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Received: 18 April 2023 | Revised: 8 July 2023 | Accepted: 27 July 2023

DOI: 10.1111/all.15843

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

REVIEW ARTICLE

Autoreactive IgE: Pathogenic role and therapeutic target in autoimmune diseases

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Funding information
Agence Nationale de la Recherche; Centre National de la Recherche Scientifique; European Research Council; Fondation pour la Recherche Médicale; Fonds Wetenschappelijk Onderzoek; Institut National de la Santé et de la Recherche Médicale; Université Paris Cité

Abstract

Autoimmunity is the break of tolerance to self-antigens that leads to organ-specific or systemic diseases often characterized by the presence of pathogenic autoreactive antibodies (AAb) produced by plasmablast and/or plasma cells. AAb are prevalent in the general population and not systematically associated with clinical symptoms. In contrast, in some individuals, these AAb are pathogenic and drive the development of signs and symptoms of antibody-mediated autoimmune diseases (AbAID). AAb production, isotype profiles, and glycosylations are promoted by pro-inflammatory triggers linked to genetic, environmental, and hormonal parameters. Recent evidence supports a role for pathogenic AAb of the IgE isotype in a number of AbAID. Autoreactive IgE can drive the activation of mast cells, basophils, and other types of FcεRI-bearing cells and may play a role in promoting autoantibody production and other pro-inflammatory pathways. In this review, we discuss the current knowledge on the pathogenicity of autoreactive IgE in AbAID and their status as therapeutic targets. We also highlight unresolved issues including the need for assays that reproducibly quantify IgE AAbs, to validate their diagnostic and prognostic value, and to further study their pathophysiological contributions to AbAID.

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KEYWORDS
antibody-mediated autoimmune diseases, autoallergy, autoreactive IgE, ligelizumab, omalizumab, UB-221

1 | INTRODUCTION

Autoimmunity is defined by a break of tolerance to self-antigens leading to either organ-specific or systemic diseases. This reactivity to self is driven by autoreactive B and/or T cells that escaped negative selection processes through mechanisms that are not yet fully characterized. Several models explaining the loss of tolerance to some self-antigens have been proposed concerning the expansion of both autoreactive B and T cells.[1–6] Some autoimmune diseases (AID) are characterized by the presence of pathogenic autoreactive antibodies (AAb) produced by plasmablast and/or plasma cells resulting from T-cell-dependent and/or T-cell-independent B-cell differentiation from both follicular and extrafollicular areas of secondary or tertiary lymphoid organs.[3,7] Pathogenic antibodies drive the development of organ injury in these antibody-mediated AID (AbAID) through mechanisms involving Fc receptor-bearing cells and/or complement pathways.[8]

In organ-specific AbAID, AAb target tissue-expressed self-antigens which lead to the development of signs and symptoms. For instance, in bullous pemphigoid, AAb against BP-180 and BP-230 (BP Ag2 and BP Ag1, respectively, key dermis–epidermis junction molecules) are responsible for blister formation.[9] In systemic diseases, AAb target non-organ specific antigens. In systemic lupus erythematosus (SLE), for instance, AAb to nuclear antigens form circulating immune complexes (CIC) that induce chronic and systemic inflammation by depositing in target organs and by activating complement and innate immune cells that amplify AAb production through various mechanisms.[7]

AAb are prevalent in the general population and are thus not systematically associated with clinical symptoms.[10] However, in some individuals, through genetic, environmental, and/or hormonal mechanisms, a pro-inflammatory trigger can amplify their production and modify their isotypes and glycosylation. Toll-like receptors (TLR) and intracellular nucleic acid sensing molecules engagement, through inflammatory signals, can lead to autoreactive B- and T-cell proliferation and maturation.[1,3,10–12] Some of these immune signals also initiate class switch recombination (CSR) allowing B cells to switch the constant region of their BCR from IgM to another isotype.[13,14]

While AAb of IgM isotype may generally be protective against AbAID, IgG AAb are mostly pathogenic. IgG subclasses differ in the activation of complement pathways and in engaging inhibitory and/or activating Fc receptors for IgG (FcγR), and differences in post-translational modifications influence their pro- or anti-inflammatory properties.[8,10] The pathogenicity of IgA and IgD AAb still needs further characterization, but recent evidence points to the pathogenicity of IgE AAb and highlights IgE as a potent therapeutic target in a number of AbAID.[15] Interleukin 4 (IL-4) and IL-13 are the main cytokines promoting IgE CSR and the generation of IgE-producing antibody-secreting cells.[14,16]

IgE binds with high affinity to FcεRI (Kd ≈ 10^{-9} M), which is expressed in its tetrameric form αβγ2 by mast cells and basophils and, in humans, in its αγ2 trimeric form mainly by some dendritic cell subsets, Langerhans cells, eosinophils, and some monocytes (either constitutively or induced).[17] FcεRI-mediated activation of mast cells and basophils leads to the immediate release of granular pro-inflammatory preformed mediators and to neosynthesis and release of arachidonic derivatives, cytokines, and chemokines.[18] These effects can be toned down through co-engagement of FcγRIIB (CD32B) or other inhibitory receptors that can block degranulation and decrease cytokine production.[19,20]

The lower affinity IgE receptor FcεRII (CD23, Kd ≈ 10^{-7}–10^{-8} M) is mainly expressed by some subsets of B cells and monocytes and is involved in the regulation of IgE synthesis and, together with FcεRI, in IgE-mediated facilitated antigen presentation.[14] Beyond its effects on IgE synthesis, little is known about CD23-mediated pathogenicity of IgE in AbAID. Its involvement in the regulation of allergic responses has been recently reviewed.[14,21]

Autoreactive IgE can drive cellular activation of mast cells, basophils, and other types of FcεRI-bearing cells[15] without necessarily inducing their degranulation due to other factors influencing their functional outcomes. Indeed, AbAID-affected patients do not have chronic anaphylactic symptoms and systematically develop pathogenic antibodies of multiple isotypes including IgG. Depending on their subclass and their affinity to the autoantigen, autoreactive IgG can induce inhibitory signals that will be integrated to FcεRI-mediated activating signals leading to a specific cellular activation (or inhibition) pattern of the targeted cell. This may result in mast cell or basophil activation without degranulation but with the production of cytokines, chemokines, or other inflammation-related compounds[22] and may potentiate the TLR9-dependent activation of dendritic cells.[23] Therefore, the term autoallergy (or allergy to self) should be used cautiously when referring to diseases where mast cell and basophil degranulation are not induced by IgE AAb.

The present review summarizes the current knowledge on the pathogenicity of autoreactive IgE in AbAID and will discuss the role of IgE as a therapeutic target in these conditions. We will also highlight the need to develop better assays for IgE AAb to validate their diagnostic and prognostic values and allow further study of their pathophysiological contribution to AbAID.

2 | AUTOREACTIVE IGE IN SYSTEMIC LUPUS ERYTHEMATOSUS AND OTHER AUTOIMMUNE CONNECTIVE TISSUE DISEASES

Systemic autoimmune rheumatic (or connective tissue) AbAID include, but are not limited to, systemic lupus erythematosus (SLE),

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rheumatoid arthritis (RA), Gougerot–Sjogren syndrome (GS), systemic sclerosis (SSc or scleroderma), and mixed connective tissue disease (MCTD). In these diseases, AAb are pathogenic drivers and diagnostic markers. They form circulating immune complexes (CIC) once engaged by their target autoantigen, complement components, and eventually rheumatoid factors. These CIC deposit in the targeted organs and activate innate immune cells that drive tissue injury and amplify AAb production.[7] All of these AbAID come with IgG AAb against nuclear antigens with established pathogenic properties.[2] The main specificities of the AAb in these diseases and their prevalence for IgG isotype are summarized in Table 1.

