Asthma phenotypes and IgE responses

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ABSTRACT The discovery of IgE represented a major breakthrough in allergy and asthma research, whereas the clinical interest given to IgE in asthma has been blurred until the arrival of anti-IgE biotherapy. Novel facets of the complex link between IgE and asthma have been highlighted by the effect of this treatment and by basic research. In parallel, asthma phenotyping recently evolved to the concept of endotypes, relying on identified/suspected pathobiological mechanisms to phenotype patients, but has not yet clearly positioned IgE among biomarkers of asthma.

In this review, we first summarise recent knowledge about the regulation of IgE production and its main receptor, FcεRI. In addition to allergens acting as classical IgE inducers, viral infections as well as air pollution may trigger the IgE pathway, notably resetting the threshold of IgE sensitivity by regulating FcεRI expression. We then analyse the place of IgE in different asthma endo/phenotypes and discuss the potential interest of IgE among biomarkers in asthma.

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We summarise regulation of IgE production, and discuss IgE in different asthma endo/phenotypes and among biomarkers http://ow.ly/TLxcW

Received: Oct 03 2014 | Accepted after revision: Oct 14 2015

Support statement: A. Froidure is funded by the Fondation Saint-Luc, Cliniques Universitaires Saint-Luc and Fondation de Vooght, Université catholique de Louvain, Belgium. C. Pilette is postdoctoral specialist of the Fonds National pour la Recherche Scientifique (FNRS 1.R.016.14), Belgium, and of the institute for Walloon Excellence in Lifesciences and Biotechnology (WELBIO CR-2012S-05).

Conflict of interest: None declared.

Introduction

Identified in 1966 as the transferable serum factor mediating the Prausnitz and Küstner reaction, *i.e.* immediate hypersensitivity, and despite the fact that it was strongly linked to asthma in epidemiological studies, IgE was given progressively less attention in asthma until the arrival of anti-IgE therapy [1]. This was partly due to a lack of evidence discriminating asthma pathobiology based on allergic phenotypes [2, 3]. In parallel, disease phenotyping has emerged in asthma as a prerequisite in severe disease to identify relevant targets for innovative therapy. Such approaches might also help in predicting future risks and potentially improve daily management. Interestingly, these two aspects merged around IgE, which has been revisited as a relevant target in patients with severe allergic asthma and prone to exacerbations [1].

Attempts to categorise, or "phenotype", asthma referred initially to a single factor-based classification. The classification by Sir Rackemann was the first, distinguishing between "extrinsic asthma", usually starting in early life and initiated through the reactivity against environmental antigens, and "intrinsic" asthma, developing later on (typically after the age of 30 years) and triggered by yet unidentified factors. This initial clinical phenotyping thus encompassed the concept of allergy and atopy, the latter defined as a genetic susceptibility to produce IgE antibodies against nonpathogenic environmental antigens, so-called allergens. Several other clinical phenotypes were subsequently described and co-existing conditions have been integrated, such as obesity [4].

A recent "clusters" analysis from the Severe Asthma Registry Program (SARP) led to the description of four different clusters based on both sputum inflammatory cells and clinical characteristics [5]. The analysis reports two clusters characterised by early-onset mild-to-moderate asthmatics with no or elevated eosinophils with fairly good asthma control and near-to-normal lung function after bronchodilation. The other two clusters were characterised by a more complex distribution of granulocytic cells, inflammation mostly dominated by neutrophils (>40%) or an increase in both neutrophils (>40%) and eosinophils (>2%) (mixed-granulocytic phenotype). In those groups, high doses of inhaled corticosteroids are usually required to control disease, whereas oral systemic corticosteroid therapy is more frequently needed in the mixed-granulocytic cluster. The latter, the smallest group, is characterised by a lower lung function and more frequent hospitalisations despite the use of additional controllers. Surprisingly, atopy was present at a similar frequency in all the four groups; this put IgE not at the centre of the phenotype, but as an additional target for therapy. (This seems particularly true for patients with neutrophilic asthma, associated or not with high sputum eosinophilia.) In a study comparing SARP and homemade clusters in a cohort of severe asthma patients, Bourdin *et al.* [6] showed that cluster analysis was unable to predict future outcomes (*e.g.* exacerbations), possibly due to important individual variability. This emphasises the need to include prospective data in cluster algorithms, and long-term follow-up is required to ascertain the validity and stability of an initial cluster class.

"Endotypes" were recently described, aiming at defining asthma entities according to identified or suspected mechanisms associated with and putatively leading to the disease. They include parameters such as clinical characteristics, biomarkers, genetics, histopathology, lung physiology and response to therapy [7]. Allergic (or atopic) asthma probably represents the most frequent endotype. However, as detailed below, the relevance of allergen sensitisation in the clinical expression of asthma remains blurred by several factors.

In this review, we will focus on recent knowledge about environmental triggers for IgE production and the role of IgE in asthma, including its potential use as a biomarker in some phenotypes of the disease.

Role of IgE and its receptors

IgE is the hallmark of type 1 hypersensitivity, but mechanisms regulating IgE production remain poorly understood [8] (figure 1). IgE synthesis is thought to occur through different biosynthetic pathways, either by "direct" class-switch recombination (CSR) from IgM, in germinal centre B-cells, or through "sequential" switch from IgM to IgG1 and then from IgG1 to IgE, which may occur outside of germinal centres. Although it is thought that IgE memory (of allergens) originally sits in IgG, it was shown that (human) blood or tonsil B-cells may undergo CSR to IgE upon CD40 ligation and activation by interleukin (IL)-4 or IL-13, produced by T-helper (Th) 2 cells, as well as also by the recently described type 2 innate lymphoid cells (ILC2) formerly referred to as "nuocytes" or "natural helper cells" [9–11]. These cells have similar morphological properties in common with lymphocytes, but lack the B- or T- cell receptor and lineage cell surface markers. This group of ILCs is characterised by the production of IL-5, IL-9 and IL-13 upon stimulation by IL-33, or by a combination of IL-2 and IL-25 [12–14]. IL-33 and IL-25 serve as alarmins in response to tissue injury or in the recognition of pattern recognition receptors by the epithelium. The recently described type 3 ILCs, however, have been reported to produce significant amounts of Th-17-like cytokines, *i.e.* IL-17 and IL-22. ILC3s appear to have a predominant role in the defence against fungal infection in mice [15] and against bacteria through IL-22 [16].

