Comparison of aeroallergen sensitization patterns in the United States and Europe

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ABSTRACT

The global prevalence of allergic diseases has increased considerably and they represent a major socio-economic burden. Asthma is a complex disease and understanding asthma phenotypes and endotypes could eventually lead to individualized management, and offer better symptom control and quality of life. In this review, we first summarize the pathogenesis of atopic asthma and delve into the assessment of sensitization to aeroallergens through skin prick testing and serological testing with total and specific immunoglobulin E testing. We will then analyze the distribution of aeroallergen sensitization patterns in the United States and Europe and its effect on the population. This review gives a comprehensive overview on atopy and it compares the prevalence and effect of atopy within various regions of both continents using data from large multicenter studies. We will conclude this review by discussing the efficacy of add-on treatments in the most prevalent severe asthma phenotypes and endotypes.

Introduction

There has been an increased prevalence of allergic diseases, such as asthma and rhinitis over the recent decades,[1] which has led to significant social and economic consequences.[2] Asthma is a complex disease, with a variable presentation depending on the underlying pathophysiology. Several different asthma phenotypes have been described in the literature, based on the clinical, physiological, biochemical, and morphological characteristics. Whereas asthma phenotype characteristics relate to observable characteristics, asthma endotypes related to the underlying pathophysiological mechanism.[3] Despite considerable advances in the understanding and management of asthma, there are many unanswered questions regarding the underlying mechanisms of these disease subgroups, which hinders drug development. The classification of asthma phenotypes and endotypes has already led to novel and successfully targeted existing treatments, hence improving asthma care.[4]

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Pathophysiology

The identification of immunoglobulin E (IgE), the hallmark of type 1 hypersensitivity, represented a major breakthrough in allergy and asthma research in 1966. IgE plays a central role in the pathophysiology of allergic diseases. Raised total IgE levels have been associated with 3 main asthmatic phenotypes: allergic (or atopic) asthma, allergic bronchopulmonary aspergillosis, hyper-eosinophilic asthma associated with nasal polyposis and *S. aureus* colonization.

Atopic asthma is genetically determined[5] and its pathogenesis is characterized by a persistent T-helper (Th)2-type driven inflammatory response upon exposure to specific inhaled allergens.[6,7] An allergen is an environmental antigen which is able to induce specific IgE antibody production. Although aeroallergens play a pivotal role in the allergic cascade, environmental factors including *Staphylococcus aureus*, viruses and air pollution act as co-factors promoting epithelial activation and allergen modification.[5]

In susceptible individuals, the aeroallergens deposit on the epithelium of the trachea, bronchi or alveoli, which cause activation of the epithelium with

subsequent upregulation and recruitment of the primary antigen presenting cells, the dendritic cell. Dendritic cells present allergens to CD4+ T-cells, inducing (Th)2 cells to produce an immune response with production of specific IgE antibodies. (Th)2 cells express cytokines including interleukin (IL)-4, IL-5 and IL-13.[8] IL-4 promotes (Th)2 cell development and B-cell class-switch recombination from IgM to IgE upon activation by IL-4 and/or IL-13. Class-switch recombination to IgE is also seen in type 2 innate lymphoid cells (ILC2s).[5] IL-4 and IL-13 affect the epithelium by chemokine production, including eotaxin, IL-8, and monocyte chemoattractant protein. Activated (Th)2 cells also produce high amounts of IL-5 and IL-13. IL-13 leads to goblet cell hyperplasia and mucus hypersecretion, with subsequent smooth muscle hypertrophy, subepithelial fibrosis, and airway hyperresponsiveness.[9,10] IL-5 plays a pivotal role in mediating eosinophil recruitment, maturation and prolonged survival in response to aeroallergen stimuli. It also promotes upregulation and differentiation of eosinophil progenitors in the bone marrow.[11] Mast cells, (Th)2 cells and ILC2 cells, secrete IL-9, which stimulates and promotes proliferation of activated T cells and mast cells. It also upregulates IgE production by B cells and increased cell surface expression of the high-affinity IgE receptor FcεRI to respond to allergens. Mast cells secrete pro-inflammatory mediators (histamine, prostaglandin D2 and leukotrienes, platelet activating factor and other mediators) increasing vascular permeability leading to bronchial edema, bronchoconstriction and inflammation.[12]