Nearly five decades ago, the presence and prevalence of IgE AAb against nuclear antigens were established for RA and SLE[24,25] and extended to other rheumatic diseases along with their abilities to drive basophil activation.[26] More recent studies characterized the prevalence of autoreactive IgE in these AbAID and their association with disease activity and particular organ damage, especially in SLE where autoreactive IgE titers are clearly associated with lupus nephritis[23,27–29] (Table 1). In lupus-like mouse models, IgE deficiency prevents, dampens, or delays the development of the disease.[27,30] The pathogenic role of autoreactive IgE in the pathophysiology of SLE includes effects on two main FcεRI-bearing cell types, namely plasmacytoid dendritic cells (pDC) and basophils[23,27,29,31] (Figure 1).

In a non-autoimmune context, IgE is known to downregulate TLR7 and TLR9 function and expression on pDCs, reducing their ability to produce IFNα.[32] However, once aggregated to nucleic acids, IgE AAb amplify IFNα production by pDC. Indeed, in human SLE, through Fcγ receptor-, FcεRI-, and TLR7/9-mediated activation, pDC are responsible for the production of high levels of type I interferons that promote autoantibody production and other pro-inflammatory pathways. Anti-DNA IgG can strongly induce pDC IFNα production by facilitating the addressing of DNA (TLR9 ligand) to the TLR9-bearing endosomal compartment. Anti-DNA IgE does the same, and the presence of anti-DNA IgE and IgG in the same immune complexes enhances the induced IFNα production.[23,29,32]

Basophil activation status correlates with SLE disease activity and is directly associated with the presence of IgE AAb in the circulation of SLE patients.[23,27–31] Sera from SLE patients induce basophil activation and IL-4 production, features that are lost after IgE depletion from the serum.[26,31,33] In SLE patients and lupus-like mouse models, activated basophils accumulate in secondary lymphoid organs (SLO) by prostaglandin D2- and CXCR4-dependent

TABLE 1 Prevalence of anti-nuclear autoreactive IgG and IgE in some autoimmune connective tissue diseases.

Autoimmune connective tissue disease	Main autoantigens	Prevalence of autoreactive IgG	Autoreactive IgG titers associated with disease activity?	Ref	Prevalence of autoreactive IgE	Autoreactive IgE titers associated with disease activity?	Ref
Systemic lupus erythematosus (SLE)	ANA	69%–90%	Yes	28,43	48–65%	Yes	24,28
	dsDNA	34%–49%	Yes	28,44	35–55%	Yes (especially with lupus nephritis[28,29])	23,27–29,33
	Sm	41%–50%	Yes	28,44	7–48%	Yes	28,44
	Ro/SS-A	34%	Yes	28,44	8–48%	Yes	28,44
	La/SS-B	7%	Yes	28,44	4–7%	Yes	28,44
Mixed connective tissue disease (MCTD)	U1-snRNP	100%		38	79%	NA	38
Gougerot–Sjögren syndrome (GS)	Ro/SS-A	73%	Yes	45	33%	NA	46
	La/SS-B	45%	Yes	45	41%	NA	46
	dsDNA	0%	NA	47	15%	NA	46
	Sm	1%–7%	NA	46,47	25%	NA	46
Rheumatoid arthritis (RA)	ANA	49%	NA	43	32%	NA	25
Systemic sclerosis (SSc)	Centromere	20%–57.8%	Yes	48	NA		
	Topoisomerase I	17%–71%	Yes	48	NA		
	RNA polymerase III	4%–20%	Yes	48	NA		
	Fibrillarin	2%–18%	Yes	48	NA		
	Elastin	0%	NA	49	20%	NA	49
	Collagen I	0%	NA	49	20%	NA	49
	Collagen IV	0%	NA	49	20%	NA	49

Abbreviations: ANA, Antinuclear antibodies; dsDNA, double-stranded DNA; NA, not assessed; Sm, Smith antigen; SS, Sjogren syndrome antigen.

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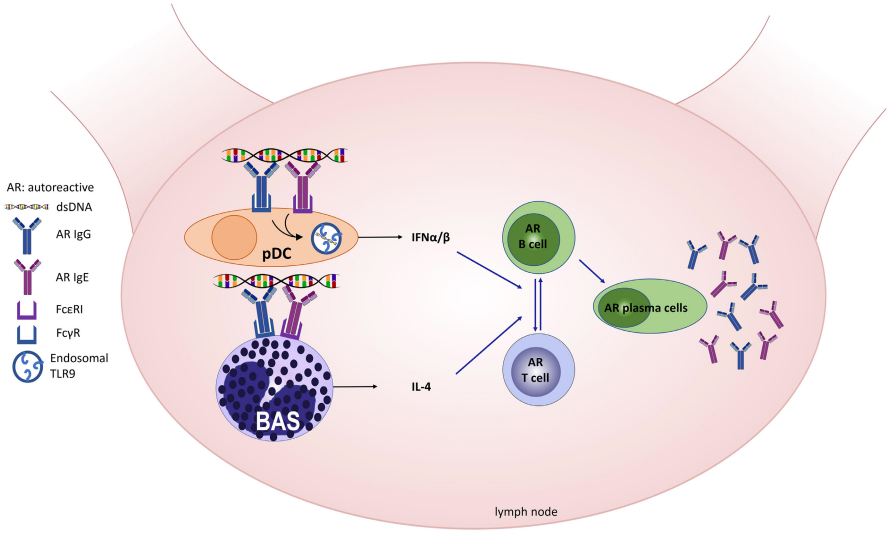


FIGURE 1 Contribution of autoreactive IgE to SLE pathophysiology. In SLE, plasmacytoid dendritic cells (pDC) and basophils (BAS) are recruited to secondary lymphoid organs. There, pDC and BAS contribute to the pathogenesis of SLE by promoting AAb production through the production of type I interferon (IFNα/β) and IL-4, respectively. IgG AAb, through Fcγ receptors, and IgE AAb, through FcεRI, cooperate to facilitate the addressing of dsDNA to TLR9 in endosomal compartments of pDC leading to increased type I IFN production. IFNα and β promote IFN-responsive gene transcription and directly act on B cells to facilitate maturation and differentiation into antibody-secreting cells (plasma cells). On basophils, autoreactive IgG may engage the inhibitory receptor for IgG, FcγRIIB, along with FcεRI engagement through autoreactive IgE. The integrated signal leads to cytokine (IL-4) production without inducing degranulation.

mechanisms,[22,27,33] and this accumulation is lost in IgE-deficient lupus-like mouse models.[27,30] In SLO, basophils promote plasmablast accumulation and AAb production most probably through their production of IL-4 that acts on both B and T cells and their expression of membrane-bound B-cell activating factor of the TNF superfamily (BAFF)[22,27,33,34] (Figure 1).