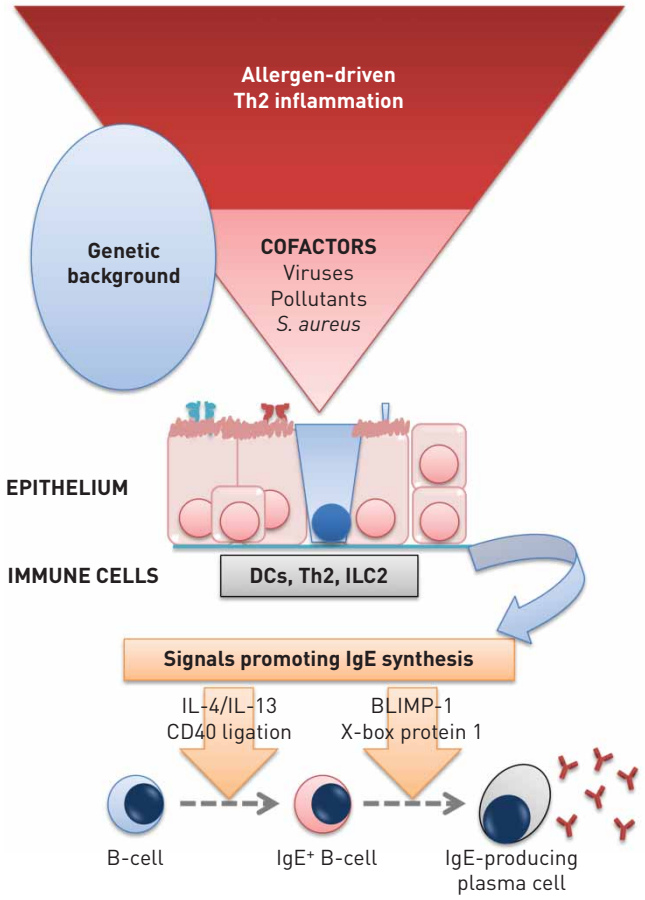

FIGURE 1 Potential factors promoting IgE production in asthma. Although allergens are the main trigger for allergic inflammation, environmental factors, including viruses and pollutants, act as cofactors through epithelium activation and allergen modification. Gene polymorphisms underlying atopy act concomitantly. The recruitment of immune cells involved in allergic inflammation, including dendritic cells (DCs), T-cells and B-cells, is orchestrated by the activated epithelium. Interleukin (IL)-4 and IL-13, the mandatory cytokines for class-switch recombination to IgE, are produced by T-helper (Th) 2 cells but also type 2 innate lymphoid cells (ILC2s). *S. aureus*: *Staphylococcus aureus*; BLIMP-1: B-cell maturation protein 1.

In situ, studies of the nasal mucosa showed that IgE^+ B-cell expansion dramatically increases upon allergen challenge, with a rate of IgE synthesis of ~3.6 million molecules·day^{-1}·mm^{-2}, mainly from IgG switching. The turnover is about half of the total synthesis, which is sufficient for the maintenance of local IgE reactivity, with the vast majority of IgE deriving from short-lived plasma cells. B-cells differentiate into IgE-secreting plasma cells under the influence of two transcription factors, *i.e.* BLIMP-1 (B-cell maturation protein 1) and X-box protein 1 [17]. A small fraction of long-lived IgE plasma cells is located in the bone marrow and could also provide sustained serum IgE. Of interest, it has been observed recently that epigenetic alterations (methylation) occurring in eosinophils contribute 13% of the level of serum IgE [18], suggesting a link between eosinophils and IgE production that will be discussed further below.

The high-affinity receptor for IgE, *i.e.* FcεRI, is constitutively expressed on mast cells and basophils as a tetramer ($\alpha\beta\gamma_2$) (figure 2). Following receptor cross-linking, a cascade of intracellular events drives Lyn kinase to phosphorylate immunoreceptor tyrosine-based activation motifs on β and γ subunits, leading to Syk activation [18], which has a pivotal role in cell activation and degranulation. FcεRI is also expressed on monocytes and dendritic cells (DCs) in a trimeric form ($\alpha\gamma_2$). The absence of a β subunit allows internalisation of the receptor following binding. This pathway underlies facilitated antigen presentation, where IgE focuses the allergen on the cell surface through FcεRI. Upon internalisation, the antigen–IgE receptor complex is processed and finally presented through major histocompatibility complex (MHC) class II molecules, lowering the threshold for T-cell activation [19, 20] and skewing the polarisation towards Th2 [21]. It was demonstrated that trimeric FcεRI also contributes to clearance of serum IgE, as antigen–IgE complexes are internalised and transferred to lysosomes where they are degraded [22].

