



Precision medicine in atopic diseases

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Purpose of review

To analyze the status of precision medicine in atopic diseases.

Recent findings

Atopic diseases are increasingly recognized as heterogeneous in nature and they can be quite different in severity, response to therapy, triggers, genetic background, ancestral risk and type of inflammation. This significant variability in the landscape of atopic diseases is not reflected in the common treatment guidelines that follow 'one fits all' approach for their management. Such an approach is largely based on minimal 'phenotype' elements, such as severity of disease and response to therapy and does not reflect the information accumulate in the last 20 years about particular pathogenic pathways (endotypes) leading to disease (phenotypes) based on biomolecular analysis of the single individuals. Accumulating data have defined asthma allergic rhinitis, food allergy based on their endotypes and clinically relevant phenotypes. In general, atopic diseases can be largely classified as high or low Th2 inflammatory status, which may explain the severity and response to therapy.

Summary

Precision medicine is aiming to use known endotype phenotype to guide specific individualized treatment. The work aimed in deep characterization of diseases to guide the disease management is crucial in light of the availability of ever more precise treatment able to target specific pathways.

Keywords

allergic rhinitis, asthma, atopic dermatitis, atopic disease, biologics, endotypes, eosinophilic esophagitis, food allergy, precision medicine, Th2 inflammation

INTRODUCTION

Atopic diseases, such as atopic dermatitis, asthma, allergic rhino-conjunctivitis and food allergy, are among the most common chronic diseases in westernized developed societies. They represent diverse inflammatory conditions [1] characterized by significant complexity, with multiple genetic and environmental factors interlinked through an inherited tendency to produce immunoglobulin E (IgE) antibodies in response to small amounts of commonly tolerated proteins known as allergens and non-IgE-associated mechanisms [2[•]]. These diseases generally begin very early in life and can persist into adult life [3]. As in patients with other chronic diseases, they often occur in the same individuals (multimorbidity) more often than expected by chance [4].

Treatment of atopic diseases is based on global highly publicized guidelines that characterize patient groups largely on minimal 'phenotype' elements, such as severity of disease and response to therapy (i.e. topical steroid and other anti-inflammatory therapies) [5–8,9[•]]. This 'one fits all' approach is being challenged by an increased recognition that atopic diseases are a heterogeneous in

nature and they can be quite different in severity, natural history, response to therapy, triggers, genetic background, ancestral risk, environmental risk factors and type of inflammation [10–17]. This significant variability has been confirmed by the information obtained with biomolecular analysis accumulated in the last 20 years about particular pathogenic pathways (endotypes) leading to disease (phenotypes) [18^{••},19^{••}]. On the basis of such knowledge, highly selective drugs targeting specific pathways are being developed and in the near future, the current management of atopic diseases

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KEY POINTS

- Atopic diseases are a heterogeneous group of diseases both clinically and pathogenetically.
- Atopic diseases are characterized in two major endotypes based on the level of Th2 inflammation: a T2 high and Th2 low.
- The mechanism of Th2-low inflammation is not well understood; however, Th1/Th17 or Th1/Th22 pathway activation, innate immune defects, tissue remodeling and neurogenic inflammation are possibly implicated.
- Current treatment approaches for patients with Th2-low inflammation have limited efficacy.

will become obsolete replaced by ‘precision medicine’ when the knowledge of ‘phenotype’ and ‘endotype’ of a patients will guide a truly individualized treatment. This progress has stimulated interest in applying systems biology approaches to biomedical research and efforts to create a personalized, predictive, preventive, and participatory (P4) medicine are increasing worldwide [20].

This review will analyze the status of precision medicine in atopic diseases.

PHENOTYPIC CLASSIFICATION

Different clinical subgroup of patients has been defined by using specific disease phenotypes that cluster together relevant clinical properties, such as age at onset, triggers, comorbidities, natural history,

biomarkers and response to treatment (Fig. 1) [21,22]. Different phenotypes have different prevalence at different ages and may have different response to therapy [23**].

For example, atopic diseases are typically chronic or chronic-relapsing in nature, tend to start at young age with a typical sequential pattern called ‘atopic march’ starting from eczema, through food allergy, asthma, to allergic rhinitis and possibly eosinophilic esophagitis (EoE) suggesting a common genetic environmental background predisposing to develop each of the single atopic diseases [24–26]. Still adult onset of single atopic diseases is not uncommon so is the fact that children affected by eczema or food allergy may never develop asthma or allergic rhinitis [26]. This different course is most likely a completely different phenotype than the one part of the atopic march starting in infancy.