Because of their effects on pDC and basophils, IgE AAb are considered as a pathogenic factor in SLE, and IgE depletion in SLE patients may constitute a valuable therapeutic strategy (see below). Other FcεRI-bearing cells are involved in SLE pathophysiology such as Langerhans cells in photosensitivity[35] or mast cells that accumulate in kidneys from lupus nephritis patients,[36] but their IgE-dependent contribution is not established. Of note, mast cell deficiency in lupus-like mouse models does not affect disease development.[27,37]

In MCTD, the main autoantigen is the 70 kDa subunit of the U1-snRNP (small nuclear ribonucleoprotein). Most MCTD patients (78%) have IgE against U1-snRNP, and this is associated with an activation of their basophils.[38] In a mouse model of MCTD, IgE deficiency fully prevented the development of the associated lung disease.[38] In RA, increased blood IgE levels, prevalence of anti-nuclear IgE (49%), and IgE-containing immune complexes in synovial fluid are associated with disease activity, as is the activation of mast cells in synovium.[15,39] Whether the latter is FcεRI- and/or IgE-mediated still needs to be investigated.[39]

As indicated in Table 1, the prevalence of IgE AAb in other autoimmune connective tissue diseases suggests that they may have a pathogenic role in these conditions (Table 1). Indeed, several FcεRI-bearing cells are involved in the pathogenesis of these conditions (for instance: mast cells in RA and SSc; pDC in RA, GS, and SSc).[15] A high prevalence of IgE AAb has been reported as well in some organ-specific autoimmune diseases affecting the thyroid, with anti-thyroid peroxidase (TPO) IgE in Graves' disease (72%) and Hashimoto disease (70%),[40] the eyes, with anti-retinal S antigen IgE in autoimmune uveitis (68%),[41] and the nervous system, with anti-myelin IgE in multiple sclerosis (100%).[42] Further studies will be required to determine the relevance of autoreactive IgE in the pathophysiology of these diseases and their value as a putative therapeutic target.

3 | AUTOREACTIVE IGE IN CHRONIC SPONTANEOUS URTICARIA

Chronic spontaneous urticaria (CSU), a common skin disease, is characterized by the recurrence of itchy wheals, angioedema, or both for more than 6 weeks.[50,51] The signs and symptoms of CSU are caused by skin mast cells and their FcεRI-mediated activation through IgG AAb to IgE or FcεRI and IgE AAb, in autoimmune and autoallergic CSU, respectively.[52,53]

The first CSU "autoallergen," TPO, was reported in 1999 by Bar-Sela and colleagues.[54] At that time, it was well known that CSU and thyroid autoimmunity often occur together, but it was unclear how the two diseases were linked mechanistically.[55,56] Since then, several studies confirmed that patients with CSU have anti-TPO IgE at varying rates up to 100%.[57–64] The reasons for the differing rates of anti-TPO IgE-positive patients across studies are currently unclear, but they likely include differences in patient populations investigated and methods used.[65,66] Other autoantigens to which CSU patients

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have autoreactive IgE include double-stranded DNA,[67] eosinophil cationic protein,[59] eosinophil peroxidase,[59] FcεRI,[68] interleukin-24 (IL-24),[53,69] thyroglobulin (TG),[60,61,68,70] tissue factor (TF),[68,70] and transglutaminase 2 (TG2)[71] (Table 2 and Figure 2). Most of them have been reported by single studies, and further verification is needed.

As of now, little is known about how the presence and levels of IgE autoantibodies in CSU are linked to demographic and clinical features. A study by Altrichter and coworkers found no difference in disease duration, urticaria activity score (UAS), and dermatology life quality index (DLQI) (all indicators of CSU disease severity) between patients with and without anti-TPO IgE.[57] Another study reported elevation of anti-TPO IgE during CSU exacerbation.[62] Cugno and colleagues showed that anti-TG and anti-TF IgE levels dropped after 1 week of omalizumab (OMZ) treatment correlating with the reduction in disease activity.[70] Anti-IL-24 IgE levels are positively linked to disease activity and negatively associated with blood basophil counts.[69]

IgE AAb contribute to the pathogenesis of CSU via "autoallergic" FcεRI-mediated activation of mast cells in the skin, which results in the release of proinflammatory mediators and the recruitment of inflammatory cells including basophils (Figure 2). Autoantigens recognized by autoreactive IgE, that is, autoallergens, lead to the cross-linking of FcεRI on mast cells and basophils and their degranulation, as shown for IgE against TPO, IL-24, and dsDNA in vitro and in vivo.[58,67,69,72] For dsDNA and TPO, patient basophils with the respective autoreactive IgE showed upregulated CD203c or CD63 expression after stimulation with different concentrations of autoallergen.[58,67,72] As of now, it is unclear why autoallergens induce IgE responses primarily in the skin. One possible explanation is cross-reactivity to skin-prominent antigens such as, for instance, anti-TPO IgE and eosinophil peroxidase in lesional CSU skin.[59]

Treatment options for urticaria target either mast cell mediators (e.g., histamine) or activators, such as autoantibodies. Currently, there is only one licensed anti-IgE treatment in CSU, OMZ. Additional IgE-targeted antibodies, that is, OMZ biosimilars, ligelizumab, and UB-221, as well as quilizumab, FB825, and dupilumab, which downregulates IgE production, have been investigated. Dupilumab is a monoclonal antibody that targets the common chain of IL-4 and IL-13 receptors (IL-4Rα).[73] These cytokines are responsible, among other central functions, for B-cell class switching to IgE. Therefore, dupilumab reduces IgE production, which has been shown to be beneficial in multiple atopic and allergic diseases[73,74] and also in CSU.[75]

4 | AUTOREACTIVE IGE IN ATOPIC DERMATITIS

Atopic dermatitis (AD) is a common chronic relapsing inflammatory skin disease characterized by pruritic (itchy), red, and dry skin lesions with an impaired skin barrier function. AD is associated with the development of food allergies, allergic asthma, allergic rhinitis, and anaphylaxis ("atopic march").[76] In patients with AD, an increased risk of co-morbid autoimmune diseases was found.[77,78] The first evidence of autoreactive responses to human dander was reported about 80 years ago[79,80] and the first human proteins reported to be reacting with autologous IgE from allergic patients and induce basophil activation were profilins and denominated "panallergens".[81,82] Several research groups have demonstrated the presence of IgE AAb in AD.[82–95] At least 140 autoantigens recognized by IgE AAb in AD patients have been identified,[96] including epidermal antigens.[84,97] A review of eight studies on the prevalence of IgE AAb described a range from 23% (40/174) to 91% (11/12) in patients with eczema and 0%–12% in controls.[98] The evaluation of studies with a sample size greater than 100 showed a range of 23%–28% in eczema patients.[98] A recent study including 672 subjects found a prevalence of 16.4% in patients with AD and atopic comorbidities, 9.6% in patients with solely AD, 9.6% in atopic controls without AD, and 2.7% in non-atopic subjects.[99]

The levels of IgE AAb in AD patients are correlated with disease severity.[84,89,91,93,100–102] Therefore, it is held that their presence is clinically relevant, but their precise pathophysiological contribution still requires further investigations. Allergen-mediated or autoallergen-mediated FcεRI-cross-linking on mast cells, basophils, Langerhans cells, and probably eosinophils in AD skin may contribute to the pathogenic activation of these cells along with IgE-independent pathways[103] (Figure 3). Of note, FcεRI-bearing mast cells and eosinophils are potent producers of IL-13, one of the key cytokine in AD pathogenesis (Figure 3).

In AD, the exact role of IgE AAb (i.e., cause, consequence, or epiphenomenon) in the disease pathophysiology is still debated.[104] It is believed that pruritus, a key feature of chronic skin inflammation in AD, incites scratching, which leads to skin damage and the release of alarmins and self-antigens.[104] These autoantigens may then be processed by antigen presenting cells and presented to lymphocytes resulting in the production of IgG and/or IgE AAb by plasma cells.[105] IgE-mediated autoimmunity in AD may also be caused by molecular mimicry due to cross-reactive peptides between environmental antigens or skin microbiome and self-antigens.[91,106–108] In addition, skin residing $CD8^+$ cytotoxic T cells with intermediate affinity to self-peptides may contribute to skin damage, and unconventional γδ T cells may also accumulate in the skin.[109,110] Finally, an extraordinary unspecific activation of the T and B cells might also underlie the response due to the conditions of an ongoing inflammation. So far, it is unclear whether the presence of IgE AAb in AD is linked to a distinct endotype or an epiphenomenon secondary to the chronic inflammation of the skin.[111] Once present, they contribute to the ongoing inflammation in a "*circulus vitiosus*" type fashion and may predict further development of type 2 comorbid diseases, such as food allergies, allergic asthma, rhinoconjunctivitis/hay fever, which is an important topic for future investigation.