DOI: 10.1183/13993003.01824-2014

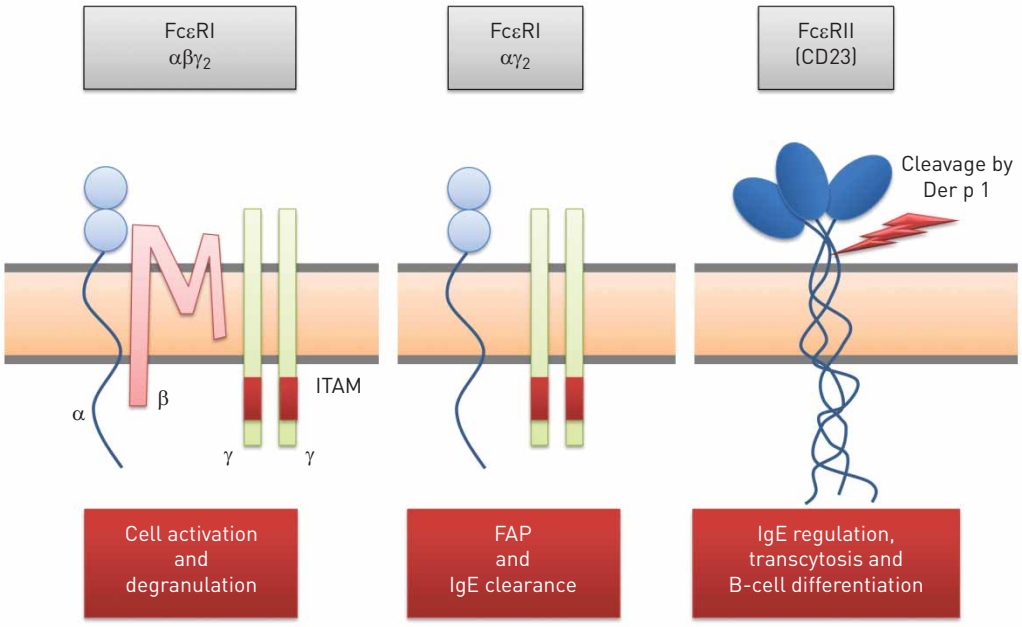

FIGURE 2 IgE receptors and their respective downstream signalling. The tetrameric FcεRI is responsible for the IgE-driven basophil and mast cell degranulation upon allergen exposure, while the trimeric form, lacking the β chain, mediates IgE-driven facilitated allergen presentation (FAP) by dendritic cells and B-cells, as well as the clearance of IgE. FcεRII (CD23) represents a low-affinity IgE receptor, regulating IgE synthesis and B-cell differentiation, as well as IgE transport across epithelial cells, which can be cleaved by the proteolytic activity of Der p 1. ITAM: immunoreceptor tyrosine-based activation motif.

In addition, cell-surface FcεRI expression is directly correlated with IgE serum load [23, 24], as IgE binding to the receptor allows its persistence at the cell surface.

FcεRII (CD23) is known as the low-affinity receptor for IgE. It is expressed mainly on B-cells, and regulates IgE production as well as B-cell differentiation, antigen presentation through CD23–MHC II [18, 25] and interactions with epithelial cells [26]. IgE only binds CD23 when complexed to an allergen by formation of a trimolecular complex. In addition, IgE can bind to other receptors, such as galectin-3 and FcγRIII. Whereas IgE-FcγRIII ligation on DCs has been shown in mice to promote Th2 responses through inhibition of IL-12 production [27], the role of these alternate receptors for IgE responses in human asthma remains unknown.

Environmental triggers of IgE responses in asthma

Allergens

Allergens are environmental antigens able to induce the production of specific IgE antibodies. The link between allergic sensitisation (atopy) and asthma has long been observed [28–30], but whether a sensitised individual will become clinically symptomatic upon allergen exposure relies on several factors, such as the

TABLE 1 Relation between IgE responses and asthma; potential links between IgE production and asthma inception, and relevance for response to anti-IgE therapy

	IgE responses	Asthma-related features		
		Mechanisms	Asthma risk (OR)	Relevance for therapy
Allergens	Allergen-specific IgE	Mast cell degranulation	2–10	Anti-IgE; allergen immunotherapy
Viruses	Virus-specific IgE?	Induction of FcεRI expression	~10[#]	Anti-IgE
Bacteria	Superantigen-specific IgE	Polyclonal B- and T-cell activation	~2	Anti-IgE?

[#]: severe lower respiratory tract infections, during early childhood.

type of allergen, the dose, the route as well as the subject's airway reactivity at a given time. IgE sensitisation to house dust mite (HDM), affects up to 25–30% of the worldwide population and represents a major risk factor for asthma [28] (table 1). In contrast, the presence of IgE to pollens, although strongly associated with allergic rhinitis, is not a clear risk factor for chronic asthma and the asthma risk associated with IgE sensitisation to cat allergen is strongly modulated by cofactors (including the level of IgG4).

Although common characteristics of allergens have been identified (the vast majority are proteins or glycoproteins <70 kDa), there is no structural feature that can discriminate allergens from nonallergenic antigens [31]. Some authors speculated that allergenic potency could be attributed to the fact that the majority of allergens have no bacterial homologues, unlike nonallergenic antigens in the same species [32]. However, this concept is challenged by the recent discovery of *Staphylococcus aureus*-specific IgE in patients with asthma associated with nasal polyposis [33]. The biological function of the allergen is probably an important factor determining the allergenicity, as well as its *asthma*genicity. For example, the major allergen Der p 1 is a member of the cysteine protease family able to cleave epithelial tight junction proteins, leading to its direct interaction with immune cells in subepithelial areas [31]. By cleaving CD23 (FcεRII) at the B-cell surface, Der p 1 also induces an increase in the level of soluble CD23. This will ultimately favour the recruitment of naive B-cells able to present antigen peptides to B-cells and consequently the production of antigen (allergen)-specific IgE.

Finally, Der p 1 may also bind and cleave DC-SIGN, a pro-Th1 and regulatory lectin-type molecule [31, 34]. Der p 2, the second major HDM allergen, is an analogue of the adapter protein MD-2 which facilitates lipopolysaccharide-mediated signalling through Toll-like receptor (TLR)-4 [35]. Moreover, it is becoming increasingly clear that proteolytic allergens are able to activate the release of epithelial-derived pro-Th2 cytokines, such as granulocyte-macrophage colony-stimulating factor, IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) [36–39]. Therefore, the tertiary structure of the antigen seems to partly determine its "allergenicity" and its ability to trigger pro-Th2 immunity or counterbalance Th1 pathways in the airway mucosa [40].

The role of allergen(s) exposure (dose, timing) in the inception of an allergic disease remains a matter of debate. It was initially considered that sensitisation occurs in a dose-dependent manner, at the least for HDM, which is thought to occur in a linear manner. In contrast, pet sensitisation seems to follow a bell-shaped relation with protective effects appearing at high-dose exposure. This difference is attributed to the aerodynamic properties of the carrier particles, which are highest for HDM (>10 μm) and confined in a dust reservoir in the absence of disturbance, and are largely airborne for pets allergens (<5 μm). These aerodynamic properties clearly affect the exposure of an individual, with exposure doses being much lower for HDM and thought to be unable to induce tolerance [41]. At the present time, no consensus has been reached regarding the age, dose and mechanism by which allergen exposure will induce sensitisation alone and/or associated clinical outcomes. Moreover, effects of allergen avoidance on clinical outcomes of asthma are variable and usually limited [42–44]. This observation suggests that allergen avoidance measures are insufficient to adequately reduce exposure levels or, alternatively, that a disease may evolve to become, at least to some extent, allergen-independent.

Viruses

The second major risk factor for asthma development is represented by severe viral respiratory infections during early childhood, particularly before the age of 3 years [45], with an odds ratio up to 10 for severe infections to rhinovirus (table 1). In addition to viral infection, IgE sensitisation to common allergens such as HDM could further increase the risk of asthma in some studies [46], but not in others [47]. It remains a matter of debate whether viral infections actually cause this increased risk or it reflects a common genetic susceptibility to both severe viral infections and asthma [48]. It is known that patients with asthma do not present with more colds than nonasthmatic controls [49, 50], but do present with more severe symptoms and a longer duration of illness. This has been observed in couples that include one asthmatic [51] and in experimental rhinoviral infection in human subjects [52]. In line with those observations, it was reported *in vitro* that asthmatic airway epithelial cells display a deficient innate immune response to rhinoviruses [53].