On allergen re-exposure, the allergen causes FcεRI cross-linking on tissue mast cells and basophils leading to a cascade of intracellular events precipitating IgE-driven cell activation and degranulation.[5] After exposure to specific aeroallergens, the number of eosinophils increase due to two main reasons: an early-phase response secondary to mast cell degranulation[13] and a late-phase response, which occurs after cell recruitment from the circulation (eosinophils, basophils and T cells).[14] Eosinophils produce a variety of chemokines and cytokines triggering epithelial damage and bronchial hyperresponsiveness.[8]

Serological testing and/or skin-prick testing (SPT) are used in patients with atopic asthma to determine the presence of specific IgE, as it is a key feature of this phenotype. Blood eosinophilia may be present in conjunction with atopic asthma and it is found in other atopy-related disorders, such as allergic rhinitis and atopic dermatitis.[5]

Skin prick testing

Skin prick testing is a reliable method to assess IgE-mediated sensitization to aeroallergens in patients with atopic asthma. It is a cheap, reproducible, fairly rapid minimally invasive test, which is readily available to accurately identify the causative aeroallergen on a suspected type 1 mediated hypersensitivity reactions.[15-18]

SPT is recommended as a result of the high degree of correlation with symptomatology, and it utilizes the presence and degree of cutaneous reactivity to an allergen as a marker for sensitization. SPTs offer high sensitivity (80-97%) and specificity (70-95%) to diagnose aeroallergens.[15,16]

In the case of asthmatic patients, SPTs should be performed when asthmatic symptoms are controlled and if peak flow is less than 70% predicted, SPT is relatively contraindicated. Prior to performing SPTs, the expiry date of the allergen solutions should be checked and ensure they are adequately stored at +2°C to +8°C when not utilized. A drug history is vital as certain medication, such as antihistamines, may interfere with proper interpretation of the final results, *e.g.* a second generation H1-blocker should be stopped 7 days prior SPT. Other medications, which are not necessarily used for the treatment of allergic disease, such as the anxiolytic imipramine or phenothiazine antipsychotics may also interfere with interpretation. The volar aspect of the forearm is used for SPT using either a test grid or a grid marked with a pen. A drop of each standardized allergen extract, including the positive and negative control should be applied at least 2 cm apart, to avoid false-positive reactions due to contamination. The drop should be immediately pricked with a new single-head metal lancet for each allergen for at least 1 second, with equal pressure applied. Penetrating the epithelial layer may cause bleeding and thus may lead to a false-positive result. Any excess allergen extract solution can be blotted using a clean tissue. Cutaneous reactivity should be tested after 15-20 min following application.[16]

The positive and negative controls should be identified and measured first. A positive result is expected with histamine dihydrochloride 0.1%, unless the patient had been on treatment affecting the outcome. The patient is evaluated for dermographism with the negative control. A test is regarded as positive if the value of the longest diameter is ≥3 mm. A permanent record of the SPT could be performed by outlining the wheal with a pen and using cellophane tape to produce a negative.[16]

SPT confirms allergen sensitization, but in order to assess atopy to a specific aeroallergen, its clinical relevance must be appropriately interpreted based on symptomatology, past medical history and other investigations such as specific IgE serological testing.[15-18]

Various population-based studies and multicenter studies have been conducted over the recent decades, namely the European Community Respiratory Health Survey (ECRHS), National Health and Nutrition Examination Surveys (NHANES), International Study of

Asthma and Allergies in Childhood (ISAAC), and the Global Allergy and Asthma European Network (GA²LEN) skin test study I and II. These studies have shown that aeroallergen sensitization varies between a geographical area and another, depending on exposure rates. Geographical and seasonal variations in aeroallergen sensitization may possibly be attributed to increasing human migration and rapid urbanization as well as climate change caused by pollution.[19] Changes in aeroallergen sensitization patterns have also been observed over time.[20]

No standard consensus protocol for SPT was available in Europe up until the last few years. A study conducted by the GA²LEN network showed that despite there being similarities in technique of SPT throughout the 29 allergy centers, procedures varied across Europe.[21] This call for standardization was followed up with the introduction of the GA²LEN protocol, which recommended a common panel of aeroallergens in order to harmonize operating procedures throughout the European centers. It also standardized the method of procedure to perform and interpret the SPT results based on published guidelines, The European Academy of Allergy and Clinical Immunology (EAACI) position paper, the Nordic Standards and the ISAAC phase II protocol. The Pan-European allergen battery (Table 1) was proven and tested in a large multicenter study involving 17 allergy centers across 14 European countries, the GA²LEN skin test study I and II.