As is the case for all diseases that come with autoreactive IgE, no commercial diagnostic test is currently available for the detection of IgE AAb in AD, which hampers their evaluation and further research on clinical relevance. Also, published differences on the prevalence might be due to the diverse diagnostic test methods used by the different research groups as described in CSU (Table 2).

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TABLE 2 Prevalence of autoreactive IgE in chronic spontaneous urticaria (CSU).

Autoreactive IgE target	Prevalence [%]	Detection Method	Association with clinical markers	Measurement of IgG antibodies against target	Reference
Double-stranded DNA (dsDNA)	n.a.	Indirect ELISA	• No significant difference in anti-dsNDA IgE levels between $ASST^+$ and $ASST^-$ patients • No correlation with total IgE and disease duration	Yes, no difference between CSU and HC	67
Eosinophil cationic protein	5.4	Direct ELISA after IgG depletion	n.a.	n.a.	59
Eosinophil Peroxidase	10.9	Direct ELISA after IgG depletion	n.a.	n.a.	59
FcεRI	30	Sandwich ELISA	n.a.	Yes, significantly higher in CSU than HC	68
Interleukin 24 (IL-24)	80	Microarray and Sandwich ELISA	• Positive correlation with disease activity (UAS7) • Negative correlation with blood basophil counts	None of the patients assessed via microarray had detectable IgG-anti-IL-24	69
	31	Site direct ELISA	• Patients with IgE autoantibodies (anti-TPO and anti-IL-24) had higher anti-TPO IgG and lower IgE and leukocyte counts compared to CSU patients without autoantibodies	n.a.	53
Thyroglobulin (TG)	5	Modified commercial ELISA	n.a.	Yes	60
	7	ELISA kit	• No difference in disease duration, UAS day and total IgE between patients with and without Anti-TG-IgE	Yes, correlation of IgE autoantibodies and IgG autoantibodies	61
	35	Sandwich ELISA	n.a.	Yes, no differences between CSU and HC	68
	87	Sandwich ELISA	• Anti-TG IgE levels dropped 1 week after omalizumab administration • This drop was correlated with drop in UAS 7 at 1 week and 2 months	Yes, most patients negative	70

(Continues)

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TABLE 2 (Continued)

Autoreactive IgE target	Prevalence [%]	Detection Method	Association with clinical markers	Measurement of IgG antibodies against target	Reference
Thyroid peroxidase (TPO)	54	Site-directed human IgE capture ELISA	• No differences in disease duration, UAS, DLQI, and total IgE between CSU patients with and without anti-TPO IgE • CSU patients with anti-TPO IgE had higher anti-TPO IgG levels, lymphocyte numbers, and complement C4	Yes, CSU patients with anti-TPO IgE had significantly higher anti-TPO IgG	57
	7.5[a]	Direct ELISA	n.a.	Yes	72
	27.2	Direct ELISA after IgG depletion	n.a.	n.a.	59
	34	Direct ELISA after IgG depletion	• No differences in UAS, DLQI, anti-TPO IgG, and total IgE between CSU with IgE-anti-TPO and patients without	Yes	58
	5	Modified commercial ELISA	n.a.	Yes	60
	18	ELISA kit	• No difference in disease duration, UAS day between CSU with anti-TPO IgE and patients without • Lower total IgE levels and antihistamine-refractory cases in patients with anti-TPO IgE	Yes, Significant correlation of IgE autoantibodies and IgG autoantibodies	61
	43	Direct ELISA after IgG depletion	• More patients with anti-TPO IgE had asthma, atopy (to mites and/or pets) and NSAID reaction than patients without anti-TPO IgE • Patients with anti-TPO IgE had lower total IgE levels than patients without anti-TPO IgE • No difference between age of onset, DLQI score, UAS score	n.a.	62
	100	Side direct ELISA	n.a.	Yes	63
	0	Modified commercial radioimmunoassay	n.a.	Yes	64
	41	Side direct ELISA	• Patients with IgE autoantibodies (anti-TPO and IL-24) had higher anti-TPO IgG and lower IgE and leukocyte counts compared to patients without	Yes	53
Tissue Factor (TF)	50	Sandwich ELISA	• Omalizumab late responders had significantly higher anti-TF IgE levels than early responders	Yes, higher in CSU than HC and higher in omalizumab late responders than early responders	68
	60	Sandwich ELISA	• Levels dropped 1 week after omalizumab administration • This drop was correlated with drop in UAS 7 at 2 months	n.a.	70
Tissue Transglutaminase 2 (TG2)	20.6	Capture ELISA	• Not linked to any demographic, clinical, and laboratory features of CSU including the presence of previously described anti-TPO and anti-IL-24 IgE	n.a.	71

Abbreviations: ASST, autologous serum skin test; DLQI, Dermatology Life Quality Index; HC, healthy controls; n.a., not assessed; NSAID, non-steroidal anti-inflammatory drugs; UAS, urticaria activity score.

[a]Aspirin intolerant chronic urticaria patients.

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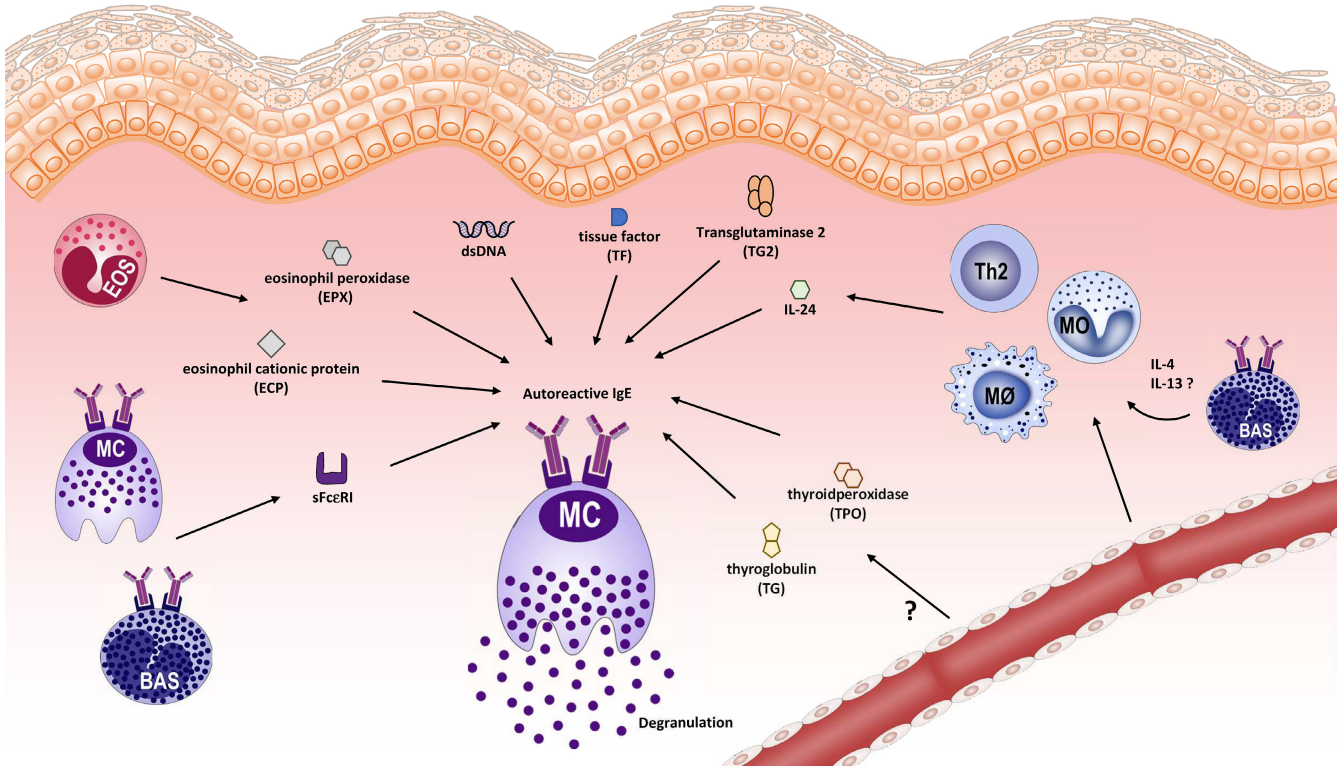