Although such phenotypes are not incorporated in clinical practice or in the design of clinical trials, mounting evidence suggests that their importance and the knowledge of different phenotype may help in the future in therapy selection as well as the design of clinical trial.

Different phenotypes of asthma, allergic rhinitis, atopic dermatitis and food allergies have been described.

Haldar *et al.* [27] have categorized asthma into five phenotypes (Table 1) through cluster analysis:

- (1) Group 1: Early-onset atopic asthma characterized by early age onset and association with atopy

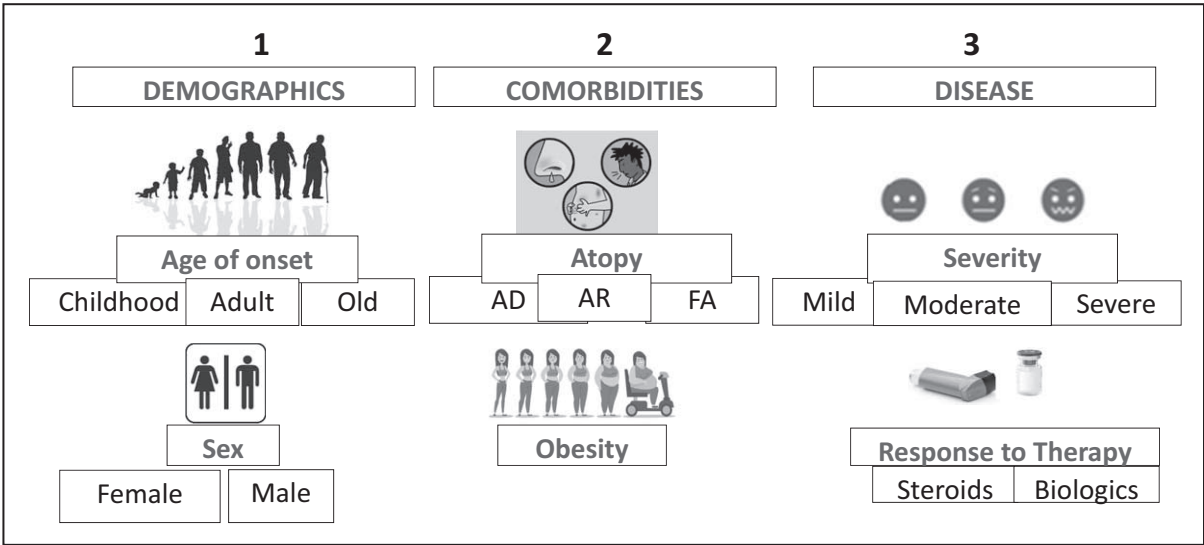


FIGURE 1. Phenotypes of atopic diseases. Phenotypes of atopic diseases, such as asthma, are based on demographic and clinical characteristics of the patients, such as age, sex (demographic), the presence of other diseases, such as atopic conditions or obesity (comorbidities) or severity of the disease and response to treatment (disease). AD, atopic dermatitis; AR, allergic rhinitis; FA, food allergy.

Table 1. Asthma phenotypes

Groups#	Age of onset	Atopy	Airways obstruction	Sputum Eos	FeNO	Respond to steroid/anti-IgE	Obesity	Sex more prevalent
1	Early onset	Yes	Reversible	Increased	Increased	Yes/yes	No	No
2	Late onset	No	Irreversible	Normal	Normal	No/no	Yes	Female
3	Early onset	Yes	Reversible	Increased	Increased	Yes/yes	No	No
4	Early onset	No	Irreversible	Normal	Normal	Yes/yes	No	No
5	Late onset	Yes	Reversible	Increased	Increased	Yes/yes	No	Male

- (2) Group 2: Obese, noneosinophilic asthma affecting mainly female sex
- (3) Group 3: Benign asthma characterized by easy to control symptoms considered benign
- (4) Group 4: Early symptom-predominant asthma characterized by frequent symptoms, association with chronic obstructive pulmonary disease and frequent overtreatment
- (5) Group 5: Inflammation-predominant asthma characterized by frequent undertreatment

Childhood asthma can be further classified into four clusters based on serum IgE level, environmental allergen sensitization, comorbidities, asthma severity and demographic characteristics [28]:

- (1) Cluster 1 was monosensitized to house dust mite and has mild asthma
- (2) Cluster 2 had pollen sensitization and severe asthma exacerbations
- (3) Cluster 3 had multiple sensitizations, eczema, moderate to severe asthma, obstruction of smaller airways and high FeNo
- (4) Cluster 4 had multiple sensitizations and mild asthma

These different asthma types may have different response to biologics where patients with IgE sensitization may be more responsive to anti-IgE and anti-interleukin (IL)-4/IL-13 biologics and those high eosinophils with low IgE sensitization burden maybe more responsive to anti-IL-5 biologics [29].

