in preventing short-term allergic sensitization. The effects of sublingual pollen-immunotherapy on symptom reduction and/or medication use have been demonstrated in randomized, double-blind, placebo-controlled studies[73–76], showing a 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 Th2 cell pathway to improve safety, effectiveness, convenience, and long-term tolerance[78]. If biologics may interrupt the allergic march has been also explored[32]. Dupilumab, a monoclonal antibody that blocks IL-4R, has been shown to be effective in treating moderate-to-severe AD, AA, chronic rhinosinusitis with nasal polyposis, and EoE, all of them driven by Th2 inflammation. A recent meta-analysis of the clinical trials with adolescents and adult patients has shown that patients treated with dupilumab presented a reduced risk of new-onset and/or worsening of preexisting allergies by 34% - 37% compared to the placebo groups. Moreover, in off-treatment follow-up, these benefits did not revert, suggesting an immunomodulatory a diseases-modifying effect, pointing out that it can attenuate the allergic march[79].

The combination of monoclonal antibody therapies with AIT, has been proposed as a complementary strategy to treat Th2-driven diseases[80]. The available data shows that Omalizumab may be 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[81].

A phase 2a, multicenter, double-blind, placebo-controlled parallel-group study, evaluated the efficacy and safety of subcutaneous AIT with dupilumab compared with subcutaneous AIT alone. The results showed that dupilumab as an add-on therapy improved the tolerability of AIT while the efficacy was not improved based on nasal symptoms after an allergen nasal challenge[82].

Tezepelumab has also been analyzed as an additional therapy in patients receiving SCIT, showing a positive impact on the efficacy of immunotherapy to improve nasal symptoms and on improving tolerance during one year of treatment[83].

Recently, immune checkpoints have been proposed as promising therapeutic targets to prevent and/or modify Th2 diseases[84].
4. Remarks and conclusions

AD is considered the initial stage of the allergic march. However, nowadays there is evidence of different trajectories in the acquisition of allergic diseases, conditioned by environmental and patients-related factors[1-6].

To decipher the complexities of AD and the allergic march, there are several hypotheses about which event or disorder occurs first: whether the barrier dysfunction allows the penetration of microbes and allergens with a subsequent immune interaction (“outside-in” hypothesis), or if it is the polarized immune response that 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 identify primary defects versus immune dysfunction.

Precision medicine applied to the concept of allergic march will allow better endophenotyping of different allergic conditions and identify risk factors for the acquisition of other disorders of the allergic spectrum. Recently, the allergic march paradigm has included other T2-driven disorders beyond AD, asthma and FA, such as EEO, and should be expanded to include other upper airway diseases, such as chronic rhinosinusitis and nasal polyps, in the near future[85-87]. This results in the definition of different disease trajectories, considering all allergic conditions present in a patient as co-existing features in a multimorbidity framework rather than as a linear sum of comorbidities. This would allow clinicians to closely monitor patients due 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 different allergic diseases are not independent, but multimorbidity does not have a specific or typical symptom sequence[20,28,34].

Adequate control and effective treatment of different allergic conditions can directly influence the allergic march, even preventing its progression. A therapeutic approach with upstream-acting therapies may be a potentially effective intervention to alter the course of the allergic march[88]. The development of more effective early intervention strategies to affect the sequential onset of these allergic disorders requires urgent advances in research to target the correct populations and avoid unnecessary recommendations or 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[73-83]. 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 underlying pathophysiology behind the different trajectories of the allergic march, will enable clinicians to have a disruptive approach to diagnosis and treatment, and more importantly, to predict individual prognoses and preventing the occurrence of the different allergic conditions.
Concluding remarks are presented in Table I.

Disclosure of potential conflict 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 has no conflicts of interest to declare related to this work.

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5. References


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Legend Figure. Etiologic features and risk factors related to the development of Allergic march and preventive interventions to impact its course.

ETIOLOGY
- Epithelial barrier dysfunction
- Environmental factors (allergens, microbiome)
- Genetic factors
- Immune disruption (Th2 immunodominance)

RISK FACTORS
- Industrial environment
- Pollution exposure
- Polysensitization
- FLG mutations
- Parental allergies
- Early onset
- Severe disease

INTERVENTIONS
- Emollients
- Topical antiinflammatory treatments
- Food introduction
- Th2 therapies (AIT, biologics)

Th2: lymphocyte T helper 2; FLG: filaggrin; AIT: allergen immunotherapy
### Table. Concluding remarks.

<table>
<thead>
<tr>
<th>Topic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is a need to better phenotype/endotype AD and identify risk factors for the allergic march</td>
<td>Possibility of studying biomarkers and microbiome using “tape strips”</td>
</tr>
<tr>
<td>Risk factors for progression: polysensitization, AD severity, early onset, parental atopy</td>
<td>Aggressive and proactive treatment of AD in the child improves AD control and possibly reduces allergic and non-allergic comorbidities</td>
</tr>
<tr>
<td>Treatment of AD, AR and type 2 asthma with disease-modifying drugs (biologics, AIT)</td>
<td>Control and “clinical remission” are plausible therapeutic goals, but there is no cure</td>
</tr>
<tr>
<td>In the future: personalised medicine, new vaccines and possibility of immunomodulation</td>
<td>AD: atopic dermatitis; AR allergic rhinitis; AIT: allergen immunotherapy</td>
</tr>
</tbody>
</table>