FIGURE 2 Contribution of autoreactive IgE to the pathogenesis of chronic spontaneous urticaria. Various autoallergens have been proposed to contribute to the pathogenesis of autoallergic CSU. These autoantigens are skin-derived, produced, and released by lesional immune cells including basophils, eosinophils, Th2 cells, and macrophages/monocytes, or reach the tissue from the circulation. Autoallergens and IgE AAb may form immune complexes. Cross-linking of FcεRI by antigen–IgE complexes results in mast cell degranulation causing the typical signs and symptoms of CSU, that is, itchy wheal and flare reactions and angioedema, as well as cytokine release causing further immune cell infiltration. In CSU, IgE AAb-driven reactions are primarily restricted to the skin presumably due to skin-prominent antigens and cross reactivity. BAS, basophil; EOS, eosinophil; MC, mast cell; Mφ, macrophage; Mo, monocyte; Th2: CD_4^+ helper type 2 cells.

Anti-IgE treatment has not been approved for the treatment of AD, due to low efficacy data in early pilot studies.[112] Radi et al. recently reviewed the promising therapeutic targets for AD. Some of them, such as alarmins, IL-4, IL-13, IL-5, and kinase inhibitors, may directly or indirectly impact levels of autoreactive IgE and their effects on FcεRI-bearing cells.[113]

5 | AUTOREACTIVE IGE IN BULLOUS PEMPHIGOID

Bullous pemphigoid (BP) is an autoimmune blistering disease characterized, in part, by the presence of IgG AAb directed against the hemidesmosomal proteins BP180 (BP antigen 2/type XVII collagen) and BP230 (BP antigen 1). Autoantibodies can be found in the bloodstream, affected tissues, and blister fluid. IgE autoreactivity in BP was first suggested by Provost et al. (1974).[114] The study utilized immunofluorescence (IF) to discover that patients with BP can exhibit IgE autoreactivity against the skin basement membrane zone (BMZ), but the specific autoantigens were unknown at that time.[114]

IgE AAb are held to contribute to the pathogenesis of BP by activating skin mast cells and basophils, similar to CSU and AD. The ability of recombinant BP-180 to activate BP patient basophils and the presence of anti BP-180 IgE on skin mast cells in BP lesions were clearly established.[115] In addition, their effects on FcεRI-expressing eosinophils accumulated in skin lesions seem to be central in the pathophysiology of BP[116] (Figure 4).

It was not until 1996 that BP230 was identified as the first IgE autoallergen in BP using a recombinant 55-kDA protein (rBP55) obtained from its cDNA sequence.[117] Four years later, BP180 was also identified as an IgE autoallergen in BP after being cloned.[118,119] With the rise and development of technologies, such as enzyme-linked immunosorbent assay (ELISA) and multi-allergen microarray (ISAC™ sIgE 112, Phadia), levels of IgE AAb against BP180 and BP230 were reported by multiple independent research groups at variable rates (Table 3). Anti-BP180 IgE positivity in BP patients varied from 0% to 89% in 18 studies, and anti-BP230 IgE varied from 22% to 76% in seven studies.[114,115,117–137] This heterogeneity in prevalence of anti-BP180/BP230 IgE in patients with BP may be due to different patient populations and different detection methods (ELISA, IF or protein microarray). The co-occurrence of IgG and IgE AAb in the same patients, competing for the same antigen and epitope, could also influence detection levels.

Currently, there is a lack of recombinant anti-BP180/230 IgE as positive control and bona fide standard available for research

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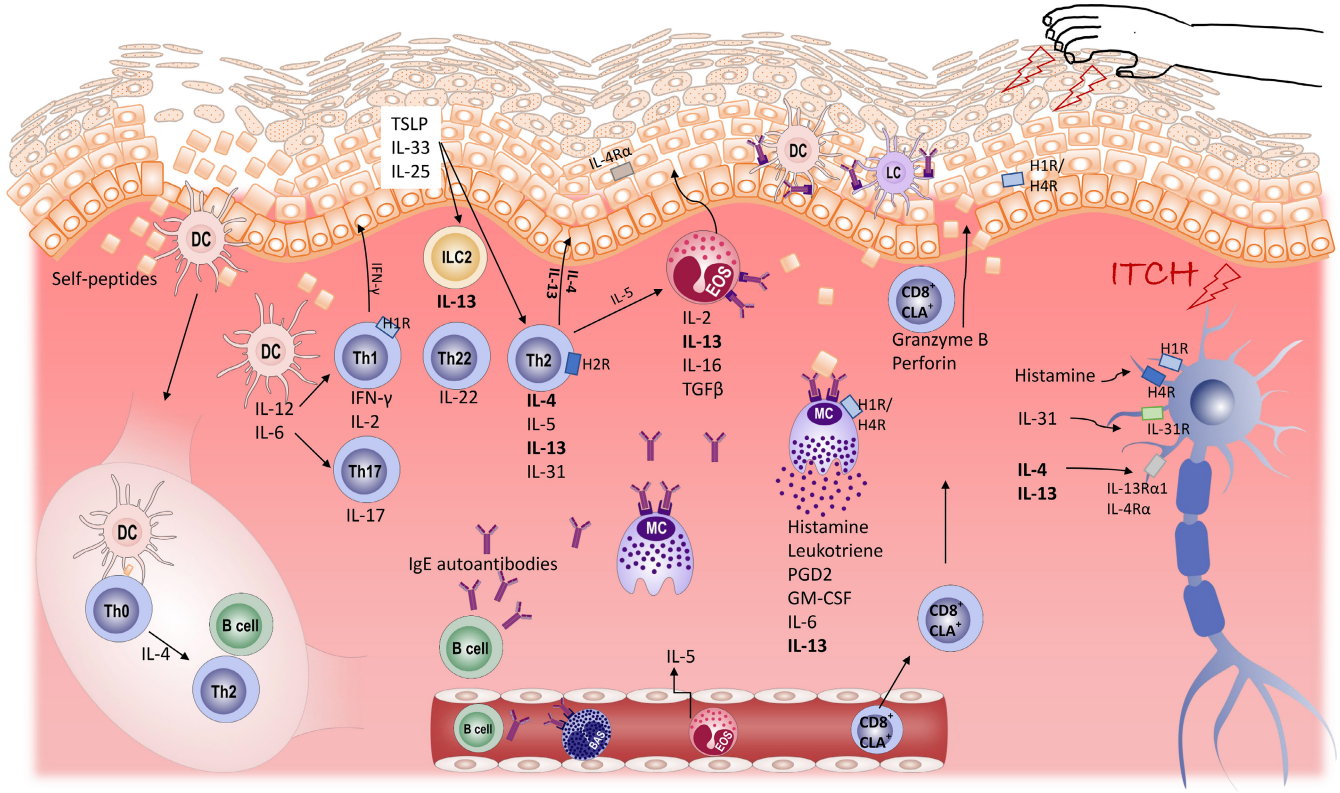