Rhinitis has also been divided into three large groups reviewed in PRACTALL EAACI document (Table 2) [30]:

Group 1: Allergic rhinitis characterized by early onset (< 20 year), frequent acute exacerbations and atopy

More recently, Kurukulaaratchy *et al.* [31] described four subphenotypes of allergic rhinitis based on a cluster analysis of young adults with rhinitis: moderate childhood-onset rhinitis, mild adolescent-onset female rhinitis, severe earliest-onset rhinitis with asthma and moderate childhood-onset male rhinitis with asthma.

Group 2: Local allergic rhinitis is similar to allergic rhinitis but allergies demonstrable only locally but not systemically (peripheral blood or skin)

Group 3: Nonallergic infectious chronic rhinosinusitis is large heterogeneous group of conditions characterized by association with chronic symptoms of obstruction, hypo or anosmia, facial pain and headache. Some examples are (idiopathic rhinitis/vasomotor rhinitis, gustatory rhinitis, chronic rhino-sinusitis with nasal polyps (CRSwNP), atrophic rhinitis, chronic infectious rhino-sinusitis, gustatory rhinitis, rhinitis of pregnancy and aspirin exacerbated respiratory disease)

Groups 2 and 3 represent challenging entity either diagnostically or therapeutically and often require a collaborative team approach with ENT.

Similarly, atopic dermatitis has been described in four major groups (Table 3) [18²²,32]:

- (1) Group 1: Infantile atopic dermatitis if chronic high risk of developing several atopic comorbidities (atopic march).

Table 2. Allergic rhinitis phenotypes

#	Age of onset	Specific-IgE	Apnea	Eos in smear>10	Acute symptoms	Respond to steroid/anti-IgE	Obesity	Sex more prevalent
1	<20 Year	Yes	Yes	Yes	Frequent	Yes/yes	No	No
2	<20 Year	No	Yes	Yes	Frequent	Yes/yes	No	No
3	>20 Year	No	No	No	No	No	No	No

Table 3. Atopic dermatitis phenotypes

#	Age of onset	Atopy	Acute lesions	Locations of lesions	Spontaneous resolution	Chronic	Atopic comorbidities	Female
1	3 months–2 years	Yes	Yes	Cheeks, scalp, neck, extensor limb-surface, trunk, diaper area sparing	60–80%	20–40%	Yes (atopic march) if chronic	No
2	2–20 years	Yes	No	Flexural limb-surface, facial periorificial areas, hands, wrists	No	Yes	Yes	No
3	>12–60	No	No	On head, neck, periorbital and flexural areas, hands	No	Yes	No	Yes
4	>60 years	No	Yes	Flexural-sparing lesions	No	Yes	No	No

- (2) Group 2: Childhood atopic dermatitis associated with xerosis and high risk of chronic disease
- (3) Group 3: Atopic dermatitis in adolescents and adults is a mild form of characterized chronic lesion, most common in women.
- (4) Group 4: Atopic dermatitis in the elderly is a severe rare form characterized by extensive highly pruritic lesions and is associated with high IgE

In terms of atopy prevention, children with infantile atopic dermatitis and allergy sensitization represent a very important group of patients, which would be the ideal target for prevention. The subgroup that has chronic diseases and IgE sensitization

is believed to have an epithelial barrier defect, which could induce a self-sustained chronic disease due to a secondary allergenic sensitization and therefore explaining the transition from atopic dermatitis to allergic asthma in the atopic march (Fig. 2). [33]. Environmental prevention, barrier restoring strategies maybe effective not only to control atopic dermatitis, but also to prevent atopic march in this group [33].

Food allergy can also be divided into two major groups: acute immediate reactions or delayed chronic reactions.