In the United States of America (USA), prevalence of aeroallergen sensitization in the general population was estimated in 3 NHANES, 2 of which, NHANES II, conducted in the late 1970s and III,[22] conducted in the late 1980s, were conducted by SPTs. NHANES 2005-2006[23] measured serum total IgE and specific IgE levels within the general population. The standard prick test panel tested for in the NHANES III is shown in Table 2.

Indoor allergens

Der p1 (*Dermatophagoides pteronyssinus*), and Der f1 (*D. farinae*) are the main species that cause allergic sensitization; Der p1 being the predominant species in Europe. During the last decade, Der f1 became increasingly more common in certain European countries. Among the European countries investigated in the GA²LEN skin test study I, house dust mite (HDM) sensitization rates were recorded the highest in the Nordic and Mediterranean countries. The mean sensitization rates to Der p1 and Der f1 in Europe were

Table 1. Standard European prick test panel for inhalant allergens.

Allergen/Control	
Hazel	*Corylus avellane*
Alder	*Alnus incana*
Birch	*Betula alba*
Plane	*Platanus vulgaris*
Cypress	*Cupressus sempervirens*
Grass mix	Smooth meadow grass (*Poa pratensis*), cock's foot grass (*Dactylis glomerata*), perennial rye (*Lolium perenne*), timothy grass (*Phleum pratense*), meadow fescue (*Festuca pratensis*) meadow oat grass (*Helictotrichon pratense*)
Olive	*Olea europaea*
Mugwort	*Artemisia vulgaris*
Ragweed	*Ambrosia artemisiifolia*
Alternaria	Alternaria alternata
Cladosporium	*Cladosporium herbarum*
Aspergillus	*Aspergillus fumigatus*
Parietaria	*Parietaria*
Cat	
Dog	
House Dust mite	*Dermatophagoides pteronyssinus, Dermatophagoides farinae*
German cockroach	*Blattella germanica*
Histamine dihydrochloride 0.1% (positive control)	
Sodium Chloride 0.9% (negative control)	

31.3% and 28.9% respectively.[17] In the population-based ECRHS sample, the sensitization rate to Der p1 was 17.8%,[24] significantly lower than in the GA²LEN skin test study I.

Sensitization to both Der p1 and Der f1 was most prominent in Mediterranean countries, such as Portugal (Der p1 68.8%; Der f1 68.0%) and Nordic countries such as Denmark (Der p1 51.5%; Der f1 51.8%). Central and Western Europe had lower rates of sensitization, for example in Poland (Der p1 22.2%; Der f1 19.1%).[17] The pattern of sensitization to Der p1 and Der f1 were also different in the ECRHS sample, as the highest rates of sensitization amongst the subsample of asthmatic patients for Der p1 was in central Europe and lower rates in northern and southern Europe.[25]

In the US, the HDM sensitization rate was 27.5%, the highest recorded in the Northeast region (*Maine, Vermont, New Hampshire, Massachusetts, Connecticut, Rhode Island, New York, New Jersey, and Pennsylvania*), 31.6% and the least prevalent in the Midwest region (*Ohio, Illinois, Indiana, Michigan, Wisconsin, Minnesota, Iowa, Missouri, Kansas, Nebraska, North Dakota, and South Dakota*).[22] SPTs cannot determine species-specificity as the allergens from these species of HDM cross react extensively.[26]

ECRHS II provided data of HDM allergen measurements from 22 cities in 10 European countries using 1 standardized protocol. Der p1 and Der p2 allergens were detectable in 68% and 53% of the samples, respectively. Latitude and longitude affected the distribution of Der p1 and Der f1 allergens. Both HDM allergens are more common with decreasing latitude, therefore are more common in southern European countries. Der p1 allergen is more common in western countries when compared to eastern locations and its concentration reduces in low winter temperatures. Longitude and low winter temperature have no effect on Der f1 allergen. Annual relative humidity and altitude were not associated with mite allergen levels. High allergen levels were also identified in households with older mattresses, a lower floor level bedroom and poor ventilation of the bedroom.[27] A study on NHANES results reached similar results, claiming older homes are associated with positive SPT to HDM and cockroach.[22] The authors concluded that HDM allergen is highly variable throughout Europe and this could be partly explained by geographic and housing characteristics. HDM allergen reduction is easily achieved by simple modifiable factors such as purchasing a new mattress, increasing ventilation of the bedroom and having a higher bedroom floor.[27]