While immune responses to viruses are classically associated with Th1 polarisation, recent studies showed that certain viruses may induce Th2-type immunity. Park *et al.* [54] and Grayson *et al.* [55] showed that infection of mice with Sendai virus, a murine analogue of respiratory syncytial virus (RSV), causes acute bronchiolitis and leads, after resolution, to a persistent asthma-like pathology including mucous hyperplasia, eosinophilic inflammation and airway hyperresponsiveness (AHR). In this model, T-cell receptor-invariant natural killer T-cells, interacting with $CD1d^+$ antigen-presenting cells and IL-13-producing macrophages are probably important [56]. Under some circumstances, virus-specific $CD8^+$ T-cells are able to switch to IL-5-producing T-cells, leading to eosinophil recruitment, as shown *in vivo* [57]. These features are associated with induction of FcεRI on lung DCs, whereas $Fc\varepsilon RI^{-/-}$ mice were protected against Sendai

 DOI: 10.1183/13993003.01824-2014

virus-driven airway mucous cell metaplasia, eosinophilia and AHR [55]. Following FcεRI cross-linking, DCs secrete CCL28, a chemokine involved in the recruitment of $CD4^+$ Th2 cells, and for which the blockade prevented the development of asthma features. It was shown by Holt *et al.* [58] that FcεRI upregulation also occurs in human asthma upon viral infection, and co-localises to monocytes and DCs.

One crucial question is what is driving FcεRI cross-linking in this viral setting? One possibility is that viral antigens first activate the production of IgE to stabilise the surface expression of FcεRI, with concomitant or early subsequent exposure to common allergens (and putative cross-reactive antigens) ultimately inducing a sustained FcεRI activation. RSV-specific IgE antibodies have been found in murine experimental models [59], but not in fluids from infected children [60]. An important consequence of FcεRI activation during airway viral infection is that it may interfere with antiviral immunity, by inhibiting the TLR-9-mediated release of type 1 interferon (IFN) by plasmacytoid DCs as observed *in vivo* [61] and *in vitro* [62], thereby presumably increasing the duration and/or severity of viral-induced airway damage. Accordingly, deficient IFN responses have been reported in blood mononuclear cells [63] as well as in epithelial cells [53] from subjects with atopic asthma, although the latter was not observed in two other studies [64]. The remarkable decrease of seasonal viral exacerbations of asthma observed with anti-IgE treatment [65] is likely due to the associated rapid downregulation of IgE receptors on innate cells with a parallel reciprocal increase in antiviral type 1 IFN production. Another mechanism presumably involved in virus-induced IgE production is virus-driven TSLP production by the airway epithelium. TSLP is an IL-7-related peptide mainly acting on DCs, notably *via* the induction of the costimulatory molecule OX40 ligand (OX40-L), and triggering Th2 and Th9-related immunity [66, 67]. It was reported that RSV infection leads to TSLP expression in the airway epithelium from murine neonates, along with DC expression of OX40-L [68], as observed *in vitro* air/liquid interface bronchoepithelial cultures [69] where the TSLP receptor is also upregulated following infection [70]. Thus, respiratory viruses and IgE responses cross at several check-points of immune pathways leading to inception and/or exacerbations of asthma.

Air pollution

Several other environmental factors may increase the immune potential of allergens [59]; in particular, evidence for a role of pollution in the rise of asthma and allergy is accumulating [71]. Diesel exhaust particles (DEPs) are of particular interest as they are able to reach distal airways due to their small size (100 nm) and to enhance local IgE synthesis [72]. It was shown in mice that fine particles have a higher capacity to induce ovalbumin-specific IgE production as compared with coarse particles [73]. In addition, such pollutants could have an effect *in utero*, as mice exposed pre-natally to DEPs and challenged with ovalbumin after birth displayed increased production of specific IgE [74], which is mediated by natural killer cells producing IL-5, IL-13 and IL-17, as well as by oxidative stress. Moreover, DEPs have the ability to stimulate OX40-L expression on DCs through induction of TSLP, similarly to allergens [75]. Other pollutants such as ozone and nitrogen dioxide may also disrupt epithelial junctions, enhance airway inflammation [34], facilitate the release of allergen granules, and induce nitration of common allergens such as Bet v 1 of birch pollen [76], which subsequently displays increased allergenic capacity.

Predisposing inherited risk factors for asthma

The genetic background of an individual greatly affects their susceptibility to develop environmental sensitisation. Complex gene–environment interactions have been reported in several studies. Consistent with the role of TLR-2 in recognising many bacterial, fungal and viral substances, variants in the *TLR2* gene have been associated with sensitisation and asthma in children living on farms and in day-care attendance [77, 78]. The combination of high-dose allergen exposure along with specific bacteria during the first year of life has been shown to induce a protective effect against atopy and wheezing [79]. The genetic susceptibility to allergen-induced Th2 responses [80, 81] may also be explained partly by polymorphisms in the genes encoding IL-4, IL-4R, IL-13, TSLP and/or IL-33 [82–85]. Polymorphisms in the gene encoding ADAM (a disintegrin and metalloproteinase) 33 actually represent the most robust association not only with asthma and bronchial hyperreactivity, but also with immune-related traits of asthma such as the levels of total IgE and blood eosinophils [86, 87]. An association between total serum IgE and an FcεRIα polymorphism has also been observed; the relative importance of this latter polymorphism resides in the enhanced facilitated antigen presentation by antigen-presenting cells that favours Th2-skewed immunity [88]. Other candidates, such as STAT6 (signal transducer and activator of transcription 6), CTLA4 (cytotoxic T-lymphocyte antigen 4) and FcεRIβ concomitantly, are also reported to participate in the variability of total IgE [89, 90]. As a whole, from genome-wide association studies we learn that almost 100 genes/loci have been identified for asthma or atopic diseases, with actually no one identified as an "atopy gene". This reflects how complex the syndrome is, and that gene–gene and gene–environment interactions may affect the susceptibility of an individual to develop allergic disease and/or asthma. Hence, respiratory allergens should not be all considered as purely *innocuous* antigens, but as

biologically active proteins profoundly affecting mucosal tissues and triggering, in susceptible individuals, IgE-specific responses.