Acute food allergy: Food-induced anaphylaxis is the most common and potentially life-threatening acute food allergy. It is characterized by IgE sensitization to food, a history of acute reaction after

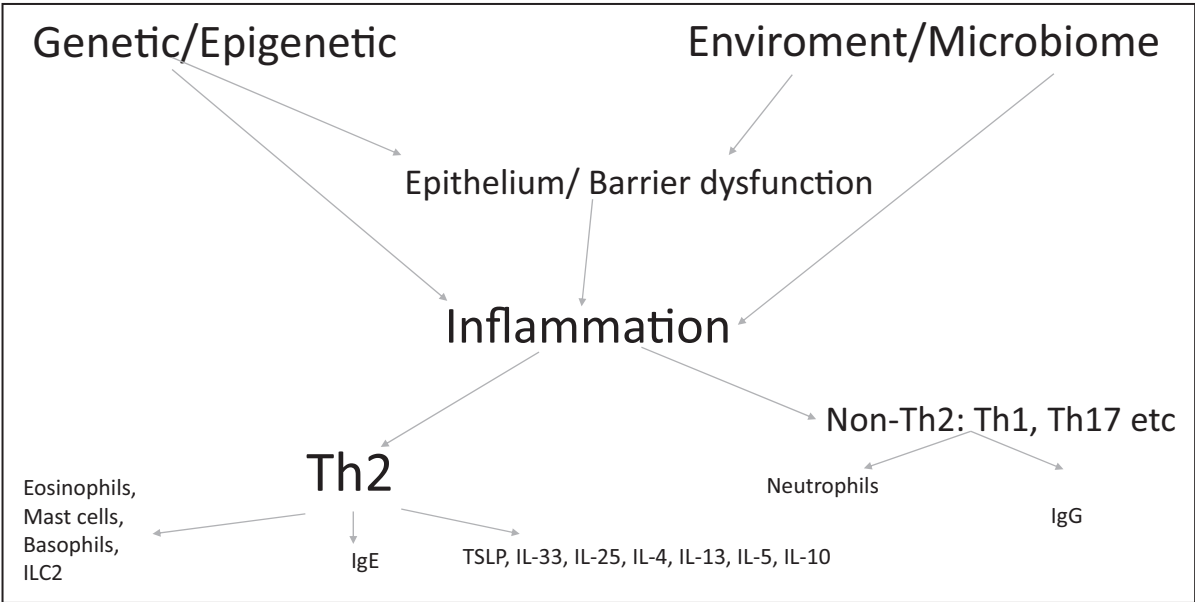


FIGURE 2. Scheme of pathogenesis of atopic disease: Th2 and Th2 endotypes. The pathogenesis of atopic diseases is due to an immunological and epithelial dysfunction. The inflammation that results is most often a Th2-type one; however, there is a less defined and difficult to treat subgroup of atopic diseases characterized by Th1-type inflammation. IgE, immunoglobulin E; IgG, immunoglobulin G; IL, interleukin; ILC2, innate lymphocyte cells type 2; Th1, T helper lymphocytes type 1; TH2, T helper lymphocytes type 2; TSLP, thymic stromal lymphopoietin.

Table 4. Phenotypes of food allergies

Type of food allergens	Animal or vegetable, baked food tolerance (for milk and egg), food matrix, molecular determinants of the allergen
Route of administration	Oral less allergenic than inhaled
Number of sensitizations	High number more allergic than single
History of allergic reaction	threshold levels, early or late onset, mild vs. severe reactions, spontaneous resolution vs. persistence, cofactor needed for reactions
Dermographics	Sex, age and ethnicity
Allergic comorbidities:	Asthma, eosinophilic esophagitis, allergic rhinitis, atopic dermatitis, immunodeficiency and post liver transplant
Cofactors to induce reactions:	Exercise, sleep deprivation, drugs (i.e. NSAIDs), infections and stress

ingesting the food that a patient is sensitized to. Severity of previous reaction does not correlate with severity of subsequent reactions [34]. Among patients allergic to food, some tend to outgrow food allergies especially to milk and egg, others have long-lasting diseases especially for peanuts, nut and shell fish. The ability to outgrow food allergy to milk and egg is clinically correlated with the ability to tolerate baked milk and egg. Precision medicine is based on many factors linked to host or food allergens (Tables 4 and 5) [35^{***}].