Cats and dogs are the most prevalent household pets worldwide. The prevalence of animal sensitization, particularly to these animals, has increased in the USA,[28] Europe, Asian countries[29] and worldwide.[30] Nordic countries also had higher sensitization rates to cat and dog allergens as compared to Central/Western and Mediterranean countries. Sensitization to cat allergen was higher in Denmark (49.3%), Finland (30.4%), and Hungary (32.5%) whilst sensitization to dog allergen was higher in Denmark (56.0%), Finland (36.5%), and Poland (34.7%). Austria recorded the lowest sensitization rates to cat (16.8%) and dog (16.1%) allergens. Belgium and Italy also recorded

Table 2. Standard NHANES III prick test panel for inhalant.

Allergen/Control	Allergens
Indoor Allergen	
House Dust mite	*Dermatophagoides pteronyssinus, Dermatophagoides farinae*
German cockroach	*Blattella germanica*
Cat	
Outdoor Allergen	
Perennial rye	*Lolium perenne*
Bermuda grass	*Cynodon dactylon*
Short ragweed	*Ambrosia sp.*
Russian thistle	*Salsola sp.*
White Oak	*Quercus alba*
Alternaria	*Alternaria alternata*
Food allergen	
Peanut	
Histamine dihydrochloride 0.1% (positive control)	
Sodium Chloride 0.9% (negative control)	

low sensitization rates to cat (18.4% and 21.3% respectively) and dog (17.8% and 17.4% respectively) allergens.[17] In the USA, allergic sensitization rate among children suffering from atopic asthma living in urban areas was 44.1% for cat and 21.1% for dog allergens.[31] The northeast region of the USA has a greater prevalence of positive skin test response to cat allergen (20.1%) as compared to the other regions.[32]

Interestingly, specific cat (Fel d 4) and dog (Can f 1 and Can f 2) allergens exhibit cross-reactivity with other mammalian species such as horses (Equ c 1), cattle (Bos d 2), rabbits (Ory c 1), and rodents.[33] The sensitization rate to horse dander is underestimated. A study performed in Italy showed higher than expected horse allergen sensitization in urban-dwelling subjects without direct or occupational exposure to horses.[34] The mean prevalence of allergic sensitization to horse in Italy was of 5.38%, with sensitization rates varying from center to center [northern (6.31%), central (5.09%), and southern (5.24%) Italy].[35] Allergic sensitization to horses can occur through passive transfer. An example of this is from clothing of a person in contact with horses, or also via cross-reactivity through allergens, particularly lipocalins and serum albumin.[34,35] Thus, several authors, support the inclusion of horse allergen testing in the standard allergen panel,[34-37] and highly atopic individuals sensitized to cat and dog dander should undergo skin prick testing and specific IgE testing before direct or indirect exposure to horses.[34,35] Studies have also shown that in cat, dog or horse-allergic children, Can f 2 and Equ c 1 sensitization was more prevalent in severe asthmatics rather than controlled asthmatic individuals.[38]

Sensitization rates to the indoor allergen, *Aspergillus fumigatus* was generally low, ranging from 0.4% (Italy) to 6.9% (Portugal). Portugal had the highest sensitization rate for cockroach (33.4%), whilst the other European countries showed sensitization rates ranging from 2.1% in Belgium to 12% in Germany.[17] The distribution of positive SPT response to cockroach in the US population represented in NHANES III was 26.1%, with increased prevalence in the Northeast region (27.8%).[22] Allergic sensitization to cockroach increases the risk of developing sensitization to crustaceans and HDM as a result of cross-reactivity.[39]

Outdoor allergens

As expected, Nordic countries have higher sensitization rates to trees typical for the region, such as hazel, alder and birch. Denmark had the most prominent rates of sensitization to hazel (49.4%), alder (47.0%) and birch (57.4%). Central/Western Europe also showed increased sensitization rates to the northern trees with Germany (hazel: 35.9%; alder: 34.8%; birch: 37.6%). As latitude decreases, the prevalence of sensitization to the northern trees decreased and were variable. Allergic sensitization to hazel ranges from 7.4% in Portugal to 11.9% in France, sensitization to alder ranges from 3.1% in Italy to 10.4% in France and birch sensitization ranges from 6.8% in Portugal to 9.4% in Italy. Plane and cypress, typical southern trees, had low risk of sensitization throughout Europe.