FIGURE 3 Contribution of autoreactive IgE to atopic dermatitis pathophysiology. IgE AAb are held to contribute to the pathophysiology of atopic dermatitis (AD). Intracellular and intranuclear peptides originating from damaged cells of the epidermis can be picked up by antigen presenting cells (dendritic cells or Langerhans cells), processed and presented to naïve T cells with intermediate affinity to self-antigens in the lymph nodes. The presence of IL-4 results in class-switch of the B cells to the production of IgE (auto)antibodies. Humoral autoimmunity may enhance the sensitization and activation of FcεR-expressing cells, such as mast cells, basophils, eosinophils, dendritic cells, and Langerhans cells. The release of inflammatory mediators decreases the skin barrier function, promotes spongiosis and hyperkeratosis, and activates the sensory nerve endings via receptor signaling. The sensation of itch promotes scratching of the skin and further damage. Also, $CD8^+$ memory T cells may participate in the pathological mechanisms by the production of granzyme B and perforin. BAS, basophil; CLA, cutaneous lymphocyte-associated antigen; DC, dendritic cell; EOS, eosinophil; GM-CSF, granulocyte-macrophage colony-stimulating factor; HR, histamine receptor; IFN, interferon; ILC, innate lymphoid cell; LC, Langerhans cell; PGD2, prostaglandin D2; TGF, transforming growth factor; Th, T helper cell; TSLP, thymic stromal lymphopoietin.

purposes. Six studies have evaluated anti-BP180 IgE and anti-BP230 IgE in the same cohort of BP patients.[118,123,124,132,133,135] Additionally, only one study has assessed IgE AAb against the intracellular domain of BP180,[125] while 17 studies have assessed IgE autoantibodies targeting the ectodomain (NC16A) of BP180.[115,118,119,122–126,128,129–133] This highlights the need for the development of standardized assays and research on autoallergen epitope mapping. These efforts are crucial for gaining a comprehensive understanding of the involvement of IgE AAb in BP pathogenesis.

The increased expression of cell-bound and soluble IgE receptors including sFcεRI and sCD23 suggests that the regulation of IgE production and the role of IgE AAb in the pathophysiology of BP are complex.[116] The studies conducted so far report no consistent relationship between IgE AAb levels and BP disease activity (Table 3), although the majority of studies reported a positive correlation with more severe clinical manifestations of BP. There is insufficient evidence to support higher IgE autoantibody levels being associated with specific clinical phenotypes of BP.[138] This lack of consistency also extends to the association between IgE AAb levels and total IgE levels, as well as the presence of IgG AAb against the same target. Therefore, future studies should comprehensively evaluate both IgE and IgG AAb levels, as well as changes in total IgE and BP activity during the course of disease, to further elucidate the role of IgE in BP pathogenesis and the potential of targeting IgE for therapeutic purposes (see below).

6 | TARGETING IGE IN NON-ALLERGIC DISEASES

Several anti-IgE monoclonal antibodies (mAbs) are at various stages of preclinical and clinical development. These mAbs have been extensively reviewed in the context of allergic diseases.[139,140] Three anti-IgE mAbs have been tested so far in patients with autoallergic and autoimmune diseases: Omalizumab (OMZ) and its biosimilars, as well as the two others: Ligelizumab (LGZ) and UB-221.

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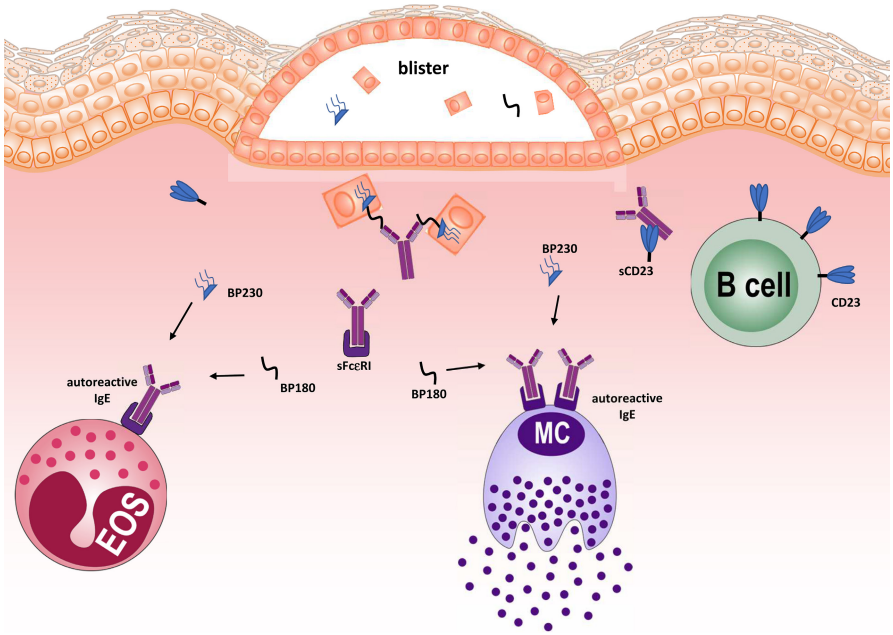


FIGURE 4 Contribution of autoreactive IgE to bullous pemphigoid pathophysiology. IgE AAb in bullous pemphigoid are directed to the intracellular hemidesmosome protein BP230 and the transmembrane ECM-linker protein BP180 located in the basement membrane zone (BMZ) of the skin. These auto-IgE have a high prevalence in BP patients and share the same epitopes with co-occurring autoreactive IgG. Cross-linking of FcεRI on mast cells and eosinophils in skin lesions of BP patients has been demonstrated, and anti-IgE therapy with omalizumab has been reported to be beneficial in a small cohort of patients. However, no consistent relationship between IgE AAb levels and disease activity in BP patients has been established yet. Increased expression of cell-bound and soluble IgE receptors in BP including sFcεRI and sCD23 further suggests a complex regulatory network of IgE production.

6.1 | Omalizumab

OMZ (Xolair®) is a humanized anti-IgE mAb that was first approved in 2003 for the treatment of moderate-to-severe asthma. In 2014, it became the first FDA-approved mAb for the treatment of CSU.[141–143] OMZ targets free IgE and precludes binding of IgE to both FcεRI and CD23.[144–146] OMZ recognizes structural epitopes in the Cε3 domain of the constant region of IgE that also contains key epitopes for binding of IgE to both FcεRI and CD23, thus preventing their binding to these receptors.[144–146] Importantly, OMZ poorly recognizes IgE already bound to FcεRI. This represents an essential safety feature as it does not induce activation of mast cells and basophils through FcεRI-cross-linking.[145,147] However, it also implies that repeated injections of OMZ are required in order to trap IgE as it slowly detaches from FcεRI. Several OMZ biosimilars such as GBR 310, CT-P39, and CMA007 are now at various stages of clinical development.[148–150]

6.2 | Ligelizumab

LGZ is an anti-IgE mAb with a K_D of 35 pM, which is 88-fold stronger than the K_D of OMZ.[151] LGZ also recognizes epitopes in the Cε3 domain of free IgE and thereby impairs binding of IgE to both FcεRI and CD23.[152] However, OMZ and LGZ have distinct inhibition profiles, due to their differences in affinity and epitopes recognized in the IgE Cε3 domain.[151] LGZ shows higher potency than OMZ at preventing binding of IgE to FcεRI, but is less potent at blocking binding of IgE to CD23.[151]

6.3 | UB-221

More recently, a novel anti-IgE mAb, UB-221, was tested in CSU in a first-in-human trial.[153] Unlike OMZ and LGZ, monomeric UB-221, in vitro, binds to CD23-bound IgE, and UB-221-IgE complexes freely engage CD23. These features may allow UB-221 to inhibit IgE production through CD23 engagement unlike LGZ and OMZ, at least ex vivo.[153] UB-221 binds IgE with a strong intermediate affinity as compared to OMZ and LGZ (LGZ > UB-221 > OMZ), is also able to prevent FcεRI-mediated basophils/mast cells activation and degranulation induced by IgE/antigen complexes, and, like LGZ, exhibits superior IgE-neutralizing activity than OMZ.