EoE is the most common chronic food allergy with significant morbidity because of symptoms, such as food impaction, vomiting and dysphagia, and carries the risk of irreversible esophageal fibrosis [36]. EoE is characterized by different types of clinical manifestations [37^{***},38]:

- (1) Group 1: Mild form responsive to all forms of treatment, including proton pump inhibitors (this type in the past was known as Proton Pump Inhibitor responsive Eosinophilic Esophagitis)

Table 5. Molecular characterization of food allergens and clinical significance

Allergen name	Allergen=Common name	Clinical relevance
Hazelnut (<i>Corilus avellana</i>)		
Cor a 1	PR-10 (Bet v 1 homologous)	
Cor a 2	Profilin	
Cor a 8	PR-14 (LPT) 9	
Cor a 9	Globulin (11S)	
Cor a 11	Vicilin (7S)	
Peanut (<i>Arachis hypogea</i>)		
Ara h 1	Seed storage proteins	Heat stable
Ara h 2	Seed storage proteins	Heat stable, associated with severe
Ara h 3	Seed storage proteins	
Ara h 4	Seed storage proteins	
Ara h 5	Profilin (Bet v 2-like)	cross-reactive other plant little clinical relevance
Ara h 6	Seed storage proteins	Homology with Ara h 2. Allergy persists
Ara h 7	Seed storage proteins	
Ara h 8	Bet v 1 family (PR-1 O, Bet v 1-like)	Responsible for cross-reactivity with birch pollen analogs
Ara h 9	LTP	Low prevalence of recognition in United States and North Europe more common in south Europe
Ara h 10	Oleolin plant lipid storage bodies	
Ara h 11	Oleolin plant lipid storage bodies	

- (2) Group 2: A more severe form largely unresponsive to PPI monotherapy but responsive to food antigen elimination (dietary treatments) or swallowed steroids (classic EoE)
- (3) Group 3: A form characterized by severe fibrosis, largely unresponsive to PPI, swallowed steroids and diet, difficult to control (fibrostenotic EoE)

ENDOTYPES

Phenotypes, despite being useful in characterization of the disease frequently overlap, are subject to change over time and do not necessarily give insights into the underlying pathogenetic mechanisms [21,22]. Thus, defining the endotypes based on key pathogenetic mechanisms has become a rational development, especially since therapy that targets specific immunological pathways is being developed at a rapid pace [39,40].

At present, two main subtypes of immune responses driving the allergic disease (endotypes) have been defined: characterized by high-level T helper 2 type (Th2) inflammation (Th2 high) and low level of Th2 inflammation (Th2 low) [41–43] (Fig. 3). Th2 high is the most common type of inflammation in allergic diseases, the current available drug work and biologics are best at treating this endotype: Th2-low endotypes have a similar disease

phenotype but a less clear pathogenetic mechanism and less clear path to treatment [18²²,40] (Fig. 2).

TH2-HIGH ENDOTYPES

The most common type of inflammation in atopic diseases is a Th2 type of inflammation (Th2 high), in which T cells recognize an antigen, mount a Th2 effector response characterized by IL-4, IL-13 and IL-5 production, and induce B cells to produce IgE class antibodies against that specific antigen (Fig. 2). IgE specific to certain antigens binds on IgE high affinity receptors on mast cells and basophils, and in the presence of the antigen, induces crosslinking of two receptors and activation of mast cells and basophils with the release of many mediators, such as histamines, leukotriens that initiate acute reactions [34]. Asymptomatic IgE sensitization to one or more allergens is very common [1,44].

In chronic atopic diseases, such as asthma, atopic dermatitis and EoE, genetically predisposed individuals have a dysfunctional epithelial barrier that tend to produce increased expression of pro-Th2 inflammatory cytokines, such as thymic stromal lymphopoietin (TSLP) or IL-33 that induce inflammatory cells to produce multiple cytokines and profibrotic factors that further disrupt epithelial layers leading to tissue damage, tissue remodeling