Countries within the Mediterranean basin have the highest rates of sensitization to olive, ranging from 18.2% in France to 23.3% in Italy. Austria and Germany also show high rates of sensitization to olive, 13.3% and 9.7% respectively. Sensitization was also noted in the Nordic countries, but far less prevalent. The higher rates of sensitization in countries not sitting on the Mediterranean basin could be explained by the cross-reactivity of the oleaceae pollens, as olive extract tests positive for both olive and European Ash (Fraxinus excelsior), which is increasingly prevalent in most areas of Europe.

The prevalence of sensitization to grasses across Europe was generally high (37.8%), ranging from 19.5% in Italy to 69.9% in Denmark. Hungary has increased rates of sensitization to the grasses, Ambrosia (53.8%) and Artemisia (44.3%) as well as both outdoor fungi investigated, Alternaria (18.6%) and Cladosporium (12.8%). Artemisia sensitization was increasingly prevalent in Nordic countries [Denmark (28.3%) and Finland (17.6%)]. The highest rates of sensitization to Parietaria were observed in the Mediterranean countries, such as Italy (33.2%), while Nordic countries show the lowest rates.[17] In the US population, the highest prevalence to outdoor allergens included rye (26.9%) and ragweed (26.2%). Rye was more prevalent in the Northeast region (32.2%) while ragweed was increasingly prevalent in the West (Washington, Oregon, California, Nevada, New Mexico, Arizona, Idaho, Utah, Colorado, Montana, Wyoming, Alaska, and Hawaii) (35%). The average prevalence of Alternaria in Europe stands at 8.9%, whilst in the US population at 12.9%. Alternaria was more prevalent in the West region of the US.[22]

Sensitization to alternaria and other fungi has been clearly established to be a risk factor for the development and persistence of asthma[40] and more importantly, is associated with greater asthma severity, increased hospital admissions and a higher incidence of severe and life-threatening asthma.[41,42] Airborne fungal spores are often 1000-fold greater than pollen counts with a protracted exposure occurring for months rather than a few weeks, as seen for pollen. Prolonged exposure to Alternaria, as seen with common indoor allergens, such as cat dander and HDM, contribute to the chronicity and severity of asthma in Alternaria sensitive individuals, mitigating (Th)2-type driven inflammatory responses.[43] A retrospective study conducted in the US showed the adjusted odds ratio of a death caused by asthma occurring on days

with fungal spore counts of ≥1000 spores/m^3 was 2.2 times higher than when the fungal spore counts were <1000 spores/m^3.[44] 76% of severe asthmatics had at least 1 positive mold SPT skin-test positive to *Alternaria alternata Aspergillus fumigatus, Penicillium notatum, or Cladosporidium herbarum* or the yeast *Candida albicans* compared with 16%-19% of patients suffering from mild to moderate asthma (P<0.0001).[42]

Serological testing

A large multicenter collaborative study, known as the ECRHS, collected data on serum specific IgE levels to common inhaled allergens and total IgE levels from 25 centers on 3 occasions (baseline, 10- and 20-year follow up) over 20 years.[45-48] Another population-based study was conducted in the USA, known as NHANES 2005-2006, which collected data regarding total serum IgE levels and asthma prevalence in the US population.[23]

The median total serum IgE in the US population was 40.8 kU/L (interquartile range, 15.5-114 kU/L)[23] while that of the European counterpart at baseline was 35.9 kU/L (interquartile range, 13.2 kU/L in Iceland to 62.2 kU/L in France). There were substantial variations in the prevalence of atopy from one area to another, ranging from 16.4% in Spain to 45.2% in New Zealand (median 35.6%).[46] The prevalence of atopy in the US population was estimated at 42.5%.[23] The variation in distribution of atopy and total serum IgE levels are independent from each other and are attributed to environmental influence.