Relation between IgE responses and nonspecific bronchial hyperreactivity in asthma

In sensitised individuals, nonspecific bronchial hyperreactivity (NSBHR) contributes to the magnitude of the response induced by the allergen [91]. Furthermore, it was shown that early allergic response could be deduced from the level of NSBHR and the magnitude of allergic hypersensitivity (*i.e.* allergic skin test) [30]. However, in 2005, Langley *et al.* [92] demonstrated that the HDM allergen Der p 1 had the ability to lower PC_{20} (provocative dose causing a 20% fall in forced expiratory volume in 1 s (FEV_1)) (hence increasing NSBHR) and increase F_{eNO} (exhaled nitric oxide fraction) even in nonsensitised atopic subjects. A similar effect was observed for the dog allergen (Can f 1), but not for the cat allergen (Fel d 1). This property was linked to a protease activity (for Der p 1) and the potential presence of endotoxins along with allergens.

Finally, whether the presence of HDM-specific IgE in the sputum of nonallergic asthma, as demonstrated by our group [93], plays a role in NSBHR remains to be further explored.

Role of IgE responses in asthma according to the disease endo/phenotype (table 1)

Allergic asthma

Allergic (or *atopic*) asthma is characterised by the development of a persistent Th2-type inflammatory process triggered upon exposure to certain inhaled allergens [31], which in susceptible individuals activate the airway epithelium and DCs, leading to the synthesis of specific IgE antibodies. Re-exposure to the allergen can then cause FcεRI cross-linking on tissue mast cells, leading to degranulation and immediate bronchoconstriction, as well as subsequent recruitment of eosinophils and late-phase inflammatory response [94]. The presence of specific IgE in the serum is a key feature of this phenotype, as evidenced by serology or, alternatively, by skin-prick testing which provides evidence of *in vivo* (skin) mast cell reactivity. Blood eosinophils are usually moderately elevated (400–1000 μL^{-1}) and other atopy-related disorders, *i.e.* allergic rhinitis (~50–90%) and atopic dermatitis (~40%), are frequently associated [38]. The atopic phenotype *per se* is genetically determined, in particular by single nucleotide polymorphisms at Th2 genes and 17q12 loci. Whereas total IgE values largely overlap between atopic and nonatopic subjects, serum IgE closely correlates with the risk of asthma [28] and with AHR [95], irrespectively of the allergen specificity. In a large study, high serum IgE was observed in children with severe asthma and in adults with early-onset asthma [96], whereas very high serum IgE (>2000 $kU{\cdot}L^{-1}$) also correlated with the severity of dermatitis [97].

The causal relationship between specific IgE antibodies (*i.e.* atopy or "allergy") and asthma involves multiple aspects [98] and is rendered complex by several factors: 1) atopic sensitisation usually concerns multiple allergens (so-called polysensitisation), each of which may have a different clinical relevance in a given patient; 2) nonallergenic factors (*e.g.* viral infections, genetic make-up, triggering/aggravating factors such as drugs, obesity or gastro-oesophageal reflux) may influence airway reactivity and symptoms; and importantly 3) allergens may cause sustained inflammation, and possibly IgE responses, that underlie disease persistency independently of allergen exposure. This last possibility is exemplified in occupational asthma, where allergen exposure can be strictly controlled and where only ~30% of patients achieve remission despite complete avoidance to the causal allergen [99]. This fact is of critical importance to support maintenance therapy, with inhaled corticosteroids as standard of care for the clinical management of persistent asthma [100].

A high level of serum total IgE is also a classical feature of allergic bronchopulmonary aspergillosis (ABPA). The IgE response underlying ABPA specifically involves IgE antibodies to Asp f 2, f 4 and f 6 allergens [101], which are not significantly observed in patients with asthma sensitised to *Aspergillus*, but without ABPA. *Aspergillus* allergens are able to activate the bronchial epithelium, inducing the release of pro-Th2 cytokines by airway epithelial cells and mucous cell metaplasia [102]. However, the fact that ABPA responds to both anti-inflammatory (*i.e.* inhaled corticosteroids) and antifungal drugs seems to indicate two sides of the same coin, *i.e.* ABPA involving both infectious and allergic processes [101]. A role for anti-IgE therapy has recently been suggested for ABPA [103, 104], including in cystic fibrosis [105].

Nonallergic asthma

The "nonallergic" phenotype of asthma, first described by Rackemann as referring to a late-onset asthma caused by an "unknown phenomenon", concerns 25–30% of patients in most series [106, 107]. Although intrinsic asthma covers several subentities, it differs from allergic asthma mainly by the absence of detectable specific IgE antibodies in the serum and negative skin-prick testing to common aeroallergens. It may also be distinguished from its allergic counterpart by some clinical features, including later onset [108], (the usual) absence of familial history of asthma, increased proportion of women, frequent

 DOI: 10.1183/13993003.01824-2014

association with chronic rhino-sinusitis with nasal polyps and aspirin hypersensitivity (often referred to as Widal or Samters' triad syndrome [109], and of more severe evolution. The low association with familial history, in contrast to atopic diseases, suggests that the environment is more important than genetics in the inception of the disease. Patients with nonallergic asthma may also exhibit elevated total serum IgE (>150 $kU \cdot L^{-1}$), as compared with healthy controls [3, 110]. The overlap between allergic and intrinsic asthma extends from immune cell infiltration [3, 110] to local IgE synthesis [111]. While the allergen specificity of this IgE remains elusive [112], a study by our group found HDM-specific IgE antibodies in bronchial secretions (*i.e.* induced sputum) from patients with intrinsic asthma to be at a similar level as that observed in allergic asthma [93]. Although this IgE was functional in terms of binding to major Der p 1 and p 2 allergens, and able to activate basophils *in vitro*, lung provocation by HDM failed to induce detectable clinical or inflammatory indices of allergic responses in these patients, in contrast to patients with allergic asthma. We suggested that this discrepancy could indicate that a "second factor" which modulates the reactivity to IgE is required to unmask the presence of local IgE. As another study recently failed to detect local specific IgE antibodies by using a microarray assessment of bronchial biopsies from intrinsic asthmatics [113], another possibility, besides technical issues related notably to the difference in sensitivity of the methods, is that the micro-localisation of IgE within the airway mucosa is critical to its activity. Although uncontrolled, a recent proof-of-concept trial in intrinsic asthma showed that the downregulatory effect of anti-IgE therapy (omalizumab) on cell surface expression of FcεRI was accompanied by a significant improvement of airway obstruction after 16 weeks of treatment [114].