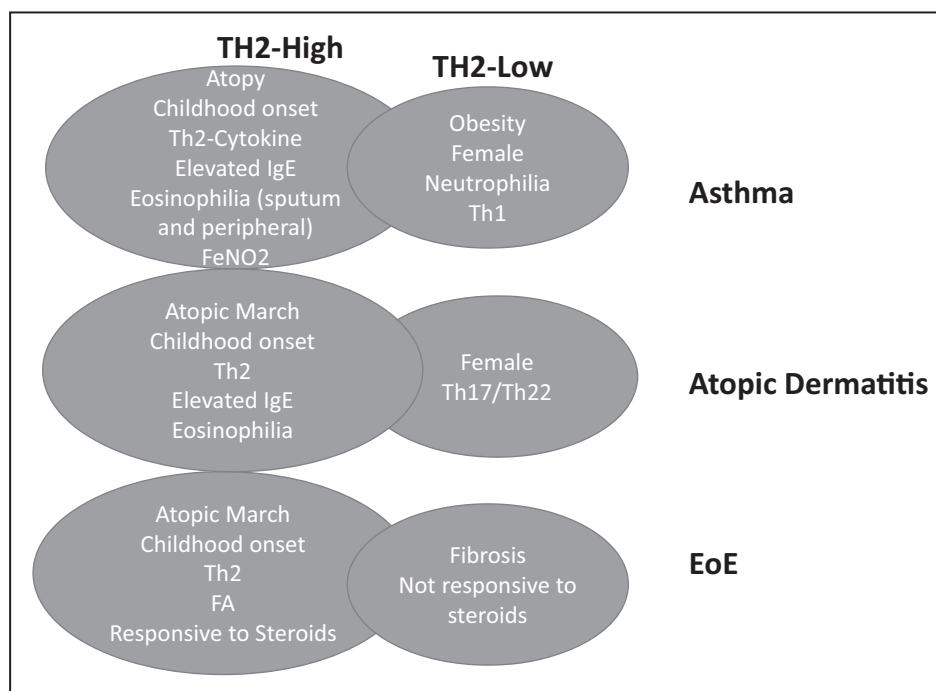


FIGURE 3. Th2-high and Th2-low endotypes for atopic diseases. The Th2-high and Th2-low endotypes of some common atopic diseases, such as asthma, atopic dermatitis and eosinophilic esophagitis, have been reported to specific phenotypes. EoE, eosinophilic esophagitis; IgE, immunoglobulin E; IgG, immunoglobulin G; Th1, T helper lymphocytes type 1; Th17, T helper lymphocytes type 17; Th2, T helper lymphocytes type 2.

and fibrosis with consequent end organ damage and loss of function [45] (Fig. 2).

Even if not applied in clinical practice, many parameters are used in research to distinguish Th2-high and Th2-low endotypes: IgE, IL-5, IL-4/IL-13, chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2), TSLP [19²²].

As we learn more about endotypes, it is clear that dynamic complex endotypes (e.g. the complex type 2 endotype) are common and consist of several subendotypes coexisting [46]. Such complexity deserves further characterization in prospective clinical studies to further advance personalized medicine.

For example, blood eosinophilia and serum IgE are common in all Th2-high endotypes [47,48], but we know that eosinophils and IgE are not the key cells in many atopic diseases characterized by Th2-high endotype. Indeed, anti-IL-5 antibodies are able to block IL-5 and eosinophilia and have been shown to benefit eosinophilic asthma [49]; however, they also have been shown to have limited or no effects on other atopic diseases characterized by eosinophilia, such as CRSwNP [50], atopic dermatitis [51] or EoE [52,53]. These data suggest that eosinophils are associated with Th2 inflammation, but are not essential in the development of all atopic diseases. Similarly, anti-IgE therapy (omalizumab) has been shown to be effective in allergic asthma [54], allergic rhinitis [30], but limited or no effects in CRSwNP [50] in atopic dermatitis [55] and EoE [56] despite all the diseases share high levels of IgE. Anti-IL4/IL-13 treatment that blocks more broadly the Th2 inflammation has been shown to be effective in the treatment of many atopic diseases suggesting that redundancy or lack of understanding of more specific endotypes may impair a more targeted treatment [57].

In asthma, analyses of peripheral blood and induced sputum cells have been used as noninvasive technique to infer and quantify inflammatory cell populations in the airways of asthmatic patients and define specific endotypes.

Asthma phenotypes defined based on the predominant inflammatory cell identified in induced sputum (eosinophilic, neutrophilic, mixed granulocytic and paucigranulocytic phenotypes) or in blood (eosinophilic asthma) are currently being used for a stratified approach to severe asthma [49,58,59, 60,61] (Fig. 3). Compared with the pauci-granulocytic phenotype, eosinophilic, neutrophilic and mixed granulocytic asthmatic patients exhibit poorer lung function [62], whereas severe asthma tends to correlate with increased neutrophil numbers rather than eosinophils in their airways (neutrophilic asthma), a phenomenon typically related

to nonallergic asthma and thought to be triggered by particulates in the air, pollution, viruses or bacteria [63].

Several biomarkers have been linked to the Th2-high endotype in asthma: total and specific serum IgE, serum periostin and dipeptidyl peptidase 4, blood and sputum eosinophils, and FeNO [19²²]. Hierarchic clustering analyses of bronchial and nasal epithelial cells separated the Th2-high changes in genes expression and transcriptome of PERIOSTIN, CLCA1, SERPINB, IL-13 and IL-5 [41,64,65]. The Th2-high endotype may predict those who would benefit from the treatment specifically targeting type 2 pathways, for example dupilumab, yet these asthmatic patients are the ones more likely to be well controlled with standard inhaled corticosteroids treatment [66].