Atopy, defined as the presence of at least one positive specific IgE, was assessed by measurements of allergen-specific IgE against a panel of inhalant allergens. A positive test result is defined as a concentration of 0.35 kU/L or greater of the specific allergen. Both ECRHS[46] and NHANES 2005-2006[23] used a different allergen battery. ECRHS investigated the presence of specific IgE against Derp p1 (*Dermatophagoides pteronyssinus*), timothy grass (*Phleum pratense*), cat dander, *Cladosporium herbarum*, and a local allergen. Depending on the location of the center involved, specific IgE for a regional allergen was assessed for; Birch (*Betula verrucosa*) in northern Europe, Parietaria (*Parietaria judaica*) in southern Europe and ragweed (*Ambrosia elatior*) in Northern America and Australasia.[47] The allergen battery used in NHANES 2005-2006 consisted of the following 15 aeroallergens: *Alternaria alternata, Aspergillus fumigatus, Bermuda grass* (*Cynodon dactylon*), birch (*Betula verrucose*), cat dander, cockroach (*Blatella germanica*), dog dander, house dust mite (Der p1 and Der f1), mouse urine proteins, oak (*Quercus alba*), ragweed (*Ambrosia elatior*), rat urine proteins, Russian thistle (*Salsola kali*), rye grass (*Lolium perenne*).[23] In the US study, the same panel was used throughout all states, and local specific IgEs were not tested for.

The level of total IgE is generally reported to decrease with age. During the ECRHS study period, specific IgE sensitization to HDM and cat, but not grass, showed a significant reduction and appeared more evident in individuals aged 40 years or older.[48] Similar results were observed in NHANES 2005-2006. The effect of socioeconomic status and ethnicity also effects the total serum IgE level; black and Hispanic race have higher levels of total serum IgE compared to the white race and lower socioeconomic status and low education level is associated with higher total serum IgE levels.[49] Gender and smoking status also affects serum IgE level outcome, as males and smoking has been reported to increase total serum IgE levels.[50,51] In both NHANES and ECRHS, bias on the impact of seasonal variation in IgE levels was minimized, patient recruitment and data collection occurred all year round.

Atopy, IgE and asthma

The prevalence of asthma in the US population represented by NHANES III, tested by SPT, was 5.2% and the prevalence of atopy, defined as the presence of at least one positive SPT response, was 54.2%. Over half of the asthmatic cases (56.3%) were attributed to atopy. Atopic asthma was predominantly found in males and associated with higher education levels and settlement in urban areas. Asthma was strongly associated with all the allergens tested for in the NHANES III, however, after adjustment by all the allergens and the subject characteristics, only cat (29.3%), Alternaria (21.1%), and white oak (20.9%) showed a positive association with asthma. The role of cat exposure in the cause of allergic sensitization and disease remains controversial. According to the NHANES III study, sensitization to cat is a strong risk factor for the development of asthma.[22]

The GA2LEN study proved that the likelihood of atopic asthma increases depending on the number of positive sensitizations. There was an increased prevalence of atopic asthma with ≥1 positive sensitization compared with no positive sensitizations [children aOR 1.96 (1.18, 3.25) and adults aOR 2.29 (1.71, 3.06)], and this increased even further with ≥7 positive sensitizations [children aOR 6.12 (2.02, 18.54) and adults aOR 5.65 (4.0, 7.97)].[17,18]

Data from NHANES 2005-2006, estimated the overall prevalence of asthma in the US population to be 8.8%, with the prevalence of atopy being 42.5%, as defined by 15 specific IgEs. The prevalence of asthma in the US population was higher amongst the

atopic subjects rather than the non-atopic (12.9% and 5.8% respectively, P<0.001), showing a strong association between asthma and atopy [odds ratio 2.41 (95% CI: 1.94-2.99)]. The total IgE level was significantly higher in the asthmatic population compared to the non-asthmatic subjects (81.1 *vs* 40.8 kU/L, P<0.0001). Total IgE closely correlates with asthma risk and with airway responsiveness. However, findings from the NHANES study demonstrate that substantial numbers of non-atopic individuals have asthma which is independent from total IgE or IgE specific.[23] This finding could be explained by two asthma phenotypes associated with low IgE levels: non-atopic asthma and (Th)2-low asthma. Non-atopic asthma is defined by the presence of asthma with the absence of detectable serum specific IgE antibodies and negative SPT to common aeroallergens. (Th)2-low asthma is a distinct phenotype, which is characterized by asthma without evidence of (Th)2 and/or eosinophilic inflammation.