Some patients with intrinsic asthma present with very clear "high-Th2" features; at the end of the spectrum is so-called "hyper-eosinophilic asthma", which refers to a late-onset nonallergic asthma, associated with nasal polyposis (or eosinophilic chronic rhino-sinusitis) and marked blood eosinophilia (>1000 μL^{-1}, or >500 μL^{-1} upon oral corticotherapy, at least two times) [115]. In this endotype, eosinophils clearly represent a valid target for biotherapies against IL-5, such as mepolizumab and reslizumab [116, 117]. Concordant blood and sputum eosinophilia is associated in severe asthma with male predominance, airflow limitation and AHR, as well as increased F_{ENO} and severe exacerbations. In contrast, isolated sputum eosinophilia is less clearly associated with poor control, but correlates with higher serum IgE levels [118]. In this phenotype, no genetic predisposition has been identified, whereas IgE responses to enterotoxin-producing *S. aureus* which colonise the upper airways of these patients have been found in serum [119]. These IgE antibodies were originally identified as more prevalent in severe asthma [33], and were recently reported in the general population with a prevalence of 29% and associated with asthma diagnosis (with an odds ratio of 2) and serum IgE, irrespectively of atopy [119]. Staphylococcal superantigens are molecules that may directly induce polyclonal T- and B-cell activation, with *S. aureus* also inducing TSLP expression in the skin from atopic dermatitis patients [120]. A role for IgE in hypereosinophilic nonallergic asthma is supported by the beneficial effect of anti-IgE in asthma associated with nasal polyposis, irrespectively of atopic status [121].

A distinct subgroup of patients presents with asthma without evidence of Th2/eosinophilic inflammation, referred to as a so-called "low Th2" asthma phenotype, with neutrophilic asthma sitting at the severe side of the spectrum [122] with resistance to corticosteroids and overlapping features with chronic obstructive pulmonary disease. With the identification of ILC2s as alternative high producers of "type 2" cytokines in asthma, this phenotype may likely be referred to more correctly as "type 2-low" asthma [123]. The role of IgE has not been studied in this asthma phenotype, whereas a role for IL-17 has been reported [124], as well as for IL-33 [125] and ADAM8 [126]. Obesity has been recently identified in population-based studies as a risk factor for both allergy [127] and asthma [4], and obesity-related asthma may represent a distinct nonallergic severe phenotype of asthma [128] associated with a loss of distal lung compliance correlated with weight gain [129]. While obesity could lower the threshold for specific IgE production in experimental asthma to ovalbumin [130], no clear mechanism links obesity to IgE responses. One study proposed a link between the imbalance in L-arginine/asymmetric dimethyl arginine in favour of the latter and reduced F_{ENO} observed in late-onset asthma associated with obesity. Of interest, those patients were less atopic and presented with low IgE levels [131]. Similarly, in exercise-induced asthma where activation of adaptive immunity is not a salient feature, the role of IgE remains elusive. It was shown that intense exercise may increase IgE production, partly due to increased (pollen) allergen exposure, but the pathophysiology of this asthma phenotype mainly relates to physical changes (*i.e.* airflow-induced shear stress and cold-induced epithelial damage) rather than IgE activation [132, 133].

In addition to the association between IgE and asthma, independently of atopy, a link between nonallergic asthma and chronic idiopathic urticaria has been suggested. In one study, 14 out of 24 nonallergic asthmatics presented with intradermal reaction to autologous serum, as observed in patients with chronic urticaria [134–136], suggesting the presence of auto-antibodies against IgE or FcεRI which were reported in ~30% of patients with intrinsic asthma [137]. However, only one serum sample from such patients was able to induce a significant histamine release *in vitro* and one positive serum sample out of four induced histamine release by IgE-stripped basophils. Several possibilities could underlie this discrepancy, including

the existence of IgE-independent mechanisms, which could contribute to degranulate mast cells in these patients, and the heterogeneity between blood basophils and skin mast cells, which differ by multiple factors, such as surface IgE density and intracellular signalling machinery. Thus, activation of the IgE pathway not only relies on IgE synthesis, but also on downstream reactivity, *i.e.* functionality of FcεRI signalling. It may thus be hypothesised that in nonatopic asthma, the discrepancy between the presence of local allergen-specific IgE antibodies and the absence of clinical reactivity upon allergen exposure [93] could relate to a defect in IgE/FcεRI/Syk signalling, which is constitutively activated in atopic subjects as well as acquired upon certain viral infections.