Similarly, blood eosinophilia and serum IgE predict therapeutic response to all currently available biologics in severe asthma (i.e. anti-IL-5, anti-IL-4/IL-13 anti-IgE targeted treatment and CRTH2 antagonists) [47,48]. Likewise, omalizumab is efficacious only in patients with high IgE with proven sensitization to perennial environmental allergy. These data point to the complexity of the Th2 high endotype.

Activation by nonallergenic stimuli of Th2-type cytokines, such as ILC2 and iNKT cells, may be one of the reasons of such complexity in the Th2 endotypes.

The classic (80%) extrinsic atopic dermatitis phenotype is characterized by a Th2-high endotype with high IgE levels, eosinophilia, personal and family atopic background, and greater rate of filaggrin (FLG) mutation. However, atopic dermatitis is also characterized by a highly diverse inflammatory repertoire (TH1/TH2/TH17/TH22 immune activation) with a compromised epidermal barrier. The initiation of acute lesions is accompanied by TH2 and TH22 cytokine upregulation, with positive correlations between IL22 mRNA levels and atopic dermatitis severity determined based on SCORAD scores. Lesser inductions of TH17 markers are also observed in acute lesions. With disease chronicity, there is intensification of TH2 and TH22 cytokine axes, with significant increases in TH1 markers in patients with chronic atopic dermatitis but no further increases in TH17 markers [19²²,67].

The atopic dermatitis Th2-high endotype is the one that responds best to anti-IL-4R treatment (Dupilumab). However, the complexity of inflammation in atopic dermatitis and the contribution of the barrier and Th17/Th1/Th22 to the pathogenesis may explain why in recent phase III dupilumab trials (SOLO 1 and 2), the outcome of Investigator's Global Assessment score reduction to 0 or 1 occurred only in 36–38% of patients with atopic dermatitis.

Food allergy has very limited useful biomarker.

For acute reaction to food, the presence of specific IgE to foods is not necessarily associated with clinical reactivity and their level cannot predict the severity of the reactions [68]. Various integrated scales combining different available diagnostics (history of previous systemic reaction, food-specific IgE levels and lung function BAT test) have been shown to be more reliable than single testing in predicting the severity of reaction, with patients having history of systemic food allergy reactions, asthma and high IgE being the ones more at risk of severe reactions [69–72]. However, those tools have still limited sensitivity and specificity and applicability in real-life food allergy reactions [69–72].

For chronic food allergy, EoE is defined by measuring eosinophil infiltration in the esophagus. Now, three different endotypes have been described: EoE1 atopic background; EoE2 with the highest expression of Th2 cytokines. EoE3 was associated with the lowest expression of epithelial differentiation genes and Th2 signal. Current treatment and research have not focused on EoE endotypes yet. As biologics becomes available to study EoE, stratification of pathogenesis and new targets will be developed.

TH2-LOW ENDOTYPE

Even more complex and less understood is the pathogenesis of all the atopic disease driven by a low T2 inflammatory process.

Low T2 asthma is defined by the absence of biomarkers of T2-high asthma with neutrophils and neutrophil-derived molecules, such as myeloperoxidase and elastase in the sputum being biomarkers of this phenotype [66,73,74]. Neutrophilic asthma has been associated with persistent bacterial inflammation, occupational exposures, smoking, viral infections and consequent IL-8 and/or IL-17-mediated or Th1 inflammation [75–83].

Experimental data coming from animal models show that IL-8 may be responsible for the steroid-resistant neutrophilic airway inflammation as it functions through a steroid insensitive NF- κ B-dependent pathway [84]. However, anti-IL-17 antibodies, such as brodalumab and secukinumab, have been tried in inadequately controlled moderate to severe asthma and ozone-induced airway neutrophilia failing to show the clinical efficacy, despite promising data in mouse casting doubts on the role of IL-17 in this disease [85–87]. Similarly, tumor necrosis factor- α (TNF- α), a proinflammatory cytokine important for Th1 and Th17 inflammation, is elevated in the serum and sputum in patients with severe neutrophilic asthma, but the enthusiasm about the role of TNF- α as a biomarker in severe

asthma has gradually faded, after the disappointing results of clinical studies with TNF- α inhibitors [88–91].