All three anti-IgE mAbs induce a rapid and pronounced serum-IgE reduction, and their efficacy has been and/or is currently being tested in the following AbAID.

6.3.1 | Chronic spontaneous urticaria

The efficacy of OMZ has been shown in many clinical trials and summarized in a recent systematic review, which identified 10 randomized controlled trials (RCTs) with a total of 1620 CSU patients.[154] Although most CSU patients respond well to OMZ, their response

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TABLE 3 Autoreactive IgE specificities, prevalence, and association with disease activity/total IgE/autoreactive IgG of same specificities in bullous pemphigoid.

Year	Ref	IgE Targets	Prevalence of autoreactive IgE	Association with disease activity	Association to total IgE levels	Association to same specificity autoreactive IgG levels	Methods
1974	[114]	BMZ	25% (4/16)	nd	nd	nd	IF
1976	[120]	BMZ	50% (2/4)	nd	nd	nd	IF
1980	[121]	BMZ	60% (15/25)	nd	nd	nd	IF
1996	[117]	BP230	63% (12/19)	POS	nd	nd	RIA
1998	[118]	BMZ, BP230, BP180	BP180: 0% (0/39); BMZ or BP230: 46%(18/39)	nd	POS	POS	IF, IB, ELISA
2000	[119]	BP180	55% (10/18)	POS	nd	POS	IB, ELISA
2003	[115]	BP180	67% (20/30)	POS	nd	nd	IB, BHRA
2005	[122]	BP180	80% (8/10)	nd	nd	POS	IB, BHRA
2008	[124]	BP180, BP230	BP180: 22% (8/37), BP230: 22% (8/37)	POS	POS	POS	ELISA
2008	[123]	BP180, BP230	BP180:30% (20/67), BP230:67% (45/67)	NEG	POS	NC	ELISA
2009	[125]	BP180	89% (16/18)	nd	NC	POS	IB
2009	[126]	BP180	77% (33/43)	POS	nd	POS	ELISA, IB, IF
2011	[127]	BMZ	43% (3/7)	nd	nd	POS	IF
2013	[128]	BP180	61% (19/31)	NC	nd	NC	ISAC
2014	[129]	BP180	75% (36/48)	POS	POS	POS	ELISA
2015	[130]	BP180	73% (27/37)	NC	NC	nd	ELISA
2015	[131]	BP180	24% (10/41)	NC	nd	POS	ELISA
2015	[132]	BP180, BP230	DIF: 18% (18/100); ELISA: 17% (3/18)	NC	nd	NC	IF, ELISA
2016	[133]	BP180, BP230	BP180: 71% (12/17), BP230:76% (13/17)	POS	nd	POS	ELISA
2016	[134]	BP180	79% (61/77)	POS	nd	POS	ELISA
2017	[135]	BP180, BP230	BP180:58% (21/36), BP230: 50% (18/36)	POS	POS	POS	ELISA
2017	[136]	BP180	40% (47/117)	POS	POS	POS	ELISA
2020	[137]	BP180	DIF: 19% (10/53)	NC	NC	POS	IF, ELISA

Abbreviations: BHRA, Basophil Histamine Release Assay; BMZ, basement membrane zone; ELISA, Enzyme-linked immunosorbent assay; IB, Immunoblotting; IF, Immunofluorescence; ISAC, Immuno solid-phase allergen chip; POS, Positive association; NC, no correlation; nd, not determined; NEG, Negative association; RIA, Radio-Immuno Assay.

to treatment in the clinical setting defined two endotypes: early responders (usually before week 4), with autoallergic CSU and IgE AAb, and late responders (after week 4 up to week 24) with type IIb autoimmune CSU and anti-FcεRI or anti-IgE IgG AAb.[155] Rapid reduction of free IgE by OMZ in patients with autoallergic CSU leads to a rapid depletion of IgE AAb and thus a rapid response to treatment,[155] whereas a slow response could be explained by FcεRI downregulation by skin mast cells, which may take months,[156] and the action of anti-IgE IgG AAb on remaining occupied FcεRI.[157] Complete non-response, seen in up to 20% of CSU patients,[158] suggests the existence of other endotype(s), with a pathogenesis not involving IgE or FcεRI.[154]

LGZ was found to outperform OMZ efficacy, in terms of rate of complete responders and longer lasting effects, in a multicenter randomized, controlled, phase IIb study including 382 patients with inadequately controlled CSU.[159,160] However, LGZ was not found superior to OMZ in phase III CSU trials, and the development for CSU was stopped. LGZ has the same drawbacks as OMZ for the treatment of type IIb autoimmune CSU and non-autoallergic endotypes. In a phase I clinical trial with 15 CSU patients, a single dose of UB-221 led to a decrease in total serum IgE levels and improved disease symptoms.[153] Of note, quilizumab, an anti-IgE mAb that binds only to membrane IgE on B cells (BCR) and not soluble IgE, was tested in CSU and reduced median serum total IgE levels by 30% at week 20.

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However, the treatment did not result in meaningful improvements in disease activity.[161]

6.3.2 | Atopic dermatitis

The efficacy of OMZ in AD has been evaluated in many case series/reports[162] and was formally evaluated in three small clinical trials. A recent randomized clinical trial (RCT) in 62 pediatric AD patients showed efficacy of OMZ in reducing AD severity and improving quality of life.[163] Two previous controlled studies (NCT00822783 and NCT01678092) did not show an overall efficacy of OMZ on the clinical course of AD patients after 16 or 24 weeks of treatment compared with AD patients in placebo groups, despite some effects on IgE levels, FcεRI expression levels, and pro- and anti-inflammatory cytokine levels.[112,164] Accordingly, LGZ did not show efficacy in a RCT including 22 patients.[165] Another anti-IgE approach with the anti-CεmX mAb FB825 targeting membrane IgE on B cells is currently under investigation (NCT04413942). In clinical practice, a subgroup of AD patients does benefit from anti-IgE treatment, as shown in case reports and smaller case series,[166–169] which implies that IgE plays an important role in the pathophysiology of AD in these patients. The efficacy of OMZ in AD patients with IgE AAb has not been investigated so far. Interestingly, one study showed that patients with a filaggrin mutation were unresponsive to omalizumab treatment, suggesting that the presence of primary skin barrier deficiency may likely be a factor for non-response.[167]

6.3.3 | Bullous pemphigoid

OMZ use in BP was analyzed in a systematic review which included 13 case series/reports and analyzed 56 patients. Complete response was achieved in 55.4% of patients with an overall response rate of 87.5%. While baseline eosinophilia was marginally associated with complete remission, no association with baseline IgE could be shown.[170] French BP Management Guidelines recommend the use of omalizumab in a subset of patients with predictors for OMZ efficacy, that is, urticarial lesions, significant blood eosinophilia, high serum IgE levels, even though the relapse rate reported was up to 80%.[171] Of note, a clinical trial (NCT01688882) to evaluate the efficacy and safety of OMZ in patients with active BP despite oral steroid treatment was terminated because the predefined criteria of efficacy were not reached. Currently, only one ongoing trial indirectly targeting IgE-associated mechanisms (dupilumab) is conducted in this indication (NCT05649579).