IgE as a therapeutic target and a biomarker in asthma

Whereas serum IgE represents an index of ongoing IgE production in the body, the epidemiological association with asthma diagnosis is probably largely explained by the close relationship between allergy and asthma. However, only a subset of allergic patients develops asthma and, in contrast, substantial numbers of nonatopic subjects have asthma. Conversely, some authors reported an inverse association between serum IgE and FEV_1 values in asthma [138], possibly in relation to the increased severity of nonatopic asthma. Although the importance of IgE for clinicians taking care of asthmatics had progressively declined, the arrival of anti-IgE therapy reversed this trend after the demonstration of its efficacy in allergic asthma, including at the severe side of the spectrum [1]. The most remarkable effect of this therapy, in addition to improvements in asthma-related symptoms and quality of life, is the reduction of viral-induced severe exacerbations [139]. However, whether IgE is a good biomarker for predicting response to omalizumab remains intriguingly unclear. Whereas a low level of serum IgE at baseline ($<76\ kU{\cdot}L^{-1}$, as the first quartile within the studied population) is associated with a lower chance of benefit [1, 140, 141], effects are not proportional to serum IgE levels. In recently conducted "real-life" studies, omalizumab was efficient in reducing exacerbations and corticosteroid use in allergic asthma regardless of the initial IgE level [142, 143], which is fixed at $>30\ kU{\cdot}L^{-1}$ in Europe (but $76\ kU{\cdot}L^{-1}$ in some countries). In addition, high levels of serum IgE ($>1300\ kU{\cdot}L^{-1}$) usually exclude patients from eligibility, due to absence of evidence of the ability for IgE quenching based on pharmacological data, and attempts to link the response to free IgE measurements have failed with efficacy still observed when free IgE remains $>50\ ng{\cdot}mL^{-1}$. This absence of any IgE dose-response is also observed during omalizumab treatment of chronic urticaria [144]. This discrepancy could relate to the existence of neutralising antibodies towards IgE, which was recently established *ex vivo* [145, 146], providing new evidence that the IgE level alone might not be sufficient to predict clinical outcome. It is also possible that IgE may act on mast cells independently of allergen-induced IgE/receptor cross-linking, to promote their survival and decrease their activation threshold by other stimuli, as suggested in the skin [147]. In contrast, eosinophilic indices (*e.g.* blood eosinophil count >2%, F_{ENO} >20 ppb) may represent better biomarkers of response to omalizumab in asthma, as discussed by Busse *et al.* [65] and Pavord and Bush [148]. In a *post hoc* analysis of biomarkers in the EXTRA study, a Th2-high profile (*i.e.* blood eosinophils $>260\ \mu L^{-1}$ or F_{ENO} >19.5 ppb) was associated with a significant reduction in asthma exacerbation rate for patients treated with omalizumab. In contrast to anti-IgE, the response rate (*e.g.* for severe exacerbations) to anti-IL-5 therapy such as mepolizumab occurs irrespective of serum IgE levels or atopy [149] and appears, as expected, proportional to blood eosinophilia. A similar trend was observed for serum periostin ($>50\ ng{\cdot}mL^{-1}$), which has been described as a potential biomarker of bronchial eosinophilic inflammation in severe asthma [150] that reflects IL-13/Th2-mediated bronchoepithelial activation. The additional value of serum periostin as a surrogate marker of sputum eosinophilia (>3%) was, however, recently challenged in a population with mild-to-moderate asthma, where blood eosinophils remained the best biomarker of airway eosinophilia [151]. Therefore, the current view is that eosinophilic biomarkers may globally indicate "Th2-mediated asthma", but it is likely there are subphenotypes that will respond differently to IgE or Th2 cytokine targeting (figure 3), probably in part as a result of a distinct cytokine profile [152]. Whether eosinophils, IgE and/or type 2 cytokines are in the "driver's seat" of asthma is the underlying issue, which will probably be addressed in the clinic through endo/phenotyping (*e.g.* with novel systemic and sputum biomarkers of response) as well as real-life studies, as randomised controlled trials only include minor subpopulations of severe asthmatics.

It is further evident that in severe asthma, the direct (treatment, exacerbations and hospitalisation) and indirect costs (work- and school-days lost) represent a major economic burden. In addition, despite the relatively high cost of omalizumab (€10 000–15 000 per year per patient [153]), this treatment remains cost-effective (by decreasing severe exacerbations) when applied to well-selected patients, with a price by quality-adjusted life-year (QALY) ranging from €26 000 to €38 000 [65, 139, 153, 154], whereas other studies in less selected asthmatics [154, 155] concluded that omalizumab was not cost-effective (from US $280 000–800 000 per QALY). This cost-effectiveness evaluation further highlights the importance of properly selecting patients for biotherapies (currently referred to as personalised medicine).

DOI: 10.1183/13993003.01824-2014

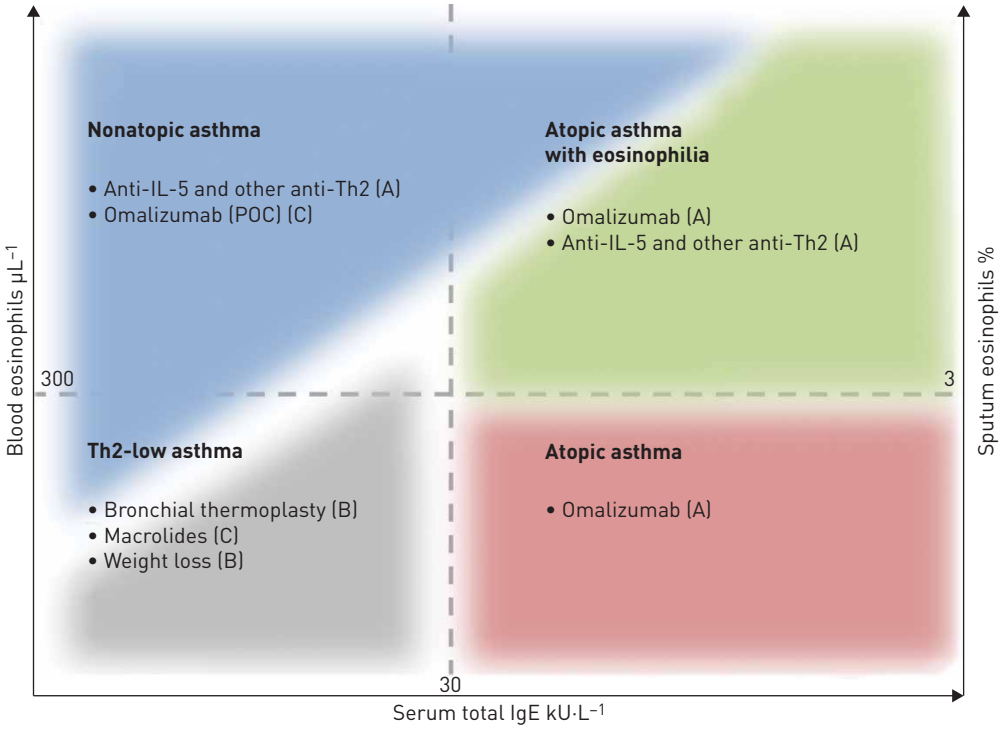

FIGURE 3 Decision chart based on the current knowledge of (proven or suspected) efficacy of add-on therapies in the most prevalent endo/phenotypes of severe asthma. The current indication of omalizumab in atopic asthma includes the allergic background to perennial allergen with increased total IgE level (>30 or 76 kU·L^{-1} according to country), whereas concomitant eosinophilic inflammation increases the chance of response. The role of (local) IgE in nonatopic asthma needs further exploration, whereas eosinophilia clearly predicts response to anti-interleukin (IL)-5. In contrast, T-helper (Th) 2-low phenotypes have no targeted therapies, but might benefit from emerging therapeutic options. A, B and C correspond to the available levels of evidence. POC: proof of concept.

Allergen-specific immunotherapy represents another treatment that, ultimately, affects IgE reactivity, and is able to induce disease remission in highly selected patients with allergic rhinitis and asthma, particularly to pollens [156]. This effect probably occurs by promoting regulatory responses involving regulatory T-cells and IgG-blocking antibodies, which quench IgE-driven effector mechanisms [157]. In this context, however, changes in IgE levels and/or affinity are poorly correlated with treatment outcomes [156], likely due to the competing effects of persistent IgG antibodies that emerge after several years of treatment [148].