Because asthma is a heterogeneous disease with clinical subphenotypes, prespecified subgroup analyses may be needed to truly understand the efficacy of specific biologics in specific subgroup. For example, in the brodalumab asthma studies, a specific analysis of different phenotypic subgroups assessed showed that clinical response (measured by Asthma Control Questionnaire) was observed in patients with high bronchodilator reversibility [86], and IL-17A has been reported to directly act on airway smooth muscle to induce increased contractility in response to bronchospasm-inducing agents (e.g. carbachol) [92].

Another explanation why these targeted therapies may not be effective in Th2-low inflammation could be that multiple non-Th2 pathways may be activated at any given time. For example, Th2-low endotype has been associated with inflammasome signatures, such interferon- γ (IFN- γ), IL-1R, IL-1 and IL-18R family members, NLRP1, NLRP3 and NLRC4 [93].

IL-1 signaling can directly impact three aspects of an airway inflammatory response: granulocyte (neutrophil/eosinophil) recruitment; nonspecific and allergen-specific airway reactivity; and mucin production [94,95]. Anakinra recombinant form of human IL-1 receptor antagonist (IL-1RA) and numerous IL-1 blocking agents are food and drug administration-approved for conditions, where the IL-1 β pathway predominates disease pathophysiology (i.e. systemic juvenile idiopathic arthritis and the cryopyrin-associated periodic syndromes), and are currently being investigated for their efficacy in asthma (<https://clinicaltrials.gov/ct2/show/NCT03513458>).

It is estimated that intrinsic T2-low atopic dermatitis accounts for 20% of patients. It affects more commonly to women, with delayed onset and preserved barrier function, as measured based on trans-epidermal water loss and normal FLG levels, but is associated with metal contact hypersensitivity [96–98].

The intrinsic endotype has increased TH1 signal (IFN- γ , CXCL9, CXCL10 and MX-1), more pronounced TH17/TH22 activation (IL-17A, CCL20, Elafin and IL-22) and levels of the antimicrobials S100A9 and S100A12, which are coregulated by IL-17/IL-22 [99–101]. The aforementioned characteristics are more similar to psoriasis than atopic diseases [99]. Several biologics effective on the Th1/Th17/Th22 pathways have been tried with various successes that may help to understand better the pathogenesis of intrinsic atopic dermatitis.

Ustekinumab (ClinicalTrials.gov: NCT01806662) that targets the IL-12/IL-23 common subunit p40 [102] showed a limited effect, but fezakinumab/ILV-094 (NCT01941537) that antagonizes IL-22 was shown to be effective at improving atopic dermatitis severity, particularly in patients with severe less fluctuating disease with high baseline IL-22 expression [103–105]. Biologics against Th17 inflammation, such as Secukinumab/Cosentyx (anti-IL-17A in phase II NCT02594098) and MOR106 (anti IL-17C in phase II-NCT03568071), are under investigation to treat intrinsic atopic dermatitis [18^{***}].

EoE like disease, with similar symptom presentation, strong familial aggregation but absence of eosinophilic infiltration and relatively low Th2 inflammation, has been described in a limited number of patients with unknown pathogenesis and unclear differences in the response to therapy [106]. The fibrostenotic endotype (EoEe3) recently described may have low T2 inflammation and limited response to steroids [37^{***}].

CONCLUSION

Classification of atopic patients based on molecular endotypes in addition to traditional clinical parameters will be needed to guide personalized interventions and improve outcomes. To achieve such a goal, molecular endotyping and biomarker need to be validated in well-characterized populations with sufficient sample power identification, and if associated with more complex analysis using transcriptomic and whole gene analysis. Recently, a European sponsored, multicenter project, MeDALL, tried to overcome such obstacles by reinforcing established collaborations among European birth cohorts and by creating a new central database. Such research approach, for example, leads to establish that monosensitization and polysensitization represent two different phenotypes of IgE-associated diseases with polysensitized representing a group with high level of comorbidities of all atopic diseases, high level of total IgE, frequent symptomatic sensitization, severe spectrum of diseases, early onset, persistence to adulthood and high level of IL-4 [2^{*}]. More data will be available as the project advance.

Precise phenotypes and endotypes can also be used to explain the development of asthma and allergies using an exposomic approach, where specific exposure at key moment of lifetime may lead to a different phenotype. This information may need to be integrated in the current knowledge of atopic disease to have a truly personalized medical approach [107,108^{***}].

Connecting science with the transformation of care and identifying priorities and needs are essential to ensure a better management of asthma and allergic diseases in the advent of big data and precision medicine together with global access to innovative and affordable diagnostics and therapeutics [109].

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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