6.3.4 | Systemic lupus erythematosus

The tolerability of OMZ was evaluated in a phase Ib clinical trial in patients with SLE with increased levels of anti-dsDNA, anti-Sm, and/or anti-SSA IgE AAb measured by ELISA assay and moderately active non-renal, non-CNS lupus.[172] SLE Disease Activity Index 2000 (SLEDAI 2K) scores but not in other measures of clinical activity improved in the OMZ group. Also, the SLE Responder Index and the absolute change in the SLEDAI 2K score were low when compared to other larger clinical trials. However, there was no worsening in other scores, and OMZ treatment showed a trend toward reduction in IFN gene signature, especially in subjects with high baseline IFN signature. Importantly, IgE AAb in SLE facilitate TLR9-mediated pDC activation and IFNα production.[23] OMZ and LGZ have both been shown to remove IgE from pDC surface and to restore TLR9 and T regulatory cells homeostasis.[173,174] The IgE-dependent basophil-mediated AAb production amplification in SLE also supports targeting IgE in this disease.[32] Hence, it will be of primary interest to confirm the therapeutic value of the anti-IgE approach for SLE in clinical trials with larger patient populations.

Patients affected by the AbAID discussed in the present review may putatively benefit from IgE-targeting therapies based on the prevalence of the identified autoreactive IgE and the FcεRI-bearing cells known to be involved in their pathophysiology. Further investigations will be required at both pathophysiological and clinical levels to validate the therapeutic values of targeting IgE and autoreactive IgE in these conditions.

7 | UNMET NEEDS IN ABAID WITH AUTOREACTIVE IGE AND CONCLUDING REMARKS

Important current challenges need to be addressed to better characterize IgE AAb as pathogenic factors and therapeutic targets. First, the extremely low concentration of these antibodies can make their quantification difficult. In this regard, new IgE detection methods are being developed, such as isotype-specific agglutination-PCR (ISAP)[175] and luciferase-linked immunosorbent assay (LuLISA),[176] which can both detect specific IgE in 1 μL of sample. Both methods have so far only been tested for measurement of IgE against allergens, but could be and should be extended to autoantigens. The high sensitivity of these approaches could allow screening of multiple potential autoantigens, and may be used for further epitope mapping studies once important autoantigens have been identified. IgE AAb detection may also be improved by purifying IgE to remove IgG AAb competing for the same antigen and epitope.[177]

Better functional tests are also needed to assess IgE AAb and their antigens for their effects on FcεRI-bearing cells. Basophil activation tests are useful to screen potential autoantigens for IgE-mediated degranulation,[178] but can be challenging to implement given the low frequency of these cells in blood samples. As an alternative approach, mast cell activation assays are now being developed,[179] and the availability of novel mast cell models such as human mast cells derived from pluripotent stem cells and mouse mast cells expressing the human FcεRI may facilitate screening of potential autoallergens.[180,181]

A deeper knowledge of the diversity and specificity of IgE repertoires in CSU and other autoimmune diseases is needed in order

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to identify key IgE clones that are likely to drive autoallergic responses. However, studying IgE repertoires is challenging due to the extremely low frequency of circulating IgE-producing B cells, making their isolation almost impossible using standard flow cytometry sorting strategies. However, Croote and colleagues have recently reported the first successful paired variable heavy (V_H) and light (V_L) chain sequencing of IgE^+ B cells from allergic subjects.[182] A similar approach could be applied to CSU, AD, and other autoimmune diseases in order to gain knowledge on the diversity of IgE repertoires in these diseases. Importantly, once identified, these paired V_H-V_L sequences could be used to produce recombinant IgE to further assess characteristics of these mAbs (affinity, epitope mapping analysis, ability to induce mast cell degranulation), and to serve as positive controls for future standardized IgE detection methods.

IgE targeting benefits many CSU patients, shows encouraging results in SLE and some limitations in subsets of type IIb autoimmune CSU, AD, and BP patients. Despite the fact that IgE- and FcεRI-bearing cells are clearly involved in the pathophysiology of these diseases, they are not the only nor the main pathogenic factors in all patients. Hence, targeting other pathogenic factors along with IgE may provide quicker and more efficient clinical benefits. For instance, IgG AAb are pathogenic in SLE and BP either through Fc receptor-mediated or complement-mediated mechanisms.[7,116] In BP, targeting B cells with rituximab (anti-CD20 mAb), IgE with OMZ, or IL-4Rα with dupilumab may lead to similar clinical benefits.[183] Combining rituximab with OMZ as an adjuvant treatment (in a small cohort of patients) showed promising add-on effects in refractory BP patients.[184] Thus, similar approaches in other AbAID, where autoreactive IgE and IgG are pathogenic and where IgE or IgG targeting are not efficacious enough, may represent a promising therapeutic strategy.

Other chronic inflammatory diseases such as vasculitis or cardiovascular diseases may involve IgE AAb and FcεRI-bearing cells in their pathophysiology. Further investigations with recently developed tools may thus identify other conditions where targeting IgE AAb could be beneficial to improve patient care. Taken together, autoreactive IgE is involved in the pathophysiology of multiple immune-mediated diseases. This rapidly evolving knowledge holds strong potential for improving diagnosis, prediction of disease course, and personalized treatment approaches.

AUTHOR CONTRIBUTIONS

All the authors wrote and edited the manuscript, designed and produced the figures and tables, read and approved the final manuscript.

ACKNOWLEDGEMENTS

This work contributed from the support of EMBRN, the European Mast Cell, and Basophil Research Network (https://embrn.eu).

FUNDING INFORMATION

This work was supported by intramural funding and, the Fondation pour la Recherche Médicale (FRM) [grant # EQU201903007794] to N.C., the French Agence Nationale de la Recherche (ANR) [grants # ANR-19-CE17-0029 BALUMET to N.C. and ANRPIA-10-LABX-0017 INFLAMEX], by the European Research Council [ERC-2021-CoG 101043749] to LLR, by the Fonds Wetenschappelijk Onderzoek (grant # G056322N) to IKK and JG.

CONFLICT OF INTEREST STATEMENT

NC is or recently was a speaker and/or advisor for and/or has received research funding from argenx and Onward Therapeutics and is inventor on patents related to compositions and methods for treating or preventing lupus (W020120710042 & WO2016128565A1); IKK received research funding from Sanofi Regeneron, Pfizer and AbbVie; EK has no conflicts of interest regarding any aspects of this study; JS has conducted studies for, received research funds/was advisor for Allakos, Ascilion, AstraZeneca, CSL Behring, Celldex, Genentech, Escient, Novartis, Sanofi, Servier, ThirdHarmonicBio, ThirdRock and ThermoFisher; SA is or recently was a speaker and/or advisor for and/or has received research funding from AstraZeneca, Allakos, CSL Behring, Sanofi, Takeda, ThermoFisher, Moxie, and Novartis; CS has no conflicts of interest regarding any aspects of this study; Y-KX has no conflicts of interest regarding any aspects of this study; JG has no conflicts of interest regarding any aspects of this study; LLR is or recently was a speaker and/or advisor for and/or has received research funding from Argenx, Novartis, Ceva and Neovacs, and is inventor on patents issued or pending relating to IgE detection and anti-IgE therapies: EP2021/060829, EP20315224-4, WO2019197607 (A1); MM is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Amgen, Aralez, ArgenX, AstraZeneca, Celldex, Centogene, CSL Behring, FAES, Genentech, GIInnovation, GSK, Innate Pharma, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Merckle Recordati, Moxie, MSD, Novartis, Pfizer, Roche, Sanofi/Regeneron, Third Harmonic Bio, UCB, and Uriach.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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How to cite this article: Charles N, Kortekaas-Krohn I, Kocaturk E, et al. Autoreactive IgE: Pathogenic role and therapeutic target in autoimmune diseases. *Allergy*. 2023;78:3118-3135. doi:10.1111/all.15843

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