It remains unclear whether local IgE production, as observed in rhinitis [152] and asthma [111] in the absence of serum allergen-specific IgE [158], could represent a better biomarker of allergic airway disease and asthma with regard to the disease endo/phenotype or response to therapy. Future studies should delineate whether bronchial IgE production closely correlates, or not, with Th2-type inflammation and eosinophilic markers [159] (figure 3).

Altogether, existing data [1, 160–162] (table 2) and emerging concepts indicate that IgE alone is not sufficient to predict the response to omalizumab, further confirming that a run-in period remains essential to determine whether a patient actually responds to the drug and suggesting that other factors, including local production, blocking antibodies and basophil/mast cell activation threshold, modulate the effect of anti-IgE and ultimately questions the real contribution of IgE-mediated allergy in asthma.

Conclusion

The epidemiological association between IgE production and asthma [28] covers several components. While allergen-specific IgE may undoubtedly mediate asthmatic responses in allergic individuals, the relation between IgE responses and clinical expression of asthma integrates several cofactors influencing airway reactivity and disease persistency. In particular, the role of microbes in initiating and/or perpetuating asthma has been unravelled, notably through the unexpected observation that respiratory viruses are able to induce FcεRI expression and signalling, and thereby to promote reactivity of the immune system to IgE. While this pathway plays an important role in the inception and exacerbation of both allergic and nonallergic asthma, the triggering mechanisms of IgE signalling in nonatopic asthma and the contribution of anti-viral IgE remain unknown. Evidence is also accumulating that IgE response to

TABLE 2 Clinical trials of anti-IgE therapy in different asthma phenotypes

Phenotypes	Patients	Asthma-related outcomes	Results	References
Allergic asthma (adults)	Placebo-controlled (n=850), 48 weeks; uncontrolled asthma with high-dose ICS+LABA with/without additional controllers	Rate of exacerbations	Incidence rate 0.66 *versus* 0.88 (omalizumab *versus* placebo), p=0.006	Hanania *et al.* 2011 [161]
	Placebo-controlled (n=419), 28 weeks; uncontrolled asthma with high-dose ICS+LABA with/without additional controllers	Exacerbation requiring systemic corticoids	Exacerbation rate 0.68 *versus* 0.91 (omalizumab *versus* placebo), p=0.42	Humbert *et al.* 2005 [1]
Allergic asthma (6–20 years old)	Placebo-controlled (n=419); patients receiving long-term therapy with symptoms or evidence of uncontrolled disease as indicated by hospitalisation or unscheduled urgent care in the previous 6–12 months, *and* patients without control therapy if they had persistent symptoms and uncontrolled asthma	Days without asthma symptoms during last 2 weeks, as assessed every 4 weeks	Mean days with symptoms 1.48 *versus* 1.96 (omalizumab *versus* baseline); 24.5% reduction as compared with placebo group, p<0.001	Busse *et al.* 2011 [65]
Nonallergic asthma (serum IgE 30–700 kU·L^{-1})	Uncontrolled nonatopic asthma (n=41) despite daily high-dose ICS treatment (>1000 μg BDP or equivalent per day)+LABA with/without maintenance OCS	Change from baseline in FcεRI expression on basophils and plasmacytoid dendritic cells (pDC2) after 16 weeks; secondary end-points: lung function, asthma control score, GETE, exacerbation rate and F_{eNO}	Significant median change in FcεRI expression on basophils (p<0.001) and plasmacytoid dendritic cells (pDC2) (p<0.001) between omalizumab group *versus* placebo group; compared with placebo, the omalizumab group showed a statistically significant (p=0.029) increase in mean FEV_1 after 16 weeks	Garcia *et al.* 2013 [160]
Allergic and nonallergic asthma	Chronic rhinosinusitis with nasal polyposis with concomitant asthma (n=23; atopic n=13, nonatopic n=10)	Asthma symptoms, lung function and quality-of-life scores	Improvement of asthma symptoms score after 16 weeks omalizumab as compared with placebo group; wheezing (p<0.02) and dyspnoea (p<0.03)	Gevaert *et al.* 2013 [121]
Occupational asthma to both high- and low-molecular weight chemicals	Occupational asthma despite workplace adjustments Severe uncontrolled asthma with high-dose ICS (mean BDP: 3200 μg)+LABA	FEV_1, asthma control, exacerbation rate, ICS daily dose and OCS daily dose	Seven out of 10 occupational asthma patients remained at work; compared with baseline, ICS daily dose was lower in five out of the 10 patients; two out of these five had their OCS therapy withdrawn; exacerbation rate fell from 5.2 to 0.5 year^{-1}	Lavaud *et al.* 2013 [162]

ICS: inhaled corticosteroid; LABA: long-acting β-agonist; BDP: beclometasone dipropionate; OCS: oral corticosteroid; GETE: physician and patient global evaluation of treatment effectiveness; F_{eNO}: exhaled nitric oxide fraction; FEV_1; forced expiratory volume in 1 s.

DOI: 10.1183/13993003.01824-2014

bacterial antigens, such as enterotoxins from *S. aureus*, may play an important role in some phenotypes of asthma, such as hyper-eosinophilic asthma associated with nasal polyposis.

Three main "high-IgE" asthma endo/phenotypes may be identified based on increased total serum IgE, *i.e.* allergic asthma (where the tendency to high IgE production is inherited), allergic bronchopulmonary aspergillosis (where IgE synthesis is *Aspergillus* driven), and hyper-eosinophilic asthma associated with nasal polyposis and *S. aureus* colonisation (where IgE production partly results from exotoxin-driven polyclonal B-cell activation). Recent proof-of-concept trials further suggest that IgE plays a role in the pathogenesis of some of these high-IgE asthma phenotypes (table 1), including in nonatopic patients. The mechanisms of the benefit observed upon anti-IgE therapy in asthma clearly overcome the blockade of allergen-specific IgE and include interference with viral-induced [59] or superantigen-induced [119] IgE/FcεRI signalling, which might be of particular importance in patients with severe disease and (partial) resistance to corticosteroids. The overlap between high-IgE and high "type 2" asthma remains unclear, however, and should be the focus of future studies in particular with regard to biotherapy of severe asthma.

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DOI: 10.1183/13993003.01824-2014

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