The US population attributable risk of asthma symptoms caused by atopy was higher than that reported by the IgE-based ECRHS, as the mean risk was 30.4%. Asthma symptoms caused by atopy varied widely between the ECRHS centers (4-61%), even within the same country (*e.g.* for HDM from 7-28% in Spain; for timothy grass 13-27% in the United Kingdom). The overall attributable risk of asthma caused by atopy increased depending on a number of variables: wheeze and bronchial responsiveness (42.6%), physician diagnosis (45.3%) and more than 12 asthma attacks in a calendar year (47.6%). There was a strong correlation of the prevalence of atopy amongst asthmatic patients and the heterogeneity of the attributable fraction of atopy at the center level (r=0.91, P<0.1), as well as the prevalence of symptoms of asthma amongst atopic patients (r=0.43).[52]

The range of prevalence for the US specific IgE panel ranged from 19.5% for rye grass to 1.1% for mouse urine proteins. 62.1% of the asthmatic US population had ≥1 positive specific IgE. The prevalence of specific IgEs to Der p1 and Der f1 was 18.8% and 18.5% respectively.[23] In the ECRHS, the median HDM prevalence was of 20.3%. The US and ECRHS populations have similar prevalence of specific IgEs to cat. In the ECRHS, the population attributable risk to cat allergen sensitization was of 14.1% in asthmatic patients. HDM and timothy grass allergen sensitization accounted for 18.2% and 17.1% of symptoms in asthma patients.[46]

Conclusions

The classification of asthma phenotypes and endotypes has already led to novel and successfully targeted existing treatments, such as allergen immunotherapy, which affects IgE reactivity by inducing tolerance to the allergen, biological therapy such as anti-IgE therapy, and biologicals targeting (Th)2 cytokines, such as anti-IL-4, IL-5 and IL-13 treatment.

Immunotherapy affects the humeral activity by increasin allergen specific IgG4 antibodies and decreasin allergen specific IgE antibodies.[53,54] It also affects regulatory T-cells by increasing IL-10 and IL-12 production which downregulates (Th)2 cell-dependent inflammation and suppresses class-switch recombination to IgE.[55] Mast cell, basophils and eosinophil activity is downregulated.

Immunotherapy should be considered in pharmacologically well controlled atopic asthma individuals where allergen sensitization is the main driver of clinical symptomatology.[53,54] According to the GINA 2018 guidelines, allergen immunotherapy is considered as an add-on therapy to achieve better asthma control by reducing symptomatology, medication burden and improving the quality of life.[56] There are two approaches to immunotherapy, either subcutaneous immunotherapy or sublingual immunotherapy (SLIT). Allergen specific immunotherapy practice patterns differ in the US and Europe. Europeans prescribe SLIT more often, and tend to treat one or two most important sensitizing aeroallergens whilst the US treat polysensitized atopic patients with mixtures including many or most of the sensitizing allergens.[57] The GINA 2018 recommends immunotherapy with extracts or regimens with proven clinical efficacy demonstrated in clinical trials, such as HDM, grasses and tree allergens.[56,58]

Omalizumab, an anti-IgE biological drug, is indicated in severe atopic asthma with increased total IgE level (>30 IU/mL) and positive SPTs to perennial aeroallergens and attenuates both the early-phase and late-phase responses to inhaled allergens.[59] It is a humanized monoclonal antibody directed against the IgE Cε3 domain preventing the interaction with the FcεRI on mast cells, basophils, eosinophils and dendritic cells.[60,61] Interestingly, a proof of concept study has shown that the effect omalizumab extends beyond decreasing IgE levels, as it is also beneficial in patients with non-atopic asthma.[62]

Patients with persistent eosinophilia and raised IgE levels may not necessarily respond to anti-IgE treatment, but may respond to treatments targeting (Th)2 cytokines, such as Anti-IL-5 therapy (mepolizumab, reslizumab and benralizumab) and therapies that inhibit both IL-4 and IL-13 (dupilumab). No targeted therapy is yet available for (Th)2-low asthma, but emerging therapeutic options still in the initial trial stages. Risankizumab, an anti-IL-23,[63] and low dose macrolide therapy[64] could offer a potential solution for patients with a (Th)2-low phenotype.

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